Pulmonary Blastomycosis

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ABSTRACT

Blastomycosis is a rare but important fungal infection diagnosed primarily in the south central and midwestern United States but also in the American and Canadian borders of the Great Lakes. Epidemics of infection related to point-source exposure include patients of all ages and both sexes, but endemic cases are usually in young to middle-aged adults, with more men than women reported. Pneumonia is the most common manifestation and the lung is almost always the organ initially infected. The lung manifestations range from illness that mimics acute bacterial pneumonia to chronic, destructive lung disease appearing like tuberculosis or lung cancer. Extrapulmonary disease can occur with or without concomitant lung disease. In descending order, cutaneous, osseous, prostatic, and central nervous system involvements are the most frequent manifestations of extrapulmonary blastomycosis. Amphotericin B is curative, but, because of toxicity, oral azole agents have replaced amphotericin B as therapy for less than overwhelming blastomycosis. Itraconazole is now considered to be the agent of choice with fluconazole, voriconazole, and posaconazole having a role in selected patients. In a patient with life-threatening or central nervous system blastomycosis amphotericin B should be given, at least initially.

KEYWORDS: Blastomycosis; *Blastomyces dermatitidis*; lung diseases, fungal

Blastomycosis is an endemic pulmonary mycosis of the United States and Canada, caused by a dimorphic fungus *Blastomyces dermatitidis*. *B. dermatitidis* exists in nature as a mold that produces conidia (mycelial phase) and converts to a broad-based budding yeast (yeast phase) at body temperature. Like histoplasmosis or coccidioidomycosis, blastomycosis can be an asymptomatic or subclinical infection with subsequent protection against progressive illness afforded by innate or specific immune mechanisms, but it may present with clinical disease with either pulmonary or extrapulmonary disease or both.[1] Diagnosis is best made by visualization of the yeast in smears or in tissue specimens or by culture.[2] Because colonization does not occur, as might with *Candida* or *Aspergillus*, identification of *B. dermatitidis* provides a definitive diagnosis.

Blastomycosis was first described by Gilchrist in Baltimore more than a century ago as a skin infection caused by a protozoan organism[3]; the infection was known as Gilchrist disease. Some errors were included in the initial description. Blastomycosis is not common in the areas surrounding Baltimore. Infection of the skin occurs secondarily rather than primarily. The organism is not a protozoan but a fungus, and Gilchrist was the first to refine portions of his own descriptions when he isolated and named the fungus *Blastomyces dermatitidis*.[4] Because skin manifestations of blastomycosis are often very striking, the initial cases were perceived as primarily dermatologic.[1,5] The concept of primary pulmonary blastomycosis was not recognized until pathological descriptions allowed the pathophysiological mechanisms to be delineated.[1] Although there have been cases of

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cutaneous inoculation of the fungus in laboratory workers and veterinarians, almost all natural cases of blastomycosis are considered to originate from a pulmonary portal of entry.[5]

ETIOLOGIC AGENT

Blastomyces dermatitidis is the imperfect (asexual) state of *Ajellomyces dermatitidis*.[6] This fungus has been recovered in many parts of the world. Examination of portions of the yeast exoantigen has allowed identification of two serotypes of *B. dermatitidis*: A antigen positive and A antigen negative.[7] *B. dermatitidis* is dimorphic, growing in a mycelial form as a fluffy white mold at 25°C and as a brown, wrinkled, folded yeast form at 37°C.[6] Primary isolation of *B. dermatitidis* in the laboratory, however, is most dependable when grown as the mycelial form at 30°C. The physiological changes causing this transition from mycelia to yeast have been described by Medoff et al as a result of heat-related cellular insults with resultant partial uncoupling of oxidative phosphorylation.[8] When examined microscopically, the branching hyphae are 2 to 3 μm in diameter and have right-angled conidiophores that have a single terminal conidia. The conidia are round or oval in shape and vary from 2 to 10 μm in diameter.[2] The conidia, which readily become airborne when the mycelia are disturbed, can be inhaled into the lungs and result in pulmonary infection. The mycelial form has no morphologically unique characteristics that allows definitive identification. Commercial test kits are available that facilitate early identification of mycelial cultures by the recognition of fungal-specific exoantigens or unique nucleic acid sequences.[9,10] Most laboratories, however, confirm the culture identification microbiologically by converting the mycelial form to the yeast form after growth at 37°C. When viewed under the microscope, the yeast cells have characteristic features that distinguish *B. dermatitidis* from other fungi. Yeast cells are usually around 8 to 10 μm in diameter and contain 8 to 12 nuclei. These cells have a thick wall that is highly refractile, with daughter cells forming from a single broad-based bud. The daughter cell often as large as the mother cell before detachment. These same characteristic features of the *B. dermatitidis* cells in vitro are also seen in tissue or secretions and support a presumptive diagnosis of blastomycosis when seen in clinical specimens. Finding the fungus in the appropriate clinical setting is almost always followed by culturing *B. dermatitidis* and should prompt the initiation of antifungal therapy.[2]

The most likely pathogenic mechanism for blastomycosis begins with inhalation of conidia from the mycelial phase into the lung followed by phagocytosis of the organism by bronchopulmonary mononuclear cells. Alveolar macrophages have been shown to kill *B. dermatitidis* conidia,[11] which may account for why some persons do not become clinically ill even though they presumably have the same exposure in an epidemic as those who become symptomatic. While transforming to the yeast phase, the fungus grows in the lung and spreads to other organs by lymphatics and the bloodstream. With the development of immunity, inflammatory reactions occur initially as a suppurative response with polymorphonuclear phagocytes and with subsequent influx of monocyte-derived macrophages.[12] This pyogranulomatous response is a distinctive feature of blastomycosis, although necrosis or fibrosis may also be found. The histological changes with this infection may prompt an erroneous diagnosis of squamous cell carcinoma or keratoacanthoma.[13] Fungal stains would demonstrate the correct diagnosis, but the misdiagnosis is usually discovered when a second distant site of infection is found. Despite spontaneous resolution of pneumonia in some cases, endogenous reactivation may occur at either pulmonary or extrapulmonary sites with or without previous therapy.[14,15]

EPIDEMIOLOGY

Because reporting of blastomycosis to public health authorities is not required except in a few states (Illinois, Wisconsin, and Mississippi) and voluntary in a few others, and since subclinical cases escape detection because of the lack of sensitive screening tests, the epidemiology of blastomycosis is not as well understood as that of several other fungal infections. The number of cases reported varies from one area of the country to the next based on the relative interest of physicians in reporting these infections. A total of 1476 cases were reported from 1896 to 1968,[16] but further prevalence studies by Furcolow and colleagues indicate rates in some geographic areas as high as 0.5 to 4.0 cases per 100,000 population per year.[17] Despite under-reporting, most clinical cases of blastomycosis occur in the states surrounding the Mississippi and Ohio Rivers and states and Canadian provinces around the Great Lakes. The states with the greatest numbers of voluntary or mandatory reporting are Arkansas, Mississippi, Kentucky, North Carolina, Tennessee, Louisiana, Illinois, and Wisconsin.[1,2] There are also pockets hyperendemic for blastomycosis. Areas around Rockford and Chicago, Illinois, and Milwaukee, Wisconsin,[18] Eagle River and Vilas County, Wisconsin,[19] Kenora, Ontario,[20] and areas in Arkansas[2] have been described as locations with hyperendemic regions for blastomycosis with rates of up to seven to 74 cases per 100,000 persons described.[20,21]

Endemic or sporadic cases account for the majority of cases of blastomycosis, but several epidemics of infection from point sources have also been described. Around a dozen well-described epidemics from North Carolina, Minnesota, Illinois, Wisconsin, and Virginia have provided information regarding the biology of

blastomycosis.[2] The association of these cases with outdoor exposure points to a common-source outbreak, but the actual site for such a source has been difficult to identify. The likely mechanism for infection is inhalation of spores from the soil. Unfortunately *B. dermatitidis* has not been isolated from soil nearly as commonly as *Histoplasma capsulatum*. Only in a handful of instances have investigators been successful in recovering the organism from soil. In two separate reports, Klein and coworkers reported the isolation of *B. dermatitidis* from soil in association with epidemics.[22,23] Both occurrences were with moist soil having high organic content, and provided evidence that the fungus exists in microfoci in soil. In both epidemics, the isolation of the fungus from soil was noted to be associated with either animals or bodies of water. Whether this association simply represents a greater exposure opportunity because of the increased occupational and recreational activities in areas with wildlife or water remains to be determined.[24]

Cellular immunity is considered to be the major protective factor in preventing progressive disease secondary to these slow-growing but pathogenic fungi. Evidence for this includes the finding that infections with fungi, such as *H. capsulatum*, evoke cellular immune responses detected by in vitro markers of antigen-induced lymphocyte reactivity. Although antibodies may be useful for diagnosis, humoral immunity does not appear critical because patients with hypogammaglobulinemia handle fungal infections adequately. The observation that patients with acquired immunodeficiency syndrome (AIDS) have multiple, relapsing infections with histoplasmosis or cryptococcosis is additional evidence that cellular immunity is the primary defense for these organisms. A relatively small number of AIDS patients have been reported to have had blastomycosis compared with histoplasmosis.[25] This likely relates to the relatively small endemic area for blastomycosis and the lower rates of human immunodeficiency virus (HIV) seropositivity in persons currently residing in the areas associated with blastomycosis; these numbers will undoubtedly increase as the HIV epidemic continues to expand.

The assessment of host response in human blastomycosis has lagged behind investigation of other fungal infections because of a lack of suitably active and specific antigen. Blastomycin, a crude mycelial-phase filtrate, had been used in the past for delayed hypersensitivity skin tests. In two large series, 59 and 100% of patients with positive cultures for *B. dermatitidis* had negative reactions to blastomycin skin tests.[1] Anergy is unlikely to be responsible for these rates, and it is more likely a reflection of poor sensitivity to the skin test material.

Experimental animal models have demonstrated that cellular immunity is the critical host defense in preventing progressive blastomycosis. Cox and Larsh developed a yeast-phase antigen from *B. dermatitidis* that has allowed specific cellular immunity testing.[26] Lymphocyte transformation assays and skin tests to this yeast antigen selectively identified *Blastomyces*-sensitized animals as compared with *Histoplasma*-sensitized animals.[27] This antigen was useful in lymphocyte transformation assays to differentiate patients with treated blastomycosis from those with histoplasmosis or those without fungal infection.[28] In additional studies, pulmonary blastomycosis patients were shown to develop this marker of specific cellular immunity over a 4-week period. Lymphocyte blastogenesis with Cox and Larsh's antigen was the most reliable indicator of infection in the Eagle River, Wisconsin, outbreak of blastomycosis, reported by Klein and coworkers.[22] Among the infected children, 44 of 48 had lymphocyte reactivity, yet only 15 of the 48 demonstrated positive skin test reactions with blastomycin. This in vitro correlate of cellular immunity has been found in patients who had been treated up to 16 years earlier[28] and is an indication of long-lasting immunity similar to that seen in other systemic fungal infections, such as histoplasmosis. Because of the potential of cross-reactivity between subclinical blastomycosis and histoplasmosis, lymphocyte reactivity assays from forestry workers by Vaaler et al[29] were performed in areas endemic for blastomycosis but not histoplasmosis (northern Minnesota and Wisconsin). Thirty percent of the workers had in vitro markers of immunity as evidence of subclinical infection with no question of *Histoplasma* cross-reactions.[29] Blastomycosis appears to have similar patterns of subclinical infection as occur with histoplasmosis and coccidioidomycosis. Recent work by Wüthrich et al has demonstrated the particular subset of CD4 + T-lymphocytes in mice that mediate resistance to infection with *B. dermatitidis*.[30]

CLINICAL MANIFESTATIONS

The clinical presentations of blastomycosis are highly variable. Nonspecific complaints, including weight loss, fever, malaise, and fatigue, are common but offer little diagnostic help. The typical patient is a male between 25 and 50 years of age who either works in or visits outdoor areas. Because dogs are infected in the same way as humans, a clinical clue to the diagnosis of blastomycosis is the history of a pet dog diagnosed with the fungus. Other than from a bite wound, blastomycosis is not contagious from the animal to the human. The observation merely represents the fact that the dog has been in the same environment and acts as a harbinger for human illness.[31] In an outbreak of blastomycosis, children and women are as likely as males to be infected. Aside from an epidemic, it is very rare for children to be diagnosed with blastomycosis.[32] The male:female ratio has been reported from 4:1 to 15:1 in series of endemic cases.[12] However, some of these studies were from

Veterans Administration medical centers, which conspicuously adds bias to the male ratio. In Arkansas, we had over a 13-year period, 78 male patients and 57 female patients referred for therapy of blastomycosis. Of these, 47% had extrapulmonary manifestations and 53% had only lung involvement. Women accounted for only 30% of the extrapulmonary cases, whereas 47% of the pneumonia cases were in women.[33]

The presentation of clinical blastomycosis for most patients is pneumonia with an alveolar or masslike infiltrate by radiography. In two series, 80 and 90% of patients had this type of radiographic appearance.[33,34] Because of the mass lesions on chest x-rays, many blastomycosis patients are initially thought to have lung cancer. Miliary or reticulonodular patterns on radiographs are the next most frequent pattern. Cavitary disease is distinctly uncommon compared with chronic pulmonary histoplasmosis or tuberculosis. Pleural disease has been stated to be distinctly unusual in this infection but in two series, 26 and 42% of patients had evidence of pleural effusion with blastomycosis.[33,35] In summary, no specific radiographic patterns are diagnostic for this fungal infection.

Widely disseminated or miliary blastomycosis may occur with adult respiratory distress syndrome as the presenting feature. One such patient reported by Evans et al had an ulcer seen at the carina on bronchoscopy, prompting the speculation that a subcarinal lymph node ruptured into the trachea, spilling enough organisms into the lungs to cause adult respiratory distress syndrome.[36] The majority of patients with this pattern of diffuse infiltrates, noncardiac pulmonary edema, and refractory hypoxemia die very quickly; three patients in one series died with this manifestation despite intensive medical and antifungal therapy.[37] A previous report suggested survival is possible if the diagnosis is quickly made and therapy is promptly begun.[38]

Clinically, patients with pneumonia due to blastomycosis have an acute presentation, a more chronic picture, or no pulmonary symptoms at all.[33] Blastomycosis patients with pulmonary infiltrates may be discovered by routine radiographs with subsequent denial of pulmonary complaints even after extensive questioning. In one group of patients, two were asymptomatic, 16 had a chronic pneumonia picture, and eight initially had acute pneumonia.[33]

Following pneumonia, cutaneous lesions are the next most common manifestation of blastomycosis. The skin lesions are either verrucous or ulcerative. The verrucous form has a raised, irregular border, often with crusting and some drainage above an abscess in the subcutaneous tissue. The borders of the ulcers are usually sharp and heaped up, and the base commonly contains exudate. These ulcers of blastomycosis originate from subcutaneous pustular lesions that spontaneously drain. Subcutaneous localization without either ulceration or the verrucous appearance may be found. These lesions are usually tender, may be confused with panniculitis, and are often associated with joint pain.[39] Aspiration of the subcutaneous mass or biopsy will reveal organisms on microscopy and culture. Osteomyelitis due to *B. dermatitidis* may be the reason the patient seeks medical attention. Granuloma, suppuration, or necrosis may be found in the bone biopsy. The vertebrae, pelvis, sacrum, skull, ribs, or long bones have been reported most frequently, but essentially any bone may be involved.[5] The radiographic appearance of bony blastomycosis is not specific and cannot be discriminated from that of other fungal, bacterial, or neoplastic disease. Debridement may be required for cure but most bone lesions resolve with antifungal therapy alone. The genitourinary system follows lung, skin, and bone in frequency of involvement, and because men are more likely to have extrapulmonary infection, prostatitis and epididymoorchitis have been reported most commonly.[1] Urine collected after prostatic massage will improve the detection of genitourinary involvement. As occurs with skin or bone infection, *B. dermatitidis* will be present at the same time in the lung as the prostate or testicle in many patients; chest radiographs should be performed in every case of blastomycosis, even if the patient does not have pulmonary complaints. Blastomycosis involves the nervous system in a small percentage of cases of disseminated disease, either as meningitis or as cranial abscesses.

Lesions of blastomycosis may occur in virtually any organ and are often misdiagnosed. A former resident of mine dubbed blastomycosis as a pneumonia unresponsive to cephalexin and a skin condition unresponsive to prednisone; I have called it the endemic mimic. Abscesses may be found in the brain, skeletal system, prostate, or any other organ, including lesions in the myocardium, pericardium, orbit, sinuses, pituitary, adrenal, or other organs as reviewed by Witorsch and Utz.[5] Lesions in the mouth and oropharyngeal area occur but are not found with the same frequency as similar lesions seen in disseminated histoplasmosis. One exception is the larynx.[40] Laryngeal biopsy reveals histological features similar to those in the skin, and the hyperplasia, acanthosis, and fungating appearance of the larynx may be confused with squamous cell carcinoma. Fixation of the vocal cords secondary to fibrosis has led, in some cases, to radiation therapy or total laryngectomy due to an incorrect diagnosis of neoplasm rather than blastomycosis.

Because blastomycosis can rarely be found in essentially any organ, several unusual manifestations have been described. We reported the cases of two women with blastomycosis who had abnormal mammograms with a strong clinical impression of carcinoma.[41] One had a computed tomographic scan that revealed

partial destruction of a vertebral body consistent with metastatic disease. Breast biopsy on both revealed *B. dermatitidis* on microscopy and subsequent culture. The breast mass in each woman resolved with antifungal therapy.

The skin lesions of blastomycosis may be confused with several alternative diagnoses, including basal cell carcinoma, squamous cell carcinoma, or pyoderma gangrenosa. We described one patient with what appeared to be condyloma acuminatum surrounding his anus.[13] Only after post-operative suppurative drainage occurred was the histology reviewed and *B. dermatitidis* found. When blastomycosis is found at sites where other diseases are more common, misdiagnosis is frequent.

Most patients with blastomycosis are immunocompetent. Infection in immunocompromised patients has been reported, including in those patients with AIDS, transplantation, sarcoidosis, or treatment with corticosteroids. Pappas et al described several patients in these categories with blastomycosis.[42] They found an increased percentage of cases of blastomycosis in immune-suppressed patients from 1978 through 1991 compared with the cases from 1956 through 1977. This could have been from a bias in referral patterns of patients, but they speculated that the continually enlarging population of patients with complicated immune compromising illnesses have lived in the endemic area for this fungus and, thereby, became infected.[42] Several cases of adult respiratory distress syndrome were described in these immunocompromised hosts as has been described with blastomycosis in AIDS patients.[25]

DIAGNOSIS

The diagnosis of blastomycosis is made by identification of the fungus in tissue or exudate followed by culture. *B. dermatitidis* is relatively easy to detect in both smears and cultures, and that detection is reliable for a firm diagnosis. Cultures are routinely positive within 2 to 4 weeks. The fungus is also readily identified on microscopy of exudate, sputum, or tissue. In addition to examinations of material by wet preparations following digestion of human cells with potassium hydroxide, cytological preparations can be used for a dependable diagnosis. Pathologists should be aware of the appearance of the fungus in sputum cytology smears; the clinical picture of chronic pneumonia due to blastomycosis may suggest a diagnosis of carcinoma of the lung, prompting cytological identification of infection from sputum and eliminating the need for surgical exploration. In areas of the country with a low frequency of this infection, many cases will be diagnosed only after invasive procedures, such as bronchoscopy.

It is fortunate that diagnosis by smear or culture is relatively easy because serological diagnostic techniques used for infections, such as complement fixation (CF) antibodies, are not reliable in blastomycosis. These assays have been useful as tools for epidemiological assessments of blastomycosis, but they have not been helpful for clinical diagnosis. Cross reactivity to antigens of various fungi, particularly *B. dermatitidis* and *H. capsulatum*, is severely limiting to specificity. For example, persons with culture-proven blastomycosis are just as apt to demonstrate CF antibodies against histoplasmin as against blastomycin.[1] Immunodiffusion (ID) percipitin band testing of serum results in sensitivity rates of up to 80%, whereas even better results have been reported with enzyme immunoassay (EIA) techniques using a yeast-phase antigen (antigen A). In the largest outbreak reported, Klein et al described antibody detection by CF, ID, and EIA techniques in 9%, 28%, and 77%, respectively.[43] EIA in general, and particularly with this antigen, is not routinely available to clinicians. Therefore, the use of serology for the diagnosis of blastomycosis is not helpful clinically. Perhaps this problem might be rectified in the future. Klein and Jones have isolated a surface protein of *B. dermatitidis* useful in detection of antibodies in patients in a research setting.[44] Confirmation of sensitivity and specificity will enhance the likelihood that this antigen may someday be used clinically.

Skin testing with blastomycin is, unfortunately, no better than serology as a diagnostic study in patients with potential infection. In two series of culture-proven blastomycosis patients, 85 and 100% had negative blastomycin skin tests.[1] This mycelial-phase antigen does not provide sufficient specificity or sensitivity for reliable patient assessment and is no longer available clinically. For the foreseeable future, the diagnosis of blastomycosis will depend on visualization of the fungus on smear, in tissue, or in culture, although the utility of urine antigen detection for blastomycosis needs further study.[45]

TREATMENT

Spontaneous resolution of chronic blastomycosis does not appear to occur and untreated blastomycosis can be associated with mortality rates approaching 60%.[2] Thus all patients with chronic pulmonary and extrapulmonary blastomycosis should receive antifungal therapy.

There has been controversy in the past regarding the need for antifungal therapy in all cases of acute pulmonary blastomycosis. Although many believe that some cases of acute blastomycosis are self-limited,[46,47] most advocate specific antifungal therapy for all cases of pulmonary blastomycosis, whether acute or chronic, particularly given that therapy other than amphotericin B is now available. Careful follow-up for several years is mandatory in patients with acute pneumonia who do not receive antifungal therapy.

Treatment of blastomycosis has expanded with the availability of the azole antifungals, namely ketoconazole,

itraconazole, and fluconazole. To date, however, no randomized, blinded studies comparing different regimens have been performed, and there are only a few comparative trials for therapy of blastomycosis. Thus the published treatment recommendations for blastomycosis are based on relatively small, open-label, controlled trials, case series, and anecdotal experience.[48]

Several studies have been performed to evaluate the role of the azoles in the treatment of non-life-threatening blastomycosis. Although ketoconazole was effective in trials, itraconazole, an oral and parenteral triazole with broad-spectrum antifungal activity, is considered to be the drug of choice for patients with non-life-threatening, non-central nervous system (CNS) blastomycosis because there is less toxicity with this agent than with ketoconazole. In a prospective, open-label, noncomparative, multicenter study, 43 of 48 (90%) patients with mild to moderate disease were cured with itraconazole at doses ranging from 200 to 400 mg daily.[49] Of 40 patients who received at least 2 months of therapy, 39 (95%) were cured. Most patients responded to the lower dose of itraconazole (200 mg), and the drug was better tolerated than ketoconazole based upon historical comparison. Based on these and other data, current recommendations for patients with non-life-threatening, non-CNS blastomycosis include treatment with itraconazole at an initial dose of 200 mg daily for at least 6 months. For patients not responding to therapy, the dose should be increased by 100 mg increments every 2 to 4 weeks to a maximum of 200 mg twice daily.[48] Some authors recommend measuring itraconazole serum levels because of erratic absorption. In patients that I treat, response to therapy with their pneumonia or skin lesions gives assurance of absorption. If the response is slow, measuring the itraconazole level or switching to the oral solution of itraconazole, which is more reliably absorbed, might be considered.

Fluconazole, another oral and parenteral triazole with broad-spectrum activity, has also been studied for the treatment of non-life-threatening, non-CNS blastomycosis. To date, two multicenter trials have been conducted using fluconazole.[50,51] The results of these studies suggest that fluconazole does not appear to be as efficacious as itraconazole for treatment of patients with mild to moderate blastomycosis; therefore, its role in treatment of this disorder is limited. The drug should be reserved for patients who are unable to tolerate itraconazole or who have potential drug–drug interactions with other required medications. Two new triazole agents, voriconazole and posaconazole, have been approved by the US Food and Drug Administration (FDA) for other indications, but both have activity against *B. dermatitidis* in vitro. In anecdotal cases, some physicians have used voriconazole and fluconazole for CNS blastomycosis,[52] and some physicians have used posaconazole for salvage therapy (personal communication).

For patients with severe, life-threatening, or CNS disease, amphotericin B deoxycholate remains the drug of choice. Little is known about the optimal dose and duration of amphotericin B or its lipid formulations. Traditionally, a cumulative dose of 1.5 t to 2.5 g of amphotericin B deoxycholate has been advocated, but this is based largely on uncontrolled trials and observational studies.[48] For patients who require amphotericin B, it is reasonable to begin at daily doses of 0.5 to 0.6 mg/kg/d, given until control of the disease is obtained, thereafter switching to an oral azole. Relapse rates with amphotericin B are probably less than 5% among immunocompetent patients. Physicians have used lipid formulations of amphotericin because many institutions have abandoned deoxycholate amphotericin B for reasons of toxicity. There are no studies of these agents for blastomycosis. Doses of 1 to 5 mg/kg/d of the liposomal formulations of amphotericin B have been used and it is likely that the 4- to 6-week course that was required to give 1.5 to 2.5 g of routine amphotericin B would be more relevant than the total dose of the liposomal amphotericin drug.

Significantly compromised patients, including those with blastomycosis who have AIDS, are transplant recipients, or are receiving chronic glucocorticosteroids should also receive initial therapy with amphotericin B. A cumulative dose of 1.5 to 2.5 g has been recommended in the past in most cases, but in selected patients, amphotericin B can be administered until the disease is under control. Subsequent therapy with an azole, such as itraconazole, is appropriate. Disease among these patients is associated with significant complications, including adult respiratory distress syndrome and CNS and multiorgan involvement, and is associated with substantially higher mortality. Thus early and aggressive therapy is essential in this population. Long-term suppressive therapy with an azole is generally advised in patients with significant ongoing immune dysfunction. Although there are no controlled trials to support this recommendation, observational studies and anecdotal data suggest a significantly higher rate of relapse among these patients, thus warranting a much more conservative approach to long-term therapy.[25,42]

REFERENCES

1. Sarosi GA, Davies SF. Blastomycosis. State of the art. Am Rev Respir Dis 1979;120:911–938
2. Bradsher RW, Chapman SW, Pappas PG. Blastomycosis. Infect Dis Clin North Am 2003;17:21–40
3. Gilchrist TC. Protozoan dermatitis. J Cutan Gen Dis 1894; 12:496–499
4. Gilchrist TC, Stokes WR. Case of pseudo-lupus vulgaris caused by *Blastomyces*. J Exp Med 1898;3:53–78
5. Witorsch P, Utz JP. North American blastomycosis: a study of 40 patients. Medicine 1968;47:169–200

6. Kwon-Chong KJ, Bennett JE. Blastomycosis. In: Medical Mycology. Philadelphia: Lea & Febiger; 1992:248–279
7. Kaufman L, Standard PG, Weeks RJ, et al. Detection of two *Blastomyces dermatitidis* serotypes by exoantigen analysis. J Clin Microbiol 1983;18:110–114
8. Medoff G, Painter A, Kobayashi GS. Mycelial to yeast-phase transitions of the dimorphic fungi *Blastomyces dermatitidis* and *Paracoccidioides brasiliensis.* J Bacteriol 1987;169:4055–4060
9. Kaufman L, Standard PG. Specific and rapid identification of medically important fungi by exoantigen detection. Annu Rev Microbiol 1987;41:209–225
10. Stockman L, Clark KA, Hunt JM, et al. Evaluation of commercially available acridine ester-labeled chemiluminescent DNA probes for culture identification of *Blastomyces dermatitidis, Coccidioides immitis, Cryptococcus neoformans* and *Histoplasma capsulatum.* J Clin Microbiol 1993;31:845–850
11. Sugar AM, Picard M. Macrophage- and oxidant-mediated inhibition of the ability of live *Blastomyces dermatitidis* conidia to transform to the pathogenic yeast phase; implications for the pathogenesis of dimorphic fungal infections. J Infect Dis 1991;163:371–375
12. Bradsher RW. Blastomycosis. Infect Dis Clin North Am 1988;2:877–898
13. Bradsher RW, Martin MR, Wilkes TD, Waltman C, Bolyard K. Unusual presentations of blastomycosis: ten case summaries. Infect Med 1990;7:10–19
14. Landis FB, Varkey B. Late relapse of pulmonary blastomycosis after adequate treatment with amphotericin B. Am Rev Respir Dis 1976;113:77–81
15. Laskey W, Sarosi GA. Endogenous activation in blastomycosis. Ann Intern Med 1978;88:50–52
16. Furcolow ML, Chick EW, Busey JF, et al. Prevalence and incidence studies of human and canine blastomycosis, I: Cases in the United States, 1885–1968. Am Rev Respir Dis 1970;102:60–67
17. Furcolow ML, Busey JF, Menges RW, et al. Prevalence and incidence studies of human and canine blastomycosis, II: Yearly incidence studies in three states, 1960–1967. Am J Epidemiol 1970;92:121–131
18. Taxy JB. Blastomycosis: contributions of morphology to diagnosis. Am J Surg Pathol 2007;31:615–623
19. Baumgardner DJ, Buggy BP, Mattson BJ, Burdick JS, Ludwig D. Epidemiology of blastomycosis in a region of high endemicity in north central Wisconsin. Clin Infect Dis 1992;15:629–635
20. Crampton TL, Light RB, Berg GM, et al. Epidemiology and clinical spectrum of blastomycosis diagnosed at Manitoba hospitals. Clin Infect Dis 2002;34:1310–1316
21. Baumgardner DJ, Knavel EM, Steber D, Swain GR. Geographic distribution of human blastomycosis cases in Milwaukee, Wisconsin, USA. Mycopathologia 2006;161:275–282
22. Klein BS, Vergeront JM, Weeks RJ, et al. Isolation of *Blastomyces dermatitidis* in soil associated with a large outbreak of blastomycosis in Wisconsin. N Engl J Med 1986;314:529–534
23. Klein BS, Vergeront JM, DiSalvo AF, et al. Two outbreaks of blastomycosis along rivers in Wisconsin: isolation of *Blastomyces dermatitidis* from riverbank soil and evidence of its transmission along waterways. Am Rev Respir Dis 1987;136:1333–1338
24. Bradsher RW. Water and blastomycosis: don't blame beaver. Am Rev Respir Dis 1987;136:1324–1326
25. Pappas PG, Pottage JC, Powderly WG, et al. Blastomycosis in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1992;116:847–853
26. Cox RA, Larsh HW. Yeast and mycelial-phase antigens of *Blastomyces dermatitidis*: comparison using disc gel electrophoresis. Infect Immun 1974;10:48–53
27. Cox RA, Larsh HW. Isolation of skin test-active preparations from yeast-phase cells of *Blastomyces dermatitidis.* Infect Immun 1974;10:42–47
28. Bradsher RW, Alford RH. *Blastomyces dermatitidis* antigen-induced lymphocyte reactivity in human blastomycosis. Infect Immun 1981;33:485–490
29. Vaaler AK, Bradsher RW, Davies SF. Evidence of subclinical blastomycosis in forestry workers in northern Minnesota and northern Wisconsin. Am J Med 1990;89:470–475
30. Wüthrich M, Filutowicz HI, Allen HL, Deepe GS, Klein BS. $V\beta1^+$ $J\beta1.1^+/V\alpha2^+$ $J\alpha49^+$ CD_4^+ T cells mediate resistance against infection with *Blastomyces dermatitidis.* Infect Immun 2007;75:193–200
31. Sarosi GA, Eckman MR, Davies SF, Laskey WK. Canine blastomycosis as a harbinger of human disease. Ann Intern Med 1979;91:733–735
32. Steele RW, Abernathy RA. Systemic blastomycosis in children. Pediatr Infect Dis 1983;2:304–307
33. Bradsher RW, Rice DC, Abernathy RS. Ketoconazole therapy of endemic blastomycosis. Ann Intern Med 1985;103:872–879
34. Halvorsen RA, Duncan JD, Merten DF, Gallis HA, Putman CE. Pulmonary blastomycosis. Radiology 1984;150:1–5
35. Kinasewitz GT, Penn RL, George RB. The spectrum and significance of pleural disease in blastomycosis. Chest 1984;86:580–584
36. Evans ME, Haynes JB, Atkins JB, Atkinson JB, Delvaux TC Jr, Kaiser AB. *Blastomyces dermatitidis* and the adult respiratory distress syndrome. Am Rev Respir Dis 1982;126:1099–1102
37. Meyer KC, McManus EJ, Maki DG. Overwhelming pulmonary blastomycosis associated with the adult respiratory distress syndrome. N Engl J Med 1993;329:1231–1236
38. Skillrud DM, Douglas WW. Survival in ARDS caused by blastomycosis infection. Mayo Clin Proc 1985;60:266–269
39. Maioriello RP, Merwin CF. North American blastomycosis presenting as an acute panniculitis and arthritis. Arch Dermatol 1970;102:92–96
40. Suen JY, Wetmore SJ, Wetzel WJ. Blastomycosis of the larynx. Ann Oto Rhinol Laryngol 1980;89:563–566
41. Farmer C, Stanley MW, Bardales RH, et al. Mycoses of the breast: diagnosis by fine needle aspiration. Diagn Cytopathol 1995;12:51–55
42. Pappas PG, Threlkeld MG, Bedsole GD, Cleveland KO, Gelfand MS, Dismukes WE. Blastomycosis in immunocompromised patients. Medicine 1993;72:311–325
43. Klein BS, Vergeront JM, Kaufman L, et al. Serologic tests for blastomycosis: assessment during a large point source outbreak in Wisconsin. J Infect Dis 1987;155:262–268
44. Klein BS, Jones JM. Isolation, purification, and radiolabeling of a novel 120KD surface protein on *Blastomyces dermatitidis* yeasts to detect antibody in infected patients. J Clin Invest 1990;85:152–161

45. Durkin M, Witt J, LeMonte A, Wheat B, Connolly P. Antigen assay with the potential to aid in diagnosis of blastomycosis. J Clin Microbiol 2004;42:4873–4875
46. Sarosi GA, Davies SF, Phillips JR. Self-limited blastomycosis: a report of 39 cases. Semin Respir Infect 1986;1: 40–44
47. Recht LD, Phillips JR, Eckman MR, Sarosi GA. Self-limited blastomycosis: a report of thirteen cases. Am Rev Respir Dis 1979;120:1109–1112
48. Chapman SW, Bradsher RW, Campbell GD, Pappas PG, Kauffman CA. Practice guidelines for the management of patients with blastomycosis. Clin Infect Dis 2000;30:679–683
49. Dismukes WE, Bradsher RW, Cloud GC, et al. Itraconazole therapy for blastomycosis and histoplasmosis. Am J Med 1992;93:489–497
50. Pappas PG, Bradsher RW, Chapman SW, et al. Treatment of blastomycosis with fluconazole: a pilot study. Clin Infect Dis 1995;20:267–271
51. Pappas PG, Bradsher RW, Kauffman CA, et al. Treatment of blastomycosis with higher doses of fluconazole. Clin Infect Dis 1997;25:200–205
52. Bariola JR, Perry PM, Pappas PG, Bradsher RW. Central nervous system (CNS) blastomycosis: review of recent experience. Program Abstract, Infectious Diseases Society of America 45th Annual Meeting; October 5, 2007; San Diego, CA