

# Clinical Practice Guidelines for the Management of Blastomycosis: 2008 Update by the Infectious Diseases Society of America

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Evidence-based guidelines for the management of patients with blastomycosis were prepared by an Expert Panel of the Infectious Diseases Society of America. These updated guidelines replace the previous management guidelines published in the April 2000 issue of *Clinical Infectious Diseases*. The guidelines are intended for use by health care providers who care for patients who have blastomycosis. Since 2000, several new antifungal agents have become available, and blastomycosis has been noted more frequently among immunosuppressed patients. New information, based on publications between 2000 and 2006, is incorporated in this guideline document, and recommendations for treating children with blastomycosis have been noted.

## EXECUTIVE SUMMARY

Blastomycosis refers to disease caused by the dimorphic fungus *Blastomyces dermatitidis*. This infection occurs most often in persons living in midwestern, southeastern, and south central United States and the Canadian provinces that border the Great Lakes and the St. Lawrence Seaway. Recent reports have shown an increase in the incidence of blastomycosis in some of these regions.

Blastomycosis is associated with a spectrum of illness ranging from subclinical infection to acute or chronic pneumonia; a subset of individuals with acute pulmonary blastomycosis can progress to fulminant multilobar pneumonia and acute respiratory distress syndrome (ARDS). Diagnostic delays are not uncommon and often result in increased morbidity and mortality.

Although blastomycosis usually remains localized to the lungs, 25%–40% of those infected will develop extrapulmonary infection manifested by cutaneous, osteoarticular, genitourinary, or CNS disease. Disseminated blastomycosis occurs more frequently in immunosuppressed individuals, such as organ transplant recipients and those infected with HIV.

In the immunocompetent host, acute pulmonary blastomycosis can be mild and self-limited and may not require treatment. However, consideration should be given to treating all infected individuals to prevent extrapulmonary dissemination. All persons with moderate to severe pneumonia, disseminated infection, or immunocompromise require antifungal therapy.

## Pulmonary Blastomycosis

1. For moderately severe to severe disease, initial

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<sup>a</sup> Private practice.

These guidelines were developed and issued on behalf of the Infectious Diseases Society of America.

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results. Accordingly, the Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances.

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treatment with a lipid formulation of amphotericin B (AmB) at a dosage of 3–5 mg/kg per day or AmB deoxycholate at a dosage of 0.7–1 mg/kg per day for 1–2 weeks or until improvement is noted, followed by oral itraconazole, 200 mg 3 times per day for 3 days and then 200 mg twice per day, for a total of 6–12 months, is recommended (A-III).

2. For mild to moderate disease, oral itraconazole, 200 mg 3 times per day for 3 days and then once or twice per day for 6–12 months, is recommended (A-II).

3. Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure (A-III).

### Disseminated Extrapulmonary Blastomycosis

4. For moderately severe to severe disease, lipid formulation AmB, 3–5 mg/kg per day, or AmB deoxycholate, 0.7–1 mg/kg per day, for 1–2 weeks or until improvement is noted, followed by oral itraconazole, 200 mg 3 times per day for 3 days and then 200 mg twice per day for a total of at least 12 months, is recommended (A-III).

5. For mild to moderate disease, oral itraconazole, 200 mg 3 times per day for 3 days and then once or twice per day for 6–12 months, is recommended (A-II).

6. Patients with osteoarticular blastomycosis should receive a total of at least 12 months of antifungal therapy (A-III).

7. Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure (A-III).

### CNS Blastomycosis

8. AmB, given as a lipid formulation at a dosage of 5 mg/kg per day over 4–6 weeks followed by an oral azole, is recommended. Possible options for azole therapy include fluconazole, 800 mg per day, itraconazole, 200 mg 2 or 3 times per day, or voriconazole, 200–400 mg twice per day, for at least 12 months and until resolution of CSF abnormalities (B-III).

### Treatment for Immunosuppressed Patients with Blastomycosis

9. AmB, given as a lipid formulation, 3–5 mg/kg per day, or AmB deoxycholate, 0.7–1 mg/kg per day, for 1–2 weeks or until improvement is noted, is recommended as initial therapy for patients who are immunosuppressed, including those with AIDS (A-III).

10. Itraconazole, 200 mg 3 times per day for 3 days and then twice per day, is recommended as step-down therapy after

the patient has responded to initial treatment with AmB and should be given to complete a total of at least 12 months of therapy (B-III).

11. Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure (A-III).

12. Lifelong suppressive therapy with oral itraconazole, 200 mg per day, may be required for immunosuppressed patients if immunosuppression cannot be reversed (A-III) and in patients who experience relapse despite appropriate therapy (C-III).

### Treatment for Blastomycosis in Pregnant Women and in Children

13. During pregnancy, lipid formulation AmB, 3–5 mg/kg per day, is recommended (A-III). Azoles should be avoided because of possible teratogenicity (A-III).

14. If the newborn shows evidence of infection, treatment is recommended with AmB deoxycholate, 1.0 mg/kg per day (A-III).

15. For children with severe blastomycosis, AmB deoxycholate, 0.7–1.0 mg/kg per day, or lipid formulation AmB, at a dosage of 3–5 mg/kg per day, is recommended for initial therapy, followed by oral itraconazole, 10 mg/kg per day (up to 400 mg per day) as step-down therapy, for a total of 12 months (B-III).

16. For children with mild to moderate infection, oral itraconazole, at a dosage of 10 mg/kg per day (to a maximum of 400 mg orally per day) for 6–12 months, is recommended (B-III).

17. Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure (A-III).

## INTRODUCTION

Blastomycosis is a systemic pyogranulomatous disease caused by the thermally dimorphic fungus *B. dermatitidis*. 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 mid-western states and Canadian provinces that border the Great Lakes, and a small area of New York and Canada adjacent to the St. Lawrence Seaway [1–5]. In these regions of endemicity, several studies have documented the presence of areas of hyperendemicity where the rate of blastomycosis is unusually high. Point-source outbreaks have been associated with occupational and recreational activities, frequently along streams or rivers, that result in exposure to moist soil enriched with decaying vegetation [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 while performing an autopsy [6]. The clinical spectrum of blastomycosis is varied, including asymptomatic infection, acute or chronic pneumonia, and disseminated disease. As defined in point-source epidemics, asymptomatic infection occurs in at least 50% of infected persons [2]. Symptomatic disease develops after an incubation period of 30–45 days. Acute pulmonary blastomycosis mimics community-acquired bacterial pneumonia. Spontaneous cures of symptomatic acute infection have been well documented, but the frequency of such cures has not been clearly defined [7].

Blastomycosis can present as chronic pneumonia with clinical manifestations that 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 [8]. Diffuse pulmonary infiltrates associated with ARDS occur infrequently but are, unfortunately, associated with a very high mortality rate [9].

Extrapulmonary disease has been described in as many as two-thirds of patients with chronic blastomycosis. In several studies, however, extrapulmonary disease was found in 25%–40% of patients with blastomycosis [4, 5, 10, 11]. The skin, bones, and genitourinary system are the most frequent sites of extrapulmonary disease. Patients frequently present with cutaneous lesions without having 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 [12].

The Panel addressed the following clinical questions:

- I. What is the treatment for pulmonary blastomycosis?
- II. What is the treatment for disseminated, extrapulmonary blastomycosis?
- III. What is the treatment for CNS blastomycosis?
- IV. What is the treatment for immunosuppressed patients with blastomycosis?
- V. What is the treatment for blastomycosis for pregnant women and children?

## PRACTICE GUIDELINES

“Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances [13]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation” [13].

## METHODS

### Panel Composition

A panel of experts prepared these guidelines; the panel was composed of the authors of the guidelines, all infectious diseases specialists from North America with expertise in blastomycosis. The panelists have both clinical and laboratory experience in blastomycosis (Appendix, table A1).

### Literature Review and Analysis

For the 2007 update, the Expert Panel completed the review and analysis of literature on the treatment of blastomycosis that has been published since 2000 and reviewed the older literature as well. Computerized literature searches of PubMed (January 2000 through July 2007) were performed. Only English-language literature was reviewed. Searches focused on studies of humans but included a few experimental animal studies and in vitro studies.

The search yielded 62 articles: 30 case reports, 16 reviews, 1 clinical practice guideline, and 15 studies. Only 1 randomized, comparative treatment trial comparing AmB with 2-hydroxystilbamidine for the treatment of blastomycosis has been reported [14]. There are no randomized, blinded trials comparing the currently available agents for the treatment of blastomycosis. However, several prospective, multicenter treatment trials of individual antifungal agents 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* and experimental animal models were considered to be relevant but of lowest importance.

### Process Overview

In evaluating the evidence with regard to the treatment of blastomycosis, the Panel followed a process used in the development of other IDSA guidelines. The process included a systematic weighting of the quality of the evidence and the grade of recommendation (table 1) [15]. Recommendations for the treatment of blastomycosis were derived primarily from case reports and nonrandomized treatment trials (table 2).

### Consensus Development Based on Evidence

The Panel met on 7 occasions via teleconference to complete the work of the guideline. The purpose of the teleconferences was to discuss the questions to be addressed, to make writing assignments, and to discuss recommendations. All members of the panel participated in the preparation and review of the draft guideline. Feedback from external peer reviews was obtained. The guideline was reviewed and approved by the Stan-

**Table 1. Infectious Diseases Society of America–United States Public Health Service grading system for ranking recommendations in clinical guidelines.**

| Category, grade            | Definition   |
|----------------------------|--|
| Strength of recommendation |  |
| A                          | Good evidence to support a recommendation for use  |
| B                          | Moderate evidence to support a recommendation for use  |
| C                          | Poor evidence to support a recommendation  |
| Quality of evidence        |  |
| I                          | Evidence from $\geq 1$ properly randomized, controlled trial   |
| II                         | Evidence from $\geq 1$ well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from $>1$ center); from multiple time-series; or from dramatic results from uncontrolled experiments |
| III                        | Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees  |

dards and Practice Guidelines Committee (SPGC) and the Board of Directors before dissemination.

### Guidelines and Conflicts of Interest

All members of the Expert Panel complied with the IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel were provided the IDSA's conflict of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested about employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

### Revision Dates

At annual intervals, the Panel Chair, the SPGC liaison advisor, and the Chair of the SPGC will determine the need for revisions to the guideline on the basis of an examination of current literature. If necessary, the entire Panel will be reconvened to discuss potential changes. When appropriate, the Panel will recommend revision of the guideline to the SPGC and the IDSA Board for review and approval.

## RESULTS

**Diagnostic issues.** *B. dermatitidis* is readily isolated from respiratory secretions in most cases of infection with lung involvement. In 1 series, culture yielded the organism in 86% of sputum and in 100% of bronchial washings in specimens from patients with documented pulmonary disease [16]. Culture

confirmation should be sought in every suspected case but is usually not the first indicator of the diagnosis [17].

Direct visualization of the organism in cytologic and histologic specimens has been the most commonly used method for rapid diagnosis of blastomycosis [16, 17]. Respiratory specimens treated with potassium hydroxide or calcofluor white or stained with Papanicolaou stain have a sensitivity of 50%–90% [16, 18]. Histopathological examination of tissue specimens with use of methenamine silver or periodic acid-Schiff (PAS) stain is the usual diagnostic method for extrapulmonary disease.

A commercial test for *Blastomyces* antigen in specimens of urine, blood, and other fluids is available as an additional method of rapid diagnosis of blastomycosis [19]. In a series of 4 pediatric cases, urine antigen detection established the diagnosis of blastomycosis in 2 of the 3 patients with negative sputum cytology results but subsequent positive culture results [20]. The urine antigen assay shows cross-reactivity with other fungi, particularly *Histoplasma capsulatum*, and the role that this test should play in the diagnosis of blastomycosis has not been established [19].

Serological testing by complement fixation and immunodiffusion methods lacks both sensitivity and specificity in the diagnosis of blastomycosis [16]. Newer EIAs have shown improved sensitivity, but there are insufficient clinical data to recommend their use as a routine diagnostic tool [21].

**Antifungal agents.** AmB is used in the treatment of patients who have severe blastomycosis and for those who have CNS involvement [22–24]. Most experience has been with the deoxycholate formulation [23]. Use of AmB deoxycholate in total doses of  $>1$  g has been reported to result in cure without relapse for 77%–91% of patients [24], and total doses of  $>2$  g have shown cure rates of 97% [21]. A large series of patients from Mississippi confirmed an 86% response rate with a relapse rate of 4% and a mortality rate of 10% for patients who were treated

**Table 2. Summary of recommendations.**

| Manifestation                                     | Preferred treatment   | Class | Comments   |
|---|---|-------|--|
| Moderately severe to severe pulmonary             | Lipid AmB, 3–5 mg/kg per day, or deoxycholate AmB, 0.7–1 mg/kg per day, for 1–2 weeks, followed by itraconazole, 200 mg bid for 6–12 months     | A-III | The entire course of therapy can be given with deoxycholate AmB to a total of 2 g; however, most clinicians prefer to use step-down itraconazole therapy after the patient's condition improves. The lipid formulations of AmB have fewer adverse effects.   |
| Mild to moderate pulmonary                        | Itraconazole, 200 mg once or twice per day for 6–12 months  | A-II  |  |
| Moderately severe to severe disseminated          | Lipid AmB, 3–5 mg/kg per day, or deoxycholate AmB, 0.7–1 mg/kg per day, for 1–2 weeks, followed by itraconazole, 200 mg bid for 12 months       | A-III | The entire course of therapy can be given with deoxycholate AmB to a total of 2 g; however, most clinicians prefer to use step-down itraconazole therapy after the patient's condition improves. The lipid formulations of AmB have fewer adverse effects. Treat osteoarticular disease for 12 months. |
| Mild to moderate disseminated                     | Itraconazole, 200 mg once or twice per day for 6–12 months  | A-II  | Treat osteoarticular disease for 12 months.  |
| CNS disease                                       | Lipid AmB, 5 mg/kg per day for 4–6 weeks is preferred, <sup>a</sup> followed by an oral azole for at least 1 year                               | B-III | Step-down therapy can be with fluconazole, 800 mg per day, itraconazole, 200 mg 2–3 times per day, or voriconazole, 200–400 mg twice per day. Longer treatment may be required for immunosuppressed patients.  |
| Immunosuppressed patients                         | Lipid AmB, 3–5 mg/kg per day, or deoxycholate AmB, 0.7–1 mg/kg per day, for 1–2 weeks, followed by itraconazole, 200 mg bid for 12 months       | A-III | Life-long suppressive treatment may be required if immunosuppression cannot be reversed.   |
| Pregnant women                                    | Lipid AmB, 3–5 mg/kg per day  | A-III | Azoles should not be used during pregnancy.  |
| Children with moderately severe to severe disease | Deoxycholate AmB, 0.7–1 mg/kg per day, or lipid AmB, 3–5 mg/kg per day, for 1–2 weeks, followed by itraconazole, 10 mg/kg per day for 12 months | B-III | Children tolerate deoxycholate AmB better than adults do; maximum dose of itraconazole should be 400 mg per day.   |
| Children with mild to moderate disease            | Itraconazole, 10 mg/kg per day for 6–12 months  | B-III | Maximum dose, 400 mg per day.  |

**NOTE.** AmB, amphotericin B; bid, twice per day.

<sup>a</sup> In animal models of fungal meningitis, liposomal AmB achieves higher CNS levels than do other lipid formulations. Hence, many infectious diseases experts recommend liposomal AmB as the preferred lipid formulation for the treatment of CNS fungal infections.



with AmB deoxycholate [11]. Although effective, AmB is now rarely used as sole therapy for blastomycosis. Step-down therapy to an azole after an initial response is noted with AmB has become the standard of care.

Lipid preparations of AmB are effective in animal models of blastomycosis [25], but they have not been studied in controlled trials involving humans. However, clinical experience indicates that the lipid formulations should be equally as efficacious as the deoxycholate formulation and are associated with less toxicity [26–30].

Ketoconazole was the first azole shown to be an effective alternative to AmB in the treatment of immunocompetent patients with mild to moderate blastomycosis. Cure rates of 70%–85% were reported from several open-label treatment trials [11, 31, 32]. However, relapse rates were 10%–14% in these trials. Although effective, this agent is seldom used because of the high incidence of serious adverse effects, especially with use of the higher dosages sometimes required for treatment.

Compared with ketoconazole, itraconazole has enhanced antimycotic activity and is better tolerated by patients. Itraconazole has replaced ketoconazole as the first-line agent for the treatment of non-life-threatening, non-CNS blastomycosis. In a prospective, phase 2 clinical trial, itraconazole was effective for 90% of patients treated with 200–400 mg per day [33]. 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 per day. Bradsher [24] noted similar success for a cohort of 42 patients treated with itraconazole at a dosage of 200 mg per day.

Itraconazole comes in 2 oral dosage forms: a 100-mg capsule and a solution of 100 mg/10 mL. It is recommended that doses of >200 mg per day be given as 2 divided doses. The capsule formulation of itraconazole is best absorbed when taken with food, and agents that decrease stomach acidity should be avoided. In contrast, itraconazole solution should be taken on an empty stomach and does not require gastric acidity for absorption.

The role of fluconazole in the treatment of blastomycosis is limited. The results of a small pilot study of treatment with 200–400 mg per day of fluconazole were disappointing, with a successful outcome noted for only 15 (65%) of the 23 patients [34]. Higher dosages of fluconazole (400–800 mg per day) showed enhanced efficacy [35]; a successful outcome was noted for 34 (87%) of 39 patients treated for a mean duration of 8.9 months. Because fluconazole has excellent penetration into the CNS, it may have some role in the treatment of CNS blastomycosis even though clinical experience in treatment of this condition is limited.

In vitro and animal data demonstrate that the extended-spectrum azoles—voriconazole and posaconazole—have activ-

ity against *B. dermatitidis* [36–39]. There have been reports of successful use of voriconazole for treatment of refractory blastomycosis and for treatment of immunosuppressed patients [40, 41]. In particular, voriconazole has been used as an alternative agent for patients who have CNS blastomycosis [29, 42–44], given its ability to achieve adequate concentrations in brain and CSF [45]. To date, there have been no reports of the use of posaconazole for the treatment of blastomycosis.

Drug-drug interactions are a major clinical issue in the use of azole antifungal agents. The azoles exert their antifungal activity through inhibition of cytochrome P450 pathways in the fungal cell membrane. Mammalian cytochrome P450 pathways are inhibited to a varying extent by each azole, and itraconazole and voriconazole are extensively metabolized by hepatic cytochrome P450 enzymes. Additionally, itraconazole is an inhibitor and a substrate of p-glycoprotein, and posaconazole is eliminated through glucuronidation, which leads to other important drug-drug interactions. Up-to-date prescribing information should be reviewed before initiating azole therapy in any patient who is taking other medications.

All azoles have been reported to cause hepatitis. Hepatic enzymes should be measured before starting therapy, at least at 2 and 4 weeks after therapy has begun, and every 3 months during therapy.

The echinocandins—caspofungin, micafungin, and anidulafungin—have intermediate to poor in vitro activity against *B. dermatitidis* and should not be used for treating blastomycosis [37, 46].

**Therapeutic drug monitoring.** Optimization of itraconazole therapy for treatment of systemic fungal infections is strongly recommended. Blood concentrations vary widely in patients receiving itraconazole. Serum concentrations are ~30% higher with use of the solution formulation than with the capsule formulation, but wide intersubject variability exists. Itraconazole concentrations in serum should be determined only after a steady state has been reached, which takes ~2 weeks. Serum levels should be determined to ensure adequate absorption, to monitor changes in the dosage of itraconazole or the addition of interacting medications, and to assess adherence. Because of its long half-life, serum concentrations of itraconazole vary little during a 24-h dosing interval, and the blood specimen can be collected at any time relative to drug administration. A serum concentration associated with treatment failure of blastomycosis has not been identified. It is recommended that a serum level >1.0 µg/mL be achieved. Similarly, a serum concentration associated with an increased risk of toxicity has not been defined, but concentrations >10.0 µg/mL are probably unnecessary and potentially toxic. When measured by high-pressure liquid chromatography, both itraconazole and its bioactive hydroxy-itraconazole metabolite are reported, the sum of which should be considered in assessing drug levels.

Because of nonlinear pharmacokinetics in adults and genetic differences in metabolism, there is both inpatient and outpatient variability in serum voriconazole concentrations [47]. Therapeutic drug monitoring, although not standard of care, may be considered in some patients receiving treatment with voriconazole, because drug toxicity has been observed when patients have higher serum concentrations and reduced clinical response has been observed when patients have lower concentrations [48–50].

**Relapse.** Relapse of blastomycosis in immunocompetent patients is uncommon with use of recommended treatment regimens but has been reported to occur even months after the end of treatment with amphotericin deoxycholate, ketoconazole, or itraconazole [11, 31, 32]. Bradsher et al. [31] noted relapse in 2 patients treated with ketoconazole for at least 6 months, with median follow-up of 17 months [31]. National Institute of Allergy and Infectious Diseases Mycoses Study Group evaluations of therapy showed 4 relapses among patients receiving ketoconazole treatment of 400 mg per day [32]. Among patients receiving itraconazole therapy for at least 2 months, 1 patient experienced relapse at 6 months after the end of treatment [33]. Physicians should consider observing patients after therapy has ended for a period of at least 6 months. When that is not possible, patients should be advised to seek further evaluation if their symptoms recur.

Data are limited, but antigen detection might prove useful in monitoring response to treatment and in predicting relapse. In a series of 4 pediatric cases, 3 patients who responded to treatment with itraconazole had significant reductions of the urine antigen levels. The fourth patient, who was nonadherent to treatment and experienced relapse after the end of treatment, had persistently high urine antigen levels [20].

## **GUIDELINE RECOMMENDATIONS FOR THE TREATMENT OF BLASTOMYCOSIS**

### **I. What Is the Treatment for Pulmonary Blastomycosis?**

#### **Recommendations**

1. For moderately severe to severe disease, initial treatment with a lipid formulation of AmB at a dosage of 3–5 mg/kg per day or AmB deoxycholate at a dosage of 0.7–1 mg/kg per day for 1–2 weeks or until improvement is noted, followed by oral itraconazole, 200 mg 3 times per day for 3 days and then 200 mg twice per day, for a total of 6–12 months, is recommended (A-III).
2. For mild to moderate disease, oral itraconazole, 200 mg 3 times per day for 3 days and then once or twice per day for 6–12 months, is recommended (A-II).
3. Serum levels of itraconazole should be determined after

the patient has been receiving treatment with this agent for at least 2 weeks, to ensure adequate drug exposure (A-III).

**Evidence summary.** The decision to treat patients with blastomycosis involves consideration of the clinical form and severity of disease, the immunocompetence of the patient, and the toxicity of the antifungal agent. In a few selected cases of acute pulmonary blastomycosis in which clinical resolution has occurred before the diagnosis is established, therapy may be withheld [7], but currently, even those patients who have resolution of radiographic findings before sputum culture results are determined to be positive for *B. dermatitidis* are usually treated with itraconazole to prevent development of extrapulmonary disease. All immunocompromised patients and patients with moderate or severe pulmonary disease should be treated.

Intravenous AmB deoxycholate, in cumulative doses of >1 g, results in cure without relapse in 70%–91% of patients with blastomycosis [24]. Currently, it is unusual for patients to be treated solely with AmB. Almost all patients who are severely ill can be treated initially with AmB, and therapy can then be changed to itraconazole after the patient's condition has stabilized. There are no firm guidelines on how to gauge the severity of illness, and the severity should be determined by clinical judgment.

Patients with mild to moderate disease should be treated with itraconazole at a dosage of 200–400 mg per day for a minimum of 6–12 months. The exact length of time that treatment should be continued beyond 6 months has not been studied. Generally, treatment will extend to a few months beyond the time of resolution of radiographic findings and clinical symptoms. Success rates approach 95% with itraconazole therapy [33]. Alternatives for those patients who are unable to tolerate itraconazole or who are unable to take this agent because of drug-drug interactions or failure to absorb the drug include ketoconazole (at a dosage of 400–800 mg per day [32]) or fluconazole (at a dosage of 400–800 mg per day) [34, 35], but these alternatives are less effective, and the toxicity of ketoconazole is greater than that of the other agents. The role of voriconazole or posaconazole is not clear, but these may also be effective agents [29, 40–44].

Increased mortality rates for patients with pulmonary blastomycosis have been associated with advanced age, chronic obstructive pulmonary disease, cancer, and African American ethnicity [1, 11]. Overwhelming pulmonary disease is the most common cause of death, and patients often die during the first few days of therapy. When ARDS occurs, mortality has a range of 50%–89% [9, 41, 51, 52]. No studies have addressed the question of determining the most appropriate therapy for overwhelming pulmonary blastomycosis with ARDS. Among patients who received the diagnosis before death, most were treated with AmB deoxycholate. Almost all of these cases were

reported before lipid formulations became available for use. In the most recent series of cases, all of which occurred in transplant recipients, lipid formulation AmB was used in 4 of 7 patients with ARDS, and 3 were cured; 2 others treated with AmB deoxycholate and 1 treated with voriconazole died [41]. Clearly, the number of cases is small, but there may be a role for higher dosages of AmB that can be given with the lipid formulations. Treatment with corticosteroids has been used in patients with ARDS, although no randomized, controlled trials have been preformed to support improved outcomes.

## II. What Is the Treatment for Disseminated Extrapulmonary Blastomycosis?

### Recommendations

4. For moderately severe to severe disease, lipid formulation AmB, 3–5 mg/kg per day, or AmB deoxycholate, 0.7–1 mg/kg per day, for 1–2 weeks or until improvement is noted, followed by oral itraconazole, 200 mg 3 times per day for 3 days and then 200 mg twice per day, for a total of at least 12 months, is recommended (A-III).

5. For mild to moderate disease, oral itraconazole, 200 mg 3 times per day for 3 days and then once or twice per day for 6–12 months, is recommended (A-II).

6. Patients with osteoarticular blastomycosis should receive a total of at least 12 months of antifungal therapy (A-III).

7. Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure (A-III).

**Evidence summary.** All patients with disseminated disease require treatment. Even patients who are thought to have had complete resection of tissue infected with *B. dermatitidis* should be treated with antifungal therapy. The presence or absence of CNS infection is a critical factor for determining which antifungal agent to use. Most patients who have CNS infection will present with clinical manifestations of headache, confusion, or focal neurological deficits. However, in immunosuppressed patients who have disseminated blastomycosis, it is recommended that imaging studies of the brain be performed to assess the presence of CNS involvement.

Patients with severe disseminated disease should be treated with AmB deoxycholate or a lipid formulation of AmB. Success rates of 70%–91% have been reported with AmB deoxycholate [11, 23, 24]. All of these reports involved patients who received AmB deoxycholate as the sole treatment for blastomycosis. As noted for pulmonary disease, it is unusual for patients who have disseminated blastomycosis to be treated solely with an AmB formulation. Almost all patients who are severely ill can be treated initially with AmB, and then therapy can be changed

to itraconazole after the patient's condition has stabilized. There are no firm guidelines on how to gauge the severity of illness, and this should be decided by clinical judgment.

Patients with mild to moderate disseminated blastomycosis that does not involve the CNS should be treated with itraconazole (200–400 mg per day) for a minimum of 6–12 months, on the basis of excellent response rates noted in a multicenter, open-label trial with this agent [33]. The exact length of time that treatment should be continued beyond 6 months has not been studied. Generally, treatment will extend to a few months beyond the time of resolution of skin or other focal lesions and clinical symptoms. Ketoconazole is less effective and more toxic than itraconazole [31, 32] and is now rarely used. Fluconazole at dosages of 400–800 mg per day is an alternative to itraconazole but is less effective [34, 35]. The role of voriconazole or posaconazole is not clear, but these may also be effective agents [40, 41]. For patients whose disease progresses during treatment with an azole or who are unable to tolerate an azole because of toxicity, treatment with an AmB formulation is recommended.

Osteoarticular blastomycosis is more difficult to treat and more likely to result in relapse [53]. Therefore, patients should receive a total of at least 1 year of treatment with an azole.

## III. What Is the Treatment for CNS Blastomycosis?

### Recommendations

8. AmB should be given as a lipid formulation at a dosage of 5 mg/kg per day for 4–6 weeks, followed by an oral azole. Possible options for azole therapy include fluconazole (800 mg per day), itraconazole (200 mg 2 or 3 times per day), or voriconazole (200–400 mg twice per day) for at least 12 months and until resolution of CSF abnormalities (B-III).

**Evidence summary.** CNS involvement in blastomycosis occurs in <5% of cases among immunocompetent patients [17], although patients with AIDS have been reported to have rates of blastomycosis involvement as high as 40% [12, 54]. CNS blastomycosis can present as a mass lesion; an abscess in the epidural space, brain parenchyma, or vertebrae; or meningitis. Ocular disease is a rare but sight-threatening complication of CNS blastomycosis [55]. Although there are few published reports of the use of lipid formulations of AmB to treat CNS blastomycosis [29, 30], these agents are preferred because of the prolonged therapy that must be given for this form of the disease. There are experimental animal data showing superior CNS penetration by liposomal AmB, when compared with AmB lipid complex and AmB deoxycholate [56]. Whether this might translate to better efficacy of this formulation in patients with CNS blastomycosis is not clear.



Azoles should not be used as primary therapy for CNS blastomycosis but should be used as follow-up therapy after an initial response to AmB. The most appropriate azole to use is not clear. Fluconazole has excellent CSF penetration but less activity against *B. dermatitidis* than do other azoles. There are a few anecdotal reports of success [57–59]. The dosage should be 800 mg per day. Itraconazole achieves minimal levels in the CSF but has greater intrinsic activity against *B. dermatitidis* than does fluconazole. There are few case reports of CNS blastomycosis treated with itraconazole [60]. Voriconazole has good CSF penetration and excellent in vitro activity against *B. dermatitidis* and has been used to treat CNS blastomycosis [29, 42–44, 59]. There is very little experience with this agent for other forms of blastomycosis [40, 41]. To date, there are no data for posaconazole as an agent for treatment of CNS blastomycosis.

For selected patients, surgery may also be important in the management of CNS blastomycosis that causes focal neurological dysfunction. Surgical drainage of an epidural abscess or other critical lesions may be important in limiting morbidity and mortality from this disorder [61].

#### IV. What Is the Treatment for Immunosuppressed Patients with Blastomycosis?

##### Recommendations

9. AmB, given as a lipid formulation, 3–5 mg/kg per day, or AmB deoxycholate, 0.7–1 mg/kg per day, for 1–2 weeks or until improvement is noted, is recommended as initial therapy for patients who are immunosuppressed, including those with AIDS (A-III).

10. Itraconazole, 200 mg 3 times per day for 3 days and then twice per day, is recommended as step-down therapy after the patient has responded to initial treatment with AmB and should be given to complete a total of at least 12 months of therapy (B-III).

11. Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure (A-III).

12. Life-long suppressive therapy, with oral itraconazole 200 mg per day, may be required in immunosuppressed patients if immunosuppression cannot be reversed (A-III) and in patients who experience relapse despite appropriate therapy (C-III).

**Evidence summary.** Immunosuppressed patients appear more likely than healthy hosts to develop severe pulmonary infection and disseminated blastomycosis and to die of the infection [12, 54]. Blastomycosis has been reported in patients with AIDS [12, 62], in a small number of solid-organ transplant recipients [54, 63–67], rarely in stem cell transplant recipients

[68], in patients with hematologic malignancies [54], and in those receiving treatment with corticosteroids [54]. The extent of disease and the response to therapy depend on the severity of immunosuppression.

On the basis of individual case reports and small case series, AmB is the agent of choice for most patients who are immunosuppressed [12, 54, 63–65]. A lipid formulation is preferred, to reduce toxicity. Few patients continue the entire treatment course with AmB; for most patients, therapy is changed to itraconazole, 200 mg twice per day, when their symptoms have improved. However, there have been no clinical trials that have specifically assessed the role of such step-down therapy, and few data exist for immunosuppressed patients.

The use of oral azoles as initial therapy for blastomycosis in immunosuppressed patients has not been studied. Reports on individual patients who had AIDS or had received a transplant note more failures than successes when azole agents were used as initial therapy, but most patients had received ketoconazole, which is now rarely used for systemic infections [12, 54, 62, 66, 67]. Itraconazole is the preferred azole [33], but unless an immunosuppressed patient has only mild or localized disease, this should be used as step-down rather than initial therapy. Fluconazole is not as effective as itraconazole [35] and should not be used. Experience is limited with voriconazole [41] and posaconazole, and neither can be recommended for immunosuppressed patients at this time.

Relapses have been well documented among immunosuppressed patients, almost all of whom had been treated initially with ketoconazole [12, 54, 66, 67]. Long-term suppressive therapy with itraconazole is recommended for immunosuppressed patients, but there are no clinical trials that have assessed the need for suppressive therapy or the length of time that suppression should be continued for patients who have blastomycosis. Studies of patients with AIDS and histoplasmosis have shown that itraconazole can be safely discontinued in patients who have a good immunologic response to antiretroviral therapy [69]. Those patients for whom discontinuation of itraconazole was successful had received at least 1 year of itraconazole therapy, had CD4 cell counts  $>150$  cells/ $\mu$ L for at least 6 months, and were receiving HAART [69]. The Panel thought that it was reasonable to apply similar parameters to patients with AIDS and blastomycosis. Suppressive therapy also may be warranted for patients with other immunodeficiency states that cannot be reversed, but there is minimal clinical experience on which to base this recommendation. In transplant recipients and other patients, this decision should be based on the amount of immunosuppression required and the period of time over which this immunosuppression likely will be maintained.

## V. What Is the Treatment for Blastomycosis in Pregnant Women and Children?

### Recommendations

13. During pregnancy, lipid formulation AmB, 3–5 mg/kg per day, is recommended (A-III). Azoles should be avoided because of possible teratogenicity (A-III).

14. If the newborn shows evidence of infection, treatment is recommended with AmB deoxycholate, 1.0 mg/kg per day (A-III).

15. For children with severe blastomycosis, AmB deoxycholate, 0.7–1.0 mg/kg per day, or lipid formulation AmB, at a dosage of 3–5 mg/kg per day, is recommended for initial therapy, followed by oral itraconazole, 10 mg/kg per day (up to 400 mg per day), as step-down therapy, for a total of 12 months (B-III).

16. For children with mild to moderate infection, oral itraconazole, at a dosage of 10 mg/kg per day to a maximum of 400 mg per day for 6–12 months, is recommended (B-III).

17. Serum levels of itraconazole should be determined after the patient has received this agent for at least 2 weeks, to ensure adequate drug exposure (A-III).

**Evidence summary.** Important issues in pregnancy include the risk of teratogenic complications of azole therapy and of transplacental transmission of *B. dermatitidis* to the fetus [70]. Transplacental transmission might be prevented by antifungal therapy before delivery, but the evidence is not adequate to make a recommendation. The placenta should be examined histopathologically for granulomas and organisms resembling *B. dermatitidis*. Furthermore, the baby should be monitored for the development of blastomycosis, in which case, treatment with AmB deoxycholate is recommended.

AmB remains the treatment of choice during pregnancy, and the lipid formulations are safe [71, 72]. The azoles are teratogenic and embryotoxic in animals and should be avoided during pregnancy, especially during the first trimester. Long-term fluconazole administration during pregnancy has been associated with congenital anomalies [73]. Reports suggesting that fetal risk is not increased [74–76] focused on low-dose, short-duration therapy and should not be used as a basis for azole treatment of pregnant women with blastomycosis.

Blastomycosis is less commonly described in children, but the clinical spectrum of disease is similar to that described in adults [1, 4, 77, 78]. A report of 10 children with blastomycosis indicated that the diagnosis in children, compared with adults,

is more difficult to establish and that the response to oral azoles is less than satisfactory [77]. Children with life-threatening or CNS disease should be treated with AmB deoxycholate or a lipid formulation of AmB [29]. In general, children tolerate the deoxycholate formulation of AmB better than adults do, and lipid formulations may not be needed. Itraconazole, at a dosage of 10 mg/kg per day, has been used successfully as treatment of a limited number of pediatric patients with non-life-threatening, non-CNS disease [77, 78]. As is the case with adults, measurement of serum itraconazole levels is recommended to ensure adequate absorption of this agent.

### PERFORMANCE MEASURES

1. Itraconazole is the preferred azole for initial therapy of patients with mild to moderate blastomycosis and as step-down therapy after treatment with AmB. When other azole agents are used, the medical record should document the specific reasons that itraconazole was not used and why other azoles were used.

2. Patients with severe or moderately severe blastomycosis should be treated with an AmB formulation initially. When AmB is used, the patient's electrolytes, renal function, and blood counts should be monitored several times per week and documented in the medical record.

3. Itraconazole drug levels should be measured during the first month in patients with disseminated or pulmonary blastomycosis, and these levels should be documented in the medical record, as well as the physician's response to levels that are too low.

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## APPENDIX

**Table A1. Expert panel.**

| Name                 | Affiliation   | Specialty           |
|----------------------|---|---------------------|
| Stanley W. Chapman   | University of Mississippi Medical Center, Jackson                                   | Infectious Diseases |
| Robert W. Bradsher   | University of Arkansas for Medical Sciences, Little Rock                            | Infectious Diseases |
| William E. Dismukes  | University of Alabama at Birmingham   | Infectious Diseases |
| Carol A. Kauffman    | University of Michigan, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI | Infectious Diseases |
| Peter G. Pappas      | University of Alabama at Birmingham   | Infectious Diseases |
| Laurie A. Proia      | Rush Medical Center, Chicago, IL  | Infectious Diseases |
| Michael G. Threlkeld | Germantown, TN  | Infectious Diseases |

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