

## Practice Guidelines for the Management of Patients with Blastomycosis

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### Executive Summary

Guidelines for the treatment of blastomycosis are presented; these guidelines are the consensus opinion of an expert panel representing the National Institute of Allergy and Infectious Diseases Mycoses Study Group and the Infectious Diseases Society of America. The clinical spectrum of blastomycosis is varied, including asymptomatic infection, acute or chronic pneumonia, and extrapulmonary disease. Most patients with blastomycosis will require therapy. Spontaneous cures may occur in some immunocompetent individuals with acute pulmonary blastomycosis. Thus, in a case of disease limited to the lungs, cure may have occurred before the diagnosis is made and without treatment; such a patient should be followed up closely for evidence of disease progression or dissemination. In contrast, all patients who are immunocompromised, have progressive pulmonary disease, or have extrapulmonary disease must be treated. Treatment options include amphotericin B, ketoconazole, itraconazole, and fluconazole. Amphotericin B is the treatment of choice for patients who are immunocompromised, have life-threatening or central nervous system (CNS) disease, or for whom azole treatment has failed. In addition, amphotericin B is the only drug approved for treating blastomycosis in pregnant women. The azoles are an equally effective and less toxic alternative to amphotericin B for treating immunocompetent patients with mild to moderate pulmonary or extrapulmonary disease, excluding CNS disease. Although there are no comparative trials, itraconazole appears more efficacious than either ketoconazole or fluconazole. Thus, itraconazole is the initial treatment of choice for non-life-threatening non-CNS blastomycosis.

### Introduction

Blastomycosis is the systemic pyogranulomatous disease caused by the thermally dimorphic fungus *Blastomyces dermatitidis*. Like histoplasmosis and coccidioidomycosis, this disease occurs most commonly in defined geographic regions, hence its designation as an endemic mycosis. In North America, blastomycosis usually occurs in the southeastern and south central states that border the Mississippi and Ohio Rivers, the midwestern states and Canadian provinces bordering the Great Lakes, and a small area of New York and Canada adjacent to the St. Lawrence River [1]. Within these regions of endemicity, several studies have documented the presence of areas of hyperendemicity where the rate of blastomycosis is unusually high [1]. Point-source outbreaks have been associated with occupational and recreational activities, frequently along streams or rivers, which result in exposure to moist soil enriched with decaying vegetation [2, 3].

Initial infection results from inhalation of conidia into the lungs, although primary cutaneous blastomycosis has infrequently been reported after dog bites and accidental inoculation in the laboratory or at autopsy. The clinical spectrum of blastomycosis is varied, including asymptomatic infection, acute or chronic pneumonia, and disseminated disease [4]. As defined in point-source epidemics, asymptomatic infection occurs in at least 50% of infected persons, which supports the hypothesis that some have natural resistance [2]. Symptomatic disease develops after an incubation period of 30–45 days. Acute pulmonary blastomycosis mimics influenza or bacterial pneumonia. Spontaneous cures of symptomatic acute infection have been well documented, but the frequency of such cures has not been clearly defined [5].

Most patients diagnosed with blastomycosis have the indolent onset of chronic pneumonia. The clinical manifestations are indistinguishable from tuberculosis, other fungal infections, and cancer. Alveolar infiltrates, mass lesions that mimic bronchogenic carcinoma, and fibronodular interstitial infiltrates are the most common radiographic findings [6]. Diffuse pulmonary infiltrates associated with the adult respiratory distress syndrome occur infrequently but are unfortunately associated with a very high mortality rate [7].

Extrapulmonary disease has been described in as many as

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two-thirds of patients with chronic blastomycosis. In 3 recent clinical studies, however, extrapulmonary disease was found in 25%–40% of patients with blastomycosis [8–10]. The skin, bones, and genitourinary system are the most frequent sites of extrapulmonary disease. Patients frequently present with cutaneous lesions without clinically active pulmonary disease. CNS involvement is rare, except in immunocompromised patients. As many as 40% of patients with AIDS who have blastomycosis have CNS disease, which is manifested as either mass lesions or meningitis [11].

Definitive diagnosis requires the growth of *B. dermatitidis* from a clinical specimen. Visualization of the characteristic budding yeast form in clinical specimens supports a presumptive diagnosis of blastomycosis and may, in the appropriate clinical setting, prompt the initiation of antifungal therapy. Because they lack both sensitivity and specificity, serological tests are generally not helpful for diagnosing blastomycosis. A negative serological test should never be used to rule out disease, nor should a positive titer be an indication to start treatment.

**Objective.** The objective of these practice guidelines is to provide recommendations for the optimal treatment of the pulmonary and extrapulmonary forms of blastomycosis.

**Outcomes.** Treatment should result in abatement of the symptoms and signs of blastomycosis and eradication of *B. dermatitidis* from involved tissues. In the immunocompromised host, a mycological cure may not be possible, and long-term suppressive therapy, usually with an azole, is often required to prevent relapse of disease.

**Evidence.** Although a single randomized trial comparing amphotericin B with 2-hydroxystilbamidine for the treatment of blastomycosis has been reported [12], there are no randomized, blinded trials comparing the currently available agents for the treatment of blastomycosis. However, several prospective, multicenter treatment trials of an individual antifungal were reviewed and accorded the greatest importance. Prospective and retrospective studies that represented the treatment experience of single institutions and individual case reports were given an intermediate importance. Finally, selected reports dealing with the *in vitro* susceptibility of *B. dermatitidis* to the azoles were considered relevant but of lowest importance.

**Values.** The highest value was placed on the ability of each individual antifungal to effect a clinical and mycological cure. Safety, tolerability, lack of drug interactions, ease of administration, and cost of therapy were also valued.

**Benefits and costs.** Before antifungal therapy became available, blastomycosis was thought to have a chronic progressive course with eventual dissemination and associated mortality rates of up to 90%. Conversely, the recent studies, which we review here, have reported cure rates of >85% and mortality rates of <10% in conjunction with the appropriate treatment of blastomycosis. Most patients whose deaths are attributed to blastomycosis have overwhelming disease associated with diffuse pulmonary infiltrates and respiratory failure.

Costs of therapy include those for acquiring the drug, administering the drug, and monitoring clinical response, drug toxicity, and drug interactions. Hospitalization may be necessary for establishing the diagnosis and initiating therapy. Most patients, however, can be managed successfully on an outpatient basis with an azole or amphotericin B.

**Treatment options.** Making the decision to treat patients with blastomycosis involves consideration of the clinical form and severity of disease, the immune competence of the patient, and the toxicity of the antifungal. In a few selected cases of acute pulmonary blastomycosis, therapy may be withheld, and the patient may be carefully observed for either spontaneous cure or progression of disease [5]. All immunocompromised patients and patients with progressive pulmonary disease or extrapulmonary disease should be treated. Treatment options include amphotericin B, ketoconazole, itraconazole, and fluconazole, although no comparative trials of these agents have been performed. Lipid preparations of amphotericin B are effective in animal models of blastomycosis, but they have not been adequately evaluated for humans. Limited clinical experience, however, indicates that these lipid preparations may provide an alternative for selected patients unable to tolerate standard amphotericin B because of toxicity. Surgery has only a limited role in the treatment of blastomycosis.

Intravenous amphotericin B, in cumulative doses of >1 g, has been described to result in cure without relapse in 70%–91% of patients with blastomycosis [13]. A recent large retrospective series of blastomycosis cases in Mississippi noted a cure rate of 86.5% and a relapse rate of only 3.9% for amphotericin B–treated patients [10]. Relapse rates depend on the total dose of amphotericin B administered [14]. Overwhelming pulmonary disease is the most common cause of death, and patients usually die during the first few days of therapy [7]. Increased mortality rates have also been associated with advanced age and concurrent illness with chronic obstructive pulmonary disease or cancer [10].

Ketoconazole was the first azole shown to be an effective alternative to amphotericin B in the treatment of immunocompetent patients with mild to moderate blastomycosis. In a prospective, randomized, multicenter trial, the Mycoses Study Group documented cure rates of 70% among patients treated with 400 mg/d of ketoconazole and 85% among patients treated with 800 mg/d [15]. Bradsher et al. [8] noted a cure rate of 76% for a cohort of 46 patients treated with 400 mg/d of ketoconazole. A recent retrospective study documented a cure rate of 82% for patients treated with ketoconazole at dosage of  $\geq 400$  mg/d [10]. Relapse rates of 10%–14% have been reported [8, 10, 15], and careful follow-up is warranted for 1–2 years after treatment with ketoconazole.

Itraconazole has proven efficacy in the treatment of blastomycosis. Compared with ketoconazole, itraconazole is more readily absorbed, has enhanced antimycotic activity, and is better tolerated. Itraconazole has replaced ketoconazole as the

**Table 1.** Guidelines for the treatment of various forms of blastomycosis.

Type of disease	Preferred treatment (category, grade) <sup>a</sup>	Alternative treatment (category, grade) <sup>a</sup>
<b>Pulmonary<sup>b</sup></b>		
Life-threatening	AmB; total dose, 1.5–2.5 g (AII)	Initiate AmB and switch to Itr after the patient's condition has stabilized (BIII)
Mild to moderate	Itr, 200–400 mg/d (AII) <sup>c</sup>	Ket, 400–800 mg/d (BII); or Flu, 400–800 mg/d (BII)
<b>Disseminated</b>		
CNS	AmB; total dose, at least 2 g (AII)	For patients unable to tolerate a full course of AmB, consider Flu, 800 mg/d (CIII)
<b>Non-CNS</b>		
Life-threatening	AmB; total dose, 1.5–2.5 g (AII)	Initiate AmB and switch to Itr after the patient's condition has stabilized (BIII)
Mild to moderate	Itr, 200–400 mg/d (AII) <sup>d</sup>	Ket, 400–800 mg/d (BII); or Flu, 400–800 mg/d (BII)
Immunocompromised host	AmB, 1.5–2.5 g (AII)	After a primary course of AmB, suppressive therapy should be continued with Itr, 200–400 mg/d (BIII); for patients with CNS disease or who cannot tolerate Itr, consider Flu, 800 mg/d (BII)
<b>Special circumstance</b>		
Pregnancy	AmB, 1.5–2.5 g (AII)	
Pediatrics	AmB; total dose, $\geq 30$ mg/kg (AII); or Itr, 5–7 mg/kg/d (BIII)	

NOTE. AmB, amphotericin B; CNS, central nervous system; Flu, fluconazole; Itr, itraconazole; Ket, ketoconazole.

<sup>a</sup> See article by Sobel [19] for definitions of categories reflecting the strength of each recommendation for or against its use and of grades reflecting the quality of evidence on which recommendations are based.

<sup>b</sup> Some patients with acute pulmonary infection may have a spontaneous cure; thus, patients with mild disease involving only the lungs may be monitored closely for resolution. Patients with progressive pulmonary disease should be treated.

<sup>c</sup> Treatment with an azole should be continued for a minimum of 6 months.

<sup>d</sup> Patients with bone disease should be treated with an azole for 12 months.

first-line agent for the treatment of non-life-threatening non-CNS blastomycosis, although it is more costly. The Mycoses Study Group, in a prospective, phase 2 clinical trial, found that itraconazole was effective for 90% of patients treated with 200–400 mg/d [16]. For compliant patients who completed at least 2 months of therapy, a success rate of 95% was noted. No therapeutic advantage was noted for patients treated with the higher doses, compared with those patients treated with 200 mg/d. Bradsher [13] noted similar success for a cohort of 42 patients treated with itraconazole at a dosage of 200 mg/d.

The role of fluconazole in the treatment of blastomycosis is limited. The results of a small pilot study of 200–400 mg/d of fluconazole were disappointing, with a successful outcome noted only for 15 (65%) of the 23 patients [17]. A recent study of higher dosages of fluconazole (400–800 mg/d) showed enhanced efficacy [18]; a successful outcome was noted for 34 (87%) of 39 patients treated for a mean duration of 8.9 months. Adverse events were uncommon. These results indicate that fluconazole is less efficacious than itraconazole and is similar in efficacy to ketoconazole at equivalent doses but with less serious toxicity. Because fluconazole has excellent penetration into the CNS, it may have some role in the treatment of blastomycotic meningitis and cerebral abscesses, although clinical experience in treating these conditions is limited to only a few cases.

## Specific Treatment Recommendations

### Pulmonary Blastomycosis

All immunocompromised patients and patients with progressive pulmonary infection should be treated. Spontaneous cure has been well documented for patients with acute pul-

monary infection [5]. Thus, in selected cases, patients may be closely monitored for resolution or progression of disease. Complicating this management decision, some patients present with serious extrapulmonary disease after the resolution of pulmonary infection. Patients must therefore be carefully evaluated for extrapulmonary disease before a decision is made to withhold therapy.

Patients with life-threatening disease, such as acute respiratory distress syndrome, should be treated with amphotericin B (0.7–1 mg/kg/d; total dose, 1.5–2.5 g; table 1) (AII; see article by Sobel [19] for definitions of categories reflecting the strength of each recommendation for or against its use and grades reflecting the quality of evidence on which recommendations are based). Therapy for some patients may be switched to itraconazole (200–400 mg/d) after clinical stabilization with an initial course of amphotericin B treatment, usually a minimum dose of 500 mg (BIII).

Patients with mild to moderate disease should be treated with itraconazole at a dosage of 200–400 mg/d for a minimum of 6 months (AII). An alternative to itraconazole includes 6 months of either ketoconazole at a dosage of 400–800 mg/d (BII) or fluconazole at a dosage of 400–800 mg/d (BII). For patients who are unable to tolerate an azole or whose diseases progress during azole treatment, therapy should be changed to amphotericin B (0.5–0.7 mg/kg/d; total dose, 1.5–2.5 g) (AII).

### Disseminated Blastomycosis, Extrapulmonary

All patients with disseminated disease require treatment. The presence or absence of CNS infection is the critical factor for determining therapy.

Patients with CNS infection should receive a dosage of amphotericin B of 0.7–1 mg/kg/d (total dose, at least 2 g) (AII).

The use of lipid formulations of amphotericin B has not been reported for CNS blastomycosis, but this treatment may be an alternative for patients unable to tolerate amphotericin B because of toxicity. Azoles should not be considered for primary treatment of patients with CNS blastomycosis (EIII). However, fluconazole, because of its excellent CSF penetration, could possibly be a consideration at higher dosages (minimum, 800 mg/d) in special circumstances (CIII).

Patients with life-threatening disseminated disease should be treated with amphotericin B (0.7–1 mg/kg/d; total dose, 1.5–2.5 g) (AII). Therapy for some patients may be switched to itraconazole after clinical stabilization with amphotericin B (BIII).

Patients with mild to moderate disseminated blastomycosis that does not involve the CNS should be treated with itraconazole (200–400 mg/d) for at least 6 months (AII). Ketoconazole and fluconazole, both at dosages of 400–800 mg/d, are alternatives to itraconazole (BII). Bone disease is more difficult to treat and more likely to relapse. Therefore, patients with blastomycotic osteomyelitis should receive at least 1 year of treatment with an azole (BIII). For patients whose diseases progress during treatment with an azole or who are unable to tolerate an azole because of toxicity, amphotericin B (0.5–0.7 mg/kg/d; total dose, 1.5–2.5 g) is recommended (AII).

#### Blastomycosis in the Immunocompromised Host

Recent reports indicate that *B. dermatitidis* may infrequently act as an opportunistic pathogen, notably in patients who are in the late stages of AIDS, transplant recipients, and patients treated with immunosuppressive or cytotoxic chemotherapy [11, 20]. Disease in these patients is more aggressive and more often fatal than disease in the normal host. Pulmonary disease is more likely to present with diffuse pulmonary infiltrates and respiratory failure. Dissemination to multiple organs, including the CNS, also occurs more frequently. Mortality rates of 30%–40% have been reported, and most deaths attributed to blastomycosis occur during the first few weeks of therapy. Thus, early and aggressive treatment with amphotericin B (0.7–1 mg/kg/d) is indicated for blastomycosis in the immunocompromised patient (AII). Most experts recommend a total dose of 1.5–2.5 g, although treatment for selected patients without CNS infection may be switched to itraconazole after clinical stabilization with amphotericin B (usually a minimum dose of 1 g) (BIII).

Despite amphotericin B treatment, frequent relapses occur in patients with AIDS and in those patients who continue immunosuppressive therapy [11, 20]. Some authorities therefore recommend chronic suppressive therapy with an azole, preferably itraconazole, for those patients who respond to a primary course of amphotericin B treatment (BIII). Treatment with ketoconazole is discouraged because relapse rates are higher (DIII). Fluconazole treatment may be given special consideration for selected patients who have had CNS disease or

patients unable to tolerate itraconazole owing to toxicity or drug interactions (BIII).

#### Special Circumstances

**Pregnancy.** Amphotericin B is the drug of choice for treating blastomycosis in pregnant women (AII). The azoles should never be used as treatment for this patient cohort because of their embryotoxic and teratogenic potential (EIII).

**Pediatrics.** Although blastomycosis is less commonly described in children, the clinical spectrum of disease is similar to that described in adults. However, a recent report has indicated that the diagnosis of blastomycosis in children, compared with adults, is more difficult to establish and that the response to oral azoles in children is less than satisfactory [21]. Children with life-threatening or CNS disease should be treated with amphotericin B (AII). Itraconazole, at a dosage of 5–7 mg/kg/d, has been used successfully as treatment of a limited number of pediatric patients with non-life-threatening non-CNS disease (BIII).

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