









~~Blastomycosis~~ Pathophysiology

The term *B dermatitidis* refers to the imperfect (asexual) stage of *Ajellomyces dermatitidis*, which grows as a yeast at 37°C and mycelial form at room temperature. Two serotypes of *B dermatitidis* have been detected by exoantigen analysis. The perfect (ie, sexual form), *A dermatitidis*, is heterothallic and requires 2 compatible mating types for spore formation. The mycelial form, which bears conidiophores, produce single terminal conidia, which measure 2-10 µm in diameter and are round or oval.

Primary infection, which may be subclinical, occurs in the lung following inhalation of fungal conidia. Transition from the mold form to the yeast form occurs after deposition in the distal airways. The phase shift occurs as a result of heat-related stress, followed by uncoupling of oxidative phosphorylation. In the absence of nonspecific host defense mechanisms, cells increase in number in the lung parenchyma. Hilar lymph nodes may become involved, and, subsequently, lymphohematogenous spread to the other organs may occur. Incubation time averages 4-6 weeks and widely varies.

Subclinical cases of blastomycosis occur in at least 50% of infected individuals, thus supporting the hypothesis that some patients have natural resistance. Cellular immune response mediated by antigen-specific T lymphocytes and lymphokine-derived macrophage's cell-mediated immunity plays a critical role in aborting fungal growth

The clinical spectrum of blastomycosis widely varies, including asymptomatic infection (in nearly one half of patients infected), acute or chronic pneumonia, and extrapulmonary disease.

- Most cases of blastomycosis are sporadic. Nearly one half of patients infected may be

asymptomatic. In one study involving 46 children and 2 adults, symptoms began 21-106 days (median 45 d) after exposure to the pathogen in a beaver pond. ⁴ Patients may complain of an influenzalike illness with the following nonspecific constitutional symptoms:

- Fever
- Chills
- Night sweats
- Weight loss
- Malaise
- Myalgia

- Acute pulmonary infection is the most frequent presentation of blastomycosis in children.

Symptoms include the following:

- Productive cough
- Dyspnea
- Wheezing
- Chest pain
- Hemoptysis (rarely)

- Symptoms of chronic pneumonia may last for 2-6 months and include weight loss, night sweats, fever, cough, and chest pain. Most adult patients diagnosed with blastomycosis have an indolent onset of chronic pneumonia.

Physical

- Signs of acute or chronic pneumonia may be noted. Life-threatening progressive lung disease and disseminated infection can occur in 10% of reported cases.

- Disseminated blastomycosis usually begins with pulmonary infection followed by cutaneous, osseous, genitourinary, or CNS involvement.

- Less commonly, primary cutaneous blastomycosis may follow after traumatic inoculation of the fungus into the skin

- Extrapulmonary disease in blastomycosis includes the following:

- Skin, most commonly (25%)
- Bone (25%)

- Prostatitis or epididymitis (17%): This is a common manifestation in adults and is not reported in prepubescent children.

- Neurologic involvement: This occurs in 3-5% of extrapulmonary infections and is

manifested as intracranial or epidural abscesses and, rarely, meningitis.

- Skin lesions are the most common manifestation of extrapulmonary disease. Cutaneous lesions favor exposed areas and enlarge over many weeks, from pimples that are minimally tender to well-circumscribed verrucous or ulcerative lesions, often with little inflammation. Verrucous lesions demonstrate raised irregular borders with crusting and purulent drainage, whereas ulcerative lesions are characterized by sharp and heaped-up borders with centrally located granulation tissue and exudate.
- Osteolytic lesions may occur in nearly any bone and present as a cold abscess or draining sinus.
- Extension to a contiguous joint may result in indolent swelling, pain, and restriction of movement. The vertebra, skull, ribs, and long bones are most commonly affected.
- Intrauterine or congenital infections are unusual.
- Other unusual metastatic sites of infection include larynx, reticuloendothelial system (liver, spleen, lymph nodes, bone marrow), oropharynx, nose, and thyroid.

Causes

B dermatitidis is a thermal dimorphic fungus that occurs in mycelial form in nature and as yeast in infected tissue.

- The fungus grows on Sabouraud agar at room temperature (25°C) as a white fluffy mold. Alternatively, at body temperature (37°C) and on blood agar, the fungus forms a brown wrinkled colony

Laboratory Studies

The following studies are indicated in patients with blastomycosis:

- Sputum examination: In general, sputum specimens processed with 10% potassium hydroxide or a fungal stain are examined first in adolescent and adult patients because specimens have a high overall yield (approximately 80%). In addition, cytologic specimens can be examined for a dependable diagnosis.
- Culture
 - The diagnosis of blastomycosis can be made by growth of the fungus in a culture of sputum, tracheal aspirates, bronchoalveolar lavage fluid, tissue biopsy specimens, cerebrospinal fluid, or urine. Because colonization with *B dermatitidis* does not occur, detection of the fungus from any sterile site is diagnostic. The organism can be cultured on

brain-heart infusion and Sabouraud dextrose agar at room temperature. In experienced hands, diagnosis of blastomycosis by visualization of the characteristic budding yeast formed in wet smear or histopathologic section is adequate.

- Because primary cutaneous blastomycosis has been reported by accidental autoinoculation, clinical laboratory personnel and pathologists should be notified about the possibility of blastomycosis in the differential diagnosis when handling potential infected tissue or body fluid specimens.

- Skin tests and serodiagnosis
- Skin testing and serodiagnosis of blastomycosis using complement fixation (CF) antibodies and immunodiffusion (ID) precipitin bands currently have very limited roles in diagnosis because of poor sensitivity and specificity, with cross-reactivity of other fungi.
- Recently developed enzyme immunoassay with the A-antigen of *B dermatitidis* has been shown to be more sensitive than CF and ID tests; however, this test has limited clinical use because it is not available in most commercial laboratories.

- Chemiluminescent DNA probes are available for identification of *B dermatitidis*.

Imaging Studies

- Chest radiography: The chest radiograph is abnormal in two thirds of cases and may reveal alveolar or masslike infiltrates, reticulonodular pattern, pleural effusion, and, rarely, cavitation

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- The mycelial form of *B dermatitidis* has been isolated from soil, although its ecologic niche is not characterized as well as other endemic fungi.
- Inhalation of the microconidia from the mold form of *B dermatitidis* into the lungs leads to infection.
- In infected tissue specimens, *B dermatitidis* appears as a characteristic thick-walled yeast cell (8- to 15-mcg diameter) with broad-based daughter cells

- Bone scanning: A radionuclide bone scan and other imaging modalities, such as CT scanning or even the more sensitive MRI, may help detect skeletal involvement in some cases of extrapulmonary blastomycosis.

Other Tests

- Skin biopsy: Blastomycosis can present with cutaneous lesions. In these situations, histology and culture on skin biopsy specimens may reveal the organism.
- Immune deficiency workup: In recent years, serious infection with blastomycosis is recognized increasingly in immunocompromised hosts, especially patients with AIDS. However, other fungal infections, such as progressive disseminated histoplasmosis or cryptococcal meningitis, are more likely to be opportunistic. Blastomycosis is not an AIDS-defining illness and no official recommendations regarding screening for human immunodeficiency virus (HIV) infection in patients diagnosed with blastomycosis are recognized.
- Lumbar puncture: Neurologic manifestations of blastomycosis include meningitis and, more commonly, epidural or cranial abscesses. Diagnosis is difficult, and evaluation of lumbar spinal fluid is rarely definitive. Ventricular fluid has been associated with higher rates of culture positivity.

Procedures

- The diagnosis of blastomycosis is more difficult in children. Children with pulmonary disease who are unable to produce sputum may require invasive procedures, such as bronchoscopy with bronchoalveolar lavage, percutaneous needle biopsy of lung, and open lung biopsy, for diagnostic confirmation.

Histologic Findings

- The definitive diagnosis of blastomycosis is based on identification of the characteristic thick-walled broad-based budding yeast cells in tissue specimens or growth of the fungus in culture.
- Pathologically, a pyogranulomatous tissue response including lymphocytes, giant cells, and neutrophils is observed with associated necrosis and fibrosis.
- Pseudoepitheliomatous hyperplasia may be striking and may lead to an erroneous diagnosis of squamous cell carcinoma.
- Typically, the granuloma of blastomycosis does not caseate or calcify as in tuberculosis.

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Medical Care

- Treatment of blastomycosis in the pediatric age group is based largely on experience with adult patients.
- Therapeutic approaches have evolved in recent years with the advent of oral azoles,

primarily itraconazole, which has replaced amphotericin B for most indications in adult patients.
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Voriconazole may have a role in the treatment of CNS blastomycosis, but further studies are necessary.

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- Close observation alone may be an option in cases of mild pulmonary blastomycosis because they can spontaneously resolve; however, reactivation of the disease may occur, and, with the availability of new oral azoles, a tendency to treat all symptomatic cases is observed.

- All immunocompromised patients and patients with progressive pulmonary disease or extrapulmonary disease should be treated.

Surgical Care

- Surgery has only a limited role in the treatment of blastomycosis.

Medication

Amphotericin B remains the antifungal agent with the most success against *B dermatitidis*. Cumulative doses less than 1 g have resulted in cure without relapse in 70-91% of adult cases of blastomycosis. A retrospective study of blastomycosis cases in Mississippi reported a cure rate of 86.5% and a relapse rate of only 3.9% for patients treated with amphotericin.

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Toxicity often necessitates interruption of therapy. Cutaneous and noncavitary lung disease should be treated for approximately 8-10 weeks. Cavitary lung disease or infection that extends beyond the lung and skin should be treated for about 10-12 weeks with a cumulative dose of 2.5 g or more of amphotericin B.

Amphotericin B is the drug of choice for treating children with life-threatening and central nervous system infections caused by blastomycosis. Most experts recommend a total cumulative dose of 30 mg/kg or higher of amphotericin B. Human trials of lipid formulations of amphotericin B in the treatment of blastomycosis have not been performed. However, limited clinical data suggest that these preparations may be used for selected patients intolerant to standard amphotericin B therapy.

The azoles are an equally effective and less toxic alternative to amphotericin B for treating adult immunocompetent patients with mild-to-moderate pulmonary or extrapulmonary disease,

excluding CNS disease. In a multicenter clinical trial involving adult patients, itraconazole was found to be more effective and associated with fewer adverse effects than ketoconazole.⁷

Most experts recommend a minimum of 6 months of oral azole therapy for mild-to-moderate pulmonary or nonmeningeal disseminated blastomycosis. Safety and efficacy data using oral azole therapy in children are limited. Itraconazole has been used successfully as treatment in a small number of pediatric patients with non-life-threatening non-CNS disease. Short courses of amphotericin B (5-10 mg/kg total dose) followed by oral itraconazole for 6 months may be used to treat extrapulmonary blastomycosis.

The oral azoles are not beneficial in treating CNS blastomycosis. If oral azole antifungal agents are used for non-life-threatening cases, patients should be closely monitored. Amphotericin B should be substituted for the oral azole agent if clinical deterioration is noted or serum levels of medications are not adequate.

Acute pneumonia complicated by acute respiratory distress syndrome and extrapulmonary disease may need treatment with moderate doses of amphotericin B (>1.5 g total dose) or short courses of amphotericin B (500 mg total dose) followed by 6 months of oral itraconazole. In pregnant women with blastomycosis, amphotericin B is the drug of choice because the oral azoles are contraindicated due to their embryotoxic and teratogenic effects.

Although unusual, in recent years, an increased number of cases of blastomycosis have been reported in compromised hosts, including patients with AIDS, bone marrow and solid organ transplant recipients, and patients receiving cytotoxic or long-term immunosuppressive therapy. Early and aggressive therapy with amphotericin B therapy is warranted because multiple organ and CNS involvement with resultant mortality is relatively common in this population. Furthermore, response to antifungal therapy may be suboptimal, and relapses are common.

Most experts recommend treating blastomycosis in children with AIDS with 30 mg/kg of amphotericin B over 4-6 weeks, followed by itraconazole for at least 6 months in those who have responded to a primary course of amphotericin B. Until more data are available, primary therapy with itraconazole should be used with caution in compromised patients with blastomycosis and considered only in mild illness without CNS infection and stable or improving disease.

Long-term suppressive therapy may be needed in immunocompromised patients. Some experts recommend itraconazole as probably the best secondary prophylaxis for AIDS patients with blastomycosis.

Antifungal agents

Their mechanism of action may involve an alteration of RNA and DNA metabolism or an intracellular accumulation of peroxide that is toxic to the fungal cell.

Amphotericin B (Amphocin, Fungizone)

Initial DOC for blastomycosis in patients with severe illness (eg, rapidly progressive infections, CNS disease), immunocompromised hosts, and special circumstances (eg, pregnancy, childhood disease).

- Dosing
- Interactions
- Contraindications
- Precautions

Adult

0.7-1 mg/kg/d IV; total cumulative dose 1.5-2.5 g; CNS disease warrants at least 2 g total dose

Pediatric

Administer as in adults; total cumulative dose >30 mg/kg IV

- Dosing
- Interactions
- Contraindications
- Precautions

Nephrotoxic drugs may cause additive toxic effects; corticosteroids may increase potassium depletion caused by amphotericin; may predispose patients receiving cardiac glycosides or skeletal muscle relaxants to toxicity secondary to hypokalemia

- Dosing
- Interactions
- Contraindications
- Precautions

Documented hypersensitivity; renal failure limits the use of amphotericin B

- Dosing
- Interactions
- Contraindications
- Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Because of the nephrotoxic potential of amphotericin, other nephrotoxic drugs should be avoided; administered by IV infusion over 2-6 h at a final concentration not to exceed 0.1 mg/mL; monitoring parameters include electrolyte levels, BUN levels, serum creatinine levels, and CBC count; regularly; monitor input and output; monitor for signs of hypokalemia (eg, muscle weakness, cramping, drowsiness, ECG changes)

Cardiovascular collapse has been reported after rapid amphotericin injection; may premedicate patients who experience mild adverse reactions with acetaminophen and diphenhydramine 30 min before the infusion; dosage adjustments not necessary with renal impairment; if decreased renal function is caused by amphotericin B, the daily dose can be decreased by 50%, or the dose can be given every other d

Risk of nephrotoxicity may be minimized by sodium loading with 10-15 mL/kg of NS infused before each amphotericin dose

Itraconazole (Sporanox)

PO itraconazole (at a dosage of 200-400 mg/d) is now the azole of choice in adult patients with indolent nonmeningeal blastomycosis of mild-to-moderate severity, whether given as primary therapy to stable patients or following a course of amphotericin B. Compared with other PO azoles, itraconazole is better absorbed and has enhanced antimycotic activity with fewer

adverse effects. In a prospective phase 2 clinical trial involving adult patients, itraconazole was effective in 90% of cases receiving 200-400 mg/d. In a cohort study of 42 patients, similar success rates were noted for patients treated with 200 mg of itraconazole.

- Dosing
- Interactions
- Contraindications
- Precautions

Adult

200-400 mg/d PO with food (to enhance absorption); 200 mg/d initially; if poor response, increase dose in 100 mg increments; not to exceed 400 mg/d in 2 divided doses

Pediatric

5-7 mg/kg/d PO qd or divided q12h

- Dosing
- Interactions
- Contraindications
- Precautions

Decreased effect of itraconazole with carbamazepine, isoniazid, rifampin, phenytoin, phenobarbital (increased metabolism); H₂-antagonists, omeprazole, antacids, didanosine (decreased absorption); inhibits CYP450 3A4 isoenzyme, thus increases effect of cyclosporine, tacrolimus (interferes with clearance); digoxin, warfarin and hypoglycemic agents (decreased metabolism); increased toxicity of terfenadine (**recalled from US market**), astemizole (**recalled from US market**), and cisapride (cardiotoxicity)

- Dosing
- Interactions
- Contraindications
- Precautions

Documented hypersensitivity; coadministration with cisapride may cause adverse

cardiovascular effects (possibly death)

- Dosing
- Interactions
- Contraindications
- Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Rare cases of serious cardiovascular adverse event, including death, ventricular tachycardia, and torsade de pointes have been observed because of increased terfenadine, astemizole, and cisapride concentrations induced by itraconazole; itraconazole solution and capsules should not be used interchangeably; PO solution is administered on an empty stomach and caps are taken with food

Ketoconazole (Nizoral)

An effective alternative agent in the treatment of immunocompetent patients with mild-to-moderate blastomycosis. In prospective randomized clinical trials conducted by the Mycoses Study Group, cure rates of 70-85% have been documented in patients treated with 400-800 mg/d. Relapse rates of 10-14% have been reported, and close follow-up monitoring is warranted for 1-2 years after therapy with ketoconazole.

- Dosing
- Interactions
- Contraindications
- Precautions

Adult

400-800 mg/d PO; divide 800 mg/d in 2 doses

Pediatric

Not established

- Dosing
- Interactions
- Contraindications
- Precautions

Drugs that decrease absorption (raise gastric pH), such as antacids, H₂-receptor blockers; drugs that decrease serum concentrations of ketoconazole (rifampin, isoniazid); potent inhibitor of CYP450 3A4, drug concentrations that are increased by ketoconazole (phenytoin, cyclosporine, cisapride, astemizole (**recalled from US market**), digoxin, theophylline, terfenadine (**recalled from US market**), warfarin); drugs that cause hepatotoxicity; alcohol may cause disulfiramlike reactions

- Dosing
- Interactions
- Contraindications
- Precautions

Documented hypersensitivity; concomitant administration with terfenadine, astemizole, or cisapride

- Dosing
- Interactions
- Contraindications
- Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Administration has been associated with hepatotoxicity, including some fatalities; high doses may depress adrenocortical function; risk of serious cardiac arrhythmias in patients receiving

concomitant terfenadine, astemizole, or cisapride

Fluconazole (Diflucan)

The role of fluconazole therapy in blastomycosis is limited. In a small pilot study involving 23 patients, a successful outcome was noted in only 15 (65%) of cases. Better results were reported recently using higher dosages of fluconazole (400-800 mg/d). A successful outcome was noted for 34 (87%) of 39 patients treated for a mean duration of 8.9 mo. Although fluconazole demonstrates excellent CNS penetration, its role in the treatment of blastomycotic meningitis and cerebral abscesses is anecdotal.

- Dosing
- Interactions
- Contraindications
- Precautions

Adult

400-800 mg/d PO

Pediatric

Not established

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