Prior to the 1980s, amphotericin B (AMB) was considered the most effective therapy for systemic histoplasmosis and blastomycosis. Over the last decade, a new group of antifungal agents, the azole compounds, have been shown to have activity against several fungal species, including *Histoplasma capsulatum* and *Blastomyces dermatitidis*. Miconazole, an imidazole compound, was the first of these agents to be tested clinically against a wide variety of systemic fungal infections. Due to its poor absorption after oral dosing, miconazole can be used only in an intravenous form to achieve adequate serum drug levels. Despite promising *in vitro* antifungal activity, significant toxicities and high relapse rates were observed when miconazole was used as a single agent in the therapy of systemic mycoses, primarily coccidioidomycosis. In the late 1970s, another imidazole compound, ketoconazole, was developed. Unlike miconazole, ketoconazole is well absorbed after oral administration and well tolerated. Most importantly, ketoconazole has been shown to be an effective alternative to AMB for the treatment of several systemic fungal diseases, including most forms of histoplasmosis and blastomycosis. Although other antifungal azoles are presently under investigation, the currently recommended therapeutic agents of choice for systemic histoplasmosis and blastomycosis are either ketoconazole or AMB, depending on the clinical setting.

**Amphotericin B**

Amphotericin B is a polyene antifungal agent that is relatively unstable in water and poorly absorbed from the gastrointestinal tract. For the treatment of systemic fungal disease, the drug is administered either intravenously or, in the case of severe central nervous system (CNS) disease, intrathecally. To achieve adequate stability and to increase its therapeutic effect, AMB is conjugated with desoxycholate, a bile salt that in turn appears to be responsible for a number of the toxic adverse reactions attributed to AMB.

These adverse effects of AMB are well known to most clinicians. Fever, rigors, nausea, vomiting, headache and phlebitis frequently occur during drug administration. Anaphylactoid reactions rarely occur. Azotemia is the most common toxicity, occurring in virtually all patients who receive more than one to two weeks of therapy. Other toxic effects on the renal tubules result in potassium, magnesium and, on occasion, bicarbonate wasting. Hematologic abnormalities are equally prominent. Anemia is universal among individuals who receive prolonged therapy. Leukopenia and thrombocytopenia occur much less commonly. Weight loss and dysesthesias also develop during prolonged therapy.

**Ketoconazole**

Ketoconazole is well absorbed from the gastrointestinal tract, has adequate bioavailability, and is primarily metabolized by the liver and excreted in the bile. An acidic gastric pH is necessary for optimal drug absorption. Consequently, ketoconazole should be used with caution in patients who have achlorhydria or who are receiving concomitant antacid, anticholinergic, or H₂ blocker therapy that cannot be discontinued. Poor penetration of the drug into the CNS and low levels of active drug in the urine and genitourinary (GU) tract are the major limitations of its use. Therefore, ketoconazole is not recommended for the treatment of CNS disease and rarely should be used for GU tract infections.

The adverse effects of ketoconazole are minor in comparison with those of AMB; however, toxicity due to ketoconazole does exist and, in rare instances, can be potentially life-threatening. The most common adverse effects are gastrointestinal (GI), with dose-dependent nausea, vomiting or anorexia occurring in 17 (400 mg/day) to 40 percent (800 mg/day) of patients on long-term therapy. However, only a few patients actually terminate therapy due to GI side effects. Skin rash, pruritis, dizziness and headache occur in fewer than 10 percent of patients.
Disorders of endocrine function represent the most unique adverse effect. Ketoconazole blocks testosterone synthesis by both the adrenal gland and testes in a dose-dependent fashion. As a result, decrease in libido, impotence, gynecomastia, and oligospermia or azospermia are reported in up to 10 to 15 percent of men on high-dose ketoconazole. Similarly, high-dose ketoconazole blocks adrenocorticosteroid synthesis; however, clinically significant adrenal insufficiency is rare. The experience of most investigators suggests that the endocrine-mediated effects of ketoconazole are reversed when therapy is discontinued.

Perhaps the most publicized adverse effect of ketoconazole is hepatotoxicity. Significant abnormalities of liver function tests (greater than three times normal) occur in only 1 to 3 percent of patients. The incidence of symptomatic hepatic dysfunction has been established to be 1 in 10,000 patients or 1 in 15,000 treatment courses. Ketoconazole-induced liver disease appears to be idiosyncratic in nature and is generally reversible if the drug is discontinued soon after significant abnormalities are noted. Nonetheless, three cases of fatal hepatitis have been attributed to the drug.

APPROACH TO THE THERAPY OF HISTOPLASMOSIS

A wide spectrum of clinical syndromes are caused by the dimorphic fungus, *H capsulatum*. Most commonly, histoplasmosis manifests as an acute, self-limited respiratory tract infection that requires no therapy. However, in a minority of cases histoplasmosis presents as severe primary pneumonitis, chronic cavitary pulmonary disease, progressive disseminated multi-organ disease, or immune-mediated disease of the mediastinum or eye. The decision whether to treat, and if so with what agent, depends on the severity of clinical symptoms and the host defense status of the infected individual.

In most cases of symptomatic acute pulmonary disease characterized by fever, cough and patchy pneumonitis on chest roentgenogram, spontaneous recovery without specific antifungal therapy is the rule. In cases of unusually severe or prolonged pulmonary disease, either ketoconazole (400 mg/day) for three to six months or AMB (0.3 to 0.5 mg/kg/day) for two to four weeks is generally effective therapy.

Chronic cavitary histoplasmosis is an indolent illness characterized by cough, weight loss, fever, malaise, chest pain and occasionally hemoptysis. Most persons with this form of histoplasmosis have underlying chronic obstructive pulmonary disease or a long history of cigarette smoking. Conservative management with restricted physical activity and no antifungal therapy is recommended for cases characterized by minimal or stable symptoms, thin-walled cavities or early pulmonary lesions. In contrast, antifungal therapy is recommended for individuals with persistent cavitation, cavity wall thickness of greater than 2 mm or progressive symptoms. Traditionally, AMB (total dose, 30 to 35 mg/kg) has been the treatment of choice for chronic cavitary histoplasmosis requiring therapy. Most recently, however, the NIAID Mycoses Study Group (MSG) has shown that ketoconazole is an effective alternative to AMB for this group of patients. Among 19 patients with chronic cavitary histoplasmosis treated at least six months with either low-dose (400 mg/day) or high-dose (800 mg/day) ketoconazole, the success rate was 84 percent, which compares favorably with reported success rates ranging from 57 to 100 percent achieved with AMB. Because the low-dose and high-dose ketoconazole regimens were equally effective and because substantially more toxicity was noted among the high-dose group, the current recommendation is to initiate ketoconazole therapy at 400 mg/day, and increase to 600 to 800 mg/day if a favorable clinical response is not achieved. Amphotericin B is recommended for those who fail ketoconazole therapy due to either inadequate clinical response or toxicity and for those who are severely immunocompromised.

Localized or disseminated histoplasmosis is characterized by constitutional symptoms such as fever, weight loss and malaise, along with evidence of extra-pulmonary disease in only one, or multiple, organ systems such as the oropharynx, lymph nodes, liver or bone marrow. Disseminated disease usually occurs in the very young, the elderly or the immunocompromised. Untreated, the disease is ultimately fatal; with treatment, mortality ranges from 10 to 30 percent, depending on the presence and severity of underlying disease. Amphotericin B (total dose, 30 to 35 mg/kg) is recommended for therapy of disseminated histoplasmosis in immunocompromised individuals and for those rare persons with CNS histoplasmosis. Ketoconazole is an acceptable alternative to AMB for individuals with non-life-threatening, non-CNS, localized or disseminated disease. In the NIAID MSG study, 17 of 31 patients with localized or disseminated histoplasmosis were successfully treated with ketoconazole. Eleven of the 14 patients who failed therapy were compromised hosts. Interestingly, the patients who were randomized to the low-dose regimen (400 mg/day) actually fared better than the high-dose (800 mg/day) group; however, five of the nine failures among high-dose patients were due to drug toxicity. Therefore, as in patients with chronic cavitary disease, the recommended initial dose of ketoconazole for patients with localized or disseminated disease is 400 mg/day, which can be advanced to 800 mg/day if no clinical improvement or disease progression is observed.

Disseminated histoplasmosis among patients with acquired immunodeficiency syndrome (AIDS) is being
reported with increasing frequency. In the patient with AIDS, histoplasmosis often presents as a subacute systemic illness with symptoms of fever, night sweats, fatigue and abdominal pain, and signs of weight loss, splenomegaly and adenopathy. In contrast to disseminated histoplasmosis in patients who are normal hosts or immunocompromised due to other causes, skin lesions are a prominent feature of disseminated histoplasmosis in HIV infected individuals. Amphotericin B is the drug of choice for histoplasmosis in AIDS patients, although the optimal dose and duration of therapy is yet to be determined. Patients treated with standard therapy (total dose, 30 to 35 mg/kg) frequently have relapses, indicating a need for prolonged therapy. Current but unsubstantiated recommendations advocate an induction course of AMB (500 to 1,000 mg given over several weeks), followed by lifelong suppressive therapy with either ketoconazole (400 mg/day) or weekly AMB (approximately 1.0 mg/kg). Studies are ongoing to address these recommendations. Recurrent disease has been reported in a few AIDS patients on long-term ketoconazole therapy; therefore, close follow-up is imperative.

Mediastinal granuloma is an uncommon immune-mediated complication of *H capsulatum* infection. Surgical therapy with enucleation or partial resection is usually effective and the long-term prognosis is excellent. Those rare patients with microbiologically or histologically proven erosive disease, such as invasion into the airways or esophagus, are candidates for antifungal therapy (either ketoconazole or AMB). Mediastinal fibrosis, a late complication of mediastinal granuloma, does not require treatment with antifungal agents. In addition, the presumed ocular histoplasmosis syndrome appears to be an immune-mediated disease and, therefore, unaffected by antifungal treatment. Laser photoagulation, intraocular corticosteroids and retinal irradiation are the primary therapeutic modalities used to treat this entity.

**Approach to the Therapy for Blastomycosis**

Blastomycosis is a systemic fungal disease caused by *B dermatitidis*, a dimorphic fungus that primarily infects the lungs but often disseminates to other tissues, such as skin, bone and the GU tract. Acute pulmonary blastomycosis in immunocompetent individuals is generally a self-limited illness requiring no therapy; however, sporadic cases of endogenous reactivation have been reported, indicating the need for close follow-up for several years for all untreated patients. Patients with severe or progressive acute pulmonary blastomycosis should be given ketoconazole, or less commonly, AMB.

Chronic pulmonary blastomycosis is characterized by fever, malaise, weight loss, cough, night sweats, hemoptysis, and bronchopneumonia or nodular masses on chest roentgenograms. Unlike chronic pulmonary histoplasmosis, patients with chronic pulmonary blastomycosis often have evidence of disseminated disease, most commonly involving the skin. Conversely, approximately 40 percent of patients with blastomycosis present with skin, bone or joint, and/or GU tract involvement without any evidence of pulmonary disease. Central nervous system disease, while exceedingly uncommon, is associated with the highest mortality rate.

Recent studies have established ketoconazole to be as effective as AMB for non-life-threatening, non-meningeal blastomycosis in immunocompetent hosts. In a prospective, randomized multicenter study, the NIAID MSG treated 80 blastomycosis patients with either low-dose (400 mg/day) or high-dose (800 mg/day) ketoconazole. Among these 80 nonimmunocompromised persons, 34 (42 percent) had pulmonary disease alone, 15 (19 percent) had pulmonary disease plus involvement of at least one other site, and the remaining 31 (39 percent) had only extrapulmonary disease involving one (21 patients) or more (10 patients) sites. Among 65 patients who completed six months or more of therapy, 59 (89 percent) were judged to be cured with a median follow-up time of 17 months; the cure rate was significantly better for those treated with high-dose (100 percent cure) vs low-dose (79 percent cure) ketoconazole. Of special note, two of five patients with blastomycotic prostatitis had relapses after therapy, perhaps due to the very low concentration of active drug excreted in the urine. Bradshaw and colleagues recently published a second study that corroborates the MSG findings. Among 44 patients who received at least two weeks of ketoconazole therapy (400 mg/day), 13 had chronic pneumonia, six had acute pneumonia, 14 had evidence of extrapulmonary disease, and two were relatively asymptomatic. Thirty-five of the 44 patients (80 percent) were cured; the mean duration of follow-up was 17 months.

Even though higher-dose ketoconazole appears to be more effective than the lower-dose drug, the 80 percent cure rate associated with low-dose ketoconazole therapy compares favorably with previously reported cure rates (66 to 93 percent) among blastomycosis patients treated with AMB. In addition, as stated previously, high-dose ketoconazole is associated with an increased frequency of adverse effects. As such, the current recommendation for the treatment of non-meningeal, non-life-threatening blastomycosis is to initiate ketoconazole at a dose of 400 mg/day, and increase to 600 to 800 mg/day in the absence of favorable clinical response. Individuals with significant GU tract disease should be treated initially with higher-dose ketoconazole (600 to 800 mg/day) and observed carefully for evidence of clinical failure.
Patients who fail or are unable to tolerate ketoconazole therapy should be treated with AMB (30 to 35 mg/kg, total dose).

For unclear reasons, blastomycosis is a very uncommon opportunistic disease among immunocompromised individuals. Rarely, cases have been observed in patients with lymphoproliferative diseases or those receiving immunosuppressive therapy, but to date there has been no case of blastomycosis reported in AIDS patients. Nonetheless, the occurrence of B dermatitidis infection in HIV infected individuals seems inevitable. Immunocompromised patients with any form of blastomycosis should be treated with AMB (30 to 40 mg/kg, total dose). Another theoretically reasonable approach to the treatment of blastomycosis in AIDS patients (when such occurs) would be to model the therapy after that of histoplasmosis, ie, give an initial induction course of AMB, and follow with lifelong suppressive therapy with either ketoconazole or AMB.

**Summary**

Prior to the development of ketoconazole, the treatment of systemic histoplasmosis and blastomycosis was limited to AMB. The convenience of oral dosing, combined with avoidance of the significant toxicities associated with AMB, make ketoconazole an attractive alternative for the treatment of selected forms of histoplasmosis and blastomycosis. Although high-dose (800 mg/day) ketoconazole is generally more effective than low-dose (400 mg/day), therapy should be initiated at the lower dose due to significantly more adverse effects at higher doses; the daily dose should be increased in patients with progressive disease. Caution should be exercised when ketoconazole is used to treat patients with GU tract disease and in patients with naturally occurring or pharmacologically induced achlorhydria. Thus, AMB remains the drug of choice for difficult to treat cases of histoplasmosis and blastomycosis; however, recent studies have established ketoconazole as the drug of choice in immunocompetent patients with non-life-threatening, non-meningeal H capsulatum and B dermatitidis disease.

**References**