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Journal of Pharmacy Practice 2006; 19; 17

DOI: 10.1177/0897190005284095

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Fungal Opportunistic Infections in HIV Disease

Melody L. Duffalo, PharmD

Fungal pathogens can lead to many of the complications seen in advanced HIV disease and are commonly identified in HIV-infected populations with decreased immune function. Common fungal organisms affecting individuals with AIDS include Cryptococcus neoformans, various Candida species, and Histoplasma capsulatum. While infection with these organisms can be fatal, appropriate identification and management of the condition can result in reduced mortality

and the opportunity for effective management of HIV disease with highly active antiretroviral therapy. This article describes the clinical presentation and treatment of 3 fungal infections common in the immunocompromised individual with AIDS. Current antifungal therapy for the management of these infections is discussed. In addition, the role of newer antifungal agents in the setting of these conditions is reviewed.

KEY WORDS: Fungal disease, opportunistic infections, HIV disease, review, treatment.

FUNGAL OPPORTUNISTIC INFECTIONS

Opportunistic infections remain a major complication of AIDS. While highly active antiretroviral therapy (HAART) has led to a dramatic reduction in the frequency of opportunistic infections in the developed world,¹ there is still significant morbidity and mortality associated with the complications of HIV disease. As of 2003, in the United States, a cumulative estimated 524,061 deaths have been attributed to complications of AIDS.² Fungal pathogens represent a significant portion of disease-causing organisms that have an impact on immunocompromised patients. While the prevalence of various fungal opportunistic infections varies geographically, several infections respond successfully with appropriate treatment. This article reviews several fungal opportunistic infections seen in the setting of HIV disease: candidiasis, cryptococcal meningitis, and histoplasmosis.

CANDIDIASIS

Overview

The most common fungal infection in individuals with HIV infection is mucocutaneous candidiasis, which is a result of the yeast *Candida*. Yeasts are fungi that grow as single cells and reproduce by budding. There are several species that cause disease in humans. *Candida albicans* is the most common cause of disease in HIV-infected individuals. Other species less frequently associated with disease include *Candida*

tropicalis, *Candida krusei*, *Candida glabrata*, and *Candida parapsilosis*. *Candida* species are distinguished by the presence or absence of capsules, the size and shape of the yeast cells, the formation of true or pseudohyphae, and the presence of sexual spores. These organisms are part of the normal flora of the human gastrointestinal tract. Most disease is a result of overgrowth of the normal flora in an individual rather than person-to-person transmission.

There are 3 forms of mucocutaneous candidiasis that are common in HIV infection: oropharyngeal, esophageal, and vulvovaginal disease. Historically, the occurrence of mucocutaneous candidiasis was common, with up to 90% of persons with advanced disease developing oropharyngeal infection, 27% to 60% of women developing vaginal candidiasis, and 10% to 20% developing esophageal disease.³ However, treatment with azole antifungals and the subsequent introduction of HAART has led to a significant decline in the incidence of candida infections among HIV-infected individuals.^{1,4-6}

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JOURNAL OF PHARMACY PRACTICE 2006, 19;1:17-30
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DOI: 10.1177/0897190005284095

Invasive candidiasis occurs in persons with more advanced disease who have other risk factors for disseminated disease (indwelling venous catheters). Bloodstream infections, meningitis, intraabdominal infections, and osteomyelitis have also been described.

Clinical Presentation

Patients presenting with oropharyngeal candidiasis typically have symptoms that include oral pain, altered taste, and mouth lesions. Lesions may be pseudo-membranous, erythematous, or hypertrophic. Pseudo-membranous candidiasis, also known as thrush, typically presents as a creamy white exudative plaque that can be removed with a tongue depressor with bleeding. Lesions may be present on the buccal mucosa, palate, or tonsils. Erythematous candidiasis presents as flat, red, atrophic plaques on mucosal surfaces. Hypertrophic candidiasis is a curdlike, nonscrapeable raised plaque, which is similar in appearance to oral hairy leukoplakia.

Angular cheilitis may be present, which are red, fissured, crusting lesions (which may ulcerate) at the corner of the mouth. Lesions are painful and result in difficulty when opening the mouth. Esophageal candidiasis is generally presumptive and based on clinical symptoms of oropharyngeal candidiasis in addition to dysphagia or odynophagia. Retrosternal burning may be present. Candida vaginitis presents with vaginal discharge, vulvar rash, and/or vaginal pruritus or pain.

Diagnosis

Oropharyngeal colonization is common, and therefore culturing of the organism is typically not necessary. The KOH slide preparation, although not mandatory, can confirm the diagnosis, demonstrating characteristic pseudohyphae and spherical budding yeast. Upper endoscopy, although not necessary in all cases, may be used to confirm esophageal involvement, specifically in patients who fail to respond to initial treatment, or to rule out other causes of esophagitis (cytomegalovirus, herpes simplex virus, aphthous ulcers). The diagnosis of *Candida* esophagitis is confirmed by the presence of yeast forms on histologic examination. In vulvovaginal disease, a KOH preparation confirms the presence of yeast forms on microscopic examination. This test should always be performed to confirm the diagnosis of candidiasis since many conditions may present with discharge or similar lesions.

Treatment

There are many options available for treatment of mucocutaneous forms of candidiasis. Options for treatment of noncomplicated disease include local and systemic therapies and are presented in Table 1.⁷ A clinical response to initial treatment is seen with most agents. Factors that determine response include choice of agent, extent and severity of infection, adherence to regimen, and pharmacokinetic and pharmacodynamic properties of the drug. For oropharyngeal disease, topical agents include the imidazoles nystatin and clotrimazole, while systemic agents usually consist of oral triazole therapy. Comparisons of topical and systemic therapies have generally shown similar response rates; however, clinical signs and symptoms of disease respond more rapidly with systemic therapy, and mycologic clearance rates are improved.^{8,9} For mild cases of oropharyngeal disease, topical therapy may be warranted. However, moderate to severe cases generally require systemic therapy. Triazole antifungals are clearly the most commonly prescribed agents for mucocutaneous disease. Choices for systemic triazole therapy include fluconazole, itraconazole, and ketoconazole. Fluconazole is superior to ketoconazole, while itraconazole is equivalent.^{10,11} The reduced efficacy of ketoconazole, along with the potential for significant drug interactions, makes ketoconazole a less than optimal choice for treatment. In addition, problems with absorption in the absence of an acidic environment and an increased risk of toxicities further limit its use. For these reasons, ketoconazole is rarely, if ever, used as treatment of oropharyngeal or esophageal disease.

Esophageal candidiasis requires systemic therapy. Oral triazole antifungals are generally indicated for treatment of esophageal disease. Several studies have compared various triazoles for use in this setting. As with oropharyngeal disease, a study comparing fluconazole 100 mg daily with ketoconazole 200 mg daily demonstrated superiority of fluconazole for management of esophageal disease, with 81% versus 66% of patients achieving symptom resolution.¹² A second study that compared fluconazole and itraconazole for the treatment of esophagitis demonstrated similar efficacy between these 2 treatment groups.¹³ The triazoles used for treatment of esophageal candidiasis are listed in Table 1. Both fluconazole and itraconazole are available in oral suspensions, which can provide added benefit because of both topical and systemic antifungal effects.^{14,15} Voriconazole, a newer triazole, has demonstrated activity against various *Candida* species and has been shown to be equivalent to fluconazole for the

Table 1
Therapeutic Options for Uncomplicated Oropharyngeal or Esophageal Candidiasis

Agent	Formulation	Administration	Duration	Side Effects
Nystatin ^a	Oral suspension, 100 000 U/mL	400-600 000 U (4-6 mL), 4 times daily	7-14 d	GI upset
Clotrimazole ^a	Troches 10 mg	10 mg (1 troche), 5 times daily	14 d	Altered taste, GI upset
Fluconazole	Tablets (50, 100, 200 mg), parenteral	200 mg day 1, then 100 mg daily	14 d ^b	GI upset, hepatitis
Itraconazole	Oral solution (10 mg/mL), Capsules (200 mg) ^c	200 mg (20 mL) swished vigorously in mouth, then swallowed	7-14 d	GI upset, hepatitis
Ketoconazole ^d	Tablets (200 mg)	200 mg daily, may increase to 400 mg daily if insufficient response	7-14 d	GI upset, hepatitis, endocrine effects

Note: GI = gastrointestinal.

a. Topical effects only. Topical therapy should not be used in esophageal candidiasis.

b. Treatment of esophageal candidiasis should be for a minimum of 3 weeks and for at least 2 weeks following resolution of symptoms.

c. Capsules are less effective than fluconazole and are generally not recommended because of variable absorption.

d. Ketoconazole is less effective than fluconazole, has variable absorption due to requirement of acidic environment, and has multiple drug interactions due to effects on cytochrome P450 3A4 inhibition. Currently not recommended in Infectious Diseases Society of America guidelines.

treatment of esophageal candidiasis.¹⁶ However, use of this agent was associated with an increased risk of toxicities. Currently, voriconazole is not considered a first-line agent for treatment of esophagitis related to candida infection. Because it has shown activity against fluconazole-resistant strains of candida, reserving its use for treatment of fluconazole-resistant disease and treatment-refractory cases may be warranted.¹⁷

Vulvovaginal candidiasis is managed effectively with topical therapy.⁷ Numerous topical preparations are available and used for the treatment of vaginal candidiasis. Short-course therapy with topical creams or suppositories is effective, and systemic therapy is often unnecessary. However, a single oral dose of fluconazole 150 mg has similar efficacy to 7 days of topical therapy and is a convenient and popular alternative to topical preparations.¹⁸

Relapse

Relapse is common in HIV-infected individuals, and many patients will develop recurrent mucosal disease. Management of relapse often involves retreatment of recurrent episodes of infection with a full course of an antifungal agent. With many patients, however, recurrent symptomatic disease leads to a need for chronic suppression with maintenance doses of an antifungal agent. Fluconazole 100 to 200 mg/d has been successful at suppressing recurrent symptoms of oropharyngeal disease and prevention of esophagitis.¹⁹

For vaginal candidiasis, single weekly doses of fluconazole 100 mg have shown to be beneficial in the prevention of recurrent vaginitis.²⁰ Although these strategies are effective, there is concern about the potential for the development of azole-resistant disease.²¹

Refractory Disease

Refractory disease is the failure to respond to antifungal treatment with appropriate doses for a standard duration of time. Because fluconazole has become the standard of treatment for management of candidiasis, much attention has been centered on fluconazole-refractory disease. Several risk factors for the development of refractory candidiasis have been identified and include advanced HIV disease (CD4 cells <50 cells/mm³), prolonged exposure to antifungal therapy, and a history of prior opportunistic illnesses.^{22,23}

Reasons for treatment failure are multifactorial and may include inadequate drug absorption, drug interactions, and drug resistance. The management of refractory disease includes an assessment of agents tried, adherence to the regimen, and the identification of potential drug interactions that may be affecting the pharmacokinetics of the drug. Identification of potential reasons for treatment failure can ultimately lead to appropriate adjustments in treatment and subsequent treatment response.

Options for refractory disease depend highly on prior exposure to antifungal therapy. In all cases, opti-

mization of antiretroviral therapy is essential and can result in improvement and resolution of complicated cases.²⁴ For fluconazole-refractory oropharyngeal disease, options include dose escalation of fluconazole to maximum doses of 800 mg/d or a switch to an alternative antifungal agent, which may include itraconazole cyclodextrin oral solution in doses of ≥ 200 mg/d, amphotericin B oral suspension, or voriconazole.⁶ Response rates for itraconazole have been reported to be approximately 60%.²⁵ Amphotericin B oral suspension is no longer commercially available; however, it can be compounded using intravenous (IV) or powder formulations.²⁶ Voriconazole at doses of 200 mg twice daily is another oral triazole recommended for treatment of refractory cases.

In instances in which oral therapy fails, systemic amphotericin B at doses of 0.5 to 1 mg/kg/d IV for 7 to 14 days may be necessary. Parenteral caspofungin in doses of 50 mg/d can also be used for refractory cases.⁷

Drug Resistance

Azole-resistant *C albicans* has been well described in HIV-infected patients.²⁷⁻³⁰ Rates of resistance to various triazole antifungals have been reported and vary widely in clinical studies, with one study demonstrating fluconazole resistance rates of up to 56%.³⁰ Several mechanisms of drug resistance contribute to treatment failure with triazole antifungal drugs. Resistance can develop as a result of reduced intracellular concentrations of the triazole. This can occur as a result of alteration of the target for azole antifungals, the cytochrome P450-dependent 14 α -demethylase. Reduced cell permeability and active efflux of the drug out of the cell by multidrug resistance gene products of the P-glycoprotein type also contribute to the development of resistance.³¹ While resistance can occur, it is not clear whether certain mechanisms of resistance may be overcome with higher doses of the drug. In AIDS patients, major factors that have been associated with resistance to fluconazole include advanced HIV disease (CD4 counts < 50 cells/mm³) and prior exposure to fluconazole, with greater likelihood of resistance in patients with longer duration of treatment with fluconazole and/or more frequent episodic treatment.^{22,29}

Because of the concern over azole resistance and the limitations with antifungals currently used for refractory disease, new azole antifungals with activity against fluconazole-resistant strains of *Candida* species are being developed. Voriconazole and caspofungin are more recent additions to the antifungal armamentarium, while posaconazole,

avuconazole, and anidulafungin are actively being developed. Micafungin (Mycamine), an agent in a new class of antifungals known as echinocandins, has recently been approved and is available in an IV formulation. All of these agents have demonstrated in vitro activity against *Candida* species. Voriconazole (Vfend) was approved in the United States in 2002 and is available in both oral and IV formulations. Voriconazole has demonstrated equivalence to fluconazole for treatment of esophageal candidiasis, although it was associated with more toxicities.¹⁶ Despite these added toxicities, treatment of fluconazole-resistant strains with voriconazole has shown some success, and use of this agent in resistant cases of disease may be warranted.¹⁷ Voriconazole is currently not licensed for this indication in the United States, awaiting additional data from ongoing clinical trials. Caspofungin, a member of a novel class of antifungals known as candins, is a parenterally administered drug that has demonstrated activity against *Candida* species, including fluconazole-resistant organisms.³²⁻³⁵ This agent may be useful in refractory disease and invasive candidemia, specifically in patients who fail or are intolerant to standard and liposomal preparations of amphotericin B. The availability of these agents both now and in the future will provide needed alternatives for refractory disease and resistant species.

CRYPTOCOCCOSIS

Background Information

Cryptococcus neoformans is an encapsulated, round to oval yeastlike fungal organism. There are 2 pathogenic varieties that are found worldwide, *Cryptococcus neoformans* var *neoformans* and *Cryptococcus neoformans* var *gattii*. The serotypes of *C. neoformans* are designated A, B, C, and D based on antigenic material found on the polysaccharide capsule.³⁶ *C. neoformans* var *neoformans* is associated with serotypes A and D and is most commonly associated with infection in AIDS patients. Serotypes B and C (*C. neoformans* var *gattii*) are endemic in Australia and Southern California and are isolated from normal hosts. The organism is a soil organism found mainly in debris around pigeon roosts and soil contaminated with decaying pigeon or chicken droppings.

Infection is believed to occur when the organism enters the host via the respiratory route. This results in colonization and respiratory infection. The organisms then spread to extrapulmonary tissues, specifically the brain tissue, where it causes meningitis. Immune status plays an important role in determining the outcome of

infection. Most serious infections occur in patients with T cell immunity dysfunction. HIV-infected individuals at greatest risk for infection are those with CD4 counts less than 50 cells/mm³.³⁷

The prevalence of cryptococcal infection varies geographically. In the United States, infection is more common east of the Mississippi River. AIDS-related cryptococcal infections are higher in Africa and Southeast Asia than in the United States but appear less often in Europe.³⁸ The incidence of cryptococcal meningitis has declined since the 1990s secondary to the availability of effective antiretroviral therapy and the introduction of azole antifungals.³⁹ However, in developing countries with limited access to medications, cryptococcal disease continues to be a leading cause of AIDS-related death.^{40,41}

Clinical Presentation

The most common clinical presentation of cryptococcal infection in AIDS patients is central nervous system (CNS) infection, presenting as meningitis. Symptoms of HIV-associated cryptococcal meningitis are insidious and can occur days to weeks prior to presentation. Symptoms may include headache, altered mental status, photophobia, and blurred vision. Nausea and vomiting are frequent, but traditional symptoms of meningitis, such as stiff neck, are uncommon. Physical findings may include fever and abnormal neurologic examination. Acute meningitis is often complicated by cerebral edema and an elevated opening pressure upon lumbar puncture.

Pulmonary cryptococcal infection is diagnosed less frequently in AIDS patients. It is, however, postulated that this organ system is the primary portal of entry for cryptococcal disease. Patients with pulmonary disease may present with cough, fever, malaise, shortness of breath, pleuritic pain, and an abnormal chest radiograph. Chest radiographs typically reveal focal or diffuse infiltrates similar to those seen with other opportunistic infections, specifically *Pneumocystis jirovecii* pneumonia.

Cutaneous cryptococcal infection is usually a sign of disseminated disease. Lesions can vary and may present as pustules, vesicles, plaques, or subcutaneous swelling. The most typical presentation appears similar to the dermatologic features of molluscum contagiosum.⁴²

Diagnosis

The diagnosis of cryptococcal meningitis is based on the evaluation of cerebrospinal fluid (CSF). Diagno-

sis can include the India ink stain, cryptococcal antigen test of serum or CSF, and the fungal culture. The most important test for initial diagnosis is the cryptococcal antigen test.

Patients who present with symptoms of cryptococcal meningitis should be tested for the presence of cryptococcal polysaccharide antigen through serum antigen testing. Antigen tests are positive in more than 99% of subjects with disease at titers >1:2048. Diagnosis can then be later confirmed with cultures.

Imaging of the brain is required prior to CSF sampling because of the potential for mass lesions within the brain. CSF sampling is critical, with examination of the sample for fungal culture, CSF cryptococcal antigen titer, glucose level, protein level, and cell count with differential. CSF opening pressure should also be measured. Elevated intracranial pressure is common in patients with cryptococcal meningitis and is present in more than 50% of patients with disease. Measurement of opening pressure should occur while the patient is in the lateral decubitus position, with elevated pressures defined as measurements greater than 200 mm H₂O.⁴³ Examination of the CSF reveals elevated protein, normal or depressed glucose levels, elevated leukocyte counts, and numerous organisms.

Treatment

The discussion on treatment of cryptococcal infection focuses on the most common presentation of cryptococcal disease in AIDS patients: cryptococcal meningitis.

Treatment of cryptococcal disease in HIV-positive patients is always indicated. Treatment generally consists of 3 phases: induction, consolidation, and maintenance. Regimens used for the treatment of cryptococcal meningitis are presented in Table 2, based on current guidelines published by the Infectious Diseases Society of America (IDSA).⁴³ There are 3 antifungals that are of benefit in the treatment of cryptococcal disease: amphotericin B, fluconazole, and flucytosine. Itraconazole appears to be less effective than fluconazole in the management of cryptococcal disease.^{44,45} Flucytosine is always used in combination regimens because of the rapid development of resistance in the setting of monotherapy.⁴⁶ There is limited data on lipid formulations of amphotericin B for treatment; however, toxicity profile advantages may warrant its use alone or in combination with flucytosine.⁴⁷

The therapeutic approach consisting of initial high-dose amphotericin combined with flucytosine followed by oral triazole therapy is the preferred regimen

Table 2
Current Infectious Diseases Society of America Recommendations for Treatment of Cryptococcal Meningitis

Stage	Preferred Regimen	Alternative Regimen
Induction	Amphotericin B 0.7-1 mg/kg IV QD plus Flucytosine 25 mg/kg PO QID	Amphotericin B 0.7-1 mg/kg IV QD or Liposomal amphotericin B 3-6 mg/kg IV QD Fluconazole 400-800 mg IV QD with or without Flucytosine 25 mg/kg PO QID
Consolidation	Fluconazole 400 mg PO QD	Itraconazole 400 mg PO QD
Maintenance	Fluconazole 200 mg PO QD	Amphotericin B 0.6-1 mg/kg IV 1-3 times per wk Itraconazole 200 mg PO QD-BID

Note: IV = intravenous; QD = every day; PO = orally; QID = 4 times a day; BID = twice a day.

for the induction phase of treatment of cryptococcal meningitis. Prior to the HIV epidemic, treatment of cryptococcal disease consisted of combination therapy with amphotericin B and flucytosine, although doses tended to be lower and treatment was often for shorter durations.^{48,49} Because of concerns over immunosuppression and response to treatment, which stemmed from one National Institute of Allergy and Infection Disease (NIAID)-sponsored study, higher doses of amphotericin and flucytosine were initially used to treat AIDS patients presenting with symptoms.⁴⁸

Problems with tolerability, poor outcomes despite therapy, and the increased incidence of disease led to further evaluation of alternative treatment strategies. While searching for more effective, tolerable, and convenient regimens continued, data continued to demonstrate superior results with the combination regimen of amphotericin B and flucytosine.^{48,49}

Current IDSA recommendations stem from a large, randomized clinical trial that evaluated combination antifungal therapy for induction therapy as well as the optimal strategy for maintenance therapy to prevent relapse.⁴⁴ The study was sponsored by the NIAID Mycosis Study Group (MSG) and AIDS Clinical Trials Group (ACTG) and investigated 2-week induction therapy with amphotericin B 0.7 mg/kg/d and flucytosine 100 mg/kg/d versus amphotericin B alone, followed by maintenance treatment with fluconazole 400 mg/d or itraconazole 200 mg twice daily. The initial phase comparison demonstrated similar response rates between amphotericin B alone and amphotericin B in combination with flucytosine, with no mortality benefit or improvement in clinical course with the combination regimen. However, flucytosine was well tolerated, and patients on the combination regimen had better CSF sterilization rates and a lower incidence of later relapse. In this same study, comparison of maintenance therapy with fluconazole versus itraconazole demonstrated no significant difference in clinical symptoms,

response rate, or mortality between the 2 triazole regimens, but trends favored fluconazole.⁴⁴ A second, smaller study showed similar results and further supports a treatment approach using amphotericin and flucytosine for 2 weeks, followed by fluconazole maintenance therapy.⁴⁹

The NIAID's MSG/ACTG trial confirmed the effectiveness of combination therapy for acute management of cryptococcal meningitis, as well as the benefit of oral triazoles for consolidation and maintenance phases of treatment. In addition, this study demonstrated an overall acute mortality of 6%, which was lower than that previously reported in any trial evaluating the treatment of cryptococcal meningitis in AIDS patients.⁴⁴

Oral regimens for acute treatment of cryptococcal meningitis have been studied. Several studies have addressed the use of oral fluconazole regimens for induction and consolidation phases of treatment. One small study evaluating fluconazole 400 mg/d versus amphotericin plus flucytosine demonstrated higher failure rates in the fluconazole group, which resulted in early study termination.⁵⁰ Another NIAID-sponsored study comparing fluconazole to amphotericin B for cryptococcal meningitis in AIDS patients failed to show any significant differences in outcomes between the 2 regimens.⁵¹ However, the median dose of amphotericin B was 0.4 mg/kg/d, and flucytosine was rarely employed in either group. In addition, while not statistically significant, mortality rates were higher during the first 2 weeks of therapy with fluconazole.

Combination oral therapy with fluconazole and flucytosine has also been studied. One study comparing combination fluconazole (400 mg/d) and flucytosine (150 mg/kg/d) versus fluconazole monotherapy demonstrated superior response rates with combination therapy, although the combination arm was associated with significantly greater side effects.⁵² In summary, while fluconazole therapy for in-

duction therapy appears to be less effective compared with amphotericin B and flucytosine, it does remain an alternative for those patients who cannot tolerate the preferred regimen.

Therapy with alternative azoles has been studied with limited success. Itraconazole 200 mg twice daily has been compared with amphotericin B 0.3 mg/kg/d plus flucytosine 150 mg/kg/d. There was a 41% failure rate in the itraconazole arm compared with no failures in the combination arm. In addition, there were more relapses in the group initially treated with itraconazole.⁵³ A second study compared itraconazole 200 mg twice daily with fluconazole 400 mg daily for primary treatment. Although no difference was seen in CSF sterilization between the 2 groups, the study was terminated early secondary to a poor response rate of approximately 40%.⁵⁴

Because of concerns with toxicity related to amphotericin B deoxycholate, there is interest in the use of liposomal amphotericin B (Ambisome, Abelcet) for management of cryptococcal disease. Several studies have evaluated liposomal formulations of amphotericin B. Two small studies have noted an earlier CSF sterilization rate in patients randomized to the liposomal preparation.^{47,55} In addition, 1 of these trials demonstrated less toxicity with the liposomal product.⁴⁷ Current IDSA guidelines recommend liposomal formulations of amphotericin B as an alternative to standard therapy in patients who cannot tolerate standard amphotericin, such as in those patients with renal insufficiency.⁴³ While the toxicities may be less significant with the liposomal product, current studies have not demonstrated superiority. This, in addition to the added cost of treatment with liposomal amphotericin, limits its usefulness as a preferred agent. Therapy with the liposomal product should be considered in patients who cannot tolerate standard amphotericin or have concurrent renal insufficiency, which would make standard amphotericin a less favorable choice. Optimal dosing of liposomal amphotericin has not been established, although doses of 4 mg/kg IV daily appear effective.

Maintenance Therapy

Patients with cryptococcal meningitis require lifelong therapy to prevent recurrence, unless immune reconstitution occurs as a result of combination antiretroviral therapy. Support for maintenance therapy comes from a randomized, double-blind, placebo-controlled trial that evaluated the effectiveness of fluconazole maintenance therapy in patients success-

fully treated for primary infection with amphotericin B alone or in combination with flucytosine. Recurrence rates were significantly higher in the placebo group compared with the fluconazole group.⁵⁶ Additional studies support the need for maintenance therapy and the efficacy of fluconazole for chronic maintenance therapy.^{57,58}

Discontinuation of maintenance therapy is safe and is recommended in patients who have a sustained immunologic response to antiretroviral therapy. Secondary prophylaxis can be discontinued in patients who have completed a course of initial therapy for cryptococcal meningitis, remain asymptomatic, and have had a sustained immune response secondary to highly active antiretroviral therapy, which is defined as CD4 counts >100 to 200 cells/mm³ for ≥6 months. Maintenance therapy should be restarted if CD4 counts fall to <100 to 200 cells/mm³.⁵⁹

Management of Intracranial Pressure

Elevated intracranial pressure occurs in more than 50% of patients with cryptococcal meningitis and contributes to morbidity and mortality.⁶⁰ Patients presenting with cryptococcal meningitis whose pressures increased between baseline and week 2 of treatment had poorer outcomes. Management of intracranial pressure is therefore recommended and includes interventions aimed at reducing intracranial pressure to normal levels. In patients with opening pressure measurements greater than 250 mm H₂O, current guidelines recommend percutaneous lumbar drainage to remove enough cerebrospinal fluid so that intracranial pressure is decreased by 50%.⁶¹ Daily lumbar punctures should be performed to maintain pressures within the reference range. Once pressures are maintained within the reference range for several days, the procedure can be stopped. For patients with extremely high opening pressures (defined as greater than 400 mm H₂O), or patients whose pressures cannot be controlled with serial lumbar punctures, lumbar drainage may be indicated.⁶¹ In addition, refractory cases may require ventriculoperitoneal shunting.⁶¹

HISTOPLASMOSIS

Background Information

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*, which is found in the temperate zones of North and Latin America, and is highly endemic in the Mississippi and Ohio River valleys of

the United States. The mold grows as a mycelial form in soil, especially in areas that birds or bats have inhabited, due to the added nutrients provided by the animals' excrement. Infection occurs when microconidia, the smaller infectious form of the organism, are inhaled. *H capsulatum* grows as a yeast form at temperatures greater than 35°C, which is what is typically found in infected tissues. Cellular immunity plays a key role in defense against the organism, and most infections in immunocompromised hosts occur in AIDS patients with CD4 counts less than 150 cells/mm³.⁶² However, localized pulmonary histoplasmosis may occur in patients with CD4 counts greater than 300 cells/mm³. *H capsulatum* is not transmissible through person-to-person contact.

Clinical Presentation

Patients infected with *H capsulatum* typically have a subacute presentation over the course of 1 to 3 months that includes fever, fatigue, and weight loss. Approximately 50% of patients will exhibit respiratory symptoms including cough and dyspnea. Physical findings include hepatosplenomegaly and lymphadenopathy. AIDS patients presenting with histoplasmosis commonly have multiorgan disease. Less frequent presentations may include sepsis, CNS involvement, gastrointestinal manifestations, and cutaneous disease. CNS involvement can occur in 10% to 20% of cases and may include lymphocytic meningitis, focal brain lesions, or diffuse encephalitis. Dermatologic findings, seen in approximately 10% of cases, include erythematous or hyperpigmented papules, pustules, plaques with ulcerations, erythema multiforme, and rosacea-like rashes.

Diagnosis

Histoplasmosis can be diagnosed through antigen testing, fungal stains, culture, and serologic tests for antibodies.⁶² Rapid diagnosis of histoplasmosis can be obtained through urine or blood antigen testing. Antigen is detected in the urine of 95% and the blood of 85% of patients with disseminated disease.⁶³ Fungal staining techniques reveal yeast cells with occasional buds and can provide a rapid diagnosis; however, the sensitivity of this approach is only 50%, which is lower than that of antigen detection and limits the usefulness of this approach. Serologic testing can be performed and is positive in approximately two thirds of cases of histoplasmosis, but serologies are rarely beneficial in the acute diagnosis of disease.

Table 3
Criteria for Intravenous Amphotericin B
in Disseminated Histoplasmosis

-
- Temperature >102°F
 - Systolic blood pressure <90 mm Hg
 - Hypoxia (pO₂ < 70)
 - Weight loss >5%
 - Karnofsky score <70
 - Hemoglobin level <10 g/dL
 - Neutrophil count <1000 cells/μL
 - Platelet count <100 000 cells/μL
 - Aspartate aminotransferase level >2.5 times normal
 - Bilirubin or creatinine level >2 times normal
 - Albumin level <3.5 g/dL
 - Coagulopathy, presence of other organ system dysfunction, or confirmed meningitis
-

Cultures should be drawn for all suspected cases of histoplasmosis. Cultures can be obtained from blood, bone marrow, respiratory secretions, or localized lesions in more than 85% of cases. Isolation of *H capsulatum* from cultures can take 2 to 4 weeks, and all cultures should be held for at least 4 weeks. Although this is the gold standard for diagnosis, awaiting the results of cultures can delay initiation of therapy.

Treatment

Recommendations for the treatment of disseminated histoplasmosis are based on the severity of illness. Signs and symptoms suggestive of more progressive illness are presented in Table 3.⁶² Patients presenting with 1 or more of the criteria listed have moderate to severe histoplasmosis and are candidates for hospitalization and treatment with IV amphotericin B. Both the liposomal and deoxycholate formulation have been evaluated and may be used for treatment; however, one study has shown the liposomal formulation to be more effective than standard amphotericin, with evidence of a more rapid and complete response, lower mortality rates, and reduced toxicity.⁶⁴ Therefore, liposomal amphotericin B (Ambisome) 3 mg/kg/d is the treatment of choice for patients with moderately severe or severe illness requiring hospitalization. Standard amphotericin B, however, is effective for patients who present with less severe illness and may be used in doses of 50 mg/d (1 mg/kg in individuals weighing <50 kg) if tolerated. IV itraconazole therapy may be used in patients who cannot tolerate amphotericin B therapy, at doses of 200 mg/d after initial high-dose induction.⁶²

Treatment consists of an induction phase of 12 weeks followed by a maintenance phase of therapy. Pa-

tients responding to initial IV amphotericin for 3 to 10 days may be switched to oral therapy to complete the induction phase of treatment. Both itraconazole and fluconazole have been evaluated in this setting; however, fluconazole appears to be less effective than itraconazole.⁶⁵ Dosing of itraconazole is 400 mg/d in capsule formulation, which is the formulation that has been evaluated in clinical trials. Oral solution would be a reasonable option given its improved absorption in absence of an acidic environment, although no studies have documented its efficacy and tolerability in this setting.⁶²

Upon completion of the induction phase of treatment, maintenance therapy is warranted. Suppressing maintenance therapy has been shown to prevent relapse, which occurs in 35% to 80% of patients who did not receive maintenance therapy.^{66,67} Current guidelines recommend itraconazole 200 mg twice daily for lifelong chronic maintenance therapy. The efficacy of this agent has been established in a prospective study, with more than 90% of patients remaining free of histoplasmosis during 97 patient years of follow-up.⁶⁸ Many experts recommend serum drug monitoring of itraconazole to maintain free concentrations of at least 1 mg/mL or free plus hydroxylated metabolite of 2 µg/mL, given that the metabolite has antifungal activity.⁶² Alternate therapies for maintenance therapy include amphotericin 50 mg/wk or 100 mg biweekly and fluconazole 100 to 400 mg daily. While amphotericin B is more than 90% effective as maintenance therapy, its use is limited by its route of administration, decreased tolerability, and lack of patient acceptance.^{67,69} Fluconazole is less effective than either itraconazole or amphotericin B for maintenance therapy and is not recommended.^{70,71} If, however, patients fail or cannot tolerate the preferred agents, fluconazole 400 to 800 mg daily could be used with extreme caution and close monitoring of urine and serum antigen levels for signs of relapse.⁷²

For mild to moderate cases of histoplasmosis not requiring hospitalization, oral therapy with itraconazole can be used. The induction phase of treatment should begin with high-dose itraconazole (200 mg 3 times daily) for 3 days, followed by 200 mg twice daily for a total of 12 weeks. Efficacy of oral therapy for mild to moderate disease was demonstrated in a prospective trial, with 85% of patients achieving remission.⁷³ Maintenance therapy should then be continued for life with oral itraconazole at doses of 200 to 400 mg/d. Monitoring of serum drug levels to ensure achievement of target concentrations is again indicated.

Antifungal Agents Used for Treatment of Opportunistic Infections

Azoles

Azole antifungals exert their activity by inhibiting the synthesis of ergosterol, which is the major sterol component in fungal cell membranes. Inhibition of ergosterol production occurs through the interference of the antifungal with the cytochrome-dependent enzyme lanosterol demethylase. The azole antifungals can be categorized into 2 groups based on the number of nitrogen atoms within the azole ring. The imidazoles contain 2 nitrogen atoms and include the agents ketoconazole, tioconazole, clotrimazole, and miconazole. The triazoles contain 3 nitrogen atoms in the azole ring and include itraconazole, fluconazole, and voriconazole.

Most of the imidazole antifungals are used for topical treatment of *Candida* infections, including mild oropharyngeal and vulvovaginal disease. Ketoconazole is the only imidazole agent available for use in systemic *Candida* infections. The use of this agent is limited, however, by a less than favorable pharmacokinetic profile. It is poorly absorbed in the absence of a highly acidic environment and has multiple drug interactions due to its strong inhibition of the cytochrome P450 3A4 enzyme. In addition, ketoconazole is associated with a high incidence of adverse effects that include gastrointestinal irritation, nausea and vomiting, and liver function abnormalities. For these reasons, ketoconazole is rarely used for the treatment of fungal infections in HIV-infected patients.

The triazole antifungals play an important role in the management of systemic fungal disease. These agents have a wide spectrum of activity that includes various *Candida*, *Cryptococcus*, and *Histoplasma* species. The individual agents differ in their pharmacokinetic characteristics, efficacy in the treatment of fungal pathogens, and resistance patterns. While efficacy has been discussed in the previous sections, a review of agent characteristics, side effects, and usefulness for resistant organisms warrants review.

Fluconazole is a triazole antifungal available in tablet, suspension, and parenteral formulations. It is well absorbed from the gastrointestinal tract with no requirement of acidity or food intake. Bioavailability exceeds 90% for both oral and parenteral formulations. Fluconazole is primarily eliminated renally, with up to 80% of a single dose appearing in the urine as unchanged drug. However, approximately 11% of the drug is metabolized in the liver, and various drug inter-

actions involving the cytochrome P450 enzyme system have been reported. However, given the limited amount of drug metabolized within the liver, interactions tend to be less frequent than with the other triazoles. Fluconazole is generally well tolerated, with the most common side effects being nausea, vomiting, or diarrhea. There is growing concern over resistance to triazoles, and fluconazole-resistant candidiasis has been reported in patients with advanced HIV disease. Resistance is associated with previous exposure to azole antifungals, lower CD4 counts, and more previously treated thrush episodes.^{22,23}

Itraconazole, a second triazole antifungal, is available in a cyclodextrin suspension, capsule, or IV formulation. This agent is commonly used in maintenance treatment of histoplasmosis infection. Itraconazole is associated with highly variable absorption when administered orally. The capsule formulation requires an acidic pH for solubilization and therefore should be given with food or a cola product.⁷⁴ This may also be a problem in the setting of treatment with acid-suppressive agents, such as proton pump inhibitors and H₂-receptor antagonists. The oral solution is better absorbed and does not require an acidic environment for absorption. In fact, with the cyclodextrin suspension, absorption is more rapid and complete when administered in the fasted state.

Itraconazole is metabolized extensively in the liver by the cytochrome P450 enzyme system, with at least 1 known active metabolite, hydroxyitraconazole.⁷⁵ In addition, itraconazole is a cytochrome P450 enzyme inhibitor and therefore has the potential for multiple drug interactions, with various antiretrovirals and other medications metabolized by this pathway. Medications that inhibit the cytochrome P450 3A4 isoenzyme can alter the metabolism of itraconazole.

It is recommended that itraconazole concentrations be measured periodically during treatment of histoplasmosis because of both the variability of absorption and the propensity for drug interactions. Therapeutic concentrations of at least 1 mg/mL (units) by bioassay are considered therapeutic for treatment of histoplasmosis.

Side effects of itraconazole include gastrointestinal effects, rash, and liver enzyme elevation.

Several new second-generation triazole antifungals are being evaluated for activity against various fungal pathogens. These newer agents have been developed in hopes of improving on various pharmacokinetic limitations of current azole agents, which include absorption problems with itraconazole and the drug interaction potential of the various agents, as well as to expand

the spectrum of activity of this class of antifungals. Three second-generation triazoles have been evaluated: voriconazole, ravuconazole, and posaconazole. Voriconazole is currently the only second-generation azole approved by the Food and Drug Administration for use in the United States.

Voriconazole is structurally related to fluconazole and is available in oral and parenteral formulations. It has extensive in vitro activity against many fungal pathogens and molds, including *Candida* and *Aspergillus* species. Voriconazole is 60 to 100 times more potent than fluconazole against *Candida* species, including *C. krusei*, which is generally resistant to fluconazole.^{75,76}

Bioavailability of the oral formulation is 96% and can be used interchangeably with the IV formulation. Oral absorption is impaired in the presence of food, and it is therefore recommended that it be administered 1 hour before or after meals. Metabolism occurs through hepatic N-oxidation, using several hepatic CYP isoenzymes, including CYP 2C19, 2C9, and 3A4. Because it is a substrate for these enzyme pathways, various drug interactions exist. Although no dosage adjustment is needed in patients with renal dysfunction, the IV formulation is prepared using sulphobutylether-b-cyclodextrin, which is renally excreted and can accumulate in patients with renal impairment. It is therefore recommended that the use of the IV formulation be avoided in patients with creatinine clearances less than 50 mL/min.⁷⁷

Side effects of voriconazole include liver abnormalities, skin rashes, photosensitivity, and visual disturbances. Hepatic enzyme elevations occurred in 12% to 20% of patients treated with voriconazole, with elevations in alanine aminotransferase and aspartate aminotransferase levels seen most frequently. Skin rashes occurred in 19% of patients in clinical studies.⁷⁷ Visual side effects are generally mild, occur early in therapy, and include photophobia or altered perception of light. Visual effects often occur 30 minutes after dose administration and last for approximately 30 minutes.

Two second-generation triazoles in current development include ravuconazole and posaconazole. Ravuconazole, like voriconazole, is structurally similar to fluconazole, with an expanded spectrum of activity. It is being evaluated in an oral formulation as well as a prodrug for IV administration. Its spectrum of activity includes various fungal pathogens, such as *Candida* species, including the more resistant strains *C. glabrata* and *C. krusei*, and *Cryptococcus* species. Posaconazole, structurally related to itraconazole,

demonstrates activity against various yeasts and molds, including activity against *Candida*, *Aspergillus*, *Cryptococcus*, and *Histoplasma* species. It is being evaluated as an oral formulation and will require frequent dose administration. Posaconazole is a CYP 3A4 inhibitor, so drug interactions will be expected.⁷⁷

Polyenes

Polyene antifungals consist of the agents nystatin and amphotericin B. These agents bind to ergosterol on the fungal cell wall and alter membrane permeability, which causes the leakage of cellular components and subsequent cell death. Nystatin is toxic when used parenterally and is therefore limited to topical use in *Candida* infections involving the skin, oral mucosa, and gastrointestinal tract. Amphotericin B, however, is a polyene antifungal agent that has a broad spectrum of activity against many fungi and molds. The primary use of amphotericin includes systemic therapy for fungal infections including cryptococcal meningitis, histoplasmosis, and invasive candidal disease. Although it is considered the standard of care in the treatment of both cryptococcal meningitis and histoplasmosis, its use is limited by its multiple toxicities, intolerability, and route of administration. Nephrotoxicity is the major dose-limiting side effect, which can present with decreased renal function, azotemia, hypokalemia, hyposthenuria, renal tubular acidosis, and nephrocalcinosis. The incidence of renal impairment can be as high as 80%. The mechanism of renal dysfunction is thought to involve the direct vasoconstriction of renal arteries. In addition, the binding of the drug to renal tubular cell sterols may alter membrane permeability and effect potassium, sodium, chloride, and hydrogen ion excretion. While the renal effects of amphotericin B are generally reversible on treatment discontinuation, it often takes days to months for renal function to return to pretreatment levels.

Infusion-related reactions are common with amphotericin B. These reactions may include fever, chills, rigors, nausea, vomiting, and headache. These reactions are more common during the first several doses of medication and are unrelated to the rate of the infusion. Treatment with acetaminophen, meperidine, corticosteroids, or diphenhydramine can alleviate symptoms and may be given to prevent symptoms with subsequent doses.

Lipid-based formulations have been developed in an effort to decrease the adverse effects noted with standard amphotericin B. The ability of the lipid for-

mulations to selectively transfer the drug to fungal cells results in a reduction in the frequency of nephrotoxicity with the liposomal products. Clinical studies, however, have failed to show a difference in the rate of infusion-related adverse effects.⁷⁸⁻⁸⁰ In addition, there is a substantial cost difference between the lipid-based products and standard amphotericin B. With the exception of histoplasmosis, for which one study demonstrated improved efficacy with liposomal amphotericin B, the use of these products are reserved for patients who fail to respond to standard amphotericin B, are intolerant of the conventional formulation, or have preexisting renal disease. Current liposomal products include amphotericin B lipid complex (Abelcet) and liposomal amphotericin B (Ambisome).

Candins

Echinocandins are glucan synthesis inhibitors, which block fungal cell wall synthesis by inhibiting the enzyme 1,3- β glucan synthase. Inhibition of this enzyme weakens the cell wall by reducing the amount of glucan polymers in the fungal cell. This results in cell lysis due to the inability for the cell to withstand osmotic pressure. Three echinocandins have been evaluated for clinical use in systemic fungal infections and include caspofungin, micafungin, and anidulafungin. All of these agents have poor bioavailability and therefore are limited to IV formulations. Caspofungin (Cancidas) and micafungin are currently approved for use in the United States.

Caspofungin is currently approved for candidemia and salvage treatment of invasive aspergillosis. It demonstrates fungicidal activity in vitro against various *Candida* species, including azole-resistant organisms. Dosing consists of a standard loading dose of 70 mg IV followed by maintenance doses of 35 to 70 mg given once daily. The drug is highly protein bound (>95%) and undergoes hepatic metabolism by spontaneous peptide hydrolysis and N-acetylation. Dose adjustments are necessary in patients with hepatic impairment, as caspofungin is thought to be metabolized by spontaneous peptide hydrolysis and N-acetylation. No dosage adjustments are necessary in renal impairment or dialysis.

Although caspofungin was not shown to inhibit cytochrome P450 enzymes in vitro, several drug interactions have been identified. Cyclosporine was shown to increase the area under the curve of caspofungin by 35%.⁸⁰ In addition, coadministration of the 2 agents resulted in increases in alanine aminotransferase levels in one study. Current recommendations therefore sug-

gest avoiding the concurrent use of cyclosporine and caspofungin unless the benefits outweigh the risks of therapy. Several other drug interactions that have resulted in decreased levels of caspofungin include coadministration with efavirenz, nevirapine, rifampin, dexamethasone, phenytoin, or carbamazepine. It is recommended to maintain doses of caspofungin at 70 mg/d when using caspofungin in the presence of these medications.⁸¹

Current use of caspofungin in HIV-infected individuals includes the treatment of invasive candidiasis, treatment of refractory candidiasis due to resistant organisms, and the treatment of invasive aspergillosis. Treatment is generally well tolerated, with few adverse events.

Antimetabolites

Flucytosine is the only available antimetabolite antifungal. The drug is a pyrimidine that is activated through deamination in the fungal cell wall to 5-fluorouracil. The 5-fluorouracil then replaces uracil in the fungal RNA, which results in inhibition of fungal cell wall synthesis.

Flucytosine (Ancobon) is currently available in oral capsules and is used in combination with amphotericin B for the treatment of cryptococcal meningitis. Monotherapy with flucytosine is limited by the rapid development of resistance to the agent and is therefore not recommended. For the treatment of cryptococcal meningitis, a dosing of 25 mg/kg/d administered 4 times daily has been shown to be efficacious. Monitoring of renal function is necessary because of the potential for changes in serum creatinine secondary to concurrent amphotericin use. Flucytosine levels are increased in the presence of renal impairment, and this could contribute to increased serum levels of the drug and subsequent toxicity. Monitoring of flucytosine levels is recommended in patients with renal impairment. Peak serum levels (2 hours after an oral dose), should be <100 mg/mL. Side effects of flucytosine include gastrointestinal intolerance and bone marrow suppression.

CONCLUSION

Fungal infections continue to cause morbidity and mortality in the setting of HIV/AIDS. Current strategies for the management of these infections with antifungal agents have proven effective in various settings. While antifungal agents are effective in the acute management of opportunistic infections, restoration of the immune system with combined antiretroviral therapy is

crucial for long-term management and the prevention of future recurrence. The availability of newer antifungal agents in both existing and novel classes will prove useful in the treatment of infections that are complicated by resistance and intolerance and in those cases refractory to conventional treatment strategies.

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