Blastomycosis is an endemic mycosis that occurs predominantly in North America in the north central United States and provinces of Canada, southern states, and those midwestern states that border the Mississippi River basin. It causes acute and chronic pneumonias and disseminated infection with cutaneous lesions as the major extrapulmonary manifestation. However, the vast majority of infected persons are asymptomatic or have mild respiratory symptoms that are not diagnosed as being caused by a fungal infection. Rarely, patients develop severe pulmonary infection that progresses to acute respiratory distress syndrome (ARDS), which has a high mortality rate. A urinary antigen test is now available to aid in diagnosis, but it is not specific and is positive in patients who have histoplasmosis as well as blastomycosis. Antibody assays remain nonspecific and insensitive, and the confirmatory diagnostic test is still growth of the organism in culture. Updated guidelines from the Infectious Diseases Society of America are available to aid clinicians in the management of the various forms of blastomycosis.

Keywords: endemic mycoses; Blastomyces dermatitidis; fungal pneumonia

Blastomycosis is caused by Blastomyces dermatitidis, a thermally dimorphic fungus that grows as a mold in the environment and as a yeast in tissues. The infection is most commonly noted in certain areas of the United States and Canada. Blastomycosis is primarily a pulmonary infection, but dissemination occurs frequently and leads to involvement of skin, osteoarticular structures, the genitourinary tract, and other organs. Newer aspects of clinical manifestations, diagnostic methods, and treatment regimens for blastomycosis will be emphasized in this review.

EPIDEMIOLOGY

The epidemiology of blastomycosis is less well defined than that of histoplasmosis and coccidioidomycosis. This is partly due to the fact that the organism is difficult to isolate from the environment (1, 2). During a recent investigation of an outbreak in dogs, a PCR-based technique successfully identified B. dermatitidis from environmental samples, giving hope that this technique might prove useful in the future to help define the environmental niche (3). In contrast to histoplasmosis, for which skin testing facilitated screening of large populations for past exposures, there have been no reliable means to screen for exposure to B. dermatitidis. Mandatory public health reporting of blastomycosis is required in only a few states or provinces, namely Illinois, Wisconsin, Mississippi, Manitoba, and Ontario. Thus, the extent of occurrence of blastomycosis is undoubtedly underestimated.

B. dermatitidis is endemic in the Mississippi and Ohio River valleys, the Midwestern states and Canadian provinces that border the Great Lakes, and the area of New York and Canada adjacent to the St. Lawrence Seaway (2, 4–6). Sporadic human cases of blastomycosis have been reported from other areas, including Hawaii, Israel, India, Africa, and Central and South America (7, 8). In states that have a high incidence of blastomycosis, such as Mississippi and Wisconsin, certain counties report a disproportionate number of cases (9). For example, one survey in Wisconsin noted that the incidence of symptomatic infection in 10 different counties ranged from 5.1 to 41.9 cases per 100,000 persons (10). Activities in watershed areas appear to carry a higher risk for acquisition of B. dermatitidis (2, 11, 12). It is thought that the moist soil enriched with decaying vegetation in these areas encourages the growth of the organism. In most series, men are more commonly infected with B. dermatitidis; the presumption is that they have a greater risk for exposure to the organism in the course of outdoor activities (5, 6, 13). Blastomycosis also occurs in dogs in the same endemic areas (14), and not infrequently, humans and dogs are ill with the disease at the same time, having experienced the same exposure.

PATHOGENESIS

The conidia produced in the environmental mold phase cause infection when aerosolized and inhaled into the alveoli, where conversion to the yeast phase occurs. Several local host factors are triggered after inhalation of the conidia. Alveolar macrophages can phagocytize and kill conidia, which can inhibit transition of some of the inoculum to the yeast phase (15, 16). Neutrophils and macrophages can phagocytize the yeast phase organisms, leading to a mixed pyogenic and granulomatous host response that is seen in tissue samples. Ultimately, control of infection with B. dermatitidis is primarily dependent on T lymphocytes that have become sensitized to Blastomyces antigens arming the macrophages to kill the phagocytized yeasts (17, 18). Humoral immunity develops, but is not crucial to containment of the infection. The primary, and in many cases the only, clinical manifestation of blastomycosis is pneumonia. However, hematogenous dissemination is common and can lead to focal disease at a distant site or disseminated infection. Not all organisms are eradicated by the immune response, and reactivation has been reported up to 40 years after the initial infection (19).

CLINICAL MANIFESTATIONS

Pulmonary Blastomycosis

Pulmonary infection is the most common manifestation of infection with B. dermatitidis. Infection is asymptomatic in more than 50% of infected individuals (13, 20–22). Of the patients who are symptomatic, illness typically begins 30 to 45 days after exposure, and the illness most often manifests as a mild self-limited pulmonary infection or “summer cold.” Several studies have suggested a seasonal predilection, with isolated pulmonary disease presenting in the late summer and autumn, and disseminated and extrapulmonary disease presenting in winter through late spring (23). Patients ill enough to seek medical care are often thought to have bacterial community-acquired pneumonia, and they are treated with antibiotics. It is
not until the patient’s symptoms fail to respond to antibacterial therapy that the diagnosis of pulmonary blastomycosis is suspected. In one series of 118 people who were found to have pulmonary blastomycosis, cough (90%) was the most common symptom, followed by fever (75%), night sweats (68%), weight loss (68%), chest pain (63%), dyspnea (54%), myalgias (50%), and hemoptysis (18%) (24). Chest radiographs reveal a patchy pneumonitis, a mass-like infiltrate, or nodules (25–27) (Figure 1). Mediastinal and hilar lymphadenopathy is not commonly seen and helps differentiate blastomycosis from histoplasmosis. Although pulmonary infection can be self-limited (21, 22), it is currently recommended that all patients in whom the diagnosis is made and who are symptomatic be treated with an antifungal agent to prevent progressive infection.

Chronic pulmonary blastomycosis is clinically indistinguishable from tuberculosis. Symptoms include cough productive of purulent and sometimes bloody sputum, fever, malaise, and weight loss (13, 28, 29). Chest radiographs reveal mass-like lesions that are often mistaken for a malignancy, upper lobe infiltrates with cavities, or scattered nodules (25–27) (Figures 2 and 3). These patients may or may not have skin lesions or other manifestations of disseminated infection. This form of blastomycosis is progressive if not treated.

Rarely, patients with pulmonary blastomycosis develop acute respiratory distress syndrome (ARDS) (Figure 4). A recent evaluation of hospitalized patients who had pulmonary blastomycosis noted that 10% received some care in the intensive care unit and that more than a third of patients who developed respiratory failure died, usually within several days of admission (29). Severe pulmonary involvement can be seen in patients with defective cell-mediated immunity, including patients who have a hematologic malignancy, have received a transplant, or have AIDS. In one series from a hyperendemic area, 3 of 9 patients with blastomycosis-associated ARDS had at least partial immunosuppression (30). However, just as frequently, the patient who develops this severe form of blastomycosis is a previously healthy person (30–33). In some patients, presentation is that of a typical community-acquired pneumonia, and then a few days to a week later acute decompensation occurs with hypoxemia requiring intubation. Others have fulminant pneumonia and appear to be septic on admission. The diagnosis of blastomycosis is often delayed, contributing to the progression to ARDS. In one report, over 60% of patients who died of blastomycosis-associated ARDS were not suspected of having a fungal infection, and the diagnosis was not made until they were desperately ill (32). Blastomycosis-associated ARDS is associated with mortality rates of 50 to 89%, even in patients receiving appropriate therapy (30–33).

**Disseminated Infection**

*B. dermatitidis* can disseminate to many different organs, but the skin, osteoarticular structures, and the genitourinary system are the most frequently involved. It is likely that dissemination occurs early in infection before the development of specific cell-mediated immunity, but most patients remain asymptomatic and will never develop systemic manifestations. Studies reported prior to the availability of antifungal agents noted rates of symptomatic dissemination in almost two-thirds of patients, but recent studies report dissemination rates of 20 to 25% (6, 13, 32). By the time extrapulmonary manifestations appear, the chest radiograph may show resolving pneumonia or no infiltrates.

Cutaneous lesions often appear on the exposed areas of the head, neck, or extremities, but they can appear anywhere. The classic lesion is verrucous and crusting with central punctate draining microabscesses, but violaceous nodules, ulcerative lesions, and pustules have been observed (13, 34) (Figures 5–7). Although single lesions have been described, most patients manifest several lesions and uncommonly, a large number of lesions. Bone involvement can underlie the cutaneous lesions,
but can also be present at multiple distant sites as well. Draining sinus tracts can develop over bony lesions. Radiographs usually show well-circumscribed osteolytic lesions (35).

Genitourinary tract involvement is most common in men, and the prostate is the usual target organ (13). Symptoms include dysuria, perineal discomfort, and obstructive symptoms. Central nervous system (CNS) infection is rare. Meningitis, brain abscesses, and cord lesions can occur (36). CNS involvement can be one manifestation of disseminated infection; this is usually the case in immunosuppressed patients. Immunocompetent patients are more likely to develop isolated chronic lymphocytic meningitis. Mortality remains high for CNS blastomycosis, especially when it is accompanied by disseminated infection.

**Blastomycosis in Immunocompromised Hosts**

Patients who have defective cell-mediated immunity have been shown to have an increased risk of developing symptomatic primary disease after exposure to *B. dermatitidis*. Most cases have been reported in patients who had AIDS (37). Acquisition has been from the environment, but it has been estimated that as many as 25% of AIDS-related cases may be due to reactivation infection (37). The manifestations of blastomycosis in patients with AIDS are generally more severe than those in immunocompetent hosts. Severe pneumonia with hypoxemia, widely disseminated infection, and CNS involvement are all more common in this population. CNS manifestations were present in 40% of cases in patients who had AIDS. The mortality of blastomycosis in the pre-HAART era was nearly 40%, and most deaths occurred within 3 weeks of diagnosis (37).

Blastomycosis has been reported uncommonly in solid organ transplant recipients and patients with hematologic malignancies (38–40). In transplant recipients, the disease is frequently associated with severe infection accompanied by ARDS and widespread dissemination (39, 40).

Seven patients with blastomycosis have been reported to the FDA registry of fungal infections in patients receiving TNF-α inhibitor therapy (41). There are no published case reports on these patients. However, blastomycosis is listed in the warning issued by the FDA on September 4, 2008 regarding increased...
risk of fulminant infections with endemic mycoses in patients receiving TNF-\(\alpha\) inhibitor therapy.

**DIAGNOSIS**

The diagnosis of blastomycosis is often elusive, and delays in diagnosis are common (13, 42, 43). For example, in Mississippi, which has the highest reported prevalence of blastomycosis in North America, only 5% of patients with pulmonary blastomycosis were correctly diagnosed at initial presentation. When pulmonary disease was associated with cutaneous involvement, the initial diagnosis was improved to 64%, as clinicians recognized the classic skin lesions of blastomycosis. A delay in diagnosis of more than 1 month was reported in half of the patients (13).

**Culture**

The difficulty in making the correct diagnosis of pulmonary blastomycosis is not so much the inadequacy of the available culture techniques, but rather the failure to consider the diagnosis. An appraisal of diagnostic techniques in patients with pulmonary blastomycosis noted that culture eventually yielded *B. dermatitidis* in 86% of patients (43). The diagnostic yields for sputum samples, tracheal secretions, and gastric washings were 75%, 100%, and 67%, respectively. When bronchoscopy was performed, the yield was even greater. The main drawback to culture methods is that it may take as long as 4 to 5 weeks for the organism to grow (44). For most clinical situations, this means that culture results provide confirmation of the diagnosis, but other techniques that give a more rapid answer must be pursued.

**Figure 5.** Verrucous, plaque-like lesion showing central microabscesses and the well-demarcated, heaped-up border typical of blastomycosis.

**Figure 6.** Painful, ulcerated lesion on the lower leg of a patient who had several other cutaneous ulcerations and also a pulmonary infiltrate; *B. dermatitidis* was grown from sputum and the cutaneous ulcers.
Smears and Histopathology

The importance of immediately looking for the organism in a smear from a respiratory or tissue sample has been emphasized. In one series of patients who had pulmonary blastomycosis, a smear and culture for fungus was ordered for only 24% of sputum samples and 55% of samples obtained by bronchoscopy (43). *B. dermatitidis* has distinctive features that include large size (8–15 μm), thick wall, and distinctive budding (daughter cell is close to the same size as the mother cell before detachment). Thus, a rapid diagnosis of blastomycosis can be made by microscopic examination of smears of respiratory secretions or histopathologic examination of tissue specimens (44). Respiratory secretions can be treated with KOH or with calcofluor white, which causes fluorescence of the fungal cell wall, and is more sensitive. Papanicolaou stains that are used for cytology preparations also show the distinctive characteristics of *B. dermatitidis* (Figure 8). The organisms are poorly seen in tissue stained with hematoxylin and eosin, but are readily seen with methenamine silver or periodic acid Schiff (PAS) stains.

Antigen Testing

A urine antigen assay for the cell wall polysaccharide of *B. dermatitidis* has been reported to have a sensitivity of 93% and a specificity of 79% (45). It is a relatively new test, and its role in diagnosis is still unclear. Currently, it appears that this assay is useful for patients who have either severe pulmonary or disseminated infection, but whether it will be helpful in those with milder infection is not known. It is also not clear if urinary antigen levels can be followed as a means of assessing the response to treatment, as has been demonstrated with urinary
emphasizing the cross-reactivity between these two assays. An antigen level is higher than that for the Histoplasma antigen, and some patients with severe infection, the Histoplasma urinary antigen level is higher than that for the Blastomyces antigen, emphasizing the cross-reactivity between these two assays.

Serological Testing

Serological testing in blastomycosis is problematic because of low rates of sensitivity and specificity (44). For example, in one large series of 25 patients with pulmonary blastomycosis, the immunodiffusion assay was positive in 40% and complement fixation in 16% (43). Extensive work has gone into trying to establish more specific and sensitive assays using different antigens specific to B. dermatitidis (47), but none are currently available. The commercially available assays for complement fixation and immunodiffusion are not useful for diagnosis.

TREATMENT

Updated practice guidelines for the treatment of blastomycosis have been published by the Infectious Diseases Society of America (IDSA) (48) (Table 1). All patients with blastomycosis, even those with a single cutaneous lesion, should be treated with an antifungal agent because of the high likelihood of progression or recurrence of the infection if not treated. In general, initial therapy for patients who have mild-to-moderate pulmonary or disseminated blastomycosis will be with an azole agent and for patients who have severe pulmonary or disseminated blastomycosis will be with an amphotericin B formulation. Immunosuppressed patients and those with central nervous system disease should be treated initially with an amphotericin B formulation (48). The major changes that have been incorporated in the 2008 IDSA guidelines as compared with the 2000 IDSA guidelines are noted below.

Amphotericin B Therapy

Lipid formulations of amphotericin B, either liposomal amphotericin B or lipid complex amphotericin B, are recommended as alternatives to amphotericin B deoxycholate, which was the only formulation recommended in 2000. There are no controlled trials proving the benefit of lipid formulations compared with standard amphotericin B deoxycholate, but in many institutions the lipid preparations are preferred for most indications that require amphotericin B therapy because they are clearly less nephrotoxic. The dosage is 3 to 5 mg/kg daily for severe pulmonary or disseminated infection. The recommendation to use amphotericin B for the entire course of therapy has been changed to encourage step-down therapy to an azole when the patient has had a satisfactory clinical response to initial amphotericin B therapy.

Despite antifungal therapy, the mortality rate of blastomycosis-associated ARDS is still 50 to 89% (30–33). The IDSA guidelines note that corticosteroids have been used in an attempt to improve the outcomes in patients with this complication, but no recommendation was made in regard to the use of these agents (48). Anecdotal case reports have shown benefit, but there are no controlled studies assessing corticosteroid use (33). One report of only two patients showed rather dramatic improvement when methylprednisolone was added to amphotericin B therapy. Extracorporeal membrane oxygenation (ECMO) has also been used in an attempt to maintain oxygenation and permit lower ventilation pressures in one patient who ultimately died of blastomycosis (49). This case was instructive in that it was documented that the serum levels of amphotericin B remained within the expected range and were not affected by changes of the membrane oxygenator or circuit tubing.

Azole Therapy

Itraconazole remains the azole of choice for mild-to-moderate blastomycosis and for step-down therapy after initial amphotericin B treatment for severe blastomycosis (48, 50). Cure rates are as high as 95% for nonmeningeal mild-to-moderate disease. The usual dosage is 200 mg once or twice daily after an initial loading dose of 200 mg three times daily for 3 days. When the daily dosage of itraconazole is 400 mg, absorption is enhanced if the drug is given as 200 mg twice daily. The main drawbacks of itraconazole are the variability in absorption and the many drug–drug interactions. The preferred formulation is the oral suspension because absorption is more predictable with this formulation. The suspension is administered on an empty stomach; unfortunately, gastrointestinal upset is common and not all patients are able to tolerate this formulation. The capsule formulation of itraconazole requires both food and gastric acid for maximum absorption. Thus, acid-inhibiting drugs cannot be prescribed when the capsule formulation is used.

Wide inter-patient variability of serum concentrations is evident with either formulation. Because of this, serum itracon-
nazole levels should be monitored. Itraconazole levels should be determined after approximately 2 weeks when steady state has been reached. A serum level greater than 1.0 μg/ml is recommended (48).

Flucytosine is not as effective as itraconazole for blastomycosis, and is not recommended (51). However, if the patient is unable to tolerate itraconazole, flucytosine can be used, but the dosage should be 800 mg daily. The guidelines acknowledge anecdotal reports that have shown the effectiveness of voriconazole for the treatment of blastomycosis (48, 52–54). Interestingly, most of these reports showed benefit when this agent was used to treat patients who had central nervous system infection. There is no experience to date for the use of posaconazole for blastomycosis, but this agent has good in vitro activity against *B. dermatitidis*.

**Central Nervous System Infection**

For patients with central nervous system blastomycosis, a lipid formulation of amphotericin B at a dosage of 5 mg/kg daily is recommended for 4 to 6 weeks, followed by therapy with an azole for a total of at least a year of antifungal therapy. The guidelines offer several options for azole step-down therapy, based entirely on anecdotal data (48). Interestingly, there is more experience with voriconazole, which is not FDA-approved for the treatment of blastomycosis, than with itraconazole or fluconazole. Although itraconazole has excellent activity against *B. dermatitidis*, cerebrospinal fluid (CSF) levels are very low; fluconazole achieves excellent CSF levels, but has only modest activity against *B. dermatitidis*. Voriconazole achieves good CSF concentrations and also has excellent activity against the organism. Depending on the response to therapy and the immune status of the patient with central nervous system blastomycosis, azole therapy may have to be continued for life to prevent relapse of the infection (48).

**Length of Therapy**

The length of therapy for pulmonary or disseminated forms of blastomycosis depends on the severity of the infection and the immune status of the host. Pulmonary blastomycosis and disseminated infection in patients who have mild-to-moderate illness is usually treated for a total of 6 to 12 months (48). Patients with disseminated infection who are severely ill and those who have osteoarticular infection should receive a total of 12 months of antifungal therapy. Although skin lesions often begin to resolve within the first few months of therapy, treatment should continue for 6 to 12 months to achieve a mycologic cure. For immunosuppressed patients, treatment with itraconazole, 200 mg daily, is recommended for life-long suppressive therapy if the immunosuppression cannot be corrected.

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