New Developments in Blastomycosis

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Abstract

Blastomyces dermatitidis, the etiologic agent of blastomycosis, is a thermally dimorphic fungus that grows as a filamentous mold in the environment and as budding yeast in human tissue. This pathogen is endemic to North America, particularly in the states bordering the Mississippi and Ohio rivers, the Great Lakes, and the St. Lawrence Seaway. Infection with *B. dermatitidis* causes a broad array of clinical manifestations ranging from asymptomatic infection to fulminant sepsis with acute respiratory distress syndrome and death. *B. dermatitidis* can infect almost any organ in the body, but has a predilection for lungs and skin. There have been recent advances in the understanding of the pathogenesis, diagnosis, and treatment of this fungus. The Infectious Diseases Society of America published updated guidelines in 2008 to guide clinicians in the treatment of this important pathogen.

Keywords
- blastomycosis
- *Blastomyces dermatitidis*
- amphotericin
- itraconazole

Historical Perspective

Blastomycosis was first described at a dermatology conference in 1894 by Thomas C. Gilchrist and in 1898, the pathologic agent was named *Blastomyces dermatitidis*.[1,2] In 1907, Walter W. Hamburger discovered that in response to changes in temperature, *B. dermatitidis* switched between mold and yeast forms.[3] In 1951, Drs. Schwarz and Baum reported that the lower respiratory tract, not the skin, was the primary portal of entry for *B. dermatitidis*.[4] In the mid-1980s, *B. dermatitidis* was successfully isolated from the soil in association with a large outbreak in northern Wisconsin.[5] Since the 1990s, several important advances at the molecular level have enhanced the understanding of how *B. dermatitidis* causes clinical disease. This includes the identification of an essential virulence factor, *Blastomyces* adhesion-1 (BAD-1; formerly WI-1), and a dimorphism-regulating kinase-1 (*DRK1*) critical for the morphologic switch from mold to yeast. In 2009, the complete genome of *B. dermatitidis* was sequenced. In 2013, genome-wide in vivo transcriptional profiling of *B. dermatitidis* yeast during experimental murine infection was performed to identify genes and gene pathways important for pathogenesis.[6]

Mycology

B. dermatitidis is a thermally dimorphic fungus that grows as yeast at 37°C and as hyphae at 22 to 25°C (►**Fig. 1**). The yeast form, which is found in human tissue, is 8 to 20 μM in diameter and is characterized by broad-based budding and a doubly refractile cell wall.[7] Uncommonly, giant yeast forms (28–40 μM) can be observed in clinical specimens and confused with *Coccidioides* spp.[8,9] At room temperature, *B. dermatitidis* grows as septate hyphae (1–2 μM diameter) that produce asexual spores (4–5 μM diameter) called conidia.[7,10] In contrast to distinctive appearance of yeast, hyphal morphology is not specific for *B. dermatitidis* and requires molecular confirmation for definitive identification.

Multilocus microsatellite typing of 112 *B. dermatitidis* isolates obtained from humans, animals, and soil demonstrated genetic heterogeneity and that *Blastomyces* can be divided into two distinct groups.[11] A subsequent analysis of 227 human *B. dermatitidis* isolates suggested group 1 isolates were more likely to be associated with disseminated disease and cause outbreaks, whereas group 2 isolates tended to cause pneumonia.[12] Moreover, recent phylogenetic analysis using genealogical concordance phylogenetic species recognition (GCPSR) suggested that the *Blastomyces* genus might

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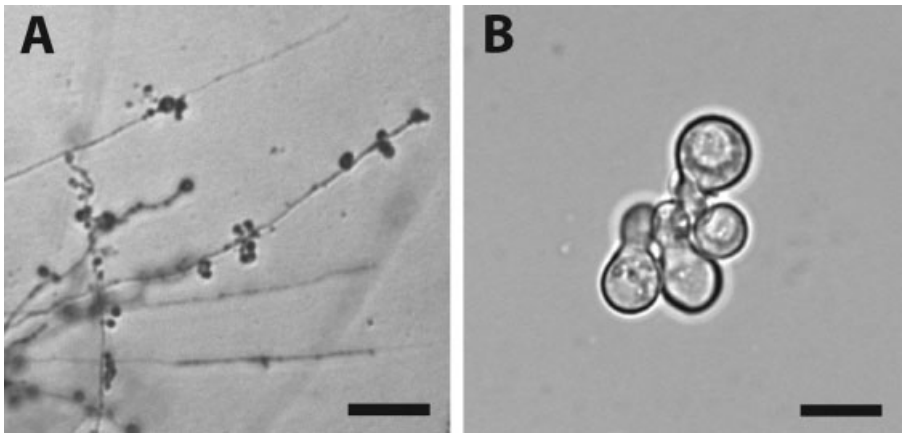

Fig. 1 *Blastomyces dermatitidis* mold and yeast. (**A**) Hyphae with conidia at 22°C. (B) Broad-based budding yeast at 37°C. Scale bar is 10 μm. (Reprinted with permission from Gauthier.[60])

have two distinct species, *B. dermatitidis* and *B. gilchristii* sp. nov.[13]

Geographic Distribution and Epidemiology

The geographic range of *B. dermatitidis* in North America is primarily limited to the Midwest, south-central, and southeastern regions of the United States and four Canadian provinces (►**Fig. 2**). This includes the Ohio–Mississippi and Saint Lawrence River valleys as well as the Great Lakes region. Within the endemic region, *B. dermatitidis* is not uniformly distributed, rather it is found in an ecological niche characterized by forested, sandy soils with an acidic pH and decaying vegetation or rotting wood that are located by water sources (e.g., rivers, lakes).[5] Similar to other fungi such as *Histoplasma capsulatum* and *Cryptococcus* spp., *B. dermatitidis* can grow in bird guano. Human activities that disrupt soil (e.g., home and road construction, exploration of beaver dams or underground forts, use of a community compost pile, hunting, clearing brush, or cutting trees) or involve water (e.g., canoeing, boating, fishing) have been associated with the acquisition of *B. dermatitidis* as well as outbreaks of disease (►**Table 1**).[5,14–28]

Epidemiologic knowledge about *B. dermatitidis* is limited because the data are based on passive surveillance and retrospective studies. Blastomycosis is reportable in six states (WI, MN, MO, AK, LA, and MS) and two provinces (Ontario, Manitoba). Serological testing has insufficient sensitivity and no skin test exists to survey large populations. Moreover, approximately 50% infected persons develop subclinical or asymptomatic illness that remains undiagnosed.[5] Thus, epidemiologic data are limited to clinically apparent infections that are diagnosed and reported. Although an underestimate, the reported annual incidence ranges from 0.2 to 1.94 cases per 100,000 persons.[29–36] Certain geographic locations are considered

Fig. 2 Geographic distribution of *B. dermatitidis* in the United States and Canada. (Reprinted with permission from Gauthier.[60])

Table 1 Outbreaks of human blastomycosis

State	Years(s)	Persons infected	Outbreak source	Reference
North Carolina	1953–1954	11	Unknown	Smith et al (1955)
Minnesota	1972	12	Cabin construction	Tosh et al (1974)
North Carolina	1975	5	Harvest at peanut farm	CDC (1976)
Illinois	1974–1975	5	Apartment complex construction	Kitchen et al (1977)
Wisconsin	1979	8	Canoeing	Cockerill et al (1984)
Wisconsin	1984	48	Visiting an abandoned beaver lodge	Klein et al (1986)
Virginia	1984	4	Raccoon hunting	Armstrong et al (1987)
Wisconsin	1985	14	Underground timber fort; fishing	Klein et al (1987)
Wisconsin	1988	32	Hotel construction	Baumgardner and Burdick (1991)
Tennessee	1989	3	Construction at a rayon factory	Frye and Seifer (1991)
Wisconsin	1989–1990	8	Unknown	Proctor et al (2002)
Colorado	1998	2	Prairie dog relocation	De Groote et al (2000)
Wisconsin	1998–2000	9	Likely related to construction/excavation	Baumgardner et al(2002)
North Carolina	2001–2002	8	Likely related to construction projects	MacDonald et al (2006)
Wisconsin	2006	21	Community yard waste site	Pfister et al (2011)
Wisconsin	2009–2010	55	Unknown	Roy et al (2013)

hyperendemic for blastomycosis including Kenora, Ontario (117.2 human cases/100,000 population); Vilas County, WI (40.4/100,000); Eagle River, WI (101.3/100,000); Washington Parish, LA (6.8/100,000); and central/south-central Mississippi ($>$ 5/100,000).[37–40] From 2007 to 2011, a total of 4,688 patients in 46 states were hospitalized for blastomycosis.[41] The majority of these patients were hospitalized in the state in which they resided; however, 8% of patients were admitted to hospitals outside of the endemic region.[41] Unlike most human pathogenic fungi, *B. dermatitidis* can infect persons with intact or impaired immune systems. Immunocompromised patients at risk for blastomycosis include those who have undergone solid-organ transplantation (SOT), received tumor necrosis factor-α (TNF-α) inhibitor therapy, have underlying malignancy, or develop HIV/AIDS (human immunodeficiency virus/acquired immunodeficiency syndrome).[42–45] Blastomycosis occurs in less than 0.2% of SOT recipients, has an onset between 0.4 and 250 months after transplantation, and can be associated with opportunistic pathogens, especially cytomegalovirus.[42,43,46] When compared with histoplasmosis or coccidioidomycosis, the frequency of blastomycosis in persons with HIV/AIDS or immunosuppressed by TNF-α inhibitor therapy is lower.[44]

Autochthonous cases of culture-proven blastomycosis have been reported from Africa and India.[47–52] Approximately 100 patients with blastomycosis have been described from 18 African countries, whereas less than 10 confirmed autochthonous cases have been reported from India.[47–52] The limited number of human and animal cases has precluded accurate discernment of the geographic distribution or ecological niche within Africa and India.

Pathogenesis

Overview

B. dermatitidis is a primary fungal pathogen because it can infect persons with normal or impaired immune defenses. Features that facilitate growth of dimorphic fungi in human tissue include the production of small-sized conidia that can penetrate deep into the respiratory tree, ability to grow at 37°C (i.e., thermotolerance), conversion to yeast morphology, expression of yeast-phase–specific virulence factors, and evasion of host immune cells.[53,54]

The Phase Transition

The conversion between hyphal and yeast morphologies, known as the phase transition, is essential for the pathogenesis for all thermally dimorphic fungi including *B. dermatitidis*. In the soil (22–25°C), *B. dermatitidis* grows as filamentous hyphae that produce conidia (asexual spores). Following soil disruption from human activities (e.g., construction), conidia and hyphal fragments are aerosolized and when inhaled into the lungs of a human host (37°C) convert into budding yeast that cause pneumonia. The predominant stimulus that induces the morphologic switch between hyphal and yeast forms is temperature. Recent investigation has demonstrated that conversion to yeast is accelerated following phagocytosis of *B. dermatitidis* spores by alveolar macrophages.[55] In addition to intracellular spore germination, yeasts are able to survive and replicate within macrophages during the early stages of infection.[55] Thus, *B.* dermatitidis exhibits an intracellular lifestyle, which is similar to other dimorphic pathogens including *H. capsulatum*, *Coccidioides* spp., and *Paracoccidioides brasiliensis*.

Previously, *B. dermatitidis* was thought to be an extracellular pathogen. Other stimuli such as estradiol, which affects the phase transition in *P. brasiliensis* or growth of *Coccidioides* spp., has minimal effect on *B. dermatitidis* morphology.[56] The development of molecular tools to manipulate gene transcription in *B. dermatitidis* has facilitated the discovery of genes important for the phase transition and virulence including *DRK1* (dimorphism-regulating kinase), *SREB* (siderophore biosynthesis repressor in *Blastomyces*), *NGT1* and *NGT2* (*N*-acetylglucosamine transporters), and *BAD1* (*Blastomyces* adhesin-1; formerly WI-1).

DRK1 encodes a histidine kinase that is essential for the conversion from hyphae to yeast following an increase in temperature from 22 to 37°C.[53] Deletion of *DRK1* in *B. dermatitidis* and *H. capsulatum* results in fungal cells that grow as hyphae (instead of yeast) at 37°C and fail to express yeast-phase–specific virulence factors (*BAD1* for *B. dermatitidis*; *CBP1* for *H. capsulatum*).[53] Moreover, these cells fail to produce conidia at 22°C and have altered distribution of cell wall carbohydrates including α-(1,3)-glucan and chitin.[53] In a murine model of pulmonary infection, *B. dermatitidis* and *H. capsulatum* strains with reduced *DRK1* transcription were avirulent.[53] This provided genetic proof that the morphologic switch is essential for virulence. *DRK1* is conserved in the dimorphic fungi with homologs identified in *Sporothrix schenckii* and *Penicillium marneffei*.[57,58] *DRK1* transcript is 24-fold more abundant in *S. schenckii* yeast than hyphae.[57] In *P. marneffei*, the *DRK1* homolog, *DRKA*, is important for germinating conidia to develop into the pathogenic yeast within macrophages at 37°C.[58]

Over the past decade, there has been increasing interest in understanding the yeast-to-hyphal transition following a drop in temperature from 37 to 22–25°C. Growth in the hyphal phase is postulated to promote environmental survival, transmission to new hosts through spores, and genetic diversity by sexual reproduction.[59,60] In *B. dermatitidis*, the SREB transcription factor and *N*-acetylglucosamine transporters influence the morphologic shift to hyphal growth.[61,62] *SREB* encodes a GATA transcription factor that promotes the conversion from yeast to mold at 22°C and regulates the biosynthesis of specialized iron gathering molecules (i.e., siderophores).[61] GATA transcription factors bind to GATA binding sites (e.g., A/T-GATA-A/G, ATC-A/T-GATA-A/G) in the promoters of target genes to induce or repress transcription. Deletion of *SREB* results in yeast cells that are unable to complete the conversion from yeast to mold after a drop in temperature and fail to accumulate substantial biomass at 22°C. The morphologic and growth defects are independent of exogenous iron concentrations. *SREB* null mutant (*SREB*Δ) cells at 22°C are viable and convert to yeast when temperature is increased to 37°C.[61] RNA interference targeting *SRE1*, a *SREB* homolog, resulted in *H. capsulatum* cells that exhibited similar defects as *SREB*Δ.[63] In addition to *SREB* (and *SRE1*), the morphologic switch is also influenced by exogenous *N*-acetylglucosamine (GlcNAc), which accelerates the transition from yeast to hyphae; this is mediated by *NGT1* and *NGT2* transmembrane transporters.[62]

BAD1 and Immune Evasion

B. dermatitidis upregulates the expression of BAD1 (formerly WI-1), which is an essential yeast-phase–specific virulence factor important for adhesion and immune evasion.[54] BAD1 is secreted extracellularly and can either bind to the yeast cell wall via interaction with chitin or remain soluble. An individual yeast cell is estimated to have 4.7×10^6 BAD1 molecules on its surface; BAD1 is not found on the cell surface of hyphae or conidia.[64,65] The 120-kDa BAD1 protein is characterized by a core region with 41 tandem repeats (10 degenerate, 31 highly conserved) of a 24 amino acid sequence, an N-terminus with Cardin-Weintraub motif, and a C-terminus with an epidermal growth factor (EGF)-like domain.[66] Each tandem repeat contains a tryptophan-rich motif that binds heparan sulfate, but not laminin or collagen.[66] Thus, BAD1 functions as a cellular adhesin to bind yeast cells to host tissue. Moreover, both bound and soluble forms of BAD1 bind macrophage receptors (CD14, CR3) to depress TNF-α production by innate immune cells (macrophages, neutrophils) in a transforming growth factor-β (TGF-β)-dependent and -independent fashion, respectively.[67–69] TNF-α is an important cytokine that contributes to host defense against *B. dermatitidis* infection, and neutralization of TNF-α in mice results in progressive lung infection.[68] In addition to its effects on innate immune cells, BAD1 inhibits $CD4^+$ T lymphocyte activation, which results in reduced interleukin-17 (IL-17) and interferon-gamma (INF-γ).[66] Deletion of *BAD1* renders *B. dermatitidis* avirulent in a murine model of pulmonary infection.[54] The lungs of mice infected with *BAD1* null (*BAD1*Δ) strains appear grossly normal and contain few granulomas.[54] In addition to facilitating adhesion and immune evasion, BAD1 can bind calcium via its tandem repeats and block deposition of complement (C3) on the yeast cell wall.[70,71] The biological impact of BAD1 calcium binding is unclear, but it appears to facilitate attachment of BAD1 to the yeast cell surface.[70]

In addition to BAD1, changes in cell wall composition associated with the morphologic switch may contribute to immune evasion. During the transition from hyphae to yeast, cell wall α-(1,3)-glucan increases and β-(1,3)-glucan decreases. β-(1,3)-glucan represents 40 to 50% of the cell wall glucan in hyphae, but less than 5% in yeast.[72] Moreover, exposed β-(1,3)-glucan molecules bind mannose-binding lectins (MBL-A, MBL-C).[73] The reduction of β-(1,3)-glucan and its binding to MBLs may impede recognition of β-(1,3)-glucan by dectin-1 receptors on innate immune cells. Clinically, the reduced amount of β-glucan in the yeast cell wall renders the (1,3)-β-D-glucan diagnostic test unreliable and echinocandins ineffective for persons infected with *B. dermatitidis*.[40,74]

Host Response

Innate and adaptive immune responses are important for combating *B. dermatitidis* infection. In contrast, antibody-mediated immunity is dispensable. In the lung, alveolar macrophages and neutrophils can kill conidia; however, under experimental conditions, not all conidia are killed.[75,76] Conidia that survive the innate immune defenses can germinate as yeast.[55] Yeasts are more difficult to kill by host cells

because they inhibit host cell cytokine production, impair $CD4^+$ T lymphocyte activation, are relatively resistant to reactive oxygen species (ROS), and actively suppress nitric oxide (NO) production.[66,69,77,78] The adaptive immune response involves Th1 and Th17 T-lymphocyte activation of macrophage fungicidal activity.[79,80] Following recovery from blastomycosis, patients develop cell-mediated immunity that can last for at least 2 years.[81]

Clinical Presentation of Human Disease

The clinical manifestations of infection with *B. dermatitidis* can be quite variable, from asymptomatic infection to fulminant sepsis with acute respiratory distress syndrome (ARDS). *B. dermatitidis* can infect nearly every organ of the body including the eye, endocrine glands, muscles, peritoneum, and breast.[82,83] It is because of the great variety of clinical manifestations that *B. dermatitidis* infection has been called "the great pretender." As noted previously, more than half of infected patients are asymptomatic.[5,84] Of the patients who do have symptoms, the majority present with pulmonary symptoms and up to 25 to 40% develop disseminated disease.[40] Common end-organ locations of extrapulmonary infection include the skin, bone, genitourinary tract, and central nervous system (CNS). Extrapulmonary manifestations can occur after a significant delay from the primary pulmonary infection, so much so that the remnants of the prior pulmonary infection are no longer present. It is also not uncommon for patients to manifest more than one location of infection at the time of presentation such as simultaneous pulmonary and cutaneous infection.[84]

Pulmonary Blastomycosis

Pulmonary infection is reported in more than 90% of patients with documented blastomycosis.[85] Pulmonary manifestations range from subclinical pneumonia to acute fulminant presentation with ARDS. In one large series of 118 people with pulmonary blastomycosis, cough (90%) was the most common symptom, followed by fever (75%), night sweats (68%), weight loss (68%), chest pain (63%), dyspnea (54%), aches or myalgias (50%), and hemoptysis (18%).[86]

Acute Pneumonia

The symptoms of acute pulmonary blastomycosis may be mild and are often mistaken for other self-limited pulmonary infection such as viral or community-acquired bacterial pneumonia. The majority of patients present with cough (productive or nonproductive) and fever. Other symptoms include headache, chills, dyspnea, chest pain, and malaise. Symptoms typically resolve in 2 to 4 weeks.[5,85,87,88] Given the brief self-limited nature of most acute pneumonias, diagnosis is rarely made in the absence of an outbreak investigation or epidemiologic study. Despite the potential for spontaneous resolution of infection, experts agree that all diagnosed cases of blastomycosis should be treated because of the risk of progressive and disseminated infection.[40]

Chronic Pneumonia

Unrecognized or untreated acute pulmonary blastomycosis can progress to chronic pneumonia. Symptoms include persistent cough with or without hemoptysis, fever, night sweats, poor appetite, weight loss, and malaise. Radiographic presentations are heterogeneous and can mimic malignancy (e.g., nodules or masses) or mycobacterial infection (e.g., cavitation). Again because this clinical picture is nonspecific, blastomycosis is frequently not clinically suspected, unless the patient has other findings such as skin lesions or has failed to respond to antibacterial therapy.[89,90] Thus, symptoms are often present for several months prior to diagnosis. Chronic pulmonary blastomycosis is nearly always progressive in the absence of specific antifungal treatment.

Acute Respiratory Distress Syndrome

Patients with acute pulmonary blastomycosis can present with a rapidly progressive infection resulting in respiratory failure or ARDS. Initially, patients may be misdiagnosed with community-acquired pneumonia that becomes fulminant in 5 to 7 days, or may present in florid septic shock that is clinically indistinguishable from bacterial sepsis and is often fatal. In a recent study of patients with pulmonary blastomycosis who required hospitalization, 10% patients received some care in the intensive care unit (ICU). More than one-third of all patients treated for respiratory failure in ICU died, and death usually occurred within several days.[91] This presentation is seen more commonly in patients with defective cell-mediated immunity such as those with hematological malignancy, SOT, or AIDS but also occurs in patients who were previously healthy.[42,92–94] In two-thirds of patients who died of ARDS caused by blastomycosis, the diagnosis was either not suspected or considered only after the patient was moribund.[95] Thus, early diagnosis of blastomycosis in patients with ARDS is critical for decreasing mortality.

Disseminated Disease

B. dermatitidis may disseminate to any organ in the body. Early studies of blastomycosis conducted prior to effective antifungal therapy reported high rates of dissemination, but more recent studies have reported dissemination rates of 20 to 25%.[33,88,95] Nearly all cases of extrapulmonary blastomycosis represent disseminated disease and should be managed as such, regardless of the number of organs involved at the time of presentation.

Cutaneous Blastomycosis

The skin is the most common extrapulmonary site of infection and skin involvement occurs in as many as 60% of those with disseminated infection.[96,97] Patients typically present with ulcerated lesions on any skin surface but exposed areas of the head, neck, or extremities are most common (►**Fig. 3**). Ulcers are characterized by well-defined edges with heaped-up borders. Other cutaneous manifestations include violaceous nodules, plaques abscesses, large verrucous lesions, or keloids.[96–99] Cutaneous infection is rarely the result of direct inoculation (e.g., penetrating trauma, accidental needle stick

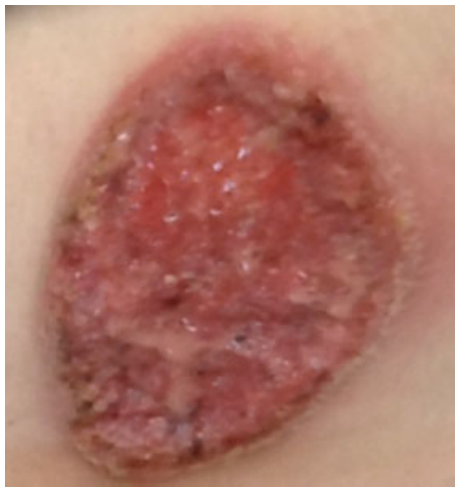

Fig. 3 Cutaneous ulcer caused by blastomycosis. Photo courtesy of Nick Haun, MD.

in laboratory workers). Moreover, disseminated disease from cutaneous inoculation has been reported.[100]

Osseous Blastomycosis

Blastomycosis has a known predilection for bone involvement. Osseous lesions are painful and often associated with draining sinus tracts. Long bones of the legs are commonly affected, and can be complicated by extension into the joint space resulting in septic arthritis. Vertebral infection represents the second most common osseous site of involvement and may clinically resemble Pott's disease. Complications of vertebral osteomyelitis include compression fractures and extension into the soft tissue resulting in paravertebral and psoas abscesses.[101] A recent case series noted that 12 of 14 patients with osseous blastomycosis were initially thought to represent malignant osseous tumors, and therefore the authors advocated for intraoperative histopathologic analysis by frozen section to reduce morbidity associated with resection of the involved areas, which could otherwise be treated with antifungal chemotherapy with better preservation of function.[102,103]

Genitourinary

Dissemination of *B. dermatitidis* to the genitourinary system is uncommon. In men, the most common sites of involvement include the prostate and epididymis. In several large case series, the prostate involvement was reported in less than 10% of patients.[29] Patients with prostatitis have urinary obstruction, dysuria, perineal or suprapubic discomfort, and may have a tender prostatic mass on examination.[104,105] Symptoms of epididymitis include testicular enlargement and pain. In women, dissemination to the genitourinary system can result in tubo-ovarian abscess and pyogranulomatous inflammation of the endometrium. Tubo-ovarian abscesses can be complicated by extension of *B. dermatitidis* into the abdominopelvic cavity resulting peritoneal and omental nodules along with new onset ascites.[83]

Central Nervous System

CNS blastomycosis is estimated to occur in less than 5 to 10% of immune competent patients with disseminated blastomycosis.[106] Dissemination to the CNS results from hematogenous spread or direct invasion from untreated osteomyelitis involving the skull.[106,107] *B. dermatitidis* may infect any part of the CNS, but most commonly causes meningitis or brain abscess. Symptoms include headache, focal neurologic defects, confusion, altered vision, and seizures. In patients with meningitis, cerebrospinal fluid (CSF) analysis demonstrates neutrophilic or lymphocytic pleocytosis along with elevated protein and hypoglycorrhachia. Less than half of patients have positive CSF cultures; however, the *B. dermatitidis* antigen test on CSF may facilitate diagnosis.[108,109]

Blastomycosis in Immunocompromised Hosts

HIV/AIDS

Patients with AIDS have been shown to have an increased risk of developing symptomatic disease after exposure to *B. dermatitidis*. Up to 25% of AIDS-related cases of blastomycosis can be caused by reactivation of a previously dormant infection.[110] Because AIDS is associated with defective cell-mediated immunity, the infection is more likely to elude initial host attempts to contain the infection. Patients with AIDS therefore manifest disease differently than do most immunocompetent hosts. For example, there is an increase in disseminated, miliary, and fatal disease. Additionally, CNS involvement is common in this population and is estimated to occur in up to 40% of cases. ARDS and miliary disease are seen in nearly 20% of patients with AIDS at the time of diagnosis.[110–112]

Solid-Organ Transplant

Transplant-associated blastomycosis typically presents as pneumonia and it is frequently complicated by severe disease including respiratory failure and ARDS.[42,43,113,114] The development of ARDS increases mortality from 33–38% to 67%.[42,43] Extrapulmonary disease occurs in 33 to 50% and most commonly affects the skin. In contrast to patients with AIDS, dissemination of *B. dermatitidis* to the CNS is uncommon in solid-organ transplant recipients.[42,43]

Patients Receiving TNF Inhibitors

There is a paucity of clinical data on patients who developed blastomycosis while receiving TNF inhibitor therapy; however, blastomycosis was listed in the warning issued by the Food Drug Administration on September 4, 2008, regarding increased risk of fulminant infections with the endemic mycosis in patients receiving TNF inhibitor therapy.[44,115]

Blastomycosis in Pregnancy

Blastomycosis in pregnancy is rare and clinical information is limited to case reports.[116–119] Infection is most commonly diagnosed in the second or third trimester and disseminated disease occurs in 62% of patients.[116] Although *B. dermatitidis*

yeasts have been identified in the placenta of an infected patient, the frequency of placental dissemination is unknown.[116,117] There is potential for the transmission of blastomycosis to the neonate during the peripartum period; however, the underlying pathogenesis is unclear and may involve either transplacental transmission or aspiration of infected vaginal secretions during delivery.[116–119]

Diagnosis

Owing to the nonspecific clinical and radiographic manifestations, a delay in the diagnosis as well as initiation of therapy for blastomycosis is common. Even in hyperendemic areas, as few as 5% of patients are correctly diagnosed at initial presentation and diagnostic delays longer than 1 month can occur in more than 50% of patients.[88,89,95] Coexisting pulmonary and cutaneous involvement is a clinical clue that can facilitate the recognition of blastomycosis. In addition, blastomycosis in a family pet such as a dog suggests a common source of exposure.[18] A detailed history regarding potential exposures such as place of residence, travel, hobbies, recent home remodeling, nearby road construction, use of a wood burning stove, or community compost pile should be obtained in patients with pneumonia. This may facilitate the diagnosis of blastomycosis, which requires a high index of clinical suspicion.

The most expeditious method to diagnose blastomycosis remains examination of stained clinical specimens. Sputum can be stained with 10% potassium hydroxide or calcofluor white, whereas tissue samples can be stained with Gomori methenamine silver (GMS) or periodic acid-Schiff (PAS).[120] *B. dermatitidis* yeasts are difficult to visualize with Gram or hematoxylin and eosin (H&E) stains. The characteristic broad-based budding pattern of yeast can lead to presumptive diagnosis before culture and nonculture diagnostic test results are available. This strategy correlated well with culture results in a recent review which demonstrated positive histopathology in nearly 80% of culture-confirmed cases.[121] Despite the utility of fungal-specific stains for diagnostic testing, this technique is often underutilized.[122] In tissue specimens, the presence of neutrophils with granulomatous inflammation should prompt a detailed examination for broad-based budding yeast.

Culture of *B. dermatitidis* provides a definitive diagnosis. The yield on culture from bronchoscopy is excellent with cultures of bronchial secretions being positive in 100% and bronchoalveolar lavage (BAL) fluid in 67% of patients.[122] Even when the specimens were obtained by noninvasive methods, sputum cultures grew *B. dermatitidis* in 86% of patients.[122] Culture requires the use of specialized media such as Sabouraud dextrose agar, potato dextrose agar, and brain–heart infusion media.[120] Most clinical laboratories incubate fungal cultures at 25 to 30°C, which results in growth of *B. dermatitidis* as a mold. Although highly specific, growth of *B. dermatitidis* in culture is slow and takes on average 5 to 14 days before fungal colonies can be visualized; however, if there is a low burden of infection, growth can take longer than 4 weeks.[120]

Molecular diagnostic systems have been developed to facilitate the rapid identification of *B. dermatitidis* from clinical specimens including culture. Currently, a chemiluminescent DNA probe assay is the most frequently used molecular test to confirm the growth of *B. dermatitidis* in culture; however, this test cross-reacts with *P. brasiliensis*.[120] In addition, real-time polymerase chain reaction (PCR) assays targeting *BAD1* and *DRK1* for amplification have been developed; however, they are not commercially available.[123,124]

Serological Testing

Antibody testing by complement fixation or immunodiffusion is not clinically useful because of poor sensitivity and specificity.[125] Recently, a newer antibody-based assay that uses microplates coated with the *B. dermatitidis* BAD1 protein has enhanced sensitivity and specificity of 87% and 94–99% in patients with active blastomycosis.[126] In contrast, the sensitivity of the immunodiffusion assay is 15%.[125,126] Moreover, this diagnostic assay can distinguish patients with blastomycosis from histoplasmosis. The combination of the BAD1 antibody test with the *Blastomyces* antigen assay can increase diagnostic sensitivity to 97%.[126]

Antigen Testing

In 2004, an antigen assay against a galactomannan component of the *B. dermatitidis* cell wall was developed and can be used to test urine, serum, BAL fluid, and CSF. The sensitivity of the urine antigen in patients with proven disease is 85.1 to 92.9% with a specificity of 79.3%.[127,128] Sensitivity of the urine antigen test can be enhanced by concentration of the urine, whereas the serum antigen test has improved sensitivity when blood samples are treated with EDTA to dissociate immune complexes.[127] False-positive tests can occur in patients with other fungal infections such as histoplasmosis, paracoccidioidomycosis, and penicilliosis. However, the clinical impact of a false-positive antigen test is mitigated by the fact that initial management with these organisms is similar. Therefore, a positive *Blastomyces* antigen test would still facilitate early initiation of appropriate antifungal therapy.[129,130] Antigen testing has been reported to enhance the diagnosis of blastomycosis when testing is done on BAL fluid and or CSF.[108,131,132] Two patients have recently been reported to have "false-positive" BAL Platelia Aspergillus enzyme immunoassay tests. This phenomenon has been previously noted with histoplasmosis and this test may suggest the diagnosis as well as prompt initiation of antifungal therapy.[133,134]

Radiographic Presentation

No pathognomonic radiographic imaging patterns have been reported for pulmonary blastomycosis. The radiographic appearance is not specific and may mimic bacterial pneumonia, tuberculosis, or lung cancer. Classic radiographic findings for pulmonary blastomycosis include diffuse or focal air-space disease (i.e., consolidation), nodular masses, interstitial disease, cavitation, and miliary disease (►**Fig. 4**). Air-space disease is the most common radiographic pattern and can be present on chest radiographs in patients without

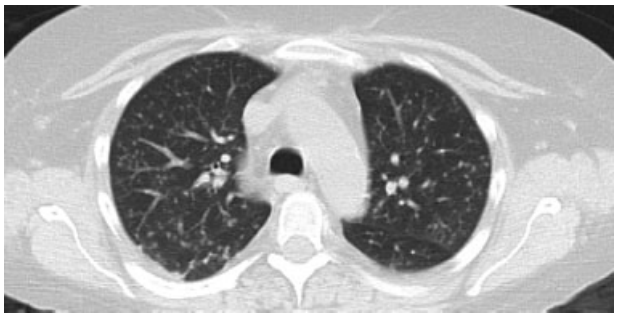

Fig. 4 Miliary pulmonary disease.

pulmonary symptoms.[135] The next most frequent radiographic presentation is either single or multiple mass lesions, which can mimic malignancy. Cavitary disease is associated with chronic blastomycosis and can be mistaken for tuberculosis. In contrast to histoplasmosis, hilar and mediastinal adenopathy as well as calcified lung lesions are uncommon in patients with blastomycosis. Pleural involvement and effusion are also rare.[135–138] For patients with CNS blastomycosis, MRI imaging is the preferred diagnostic technique and nearly all patients with CNS involvement have abnormal imaging findings.[108,109]

Treatment

In 2008, Infectious Diseases Society of America published guidelines for the diagnosis and treatment of blastomycosis.[40] Treatment recommendations are based on the site and severity of infection, immune status of the host, and pregnancy (►**Table 2**). Prior to starting amphotericin B (AmB) or azole-base therapy, baseline laboratory testing of hepatic and renal function along with a thorough evaluation for potential drug–drug interactions should be performed. All women of childbearing age must be tested for pregnancy because prolonged use of high-dose azole antifungals can induce fetal deformities or cause spontaneous abortion.[139–141]

Itraconazole

Itraconazole has demonstrated excellent efficacy and tolerability and is the first-line agent for the treatment of mild to moderate, non-CNS blastomycosis, and for step-down therapy after treatment with AmB.[40,142] Oral administration of itraconazole results in variable serum concentrations and the use of therapeutic drug monitoring is necessary to ensure appropriate dosing. Serum concentrations are approximately 30% higher with use of the solution formulation than with the capsule formulation, but wide interpatient variability is evident with any of the formulations. Itraconazole capsules should be taken with food and an acidic beverage (e.g., orange juice, soda). Gastric acidity is required for optimal absorption of the capsule formulation. In contrast, itraconazole solution can be taken without food and does not require gastric acidity for absorption. Thus, in patients who are taking H_2-blockers or proton-pump inhibitors, itraconazole solution is the preferred formulation. Itraconazole concentrations in serum should be determined after 2 weeks of therapy, which is when a steady state concentration is reached. Because of the long half-life of itraconazole (~24 hours), serum levels can be obtained independent of the time of drug administration. A total serum level of >1.0 μg/mL is recommended (both itraconazole and hydroxy-itraconazole levels are added together). Serum levels >10.0 μg/mL are unnecessary and increase the risk for drug toxicity. In addition to therapeutic drug monitoring, liver function tests should be obtained at baseline, 2 and 4 weeks into therapy, and then every 3 months.[40]

Amphotericin B Formulations

AmB products are recommended for all serious infections with *B. dermatitidis*, which includes patients with underlying immunocompromise, severe pulmonary or disseminated infection, and CNS involvement. In addition, AmB formulations are the drug of choice for neonates and pregnant women. Large case series have reported excellent clinical response to AmB products with clinical cure rates between 77 and 91%.[40,88] Despite the well-demonstrated efficacy, the use of AmB is associated with significant cumulative toxicity. Nephrotoxicity is the most treatment-limiting toxicity and occurs in more than 30% of treated patients.[143] Other adverse effects include nausea, vomiting, rigors, fever, hypertension or hypotension, electrolyte abnormalities, hepatotoxicity, and hypoxia. Renal toxicity is mitigated by saline loading patients, avoiding diuretics and other nephrotoxic agents. Careful attention must be paid to electrolyte management because of the frequent occurrence of hypokalemia and hypomagnesemia.

Lipid formulations of AmB (e.g., liposomal amphotericin, AmB lipid complex, and AmB colloidal dispersion) have largely replaced AmB deoxycholate in the treatment of blastomycosis, mainly because of a lower incidence of toxicity. Although lipid formations have not been directly compared with AmB deoxycholate in patients with blastomycosis, a study in AIDS patients with disseminated histoplasmosis demonstrated improved outcomes for those treated with liposomal AmB versus AmB deoxycholate.[144] At least one case report has described the successful use of continuous infusion AmB deoxycholate in a patient with blastomycosis who was failing therapy with liposomal AmB.[145] The authors postulated that although lipid formulations produce much higher drug concentrations than conventional AmB, they might be physiologically less active while bound to plasma proteins or contained within liposomes. The role of continuous infusion AmB deoxycholate represents an intriguing area of research in blastomycosis treatment.

New Triazoles

The new triazoles, voriconazole and posaconazole, have been demonstrated to have excellent in vivo and in vitro activity against *B. dermatitidis*.[146–148] There have been several reports of successful use of voriconazole for the treatment of blastomycosis.[42,108,149,150] Owing to its excellent CNS penetration, it has been used most frequently to treat CNS disease.[108,149–151] Use of posaconazole for the treatment of

Table 2 Summary of clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America

Site of infection	Disease severity	Initial therapy	Step-down therapy
Pulmonary blastomycosis	Mild to moderate	Oral itraconazole 200 mg 3 times per day for 3 d and then once or twice per day for 6–12 mo[a]	N/A
	Moderately severe to severe	Lipid formulation of AmB 3–5 mg/kg per day or AmB deoxycholate 0.7–1 mg/kg per day for 1–2 wk or until improvement is noted	Oral itraconazole 200 mg 3 times per day for 3 d and then 200 mg twice per day for 6–12 mo[a]
Disseminated extrapulmonary blastomycosis	Mild to moderate	Oral itraconazole 200 mg 3 times per day for 3 d and then once or twice per day for 6–12 mo[a,b]	N/A
	Moderately severe to severe	Lipid formulation AmB 3–5 mg/kg per day, or AmB deoxycholate 0.7–1 mg/kg per day for 1–2 wk or until improvement is noted	Oral itraconazole 200 mg 3 times per day for 3 d and then 200 mg twice per day for a total of at least 12 mo[a,b]
CNS disease		Lipid formulation AmB 5 mg/kg per day for 4–6 wk	Possible options include Fluconazole (800 mg per day) Itraconazole (200 mg 2 or 3 times per day Voriconazole (200–400 mg twice per day) for at least 12 months and until resolution of CSF abnormalities
Immunocompromised patients		Lipid formulation AmB 3–5 mg/kg per day or AmB deoxycholate 0.7–1 mg/kg per day for 1–2 wk or until improvement is noted	Oral itraconazole, 200 mg 3 times daily for 3 d and then 200 mg twice daily for a total of 12 mo[a,c]
Pregnant women	Any	Lipid formulation AmB 3–5 mg/kg per day	Azoles should be avoided because of risks for teratogenicity and spontaneous abortion
Newborn	Any	AmB deoxycholate 1.0 mg/kg per day	N/A
Children	Mild to moderate	Oral itraconazole 10 mg/kg per day (maximum of 400 mg/d) for 6–12 mo[a]	N/A
	Severe	AmB deoxycholate 0.7–1.0 mg/kg per day or lipid formulation AmB, at a dosage of 3–5 mg/kg per day until improvement	Oral itraconazole 10 mg/kg per day (up to 400 mg/d) as step-down therapy for a total of 12 mo[a]

Abbreviations: CNS, central nervous system; N/A, not applicable.
[a]Therapeutic drug monitoring of serum itraconazole levels is required.
[b]Patients with osteoarticular blastomycosis should receive a total of at least 12 months of antifungal therapy.
[c]Life-long suppressive therapy with oral itraconazole, 200 mg/day 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.

blastomycosis has also recently been reported.[152,153] Voriconazole should be taken without food to optimize absorption. In contrast, the liquid formulation of posaconazole should be administered with a high-fat meal. The absorption of the new tablet formulation of posaconazole is not affected by food or administration of gastric acid inhibitors (e.g., H_2-blockers, proton-pump inhibitors). Similar to itraconazole, therapeutic drug monitoring along with periodic assessment of liver

function tests is needed for patients treated with voriconazole and posaconazole.[154] The goal serum trough concentration for voriconazole is > 1 and < 5.5 μg/mL. The optimal serum concentration that correlates with clinical efficacy for posaconazole is unclear, but most experts recommend serum trough levels > 0.5 to 1 μg/mL.[154] Isavuconazole and ravuconazole have potent in vitro activity against *B. dermatitidis* and have the potential to be added to the therapeutic armamentarium against blastomycosis.[155,156]

Echinocandins

The echinocandins have poor in vitro activity against *B. dermatitidis* yeast and are not recommended for treatment of blastomycosis. At least one case report has described successful use of caspofungin for chronic pulmonary blastomycosis in a patient intolerant of other therapies; this should be considered only a last resort. The authors do not advocate this strategy because of the minimal amount of drug target, β-(1,3)-glucan, in the cell wall of *B. dermatitidis*.[72,157]

Adjunctive Therapy

Despite adequate antifungal therapy, the mortality rate of blastomycosis-induced ARDS remains high.[92,93,95] There is considerable interest in the role of adjunctive steroids for the treatment of patients with ARDS caused by *B. dermatitidis*. Although clinical data are limited, a few case reports suggest the potential for adjunctive steroids to improve survival.[158,159] However, it is unclear if these findings can be applied to all patients with ARDS from *B. dermatitidis*.[158,159] Moreover, the steroid doses used in these case reports were not standardized and were higher than recommended for patients with severe pulmonary histoplasmosis. Additional research is needed regarding the dose, duration, and efficacy of adjunctive steroids for the treatment of patients with severe pulmonary blastomycosis complicated by respiratory failure and ARDS. In addition to steroids, extracorporeal membrane oxygenation has been used in a single patient with blastomycosis-induced ARDS; however, this did not result in patient survival.[160]

Mortality

The case fatality rate reported in a large group of patients from Wisconsin from 1986 to 1995 was 4.3% (29 of 670 patients),[33] and from a large series in Manitoba the observed mortality rate was 6.3%.[32] Mortality has been associated with shorter duration of symptoms likely suggesting more fulminant presentation as well as with a compromised immune status of the host. Blastomycosis-induced ARDS is associated with 50 to 89% mortality rate, even in patients receiving appropriate therapy.[92,93] The mortality of blastomycosis in patients who have AIDS is nearly 40%, and most deaths occur within 3 weeks of diagnosis.[110]

Conclusion

Over the past two decades, there have been significant advances in the pathogenesis, immunology, diagnosis, and treatment of *B. dermatitidis*. Basic science research that led to the discovery of *BAD1* and *DRK1* is beginning to impact clinical diagnostics with the implementation of the BAD1 antibody test and the use of *DRK1* as a target for real-time PCR analysis of clinical specimens. Although the *Blastomyces* antigen test has revolutionized how clinicians diagnose blastomycosis, fungal smear and culture remain important. The ability to recognize the diverse clinical manifestations and consider blastomycosis as a potential diagnosis is essential. The newer azole antifungals such as voriconazole have been successfully used for treatment of blastomycosis, including patients with CNS infection. In contrast, the echinocandins, which represent the newest class of antifungals, have poor activity against *B. dermatitidis* yeast. AmB lipid formations have facilitated the treatment of patients with severe blastomycosis while minimizing (but not eliminating) nephrotoxicity. Despite these advances, the treatment of patients with blastomycosis-induced ARDS remains challenging and new approaches are needed to reduce mortality in this patient population.

References

1 Gilchrist TC. Protozoan dermatitis. J Cutan Genitourin Dis 1894; 12:496
2 Gilchrist TC, Stokes WR. A case of pseudo-lupus vulgaris caused by a *Blastomyces*.. J Exp Med 1898;3(1):53–78
3 Hamburger WW. A comparative study of four strains of organisms isolated from four cases of generalized blastomycosis. J Infect Dis 1907;4:201–209
4 Schwarz J, Baum GL. Blastomycosis. Am J Clin Pathol 1951;21(11): 999–1029
5 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(9):529–534
6 Marty AJ, Wüthrich M, Carmen JC, et al. Isolation of *Blastomyces dermatitidis* yeast from lung tissue during murine infection for in vivo transcriptional profiling. Fungal Genet Biol 2013;56:1–8
7 Wolf PL, Russell B, Shimoda A, eds. Practical Clinical Microbiology and Mycology: Techniques and Interpretations. Section X: Identification of Dimorphic Fungi Causing Systemic Mycosis. New York: John Wiley & Sons; 1975:486–488
8 Wu SJ, Valyi-Nagy T, Engelhard HH, Do MA, Janda WM. Secondary intracerebral blastomycosis with giant yeast forms. Mycopathologia 2005;160(3):253–257
9 Walker K, Skelton H, Smith K. Cutaneous lesions showing giant yeast forms of *Blastomyces dermatitidis*. J Cutan Pathol 2002; 29(10):616–618
10 Winn W, Allen S, Janda W, et al , eds. Koneman's Color Atlas and Textbook of Diagnostic Microbiology, 6th ed. Mycology. Philadelphia, PA: Lippincott Williams & Wilkens; 2006:1194–1198
11 Meece JK, Anderson JL, Fisher MC, Henk DA, Sloss BL, Reed KD. Population genetic structure of clinical and environmental isolates of *Blastomyces dermatitidis*, based on 27 polymorphic microsatellite markers. Appl Environ Microbiol 2011;77(15): 5123–5131
12 Meece JK, Anderson JL, Klein BS, et al. Genetic diversity in *Blastomyces dermatitidis*: implications for PCR detection in clinical and environmental samples. Med Mycol 2010;48(2):285–290
13 Brown EM, McTaggart LR, Zhang SX, Low DE, Stevens DA, Richardson SE. Phylogenetic analysis reveals a cryptic species *Blastomyces gilchristii*, sp. nov. within the human pathogenic fungus *Blastomyces dermatitidis*. PLoS ONE 2013;8(3):e59237

14 Smith JG Jr, Harris JS, Conant NF, Smith DT. An epidemic of North American blastomycosis. J Am Med Assoc 1955;158(8):641–646
15 Tosh FE, Hammerman KJ, Weeks RJ, Sarosi GA. A common source epidemic of North American blastomycosis. Am Rev Respir Dis 1974;109(5):525–529
16 Kitchen MS, Reiber CD, Eastin GB. An urban epidemic of North American blastomycosis. Am Rev Respir Dis 1977;115(6): 1063–1066
17 Cockerill FR III, Roberts GD, Rosenblatt JE, Utz JP, Utz DC. Epidemic of pulmonary blastomycosis (Namekagon fever) in Wisconsin canoeists. Chest 1984;86(5):688–692
18 Armstrong CW, Jenkins SR, Kaufman L, Kerkering TM, Rouse BS, Miller GB Jr. Common-source outbreak of blastomycosis in hunters and their dogs. J Infect Dis 1987;155(3):568–570
19 Klein BS, Vergeront JM, DiSalvo AF, Kaufman L, Davis JP. 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(6): 1333–1338
20 Centers for Disease Control and Prevention (CDC). Blastomycosis – North Carolina. MMWR Morb Mortal Wkly Rep 1976; 25:205–206
21 Baumgardner DJ, Burdick JS. An outbreak of human and canine blastomycosis. Rev Infect Dis 1991;13(5):898–905
22 Frye MD, Seifer FD. An outbreak of blastomycosis in eastern Tennessee. Mycopathologia 1991;116(1):15–21
23 De Groote MA, Bjerke R, Smith H, Rhodes LV III. Expanding epidemiology of blastomycosis: clinical features and investigation of 2 cases in Colorado. Clin Infect Dis 2000;30(3):582–584
24 Proctor ME, Klein BS, Jones JM, Davis JP. Cluster of pulmonary blastomycosis in a rural community: evidence for multiple high-risk environmental foci following a sustained period of diminished precipitation. Mycopathologia 2002;153(3):113–120
25 Baumgardner DJ, Egan G, Giles S, Laundre B. An outbreak of blastomycosis on a United States Indian reservation. Wilderness Environ Med 2002;13(4):250–252
26 MacDonald PD, Langley RL, Gerkin SR, Torok MR, MacCormack JN. Human and canine pulmonary blastomycosis, North Carolina, 2001-2002. Emerg Infect Dis 2006;12(8):1242–1244
27 Pfister JR, Archer JR, Hersil S, et al. Non-rural point source blastomycosis outbreak near a yard waste collection site. Clin Med Res 2011;9(2):57–65
28 Roy M, Benedict K, Deak E, et al. A large community outbreak of blastomycosis in Wisconsin with geographic and ethnic clustering. Clin Infect Dis 2013;57(5):655–662
29 Carlos WG, Rose AS, Wheat LJ, et al. Blastomycosis in Indiana: digging up more cases. Chest 2010;138(6):1377–1382
30 Hussein R, Khan S, Levy F, Mehta JB, Sarubbi FA. Blastomycosis in the mountainous region of northeast Tennessee. Chest 2009; 135(4):1019–1023
31 Cano MV, Ponce-de-Leon GF, Tippen S, Lindsley MD, Warwick M, Hajjeh RA. Blastomycosis in Missouri: epidemiology and risk factors for endemic disease. Epidemiol Infect 2003;131(2): 907–914
32 Crampton TL, Light RB, Berg GM, et al. Epidemiology and clinical spectrum of blastomycosis diagnosed at Manitoba hospitals. Clin Infect Dis 2002;34(10):1310–1316
33 Centers for Disease Control and Prevention (CDC). Blastomycosis —Wisconsin, 1986-1995. MMWR Morb Mortal Wkly Rep 1996; 45(28):601–603
34 Manetti AC. Hyperendemic urban blastomycosis. Am J Public Health 1991;81(5):633–636
35 Klein BS, Davis JP. A laboratory-based surveillance of human blastomycosis in Wisconsin between 1973 and 1982. Am J Epidemiol 1985;122(5):897–903
36 Furcolow ML, Chick EW, Busey JF, Menges RW. Prevalence and incidence studies of human and canine blastomycosis. 1. Cases in the United States, 1885-1968. Am Rev Respir Dis 1970;102(1): 60–67
37 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(4):629–635
38 Dwight PJ, Naus M, Sarsfield P, Limerick B. An outbreak of human blastomycosis: the epidemiology of blastomycosis in the Kenora catchment region of Ontario, Canada. Can Commun Dis Rep 2000; 26(10):82–91
39 Lowry PW, Kelso KY, McFarland LM. Blastomycosis in Washington Parish, Louisiana, 1976-1985. Am J Epidemiol 1989;130(1): 151–159
40 Chapman SW, Dismukes WE, Proia LA, et al; Infectious Diseases Society of America. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis 2008;46(12):1801–1812
41 Seitz AE, Younes N, Steiner CA, Prevots DR. Incidence and trends of blastomycosis-associated hospitalizations in the United States. PLoS ONE 2014;9(8):e105466
42 Gauthier GM, Safdar N, Klein BS, Andes DR. Blastomycosis in solid organ transplant recipients. Transpl Infect Dis 2007;9(4): 310–317
43 Grim SA, Proia L, Miller R, et al. A multicenter study of histoplasmosis and blastomycosis after solid organ transplantation. Transpl Infect Dis 2012;14(1):17–23
44 Smith JA, Kauffman CA. Endemic fungal infections in patients receiving tumour necrosis factor-alpha inhibitor therapy. Drugs 2009;69(11):1403–1415
45 Pappas PG, Threlkeld MG, Bedsole GD, Cleveland KO, Gelfand MS, Dismukes WE. Blastomycosis in immunocompromised patients. Medicine (Baltimore) 1993;72(5):311–325
46 Kauffman CA, Freifeld AG, Andes DR, et al. Endemic fungal infections in solid organ and hematopoietic cell transplant recipients enrolled in the Transplant-Associated Infection Surveillance Network (TRANSNET). Transpl Infect Dis 2014;16(2): 213–224
47 Baily GG, Robertson VJ, Neill P, Garrido P, Levy LF. Blastomycosis in Africa: clinical features, diagnosis, and treatment. Rev Infect Dis 1991;13(5):1005–1008
48 Carman WF, Frean JA, Crewe-Brown HH, Culligan GA, Young CN. Blastomycosis in Africa. A review of known cases diagnosed between 1951 and 1987. Mycopathologia 1989;107(1):25–32
49 Frean JA, Carman WF, Crewe-Brown HH, Culligan GA, Young CN. *Blastomyces dermatitidis* infections in the RSA. S Afr Med J 1989; 76(1):13–16
50 McCullough MJ, DiSalvo AF, Clemons KV, Park P, Stevens DA. Molecular epidemiology of *Blastomyces dermatitidis*. Clin Infect Dis 2000;30(2):328–335
51 Rao GR, Narayan BL, Durga Prasad BK, Amareswar A, Sridevi M, Raju B. Disseminated blastomycosis in a child with a brief review of the Indian literature. Indian J Dermatol Venereol Leprol 2013; 79(1):92–96
52 Randhawa HS, Chowdhary A, Kathuria S, et al. Blastomycosis in India: report of an imported case and current status. Med Mycol 2013;51(2):185–192
53 Nemecek JC, Wüthrich M, Klein BS. Global control of dimorphism and virulence in fungi. Science 2006;312(5773):583–588
54 Brandhorst TT, Wüthrich M, Warner T, Klein B. Targeted gene disruption reveals an adhesin indispensable for pathogenicity of *Blastomyces dermatitidis*. J Exp Med 1999;189(8):1207–1216
55 Sterkel AK, Mettelman R, Wüthrich M, Klein BS. The unappreciated intracellular lifestyle of *Blastomyces dermatitidis*. J Immunol 2015;194(4):1796–1805
56 Powell BL, Drutz DJ, Huppert M, Sun SH. Relationship of progesterone- and estradiol-binding proteins in Coccidioides immitis to coccidioidal dissemination in pregnancy. Infect Immun 1983; 40(2):478–485

57 Hou B, Zhang Z, Zheng F, Liu X. Molecular cloning, characterization and differential expression of DRK1 in *Sporothrix schenckii*. Int J Mol Med 2013;31(1):99–104

58 Boyce KJ, Schreider L, Kirszenblat L, Andrianopoulos A. The two-component histidine kinases DrkA and SlnA are required for in vivo growth in the human pathogen *Penicillium marneffei*. Mol Microbiol 2011;82(5):1164–1184

59 Li W, Sullivan TD, Walton E, et al. Identification of the mating-type (MAT) locus that controls sexual reproduction of *Blastomyces dermatitidis*. Eukaryot Cell 2013;12(1):109–117

60 Gauthier GM. Blastomyces dermatitidis and blastomycosis. In: Sullivan DJ, Moran GP, eds. Human Pathogenic Fungi: Molecular Biology and Pathogenic Mechanisms. Norfolk, UK: Caister Academic Press; 2014:273–295

61 Gauthier GM, Sullivan TD, Gallardo SS, et al. SREB, a GATA transcription factor that directs disparate fates in *Blastomyces dermatitidis* including morphogenesis and siderophore biosynthesis. PLoS Pathog 2010;6(4):e1000846

62 Gilmore SA, Naseem S, Konopka JB, Sil A. N-acetylglucosamine (GlcNAc) triggers a rapid, temperature-responsive morphogenetic program in thermally dimorphic fungi. PLoS Genet 2013; 9(9):e1003799

63 Hwang LH, Seth E, Gilmore SA, Sil A. SRE1 regulates iron-dependent and -independent pathways in the fungal pathogen *Histoplasma capsulatum*. Eukaryot Cell 2012;11(1):16–25

64 Klein BS, Jones JM. Isolation, purification, and radiolabeling of a novel 120-kD surface protein on *Blastomyces dermatitidis* yeasts to detect antibody in infected patients. J Clin Invest 1990;85(1): 152–161

65 Rooney PJ, Sullivan TD, Klein BS. Selective expression of the virulence factor BAD1 upon morphogenesis to the pathogenic yeast form of *Blastomyces dermatitidis*: evidence for transcriptional regulation by a conserved mechanism. Mol Microbiol 2001;39(4):875–889

66 Brandhorst TT, Roy R, Wüthrich M, et al. Structure and function of a fungal adhesin that binds heparin and mimics thrombospondin-1 by blocking T cell activation and effector function. PLoS Pathog 2013;9(7):e1003464

67 Brandhorst TT, Wüthrich M, Finkel-Jimenez B, Warner T, Klein BS. Exploiting type 3 complement receptor for TNF-alpha suppression, immune evasion, and progressive pulmonary fungal infection. J Immunol 2004;173(12):7444–7453

68 Finkel-Jimenez B, Wüthrich M, Brandhorst T, Klein BS. The WI-1 adhesin blocks phagocyte TNF-α production, imparting pathogenicity on *Blastomyces dermatitidis*. J Immunol 2001;166(4): 2665–2673

69 Finkel-Jimenez B, Wüthrich M, Klein BS. BAD1, an essential virulence factor of *Blastomyces dermatitidis*, suppresses host TNF-α production through TGF-β-dependent and -independent mechanisms. J Immunol 2002;168(11):5746–5755

70 Brandhorst TT, Gauthier GM, Stein RA, Klein BS. Calcium binding by the essential virulence factor BAD-1 of *Blastomyces dermatitidis*. J Biol Chem 2005;280(51):42156–42163

71 Zhang MX, Brandhorst TT, Kozel TR, Klein BS. Role of glucan and surface protein BAD1 in complement activation by *Blastomyces dermatitidis* yeast. Infect Immun 2001;69(12):7559–7564

72 Kanetsuna F, Carbonell LM. Cell wall composition of the yeastlike and mycelial forms of *Blastomyces dermatitidis*. J Bacteriol 1971; 106(3):946–948

73 Koneti A, Linke MJ, Brummer E, Stevens DA. Evasion of innate immune responses: evidence for mannose binding lectin inhibition of tumor necrosis factor alpha production by macrophages in response to *Blastomyces dermatitidis*. Infect Immun 2008;76(3): 994–1002

74 Girouard G, Lachance C, Pelletier R. Observations on (1-3)-beta-D-glucan detection as a diagnostic tool in endemic mycosis caused by *Histoplasma* or *Blastomyces*. J Med Microbiol 2007; 56(Pt 7):1001–1002

75 Sugar AM, Picard M, Wagner R, Kornfeld H. Interactions between human bronchoalveolar macrophages and *Blastomyces dermatitidis* conidia: demonstration of fungicidal and fungistatic effects. J Infect Dis 1995;171(6):1559–1562

76 Drutz DJ, Frey CL. Intracellular and extracellular defenses of human phagocytes against *Blastomyces dermatitidis* conidia and yeasts. J Lab Clin Med 1985;105(6):737–750

77 Sugar AM, Chahal RS, Brummer E, Stevens DA. Susceptibility of *Blastomyces dermatitidis* strains to products of oxidative metabolism. Infect Immun 1983;41(3):908–912

78 Rocco NM, Carmen JC, Klein BS. *Blastomyces dermatitidis* yeast cells inhibit nitric oxide production by alveolar macrophage inducible nitric oxide synthase. Infect Immun 2011;79(6): 2385–2395

79 Bradsher RW, Balk RA, Jacobs RF. Growth inhibition of *Blastomyces dermatitidis* in alveolar and peripheral macrophages from patients with blastomycosis. Am Rev Respir Dis 1987;135(2): 412–417

80 Wüthrich M, Gern B, Hung CY, et al. Vaccine-induced protection against 3 systemic mycoses endemic to North America requires Th17 cells in mice. J Clin Invest 2011;121(2):554–568

81 Klein BS, Bradsher RW, Vergeront JM, Davis JP. Development of long-term specific cellular immunity after acute *Blastomyces dermatitidis* infection: assessments following a large point-source outbreak in Wisconsin. J Infect Dis 1990;161(1):97–101

82 Propeck PA, Scanlan KA. Blastomycosis of the breast. AJR Am J Roentgenol 1996;166(3):726

83 Barocas JA, Gauthier GM. Peritonitis caused by *Blastomyces dermatitidis* in a kidney transplant recipient: case report and literature review. Transpl Infect Dis 2014;16(4):634–641

84 Sarosi GA, Davies SF. Blastomycosis. Am Rev Respir Dis 1979; 120(4):911–938

85 Sarosi GA, Davies SF, Phillips JR. Self-limited blastomycosis: a report of 39 cases. Semin Respir Infect 1986;1(1):40–44

86 Baumgardner DJ, Halsmer SE, Egan G. Symptoms of pulmonary blastomycosis: northern Wisconsin, United States. Wilderness Environ Med 2004;15(4):250–256

87 Vaaler AK, Bradsher RW, Davies SF. Evidence of subclinical blastomycosis in forestry workers in northern Minnesota and northern Wisconsin. Am J Med 1990;89(4):470–476

88 Chapman SW, Lin AC, Hendricks KA, et al. Endemic blastomycosis in Mississippi: epidemiological and clinical studies. Semin Respir Infect 1997;12(3):219–228

89 Lemos LB, Baliga M, Guo M. Blastomycosis: The great pretender can also be an opportunist. Initial clinical diagnosis and underlying diseases in 123 patients. Ann Diagn Pathol 2002;6(3): 194–203

90 Recht LD, Philips JR, Eckman MR, Sarosi GA. Self-limited blastomycosis: a report of thirteen cases. Am Rev Respir Dis 1979; 120(5):1109–1112

91 Kralt D, Light B, Cheang M, et al. Clinical characteristics and outcomes in patients with pulmonary blastomycosis. Mycopathologia 2009;167(3):115–124

92 Lemos LB, Baliga M, Guo M. Acute respiratory distress syndrome and blastomycosis: presentation of nine cases and review of the literature. Ann Diagn Pathol 2001;5(1):1–9

93 Meyer KC, McManus EJ, Maki DG. Overwhelming pulmonary blastomycosis associated with the adult respiratory distress syndrome. N Engl J Med 1993;329(17):1231–1236

94 Ascioglu S, Rex JH, de Pauw B, et al; Invasive Fungal Infections Cooperative Group of the European Organization for Research and Treatment of Cancer; Mycoses Study Group of the National Institute of Allergy and Infectious Diseases. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 2002;34(1):7–14

95 Vasquez JE, Mehta JB, Agrawal R, Sarubbi FA. Blastomycosis in northeast Tennessee. Chest 1998;114(2):436–443

96 Body BA. Cutaneous manifestations of systemic mycoses. Dermatol Clin 1996;14(1):125–135

97 Smith JA, Riddell J IV, Kauffman CA. Cutaneous manifestations of endemic mycoses. Curr Infect Dis Rep 2013;15(5):440–449

98 Steck WD. Blastomycosis. Dermatol Clin 1989;7(2):241–250

99 Saucier J, Gauthier G. Photo quiz. Verrucous lesions and ectropion in an immunocompetent individual. Clin Infect Dis 2012;55(10): 1390–1391, 1426–1428

100 Emer JJ, Spear JB. Primary cutaneous blastomycosis as a cause of acute respiratory distress syndrome: case report and literature review. J Clin Aesthet Dermatol 2009;2(3):22–30

101 Saccente M, Abernathy RS, Pappas PG, Shah HR, Bradsher RW. Vertebral blastomycosis with paravertebral abscess: report of eight cases and review of the literature. Clin Infect Dis 1998; 26(2):413–418

102 Jain R, Singh K, Lamzabi I, Harbhajanka A, Gattuso P, Reddy VB. Blastomycosis of bone: a clinicopathologic study. Am J Clin Pathol 2014;142(5):609–616

103 Oppenheimer M, Embil JM, Black B, et al. Blastomycosis of bones and joints. South Med J 2007;100(6):570–578

104 Seo R, Oyasu R, Schaeffer A. Blastomycosis of the epididymis and prostate. Urology 1997;50(6):980–982

105 Wise GJ, Talluri GS, Marella VK. Fungal infections of the genitourinary system: manifestations, diagnosis, and treatment. Urol Clin North Am 1999;26(4):701–718, vii

106 Lemos LB, Guo M, Baliga M. Blastomycosis: organ involvement and etiologic diagnosis. A review of 123 patients from Mississippi. Ann Diagn Pathol 2000;4(6):391–406

107 Fanella S, Skinner S, Trepman E, Embil JM. Blastomycosis in children and adolescents: a 30-year experience from Manitoba. Med Mycol 2011;49(6):627–632

108 Bariola JR, Perry P, Pappas PG, et al. Blastomycosis of the central nervous system: a multicenter review of diagnosis and treatment in the modern era. Clin Infect Dis 2010;50(6):797–804

109 Bush JW, Wuerz T, Embil JM, Del Bigio MR, McDonald PJ, Krawitz S. Outcomes of persons with blastomycosis involving the central nervous system. Diagn Microbiol Infect Dis 2013;76(2):175–181

110 Pappas PG, Pottage JC, Powderly WG, et al. Blastomycosis in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1992;116(10):847–853

111 Pappas PG, Dismukes WE. Blastomycosis: Gilchrist's disease revisited. Curr Clin Top Infect Dis 2002;22:61–77

112 Guccion JG, Rohatgi PK, Saini NB, French A, Tavaloki S, Barr S. Disseminated blastomycosis and acquired immunodeficiency syndrome: a case report and ultrastructural study. Ultrastruct Pathol 1996;20(5):429–435

113 Butka BJ, Bennett SR, Johnson AC. Disseminated inoculation blastomycosis in a renal transplant recipient. Am Rev Respir Dis 1984;130(6):1180–1183

114 Serody JS, Mill MR, Detterbeck FC, Harris DT, Cohen MS. Blastomycosis in transplant recipients: report of a case and review. Clin Infect Dis 1993;16(1):54–58

115 FDA Alert September 2008, Tumor necrosis factor-alpha blockers (TNF blockers), Cimzia (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab), and Remicade (infliximab)

116 Lemos LB, Soofi M, Amir E. Blastomycosis and pregnancy. Ann Diagn Pathol 2002;6(4):211–215

117 MacDonald D, Alguire PC. Adult respiratory distress syndrome due to blastomycosis during pregnancy. Chest 1990;98(6): 1527–1528

118 Maxson S, Miller SF, Tryka AF, Schutze GE. Perinatal blastomycosis: a review. Pediatr Infect Dis J 1992;11(9):760–763

119 Watts EA, Gard PD Jr, Tuthill SW. First reported case of intrauterine transmission of blastomycosis. Pediatr Infect Dis 1983;2(4): 308–310

120 Saccente M, Woods GL. Clinical and laboratory update on blastomycosis. Clin Microbiol Rev 2010;23(2):367–381

121 Patel AJ, Gattuso P, Reddy VB. Diagnosis of blastomycosis in surgical pathology and cytopathology: correlation with microbiologic culture. Am J Surg Pathol 2010;34(2):256–261

122 Martynowicz MA, Prakash UB. Pulmonary blastomycosis: an appraisal of diagnostic techniques. Chest 2002;121(3):768–773

123 Babady NE, Buckwalter SP, Hall L, Le Febre KM, Binnicker MJ, Wengenack NL. Detection of *Blastomyces dermatitidis* and *Histoplasma capsulatum* from culture isolates and clinical specimens by use of real-time PCR. J Clin Microbiol 2011;49(9):3204–3208

124 Sidamonidze K, Peck MK, Perez M, et al. Real-time PCR assay for identification of *Blastomyces dermatitidis* in culture and in tissue. J Clin Microbiol 2012;50(5):1783–1786

125 Klein BS, Vergeront JM, Kaufman L, et al. Serological tests for blastomycosis: assessments during a large point-source outbreak in Wisconsin. J Infect Dis 1987;155(2):262–268

126 Richer SM, Smedema ML, Durkin MM, et al. Development of a highly sensitive and specific blastomycosis antibody enzyme immunoassay using *Blastomyces dermatitidis* surface protein BAD-1. Clin Vaccine Immunol 2014;21(2):143–146

127 Bariola JR, Hage CA, Durkin M, et al. Detection of *Blastomyces dermatitidis* antigen in patients with newly diagnosed blastomycosis. Diagn Microbiol Infect Dis 2011;69(2):187–191

128 Connolly P, Hage CA, Bariola JR, et al. *Blastomyces dermatitidis* antigen detection by quantitative enzyme immunoassay. Clin Vaccine Immunol 2012;19(1):53–56

129 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(10):4873–4875

130 Mongkolrattanothai K, Peev M, Wheat LJ, Marcinak J. Urine antigen detection of blastomycosis in pediatric patients. Pediatr Infect Dis J 2006;25(11):1076–1078

131 Hage CA, Davis TE, Egan L, et al. Diagnosis of pulmonary histoplasmosis and blastomycosis by detection of antigen in bronchoalveolar lavage fluid using an improved second-generation enzyme-linked immunoassay. Respir Med 2007;101(1):43–47

132 Hage CA, Knox KS, Davis TE, Wheat LJ. Antigen detection in bronchoalveolar lavage fluid for diagnosis of fungal pneumonia. Curr Opin Pulm Med 2011;17(3):167–171

133 Van Der Veer J, Lewis RJ, Emtiazjoo AM, Allen SD, Wheat LJ, Hage CA. Cross-reactivity in the Platelia™ Aspergillus enzyme immunoassay caused by blastomycosis. Med Mycol 2012;50(4): 396–398

134 Wheat LJ, Hackett E, Durkin M, et al. Histoplasmosis-associated cross-reactivity in the BioRad Platelia Aspergillus enzyme immunoassay. Clin Vaccine Immunol 2007;14(5):638–640

135 Halvorsen RA, Duncan JD, Merten DF, Gallis HA, Putman CE. Pulmonary blastomycosis: radiologic manifestations. Radiology 1984;150(1):1–5

136 Brown LR, Swensen SJ, Van Scoy RE, Prakash UB, Coles DT, Colby TV. Roentgenologic features of pulmonary blastomycosis. Mayo Clin Proc 1991;66(1):29–38

137 Fang W, Washington L, Kumar N. Imaging manifestations of blastomycosis: a pulmonary infection with potential dissemination. Radiographics 2007;27(3):641–655

138 Winer-Muram HT, Beals DH, Cole FH Jr. Blastomycosis of the lung: CT features. Radiology 1992;182(3):829–832

139 Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. Clin Infect Dis 1996;22(2):336–340

140 Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. Am J Obstet Gynecol 2000;183(3):617–620

141 De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. Drug Saf 2009;32(3): 239–244

142 Dismukes WE, Bradsher RW Jr, Cloud GC, et al; NIAID Mycoses Study Group. Itraconazole therapy for blastomycosis and histoplasmosis. Am J Med 1992;93(5):489–497
143 Girois SB, Chapuis F, Decullier E, Revol BG. Adverse effects of antifungal therapies in invasive fungal infections: review and meta-analysis. Eur J Clin Microbiol Infect Dis 2005;24(2):119–130
144 Johnson PC, Wheat LJ, Cloud GA, et al; U.S. National Institute of Allergy and Infectious Diseases Mycoses Study Group. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. Ann Intern Med 2002;137(2):105–109
145 Ariano RE, Mitchelmore BR, Lagacé-Wiens PR, Zelenitsky SA. Successful treatment of pulmonary blastomycosis with continuously infused amphotericin B deoxycholate after failure with liposomal amphotericin B. Ann Pharmacother 2013;47(6):e26
146 Li RK, Ciblak MA, Nordoff N, Pasarell L, Warnock DW, McGinnis MR. In vitro activities of voriconazole, itraconazole, and amphotericin B against *Blastomyces dermatitidis*, Coccidioides immitis, and *Histoplasma capsulatum*. Antimicrob Agents Chemother 2000;44(6):1734–1736
147 Espinel-Ingroff A. Comparison of In vitro activities of the new triazole SCH56592 and the echinocandins MK-0991 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. J Clin Microbiol 1998;36(10):2950–2956
148 Sugar AM, Liu XP. In vitro and in vivo activities of SCH 56592 against *Blastomyces dermatitidis*. Antimicrob Agents Chemother 1996;40(5):1314–1316
149 Borgia SM, Fuller JD, Sarabia A, El-Helou P. Cerebral blastomycosis: a case series incorporating voriconazole in the treatment regimen. Med Mycol 2006;44(7):659–664
150 Lutsar I, Roffey S, Troke P. Voriconazole concentrations in the cerebrospinal fluid and brain tissue of guinea pigs and immunocompromised patients. Clin Infect Dis 2003;37(5):728–732
151 Ta M, Flowers SA, Rogers PD. The role of voriconazole in the treatment of central nervous system blastomycosis. Ann Pharmacother 2009;43(10):1696–1700
152 Proia LA, Harnisch DO. Successful use of posaconazole for treatment of blastomycosis. Antimicrob Agents Chemother 2012; 56(7):4029
153 Day SR, Weiss DB, Hazen KC, Moore CC. Successful treatment of osseous blastomycosis without pulmonary or disseminated disease and review of the literature. Diagn Microbiol Infect Dis 2014; 79(2):242–244
154 Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother 2009;53(1):24–34
155 Falci DR, Pasqualotto AC. Profile of isavuconazole and its potential in the treatment of severe invasive fungal infections. Infect Drug Resist 2013;6:163–174
156 González GM. In vitro activities of isavuconazole against opportunistic filamentous and dimorphic fungi. Med Mycol 2009; 47(1):71–76
157 Mardini J, Nguyen B, Ghannoum M, Couture C, Lavergne V. Treatment of chronic pulmonary blastomycosis with caspofungin. J Med Microbiol 2011;60(Pt 12):1875–1878
158 Lahm T, Neese S, Thornburg AT, Ober MD, Sarosi GA, Hage CA. Corticosteroids for blastomycosis-induced ARDS: a report of two patients and review of the literature. Chest 2008;133(6): 1478–1480
159 Plamondon M, Lamontagne F, Allard C, Pépin J. Corticosteroids as adjunctive therapy in severe blastomycosis-induced acute respiratory distress syndrome in an immunosuppressed patient. Clin Infect Dis 2010;51(1):e1–e3
160 Dalton HJ, Hertzog JH, Hannan RL, Vezza P, Hauser GJ. Extracorporeal membrane oxygenation for overwhelming *Blastomyces dermatitidis* pneumonia. Crit Care 1999;3(4):91–94