Clinical Manifestations and Treatment of Blastomycosis

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INTRODUCTION

*Blastomyces dermatitidis* and *Blastomyces gilchristii* are the causal agents of blastomycosis. *Blastomyces* spp are thermally dimorphic fungi that grow as a filamentous mold in the environment and as a yeast in human tissues. Blastomycosis is endemic to North America, particularly states/provinces bordering the Mississippi, Ohio and St Lawrence Rivers, and the Great Lakes. The clinical manifestations of blastomycosis are broad, ranging from asymptomatic infection to acute respiratory distress syndrome. Diagnosis of blastomycosis requires a high degree of clinical suspicion and involves the use of culture and nonculture diagnostic methods. Blastomycosis should be considered in patients who live in or visit regions where *Blastomyces* is endemic and have unresolved pneumonia despite antibiotic therapy, concomitant pulmonary and cutaneous infection, acute respiratory distress syndrome, or a compatible illness following recognizable risk factors for *Blastomyces* exposure.

MYCOLOGY

Recent phylogenetic analysis has divided *Blastomyces* into 2 species, *B dermatitidis* and *B gilchristii*.1 *Blastomyces* spp belong to a group of fungi that includes *Histoplasma capsulatum*, *Coccidioides immitis* and *Coccidioides posadasi*, *Paracoccidioides brasiliensis* and *Paracoccidioides lutzii*,...
Sporothrix schenckii, and Talaromyces marneffei (formerly Penicillium marneffei). Blastomyces undergoes a reversible morphologic switch between hyphae at 22°C to 25°C and yeast at 37°C. Blastomyces yeast forms (8–20 μm diameter) are characterized by a broad-based bud (4–10 μm) and doubly refractile cell wall (Fig. 1).² Although this appearance is unique among dimorphic fungi, giant forms (28–40 μm diameter) have been described and can be confused with Coccidioides species.³ The mycelial form is characterized by septate hyphae (1–2 μm diameter) that produce asexual spores (4–5 μm diameter).² In contrast with the yeast, hyphal morphology is not distinct and requires molecular confirmation or transition to yeast for identification.

GEOGRAPHIC DISTRIBUTION AND EPIDEMIOLOGY

Knowledge about the geographic distribution and epidemiologic risks is important for including blastomycosis in the differential diagnosis in patients with pulmonary, cutaneous, bone, and central nervous system (CNS) infections. In North America, Blastomyces is endemic to the midwestern, south-central, and southeastern regions of the United States and 4 Canadian provinces from Saskatchewan to Quebec (Fig. 2). In the endemic region, Blastomyces is not uniformly distributed; it inhabits an ecologic niche that is characterized by forested, sandy soils with an acidic pH, decaying vegetation or organic material, and rotting wood located near water sources.⁴ Similar to H capsulatum and Cryptococcus, Blastomyces can grow in bird guano. Although most infections are sporadic, occupational and recreational activities that disrupt soil (e.g., construction, exploration of beaver dams or underground forts, use of community compost piles, clearing brush or cutting trees, hunting, canoeing, boating, tubing, fishing) have all been associated with outbreaks of the disease (Table 1).⁴,⁵

Rare autochthonous cases of culture-proven blastomycosis have been reported outside of North America. Approximately 100 cases have been described in 18 African nations, whereas fewer than 10 confirmed autochthonous cases have been reported in India.⁶,⁷ Blastomyces is not considered endemic to Central America, South America, Europe, Australia, or Asia outside India.

The epidemiology of blastomycosis in North America is based mainly on retrospective studies and passive surveillance. Within endemic zones, 6 American states (Arkansas, Louisiana, Michigan, Minnesota, Missouri, and Wisconsin) and 2 Canadian provinces (Manitoba and Ontario) require reporting of new cases. In North America, the annual incidence of blastomycosis ranges from 0.2 to 1.94 cases per 100,000 persons.⁸⁻¹¹ Several hyperendemic regions exist, including Kenora, Ontario (117.2 human cases per 100,000 population); Eagle River, Wisconsin (101.3 per 100,000); Vilas County, Wisconsin (40.4 per 100,000); Washington Parish, Louisiana (6.8 per 100,000); and central/south-central Mississippi (>5 per 100,000).¹²⁻¹⁵ The true incidence of blastomycosis is likely greater than the reported numbers. Reliable skin and serologic tests are not available. Moreover, approximately 50% of infected persons have subclinical or asymptomatic illness.⁴ Thus, epidemiologic data are limited to patients with clinically apparent infection that is diagnosed and reported. In the United States from 2007 to 2011 a total of 4688 patients in 46 states were hospitalized for blastomycosis.¹⁶ Most of these patients were hospitalized in the state in which they resided; however, 8% of patients were admitted to hospitals outside of known endemic regions.¹⁶

Most blastomycosis cases occur in adults, with less than 13% occurring in the pediatric population.⁵,¹⁷ Similar to histoplasmosis and coccidioidomycosis, blastomycosis epidemiologic studies of adults show a slight male predominance. Blastomyces is a primary fungal pathogen because it causes invasive disease in immunocompetent hosts; most patients with blastomycosis are immunocompetent. Patients who are immunocompromised by solid organ transplant (SOT), tumor necrosis factor-alpha (TNF-α) inhibitors, malignancy, or human immunodeficiency virus
(HIV)/AIDS (acquired immunodeficiency syndrome) can develop more severe disease.\textsuperscript{18–22} The higher incidence of blastomycosis in some ethnic groups, including aboriginal ethnicity in Canada and Hmong populations in Wisconsin, may signal genetic predisposition.\textsuperscript{9,23}

**PATHOGENESIS**

**The Phase Transition**

The ability to convert from mold to yeast is an essential event in the pathogenesis of all dimorphic fungi, including *Blastomyces* spp. This morphologic shift or phase transition is primarily influenced by a change in temperature and is a complex process involving global changes in transcription, metabolism, cell signaling, cell wall composition, and plasma membrane lipid content.\textsuperscript{24} In the soil (22°C–25°C), *B dermatitidis* and *B gilchristii* grow as mold that produces infectious conidia (spores). After disruption of soil, often through human activity, aerosolized conidia and mold fragments inhaled into the lungs of a human host (37°C) convert to pathogenic yeast, which evades host immune defenses to cause infection. Moreover, conidia phagocytized by lung macrophages are able to survive and convert into yeast.\textsuperscript{25} This intracellular lifestyle is not unique to *Blastomyces*; other dimorphic pathogens, including *H capsulatum*, *Coccidioides* spp, and *Paracoccidioides* spp, show similar intracellular preferences. For fungi such as *H capsulatum* and *Cryptococcus neoformans*, survival in macrophages promotes dissemination; however, it is unknown whether *B dermatitidis* uses this so-called Trojan horse method for extrapulmonary dissemination.\textsuperscript{26}

The development of molecular tools to genetically manipulate the dimorphic fungi has enabled the discovery of genes critical for the phase transition to yeast and virulence, including *DRK1* (dimorphism-regulating kinase-1) and *BAD1* (Blastomyces adhesion-1; formerly WI-1). *DRK1* encodes a hybrid histidine kinase that is essential for the conversion of mold to yeast in *B dermatitidis*, *B gilchristii*, and *H capsulatum* in response to a
shift in temperature from 22°C to 37°C. Deletion of DRK1 results in Blastomyces and Histoplasma cells that fail to convert to yeast and grow as hyphae at 37°C. DRK1 null mutants (DRK1Δ) also have altered distribution of cell wall carbohydrates, such as α-(1,3)-glucan and chitin, and fail to express BAD1, an essential virulence factor. These findings offer genetic proof that the morphologic switch to yeast is essential for pathogenicity.

In the yeast phase, B dermatitidis expresses BAD1, a 120-kDA protein that facilitates adhesion and immune evasion. BAD1 is secreted by B dermatitidis yeast into the extracellular milieu and binds back to the cell surface via interactions with chitin in the cell wall. BAD1 functions as an adhesin that attaches yeast cells to host tissue by binding heparin sulfate. BAD1 functions as an adhesin that attaches yeast cells to host tissue by binding heparin sulfate. BAD1 enables immune evasion by repressing TNF-α production through transforming growth factor-β (TGF-β)–dependent and TGF-β–independent mechanisms. TNF-α is an important cytokine that contributes to host defense against blastomyces infection. In mice, neutralization of TNF-α results in progressive pulmonary blastomycosis. In addition to its effects on innate immunity, BAD1 alters adaptive immunity through inhibiting CD4+ T-lymphocyte activation, which in turn reduces production of interleukin-17 and interferon gamma. Moreover, the lungs of mice infected with BAD1Δ strains appear grossly normal and contain few granulomas. In addition to its effects on innate immunity, BAD1 alters adaptive immunity through inhibiting CD4+ T-lymphocyte activation, which in turn reduces production of interleukin-17 and interferon gamma. Moreover, the lungs of mice infected with BAD1Δ strains appear grossly normal and contain few granulomas.

### Table 1

<table>
<thead>
<tr>
<th>Number</th>
<th>State</th>
<th>City or County</th>
<th>Years</th>
<th># Infected</th>
<th>Outbreak Source</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>North Carolina</td>
<td>Pitt</td>
<td>1953–1954</td>
<td>11</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>Minnesota</td>
<td>Bigfork</td>
<td>1972</td>
<td>12</td>
<td>Cabin construction</td>
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<tr>
<td>3</td>
<td>North Carolina</td>
<td>Enfield</td>
<td>1975</td>
<td>5</td>
<td>Harvest at peanut farm</td>
</tr>
<tr>
<td>5</td>
<td>Wisconsin</td>
<td>Hayward</td>
<td>1979</td>
<td>8</td>
<td>Canoeing</td>
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<tr>
<td>6</td>
<td>Wisconsin</td>
<td>Eagle River</td>
<td>1984</td>
<td>48</td>
<td>Visiting an abandoned beaver lodge</td>
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<tr>
<td>7</td>
<td>Virginia</td>
<td>Southampton</td>
<td>1984</td>
<td>4</td>
<td>Raccoon hunting</td>
</tr>
<tr>
<td>8</td>
<td>Wisconsin</td>
<td>Portage and Waupaca</td>
<td>1985</td>
<td>14</td>
<td>Underground timber fort; fishing</td>
</tr>
<tr>
<td>9</td>
<td>Wisconsin</td>
<td>Vilas</td>
<td>1988</td>
<td>32</td>
<td>Hotel construction</td>
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<tr>
<td>10</td>
<td>Tennessee</td>
<td>Elizabethton</td>
<td>1989</td>
<td>3</td>
<td>Construction at rayon factory</td>
</tr>
<tr>
<td>11</td>
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<td>Oconto</td>
<td>1989–1990</td>
<td>8</td>
<td>Unknown</td>
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<tr>
<td>12</td>
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<td>Prairie dog relocation</td>
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<td>13</td>
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<td>Indian reservation</td>
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<td>Likely related to construction/ excavation</td>
</tr>
<tr>
<td>14</td>
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<td>Duplin</td>
<td>2001–2002</td>
<td>8</td>
<td>Likely related to construction projects</td>
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<tr>
<td>15</td>
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<td>Merrill</td>
<td>2006</td>
<td>21</td>
<td>Community yard waste site</td>
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<tr>
<td>16</td>
<td>Wisconsin</td>
<td>Marathon</td>
<td>2009–2010</td>
<td>55</td>
<td>Unknown</td>
</tr>
<tr>
<td>17</td>
<td>Wisconsin</td>
<td>Waupaca</td>
<td>2015</td>
<td>90</td>
<td>Tubing on Little Wolf River</td>
</tr>
</tbody>
</table>

b See Fig. 2.
c The specific Indian reservation was not published and thus the location is not reflected in Fig. 2.
of β-(1,3)-glucan assays for diagnosis and renders echinocandins ineffective.

The transition in the opposite direction, yeast to mycelia, is important for environmental survival, mating to promote genetic diversity, and transmission to mammalian hosts. Recent genetic analyses identified a GATA transcription factor encoded by SREB that mediates the conversion from yeast to mycelia after a reduction in temperature from 37°C to 22°C. SREB null mutants (SREBΔ) have a defect in the morphologic shift that corresponds with a reduction in neutral lipid (ergosterol, triacylglycerol) biosynthesis and lipid droplet formation. In B dermatitidis and H capsulatum, N-acetylglucosamine transporters NGT1 and NGT2 accelerate the transition to mycelia at 22°C.

HOST RESPONSE

Both the innate and adaptive immune responses are required to combat blastomycosis infection, whereas humoral immunity is dispensable. Following inhalation of aerosolized conidia, alveolar macrophages and neutrophils phagocytize and kill conidia. However, conidia that survive phagocytosis germinate to yeast, which is more challenging for the host immune system to kill. B dermatitidis yeast actively subverts host immune defenses by inhibiting host cell cytokine production, impairing CD4+ T-lymphocyte activation, and suppressing nitric oxide production. Moreover, Blastomyces yeasts are fairly resistant to reactive oxygen species produced by macrophages and neutrophils. Following recovery from blastomycosis, hosts develop cell-mediated immunity that lasts at least 2 years and likely longer.

CLINICAL MANIFESTATIONS

The clinical manifestations of blastomycosis are heterogeneous and range from asymptomatic infection to pneumonia to acute respiratory distress syndrome (ARDS). Because of this clinical variability, blastomycosis has been described as “the great pretender.” The lung is the primary portal of entry for aerosolized conidia following disruption of soil. Traumatic inoculation of skin (eg, laboratory accidents) is rare but has been reported. Onset of symptoms occurs 3 weeks to 3.5 months following inhalation of mycelial fragments or spores. When symptomatic, approximately 25% to 40% of patients develop extrapulmonary dissemination. Common sites for disseminated disease are the skin, bone, genitourinary tract, and CNS; however, Blastomyces can infect nearly every organ in the body.

PULMONARY BLASTOMYCOSIS

Pulmonary infection is reported in more than 79% of patients with documented blastomycosis. The spectrum of pulmonary infection is broad and varies from subclinical pneumonia to ARDS. In both adult and pediatric populations, symptomatic pneumonia presents with fevers, chills, headache, productive or non-productive cough, dyspnea, chest pain, and malaise. Acute pulmonary blastomycosis may be mild and can be mistaken for other lower respiratory tract infections, including bacterial community-acquired pneumonia (CAP); moreover, consolidation is the most common chest radiographic finding and is indistinguishable from CAP. Undiagnosed or untreated acute pulmonary blastomycosis can progress to ARDS or chronic pneumonia (Figs. 3 and 4). Symptoms and radiographic findings for chronic pulmonary blastomycosis are nonspecific and can mimic other diagnoses, such as lung neoplasm or tuberculosis. Symptoms can include fever, persistent cough, hemoptysis, night sweats, anorexia, weight loss, and malaise. Chest radiography can show nodules, masses, or cavitation (see Fig. 4). Because the clinical picture is
nonspecific, blastomycosis is often not included in the differential diagnosis unless the patient has other findings such as skin lesions, fails to respond to antibacterial therapy, or has recognized risk factors for exposure to blastomycosis. Therefore, symptoms may be present for several months before diagnosis.

A subset of patients with acute pulmonary blastomycosis have a rapidly progressive infection resulting in respiratory failure or ARDS (see Fig. 3). In retrospective analyses of patients from Mississippi and Tennessee, ARDS was encountered in 8.4% to 14.8% of hospitalized patients with pulmonary blastomycosis. A delay in diagnosis of blastomycosis-induced ARDS is common with patients initially misdiagnosed with CAP that becomes fulminant in 5 to 7 days or progressive CAP that fails to respond to multiple courses of antibiotic therapy. Mortality caused by ARDS is high, often greater than 50%. In most patients who die of blastomycosis-induced ARDS, the diagnosis was either not suspected or was considered after the patient was moribund. Thus, early diagnosis of blastomycosis-induced ARDS is critical to decrease mortality.

**EXTRAPULMONARY AND DISSEMINATED BLASTOMYCOSIS**

**Overview**

*Blastomyces* can disseminate to any organ in the body. Evidence of dissemination occurs in approximately 25% to 40% of cases. Aside from rare cases of direct inoculation through penetrating trauma, accidental needle stick, or laboratory exposure, extrapulmonary blastomycosis represents disseminated disease and should be treated accordingly.

**Cutaneous Blastomycosis**

The skin is the most common extrapulmonary site of infection and cutaneous involvement occurs in up to 40% to 80% of patients with disseminated disease. Cutaneous disease often begins as papulopustular lesions that progress to ulcerative, verrucous, or crusted lesions (Fig. 5). Other manifestations include violaceous nodules, plaques, and abscesses. Although erythema nodosum is common in patients with histoplasmosis or coccidiodomycosis, it is rarely described in blastomycosis infection. Cutaneous lesions can expand in an asymmetric fashion creating ulcerations and...
necrosis that can lead to disfigurement, including permanent scarring. Less commonly, cutaneous blastomycosis manifests as a draining sinus tract or ulcer from underlying osteomyelitis. Skin lesions can occur anywhere on the body but are often found on exposed areas, including the head and extremities. Blastomycosis is much less likely than H capsulatum or Paracoccidioides spp to involve the mucous membranes; however, intraoral, nasal, and pharyngeal lesions have rarely been described. Although uncommon, cutaneous involvement of the eyelid is the most common ophthalmologic finding. Endophthalmitis and orbital abscess are exceedingly rare. Involvement of the periorbital skin can be complicated by ectropion, which can require surgical correction following successful treatment of infection.

Osseous Blastomycosis

The bone is the second most common site for dissemination of Blastomyces and occurs in approximately 5% to 25% of patients. Most patients with osteomyelitis have concomitant pulmonary blastomycosis. Osseous lesions are painful and can be associated with soft tissue abscess, draining sinus tracts, or cutaneous ulcers. Osseous invasion by Blastomyces is characterized by lytic destruction, periosteal reaction or sclerotic margins on radiography, and granulomatous inflammation on histopathology. Although any bone can be infected, the most common sites include the long bones, vertebrae, skull, and ribs. Blastomycosis of the bone can mimic malignancy (eg, sarcoma, giant cell tumor, metastases) and Pott disease (Mycobacterium tuberculosis). Through direct extension, infection can spread from bones to nearby joints and soft tissue, resulting in septic arthritis and abscess, respectively. Progressive bone destruction can result in pathologic fracture (eg, vertebral body collapse).

Genitourinary Blastomycosis

Case series published in the 1950s estimated the rate of genitourinary (GU) dissemination to be as high as 20% to 30%; however, modern case series report prostate involvement in less than 10% of patients. In men, the most common sites of GU involvement are the prostate and epididymis. Symptoms of prostatitis include urinary obstruction, dysuria, and perineal or suprapubic discomfort. Epididymitis presents with pain, scrotal swelling, testicular enlargement, and (rarely) a draining sinus. In women, dissemination to the GU system can cause tubo-ovarian abscess, endometritis, and salpingitis. This condition can be complicated by extension to the peritoneum and omentum with or without new-onset ascites. A single case of sexual transmission has been described following intercourse between a man with Blastomyces prostatitis and his wife who had endometrial adenocarcinoma.

Central Nervous System Blastomycosis

CNS blastomycosis is estimated to occur in less than 5% to 10% of immunocompetent patients. Dissemination to the CNS results from either hematogenous seeding or direct invasion through untreated skull-based osteomyelitis and can manifest as meningitis, epidural abscess, or brain abscess. Presenting symptoms can include headache, focal neurologic defects, confusion, visual disturbances, and seizures. In patients with meningitis, cerebrospinal fluid (CSF) analysis reveals a lymphocytic or neutrophilic pleocytosis with increased protein levels and hypoglycorrhachia. Blastomyces grow about 45% of the time from CSF cultures; however, a positive CSF Blastomyces antigen test may facilitate diagnosis. A wide range of CNS complications have been reported, including hydrocephalus, mass effect from edema, cerebral herniation, infarction, seizures, panhypopituitarism, weakness, and impaired ability to function at school.

BLASTOMYCOSIS IN IMMUNOCOMPROMISED HOSTS

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome

In contrast with histoplasmosis, blastomycosis is an uncommon infection in patients with HIV/AIDS. Most patients with HIV with blastomycosis have a CD4+ T-lymphocyte count less than 200 cells/mm³ and two-thirds have a history...
of prior opportunistic infections. Patients with AIDS are more likely to have severe pulmonary disease (eg, ARDS, miliary disease) and up to 40% have dissemination to the CNS. In one case series, approximately one-quarter of AIDS-related blastomycosis was postulated to be caused by reactivation of latent infection. Before the era of modern antiretrovirals, mortality in patients with AIDS and blastomycosis exceeded 50%.

**Solid Organ Transplant**

Blastomycosis is an uncommon infection in SOT recipients, with a cumulative incidence of 0.13% to 0.14% in SOT patients from an endemic region. This rate is lower than the reported incidence of posttransplant histoplasmosis or coccidioidomycosis. The onset of disease after transplant ranges from 12 days to 250 months. This variability may reflect different disease pathogenesis including (1) primary infection; (2) reactivation of latent disease; (3) and conversion of recently acquired, pretransplant, asymptomatic infection to symptomatic disease. Mortality for transplant-associated blastomycosis ranges from 33% to 38% but increases to 67% in patients with ARDS. Lifelong suppressive antifungal therapy is generally not required following appropriately treated blastomycosis.

**Anti–Tumor Necrosis Factor Alpha Therapy**

TNF-α is a critical cytokine for host defense against blastomycosis. In murine models, antibody-mediated neutralization of TNF-α results in progressive pulmonary infection. Clinical data on blastomycosis in the setting of TNF-α exposure are sparse and are limited to case reports. Nevertheless, blastomycosis was listed in the 2008 warning issued by the US Food and Drug Administration regarding increased risk of fulminant infections with endemic mycosis in patients receiving TNF inhibitor therapy.

**BLASTOMYCOsis IN PREGNANCY AND NEWBorns**

Blastomycosis in pregnancy and the newborn is rare and clinical information is limited to case reports. Women can be infected in any trimester but the disease is most frequently diagnosed in the second or third trimester. Case reports suggest disseminated disease (62%) is more common than isolated pulmonary infection (38%). Reliable data regarding the frequency of placental infection are lacking because examination by culture or histology has been conducted in only one-third of clinical cases; however, placental involvement has been reported. Blastomycosis does not seem to increase risk for congenital malformations, but there is potential for transmission during the peripartum period. Neonatal pulmonary blastomycosis is rare and can be fatal. The underlying pathogenesis of neonatal blastomycosis is not well defined and may involve transplacental transmission or aspiration of infected vaginal secretions.

**DIAGNOSIS**

The clinical presentation, physical examination, and the radiographic manifestations of blastomycosis are nonspecific; therefore, a high index of suspicion is essential for prompt diagnosis. Delays in diagnosis are common, even in endemic areas, because few patients are correctly diagnosed at initial presentation and delays in diagnosis exceeding 1 month occur in more than 40% of patients. A detailed history to identify possible exposures and at-risk hosts can facilitate a diagnosis. In patients with pneumonia, medical histories should include place of residence, travel, outdoor activities (eg, fishing, canoeing, rafting), hobbies, recent home remodeling, exposure to road construction, and use of a wood-burning stove or community compost pile. Blastomycosis in a household pet, such as a dog, suggests a common source of exposure and can serve as a harbinger of human infection. In patients with concomitant pulmonary and cutaneous disease, blastomycosis must be considered in the differential diagnosis.

**Microscopic and Culture-Based Diagnostics**

The most expeditious method to diagnose blastomycosis remains the examination of stained clinical specimens. Although Blastomyces is not well visualized with Gram or hematoxylin and eosin stains, sputum or tissue samples stained with 10% potassium hydroxide, calcofluor white, Gomori methenamine silver, or periodic acid–Schiff can facilitate visualization of the characteristic Blastomyces yeast. The discovery of the characteristic yeast forms (8–20 µm) with broad-based budding and a doubly refractile cell wall can lead to a presumptive diagnosis of blastomycosis before the results of culture and non-culture tests are available. In one case series, the use of appropriately stained clinical specimens identified nearly 80% of culture-confirmed cases. Despite
the effectiveness of fungal-specific stains in diagnosis, this technique is often underused. In tissue specimens, the presence of neutrophilic infiltration with noncaseating granulomas (ie, pyogranulomatous inflammation) can suggest blastomycosis and thorough microscopic examination for Blastomyces yeast should be performed.

Culture of Blastomyces provides a definitive diagnosis. In the setting of pulmonary blastomycosis, the yield of culture from invasive bronchoscopy is excellent. One study showed a 92% diagnostic yield for bronchoscopy. Even noninvasive methods, including cultures from sputum, tracheal secretion, or gastric washings, yielded Blastomyces growth in 86% of samples. Specialized media, including Sabouraud dextrose agar, potato dextrose agar, and brain-heart infusion media, are required for growth. Incubator temperatures used in most clinical laboratories (25°C to 30°C) promote the growth of Blastomyces as a mold. Although highly specific, Blastomyces grows slowly in culture. Fungal colonies take an average of 5 to 14 days to be visualized; however, when burden of infection is low, growth can take longer.

**Non-culture Diagnostics**

Classic antibody testing by complement fixation (CF) or immunodiffusion (ID) is not clinically useful for the diagnosis of blastomycosis because of poor sensitivity and specificity. A newer enzyme immunoassay that uses microplates coated with BAD1 protein has enhanced sensitivity (87%) and specificity (94%–99%); however, it is not yet commercially available. Because BAD1 is unique to Blastomyces, BAD1 assays can distinguish between histoplasmosis and blastomycosis.

An antigen assay that detects a galactomannan component in the cell wall of Blastomyces has supplanted CF and ID, and can be used to test urine, serum, bronchoalveolar lavage fluid, and CSF specimens. Sensitivity of antigenuria in patients with proven disease is 76.3% to 92.9% and specificity is 79.3%. False-positives can occur in the setting of other fungal infections, such as histoplasmosis, paracoccidioidomycosis, and penicilliosis (talaromycosis). The clinical impact of a false-positive test is often minimal because paracoccidioidomycosis and penicilliosis (talaromycosis) can be removed from the differential diagnosis if the patient has not traveled to Central and South America (paracoccidioidomycosis), or southeast Asia and China (talaromycosis). Moreover, the treatment of blastomycosis is similar to that of histoplasmosis. Serial urine antigen concentrations can be used to monitor response to treatment. Following initiation of therapy, an increase in antigenuria can occur (median of 11 days), which is followed by progressive decline in antigen titer with successful therapy. Initial posttreatment increase in titer may reflect increased urinary excretion of antigen caused by fungal cell death.

**RADIOGRAPHIC MANIFESTATIONS**

There are no pathognomonic radiographic patterns for pulmonary blastomycosis. Radiographic findings are nonspecific and may mimic bacterial pneumonia, tuberculosis, or malignancy. Radiographic abnormalities may include diffuse airspace disease, consolidation, nodular masses, interstitial disease, cavitation disease, or miliary disease (see Figs. 3 and 4). Consolidation is the most common radiographic finding and may be present in the absence of pulmonary symptoms. Calcified lung lesions, hilar/mediastinal adenopathy, and pleural effusions are uncommon. MRI is the preferred imaging modality for CNS disease and is frequently abnormal in patients with CNS blastomycosis.

**TREATMENT**

Guidelines for the diagnosis and treatment of blastomycosis are published by the Infectious Disease Society of America and the American Thoracic Society (Table 2). Treatment recommendations are based on the site and severity of infection, host immune status, and pregnancy. Antifungal treatment is recommended for all patients diagnosed with blastomycosis, including those with resolution of clinical symptoms before receiving therapy. Before the initiation of therapy, baseline evaluation of hematologic, hepatic, and renal function should be obtained. Careful review of all medications is required to limit drug interactions commonly associated with azole antifungals. Itraconazole, voriconazole, posaconazole, and fluconazole can lengthen the QT interval, especially when administered with other medications that prolong the QT interval. In contrast, isavuconazole can shorten the QT interval and is contraindicated in patients with familial short QT syndrome. Itraconazole has a negative inotropic effect and the potential to exacerbate existing congestive heart failure and should be used with caution in patients with ventricular dysfunction. Azole antifungals increase the serum concentration of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors metabolized by cytochrome P450 3A4, which can increase the risk for statin-induced rhabdomyolysis. Pravastatin can...
### Table 2
Summary of clinical practice guidelines for antifungal therapy against blastomycosis

<table>
<thead>
<tr>
<th>Site of Infection</th>
<th>Disease Severity</th>
<th>Initial Therapy</th>
<th>Step-Down Therapy</th>
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<tbody>
<tr>
<td><strong>Pulmonary blastomycosis</strong></td>
<td>Mild to moderate</td>
<td>Oral itraconazole 200 mg 3× daily for 3 d and then 1× or 2× daily for 6–12 mo&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Moderately severe to severe</td>
<td>Lipid formulation of AmB 3–5 mg/kg daily or AmB deoxycholate 0.7–1 mg/kg daily for 1–2 wk or until improvement is noted</td>
<td>Oral itraconazole 200 mg 3× daily for 3 d and then 2× daily for 6–12 mo&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Disseminated or extrapulmonary blastomycosis</strong></td>
<td>Mild to moderate</td>
<td>Oral itraconazole 200 mg 3× daily for 3 d and then 1× or 2× daily for 6–12 mo&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Moderately severe to severe</td>
<td>Lipid formulation of AmB 3–5 mg/kg daily or AmB deoxycholate 0.7–1 mg/kg daily for 1–2 wk or until improvement is noted</td>
<td>Oral itraconazole 200 mg 3× daily for 3 d and then 2× daily for at least 12 mo&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<tr>
<td><strong>Central nervous system disease</strong></td>
<td>—</td>
<td>Lipid formulation AmB 5 mg/kg/d for 4–6 wk</td>
<td>Options include:</td>
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<tr>
<td></td>
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<td>1. Oral fluconazole 800 mg daily</td>
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<td></td>
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<td></td>
<td>2. Oral itraconazole 200 mg 2× or 3× daily</td>
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<td>3. Voriconazole (200–400 mg 2× daily)</td>
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<td>Treatment should continue for at least 12 mo and until resolution of CSF abnormalities</td>
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<tr>
<td><strong>Immunocompromised patients</strong></td>
<td>—</td>
<td>Lipid formulation of AmB 3–5 mg/kg daily or AmB deoxycholate 0.7–1 mg/kg daily for 1–2 wk or until improvement is noted</td>
<td>Oral itraconazole 200 mg 3× daily for 3 d and then 2× daily for at least 12 mo&lt;sup&gt;a,c&lt;/sup&gt;</td>
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<tr>
<td><strong>Pregnant women</strong></td>
<td>All disease</td>
<td>Lipid formulation of AmB 3–5 mg/kg/d</td>
<td>Azoles should be avoided because of risks of teratogenicity and spontaneous abortion</td>
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<tr>
<td><strong>Newborn</strong></td>
<td>All disease</td>
<td>AmB deoxycholate 1.0 mg/kg/d</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td>Mild to moderate (nonmeningeal)</td>
<td>Oral itraconazole 10 mg/kg/d (maximum of 400 mg/d) for 6–12 mo&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>AmB deoxycholate 0.7–1.0 mg/kg daily or lipid AmB at 3–5 mg/kg daily until improvement</td>
<td>Oral itraconazole 10 mg/kg/d (maximum of 400 mg/d) for 12 mo&lt;sup&gt;a&lt;/sup&gt;</td>
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</table>

**Abbreviations:** AmB, amphotericin B; CSF, cerebrospinal fluid.

<sup>a</sup> Therapeutic drug monitoring is required with goal serum levels (sum of itraconazole + hydroxy-itraconazole concentrations) of greater than or equal to 1 μg/mL.

<sup>b</sup> Osteoarticular blastomycosis should be treated with at least 12 months’ total antifungal treatment.

<sup>c</sup> Lifelong suppressive therapy with oral itraconazole, 200 mg/d may need to be considered in select patients including those with immunosuppression that cannot be reversed and in those who experience relapse despite appropriate therapy.
safely be used with azoles because it is not metabolized by P450 3A4.\textsuperscript{42} Other significant azole drug-drug interactions include immunosuppressive medications, dihydropyridine calcium channel blockers, sulfonyleureas, and anticonvulsants. Because of adverse effects of azole exposure on pregnancy, including teratogenicity, all women of childbearing age should be screened for pregnancy.\textsuperscript{74,75}

**Amphotericin B**

Polyene amphotericin B (AmB) formulations are recommended for the treatment of patients with severe pulmonary infection, disseminated disease, CNS involvement, and underlying immunosuppression (eg, HIV/AIDS, SOT). AmB is also the first-line agent for neonates and pregnant women.\textsuperscript{42,43} AmB deoxycholate has a long track record of clinical success with high cure rates.\textsuperscript{15,42} Despite well-proven efficacy, the use of AmB is associated with significant cumulative toxicity. Nephrotoxicity is the most common treatment-limiting toxicity and occurs in more than 30% of treated patients.\textsuperscript{76} Other adverse effects include infusion reactions (eg, fever, rigors, hypoxia, nausea, vomiting, hypertension, hypotension) and electrolyte disturbances (hypokalemia, hypomagnesemia).\textsuperscript{76} The risks of nephrotoxicity can be minimized by 0.9% normal saline infusions administered before and after AmB, and by avoidance of diuretics and nephrotoxic agents. Most patients require scheduled replacement potassium and magnesium to offset renal loss of these electrolytes. Frequent monitoring of electrolytes and creatinine is essential during AmB therapy (eg, at 2–3 times per week). Lipid AmB preparations (eg, liposomal amphotericin, AmB lipid complex, and AmB colloidal dispersion) are preferred to AmB deoxycholate because these formulations have lower rates of nephrotoxicity. For CNS blastomycosis, liposomal amphotericin is the preferred polyene because it has the best penetration of the blood-brain barrier among the lipid formulations.\textsuperscript{42}

**Triazoles**

In contrast with AmB, azole antifungal agents are fungistatic against *Blastomyces*. Itraconazole is the first-line agent for the treatment of mild to moderate, non-CNS blastomycosis, and for step-down therapy following induction treatment with AmB.\textsuperscript{42,43} Oral itraconazole can be prescribed as a solution or a capsule; however, administration of these formulations is not equivalent. Therapeutic drug monitoring (TDM) is important to optimize itraconazole dosing because serum concentrations are influenced by formulation, dosage, and interpatient variability in drug metabolism. Serum concentrations are approximately 30% higher with the use of solution than with capsule formulation.\textsuperscript{42} Itraconazole solution can be taken without regard to food and does not require gastric acidity for absorption. In contrast, itraconazole capsules must be taken with food and an acidic beverage to maximize absorption.\textsuperscript{42,43} Therefore, in patients who are taking H2-blockers or proton-pump inhibitors, itraconazole solution is the preferred formulation. Itraconazole levels should be obtained after 2 weeks of therapy when a steady-state concentration is reached. Because of a long half-life of approximately 24-hours, serum specimens for TDM can be obtained at any time, independent of when the itraconazole dose was administered. Total itraconazole level is calculated by adding itraconazole and hydroxy-itraconazole concentrations with a goal level between 1 and 5.5 \(\mu\text{g/mL}\). Hydroxy-itraconazole, which is a metabolite of itraconazole, has antifungal activity. Serum levels of greater than or equal to 10.0 \(\mu\text{g/mL}\) are unnecessary and associated with drug toxicity.\textsuperscript{42} Liver function tests should be obtained at baseline and at 2 and 4 weeks into therapy and then every 3 months thereafter.\textsuperscript{42}

Newer triazoles, including voriconazole, posaconazole, and isavuconazole, have activity against *B dermatitidis*.\textsuperscript{77–79} Voriconazole should be taken in the absence of food to optimize absorption. The goal serum trough concentration for voriconazole is between 1 and 5.5 \(\mu\text{g/mL}\).\textsuperscript{80} The absorption of posaconazole solution is maximized by high-fat meals, whereas posaconazole delayed-release tablets are not affected by food or gastric acid inhibitors. The target posaconazole level is not well defined but most experts recommend levels greater than 0.5 to 1 \(\mu\text{g/mL}\).\textsuperscript{80} Isavuconazole capsules can be administered without regard to food or stomach acidity and TDM is not needed. Parenteral formations are available for voriconazole, posaconazole, and isavuconazole. Voriconazole and posaconazole have been successfully used to treat blastomycosis, including the use of voriconazole for CNS infection.\textsuperscript{77,78}

**Steroids and Acute Respiratory Distress Syndrome**

Despite appropriate antifungal therapy, the mortality of blastomycosis-induced ARDS remains high.\textsuperscript{45–47} Case reports have suggested the potential for adjunctive steroids to improve survival; however, a recent retrospective analysis of 43 patients (1992–2014) with ARDS caused by blastomycosis did not show reduced mortality in patients who received steroids.\textsuperscript{81–83} Nevertheless, additional
research is needed regarding the dose, duration, and efficacy of adjuvant steroids in ARDS.

**Mortality**

Large case series from Wisconsin and Manitoba report a case fatality rate between 4.3% and 6.3%.\(^6\, 16\, 17\) Mortality has been associated with a shorter duration of symptoms, likely suggesting more fulminant presentation and a compromised immune status of the host. Blastomycosis-induced ARDS is associated with high mortality even in patients receiving appropriate antifungal treatment.\(^18\, 19\, 45\, 47\, 83\) The mortality of blastomycosis in patients with AIDS in the absence of immune reconstitution is nearly 40% and most deaths occur within 3 weeks of diagnosis.\(^22\) Similarly, the mortality of patients immunosuppressed by SOT is 33% to 38% and increases in the setting of respiratory failure.\(^18\, 19\)

**SUMMARY**

Blastomycosis is often a diagnostic and therapeutic challenge. Even in endemic areas, the nonspecific clinical manifestations of blastomycosis frequently lead to a delay in diagnosis. For physicians within areas of Blastomyces endemicity, certain clinical characteristics should trigger suspicion, including (1) unresolving pneumonia despite appropriate CAP management, (2) simultaneous pulmonary/cutaneous infection, (3) ARDS, and (4) illness following recognizable risk factors for Blastomyces exposure. The knowledge that Blastomyces spp can infect, and disseminate, in both the immunocompromised and the immunocompetent is essential. An understanding of phase transition reminds clinicians that β-(1,3)-glucan assays and echinocandin antifungals have no role in diagnosis or therapy for blastomycosis. Ultimately, an awareness of common issues confronting clinicians using polyene and azole antifungals decreases the risks associated with treatment.

**REFERENCES**


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