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EPIDEMIOLOGICAL ASPECTS OF FUNGAL INFECTIONS (T CHILLER AND J BADDLEY, SECTION EDITORS)

Epidemiologic and Ecologic Features of Blastomycosis: A Review

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Abstract Blastomycosis is a potentially fatal infection caused by *Blastomyces dermatitidis*, a fungus endemic to North America in areas surrounding the Ohio and Mississippi River valleys and the Great Lakes. The clinical manifestations, diagnostic techniques, and treatment strategies for blastomycosis are relatively well-described in the literature; however, the epidemiologic features of disease are not as clearly defined as those of other endemic mycoses, such as histoplasmosis and coccidioidomycosis. We review the ecologic and epidemiologic aspects of *B. dermatitidis* and blastomycosis, including geographic distribution, environmental niche, seasonality, and possible risk factors.

Keywords Blastomycosis · Blastomyces · Fungus · Epidemiology · Ecology · Risk factor · Prevention

Introduction

Blastomycosis is a potentially fatal infection of humans and animals caused by *Blastomyces dermatitidis*, a thermally dimorphic fungus that exists as a mold in the environment and transforms into a yeast at body temperatures. The endemic areas are largely restricted to North America, although locally acquired cases have been reported elsewhere [1, 2]. Following inhalation of spores, the infection typically results in pulmonary illness, which can range from asymptomatic to life-threatening disease. The clinical manifestations of blastomycosis are generally well-described in the literature, and significant progress has been made during the past several years regarding the diagnosis and management of the disease; however, comparatively little is known about its epidemiologic features. Consistently demonstrated risk factors for blastomycosis have not been definitely established, and the true public health burden of disease is likely underestimated. Here, we review the epidemiologic and ecologic aspects of blastomycosis and *B. dermatitidis*, including geographic distribution, environmental niche, seasonality, and possible risk factors.

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Clinical Presentation, Diagnosis, and Treatment

B. dermatitidis infections primarily occur following inhalation of air-borne conidia, and the incubation period ranges from approximately 3 to 15 weeks [1]. The spectrum of illness can vary from asymptomatic to serious, life-threatening disease [1]. Infection usually involves the respiratory system and can range from mild, self-limiting illness to severe acute respiratory distress syndrome [3, 4]. Less frequently, primary cutaneous infection can occur following accidental inoculation or a bite from an infected animal [5, 6].

The most common signs and symptoms of the acute and chronic forms of pulmonary blastomycosis mimic those of other, more common respiratory infections and include cough, fever, night sweats, weight loss, chest pain, and dyspnea [7]. Extrapulmonary infection is uncommon, but sites of dissemination include the skin, bones, genitourinary system, central nervous system, liver, spleen, heart, lymph nodes, and muscle [8].

Culture is the most sensitive method for diagnosis of blastomycosis, and can be performed on a variety of specimens; however, the organism sometimes takes several

weeks to grow in culture media, which can lead to delays in diagnosis and treatment [9•, 10]. More rapid diagnosis can be achieved through direct observation of the yeast cells in smears or tissue specimens using microscopy or histopathology [9•, 10]. These methods are less sensitive than culture, so negative results do not necessarily exclude a diagnosis of blastomycosis [10]. Antibody tests, including complement fixation and immunodiffusion are available, but their diagnostic utility is limited because of low sensitivity or specificity; enzyme immunoassay for the diagnosis of blastomycosis is more sensitive than immunodiffusion, but less specific [11–13]. Antigen detection methods, recently modified to enable quantification, may be helpful in establishing a diagnosis, but careful interpretation of test results is necessary because cross-reactivity with *Histoplasma* is common [14]. Newly developed real-time PCR assays are promising for the rapid detection of *Blastomyces* directly from clinical specimens [15•, 16]. While not used in any currently licensed tests, a highly conserved 120-kDa surface protein (WI-1) on *B. dermatitidis* yeasts that reacts with antibodies to *Blastomyces* is an important antigenic target of humoral and cellular responses during infection of humans and experimental animals [17]. When compared to the A-factor antigen of *B. dermatitidis* used to detect antibodies in human serum, WI-1 is more reactive and specific for the binding of serum antibodies to *Blastomyces* [18]. WI-1 has demonstrated very good accuracy when used as a target in a radioimmunoassay to test serum samples from ill patients and healthy controls among a variety of subpopulations, including blood donors in Wisconsin, suggesting that WI-1 serologic testing may be useful for diagnosing blastomycosis in endemic areas [19].

The recommended treatment for blastomycosis in immunocompetent persons is a lipid formulation of amphotericin B for severe pulmonary or disseminated disease, and oral itraconazole for mild to moderate pulmonary disease. In immunosuppressed patients, a lipid formulation of amphotericin B followed by itraconazole step-down therapy is the preferred treatment [20]. Other azoles, including ketoconazole and fluconazole, have also been shown to be effective in treating non-life-threatening blastomycosis; however, these are not considered first-line agents [21, 22].

Geographic Distribution and Incidence

Blastomycosis is considered endemic to the Midwestern, Southern, and Southeastern states bordering the Ohio and Mississippi rivers and in areas bordering the Great Lakes and the Saint Lawrence River in the US and Canada [1, 2] (Fig. 1). While the vast majority of blastomycosis cases occur in North America, a small number of cases have also been described in other areas of the world, including Africa and India [23, 24]. Estimations of the geographic distribution of blastomycosis are based almost exclusively on case reports of symptomatic patients rather than extensive skin test surveys, because a reliable skin test for blastomycosis is not available [2, 25]. As a result, the endemic regions for blastomycosis are not as well defined as those of the other endemic North American fungal infections, namely, histoplasmosis and coccidioidomycosis [1]. While the vast majority of blastomycosis cases occur within the defined endemic area, a recent analysis based on Medicare claims data revealed that up to 14 % of the study population did not reside in or file a claim in a known endemic region [26]. Although the study was not able to assess travel history, the finding suggests that a small subset of cases may result from exposure in areas not traditionally considered to be endemic. At least 15 outbreaks of blastomycosis have occurred in the US since 1953 [27–38, 39•] (Table 1). Among these outbreaks, nine occurred in Wisconsin, two occurred in North Carolina, and one each occurred in Illinois, Minnesota, Tennessee, and Virginia. The geographic distribution of these outbreaks has helped to further refine our understanding of the likely region of *B. dermatitidis* distribution in North America (Fig. 1).

Because blastomycosis is not a nationally notifiable condition, estimating the burden of disease is challenging, even in known endemic areas. However, the infection is currently reportable in five states: Louisiana, Michigan, Minnesota, Mississippi, and Wisconsin. Most cases occur sporadically, although some occur in association with outbreaks presumably resulting from shared environmental exposures. Reporting of sporadic infections and outbreak events suggests that blastomycosis is more common in some endemic areas than others. However, it is unclear whether this observation reflects actual differences in the burden of disease, differences in surveillance practices, or some combination of these factors. Wisconsin has the highest reported number of cases and annual incidence of any state, with an annual mean of 125 cases during 2001–2010 (Wisconsin Division of Public Health, WDPH, unpublished data). Nearly half of all Wisconsin cases occur in residents of the northern portion of the state. The annual incidence rates in at least seven northern Wisconsin counties range from 10 to 40 cases per 100,000 persons [40]. Recent data suggest that the incidence of blastomycosis may be increasing in Wisconsin and some other endemic regions. In Wisconsin, the statewide mean annual reported incidence increased from 1.32 cases per 100,000 during 1985–1994 [40] to 1.82 cases per 100,000 during 2001–2005 and 2.63 cases per 100,000 during 2006–2010 (WDPH, unpublished data). The reported incidence in Illinois increased from 0.38 cases per 100,000 in 2001 to 1.07 cases per 100,000 in 2007 [41], a hospital-based study in Indiana demonstrated a similar increase from 0.12 to 1.15 cases per 100,000 during 2003–2006 [42], and a laboratory-

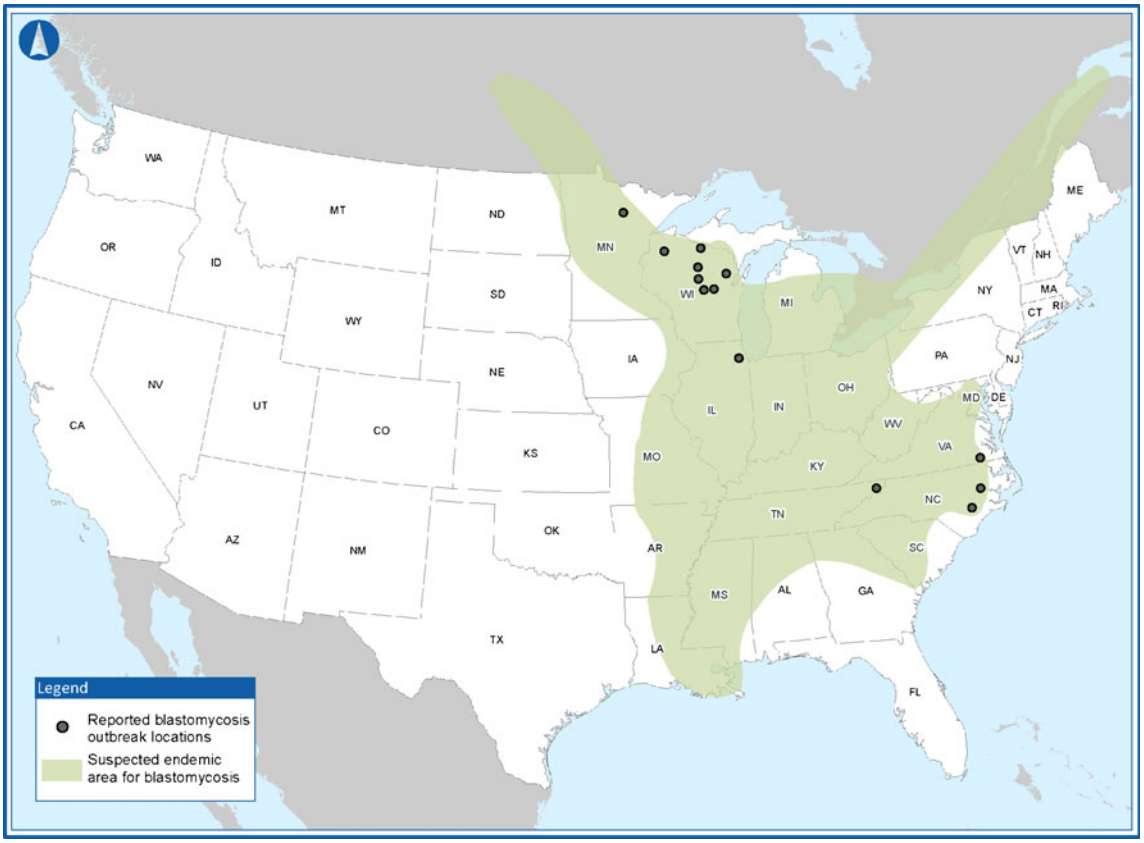

Fig. 1 Suspected endemic areas for blastomycosis and reported US blastomycosis outbreak locations

based case-finding study in Ontario, Canada, demonstrated an overall increase in incidence during 1994–2003, with an average annual incidence of 0.3 cases per 100,000 [43].

Whether these observed increases in blastomycosis incidence reflect a true increase in morbidity or improved healthcare provider or community awareness of the infection is unclear. Generally, the public health burden of blastomycosis is likely underestimated even in known endemic areas because 30–50 % of *B. dermatitidis* infections may be asymptomatic [31, 44], and among symptomatic infections, the nonspecific clinical presentation can result in a low index of suspicion for blastomycosis [45]. Blastomycosis can be commonly mistaken for other pulmonary infections such as tuberculosis or bacterial pneumonia [9•].

Ecologic Features and Seasonality

The ecologic features of *B. dermatitidis* are not well understood, primarily because of the difficulty associated with isolating the organism from the environment. *B. dermatitidis* was first successfully isolated from soil in 1961 [46], and since then, the fungus has been recovered from the environment fewer than two dozen times despite thousands of attempts [47]. Testing of environmental samples has traditionally relied on application of culture methods. However, newer molecular methods such as PCR have demonstrated promise in detection of *B. dermatitidis* DNA in environmental samples [48].

The small number of environmental samples positive for *B. dermatitidis* includes soil as well as silt, manure, and debris such as rotting wood and leaves, or other decaying organic matter [31, 33, 49–52]. These findings provide insight into the natural habitat of the fungus, but the precise conditions necessary for its growth and persistence are still somewhat unclear [1]. Some evidence suggests that *B. dermatitidis* is short-lived in the environment [50], whereas other studies based on the occurrence of multiple cases of blastomycosis from the same property during a period of several years suggest that the fungus can persist in specific areas for long periods of time [53]. In addition, laboratory studies have demonstrated that *B. dermatitidis* may be able to survive in quickly changing conditions, including high-ammonia microenvironments [54].

Although factors which determine its persistence in the environment are not completely understood, moisture is widely believed to be an important factor for the growth and dispersal of *B. dermatitidis*. Laboratory studies have demonstrated that infectious conidia are readily dispersed by air currents only after exposure to water [55]. In addition,

Table 1 Features of documented US human blastomycosis outbreaks, 1953–2012

Reference	Occurrence, year(s)	No. of proven and probable cases	Location	*B. dermatitidis* recovered from environment?	Common exposures
[27]	1953–1954	11	Eastern North Carolina (Pitt County)	Not attempted	None identified
[28]	1972	12	Northern Minnesota (Bigfork, Itasca County)	No	Lakeshore point source: cabin construction
[29]	1974–1975	5	Northeastern Illinois (Westmont) (urban)	No	Road construction site (presumed)
[30]	1979	8	Northwestern Wisconsin (Hayward)	No	Campsite during canoe trip (Namekagon River)
[31]	1984	48	Northern Wisconsin (Vilas County)	Yes (beaver lodge and beaver dam specimens)	Trip to beaver pond. Common exposure to beaver lodge (Eagle River)
[32]	1984	4	Eastern Virginia (Southampton County)	No	Raccoon hunting in wooded, swampy area
[33]	1985	7	Central Wisconsin (Portage County)	Yes (soil)	Riverbank fishing (Tomorrow River)
[33]	1985	6	Central Wisconsin (Waupaca County)	No	Climbing into an underground timber fort on Crystal River riverbank
[34]	1988	22	Northern Wisconsin (Vilas County)	Not attempted	Hotel excavation site (presumed)
[35]	1989	3	Eastern Tennessee (Carter County)	No	Driving past construction site (presumed)
[36]	1990	8	Northeastern Wisconsin (Oconto County)	No	Digging/earth-disturbing activities (risk factor)
[37]	1998–2000	9	Northern Wisconsin (Vilas County)	Not attempted	Excavation on a Native American reservation
[38]	2001–2002	8	Eastern North Carolina (Duplin County)	Not attempted	None identified
[39•]	2006	21	North central Wisconsin (Lincoln County)	Yes (non-outbreak strain nucleic acid evidence from yard waste pile)	Yard waste site
[73]	2009–2010	55	North central Wisconsin (Marathon County)	Yes (nucleic acid evidence from indoor air sample)	Independent risk factors: Hmong ethnicity and presence of an underlying medical condition

many cases of human and canine blastomycosis, both sporadic and outbreak-related, have been observed in proximity to waterways [1, 33, 56–58]. Analyses of the residential locations of human and canine blastomycosis patients in Vilas County, Wisconsin, have shown that a high proportion of cases occur near waterways at low elevations (less than 500 m) and in association with sandy soils prone to fluctuations in moisture level [58]. Ecologic niche modeling for *B. dermatitidis* has provided further evidence that moist soils near waterways, in both urban and rural environments, likely provides the most suitable natural habitat for the fungus [47].

Climate and weather undoubtedly influence the environmental conditions that support the growth and dispersal of *B. dermatitidis*. Clusters of blastomycosis cases have been observed following periods of diminished precipitation and in association with rainfall events [31, 33, 36, 39•]. This suggests that there may be similarities in the growth and dispersal mechanisms of *B. dermatitidis* and *Coccidioides*, which are thought to proliferate in the environment following periods of heavy rainfall, and then disperse as the soil dries and is exposed to air currents [59]. The potential effects of global climate change on the natural habitat of *B. dermatitidis* have not yet been determined, and will likely be an important consideration in the future. In general, the prevalence of mammalian fungal diseases is hypothesized to increase as global warming occurs, partially because selection may favor fungi which are capable of surviving at higher temperatures (i.e., body temperature) [60].

Meteorologic factors also likely affect the observed seasonality of blastomycosis. However, seasonal patterns of infection have been difficult to establish definitively because the incubation period for blastomycosis can range from weeks to months. During the first decade that blastomycosis was reportable in Wisconsin (1985–1994), no clear seasonal patterns of infection were observed [40]. During 2001–2010, a total of 1,245 cases were reported in Wisconsin. The peak months were November to January (12 to 15 illness onsets per month), and the nadir months were July to September (8 illness onsets per month) (WDPH, unpublished data). Studies that examined shorter periods of time or were limited in geographic scope provide differing conclusions regarding seasonality, including similar observed peaks during winter months [57, 61] or no apparent seasonality [62–64]. Investigations in Manitoba and northwestern Ontario suggest seasonal variations in the clinical presentation of the disease, with the majority of localized pulmonary infections occurring during autumn and winter, and diffuse pulmonary infection occurring predominantly during the spring [65]. Following this Canadian study, the authors hypothesized that this pattern represents acquisition of the infection during the summer months, resulting in localized pneumonia one to six months later, followed by slow progression of disease within four to nine months among a small proportion of patients [65]. Ultimately, the observed seasonal aspects of blastomycosis likely result from a combination of factors including geography, the climate and weather conditions which affect the growth and dispersal of the fungus, and individual risk factors related to seasonal likelihood of environmental exposure.

Risk Factors

Age and Sex

Blastomycosis is generally more common among adults than children. In Wisconsin, data derived from laboratory-based surveillance during 1973–1982 and statewide reporting of cases during 1985–1994 demonstrated virtually identical mean patient age (43.8 years and 44.0 years) during each study interval [40, 66]. During 2001–2010 in Wisconsin, 67 % of cases occurred among persons aged 25 to 64 years, and the mean ages were similar among males (43.1 years) and females (45.7 years) (WDPH, unpublished data). Studies in Illinois and Canada have demonstrated older age to be associated with higher mortality rates, but the analyses did not consider presence of underlying medical conditions as a potential confounder [61, 67].

With regard to sex disparities in blastomycosis, state-specific studies of reported blastomycosis cases or cases identified using hospital or laboratory records or official report data have demonstrated a higher proportion of cases among males [40, 64, 66–70]. Statewide Wisconsin data reported during 2001–2010 demonstrated that the mean annual incidence was 2.9 cases per 100,000 among males and 1.5 cases per 100,000 among females, and the sex disparity was greatest among persons aged 25 to 44 years (WDPH, unpublished data). A national population-based study demonstrated that the numbers of hospitalizations for blastomycosis during 2002 were similar among male (31 patients) and female (37 patients) children, but were substantially greater among men (407 patients) than among women (296 patients) [71]. However, case-control analyses in both outbreak and non-outbreak settings have not shown male sex to be an independent risk factor for infection [39•, 63, 72]. Altogether, these findings suggest that demographic factors such as age and sex may reflect the likelihood of occupational or recreational environmental exposures rather than actual susceptibility to infection.

Race/Ethnicity

Racial and ethnic disparities in blastomycosis rates have been documented. Persons of Aboriginal ethnicity were found to be disproportionately affected in Canada [67, 70].

In Wisconsin during 2001–2010, the mean annual reported incidence per 100,000 population was substantially greater among Asians (6.6) and American Indians (7.2) than among African Americans (2.0) and whites (1.6) (WDPH, unpublished data). In Louisiana and Illinois, higher incidence rates [63] and mortality rates [61] among blacks have been observed, and a Mississippi study found black race to be an independent risk factor for infection [68]. More recently, a Wisconsin outbreak occurring during 2009–2010 affected a disproportionately large number of persons of Hmong ethnicity [73]. Variations in immune response or other genetic factors may account for these observed racial and ethnic disparities, but other possible explanations involve differences in socioeconomic status, access to medical care, or other unmeasured sociocultural factors.

Outdoor Activities and Place of Residence

A variety of specific outdoor activities have been identified as risk factors for blastomycosis, as infection is presumed to result primarily from exposure to soil, dust, or organic matter, particularly where it has been disturbed, such as during construction or excavation. Studies of case series in Indiana and Tennessee have shown an increased number of cases coinciding with local excavation or construction projects [42, 64]. Accordingly, results of some studies suggest that blastomycosis is more common among persons with outdoor occupations that expose them to soil [68, 69].

Outbreak investigations provide opportunities to learn about the environmental risk factors for acquiring blastomycosis, although the delay (weeks to months) between exposure and symptom development may limit an infected individual's ability to accurately recall all of the instances during which they may have been exposed to *B. dermatitidis*. Among 15 documented outbreaks, 12 involved a confirmed or presumed shared exposure: five of these involved common activities, such as hunting, camping, or fishing, and six involved actual or presumed exposures to construction, excavation sites or digging activities (Table 1). Among six point source outbreaks, five involved participation in activities along a riverbank or lakeshore, and one was associated with proximity to a yard waste site (Table 1).

In contrast, investigation of other outbreaks, case series, and veterinary cases occurring among strictly indoor pets do not implicate specific outdoor activities as risk factors [38, 53, 63, 72, 74]. Outbreaks apparently unrelated to shared exposures may support the hypothesis that place of residence plays a larger role in the acquisition of blastomycosis than participation in specific outdoor activities. Exposures near the home may be a particularly likely explanation in hyperendemic areas, where ecologic conditions that support the growth of the fungus are thought to be most favorable. The occurrence of multiple cases of blastomycosis among members of the same household during a period of several years supports this hypothesis [53]. Canine blastomycosis has long been believed to act as a sentinel for human disease, presumably because dogs are likely to have more outdoor exposures, particularly exposures near the home, than their human counterparts [74]. Recently, evidence of the organism from the air in a basement further supports the theory that blastomycosis may result from exposure to *B. dermatitidis* in or near the home [75].

Immunosuppression

Blastomycosis appears to primarily affect immunocompetent persons, and is not considered to be an opportunistic infection, though the presence of underlying medical conditions or immunosuppression has been occasionally recognized as a risk factor for blastomycosis. For example, a Canadian case-control study demonstrated immunosuppression for any reason and collagen vascular disease to be independent risk factors for illness [69].

There are few comprehensive data characterizing blastomycosis among immunosuppressed persons, but extensive pulmonary involvement and complications such as respiratory failure are more common among immunocompromised patients than among healthy persons [76]. Extrapulmonary infection, including cutaneous involvement, multiple visceral organ involvement, and central nervous system disease, has also been observed to be more common among immunocompromised patients [76, 77•].

Unlike other infections caused by dimorphic fungi, blastomycosis is not a typical AIDS-defining illness. The illness may result from endogenous reactivation of *B. dermatitidis* in nearly 30 % of patients with AIDS who are diagnosed with blastomycosis [78]. Blastomycosis is similarly uncommon among solid organ transplant recipients. Retrospective review data from three Midwestern medical centers suggest a post-transplant combined histoplasmosis and blastomycosis incidence rate of 0.5 %, and cases were associated with high rates of disseminated infection, graft loss, and overall mortality [77•].

Prevention

Blastomycosis can be debilitating and costly. The median hospital charge in 2006 for treating an adult infection was estimated to exceed $20,000 [71]. Because there are currently no recommendations or guidelines for preventing blastomycosis, there is an increasing need to focus public health research efforts on prevention of this infection. Specifically, further insight into the pathogenesis of blastomycosis and host immune response to blastomycosis is

warranted. For example, the interleukin-12/interferon-γ pathway is thought to mediate the adaptive immune response against fungal infections, and defects in this pathway have been shown to be associated with increased susceptibility to developing severe or disseminated infections that are similar to blastomycosis (histoplasmosis, coccidioidomycosis, and paracoccidioidomycosis) [79–81]. Research examining the role of this pathway and other aspects of the host immune response against blastomycosis may help to delineate future opportunities for prevention.

The WI-1/BAD-1 adhesion protein has been identified as a major virulence factor and is the primary antigen target for immune response against blastomycosis [82]. Recently, a live attenuated strain of *B. dermatitidis* lacking BAD-1 was used to develop a vaccine against blastomycosis which was proven to be safe and immunogenic in dogs [83•]. Additional research into the development of a human vaccine against blastomycosis is warranted. A vaccine could ultimately benefit individuals thought to be at greater risk of acquiring the infection or immunosuppressed persons at greater risk of developing complications resulting from blastomycosis.

Other methods which may help to reduce the overall burden of disease include the development of more rapid and specific serologic and molecular diagnostic methods that would help to minimize delays in diagnosis and treatment [14, 15•]. Similarly, improved culture and molecular tools for detecting *B. dermatitidis* in the environment would facilitate a better understanding of its ecologic niche, which may inform directions for prevention. In the future, predictive models may be able to more precisely characterize the risk of blastomycosis based on location, climate, and other environmental factors.

Conclusions

The epidemiologic and ecologic features of blastomycosis are not as well understood as those of other mycoses endemic to North America. Knowledge about the burden and distribution of blastomycosis relies on evidence from reporting of patients with symptomatic illnesses, and our understanding of the natural habitat of *B. dermatitidis* is hindered by the difficulty associated with isolating it from the environment.

Despite these limitations, the public health burden of blastomycosis appears to have been increasing during the past several years. The reasons for this observed increase are unclear, and may represent improved awareness, recognition, or reporting of the disease. An alternative or concomitant hypothesis involves environmental modification: anthropogenic dispersal and the growing threat of global climate change have the potential to alter the natural habitats of pathogenic fungi in ways which are not yet fully apparent [60, 84].

Because the clinical signs and symptoms of blastomycosis are commonly indistinguishable from those of other respiratory infections, increasing healthcare provider and community awareness is an important method to combat the public health burden of this infection, the magnitude of which is likely underestimated. Further collaboration between healthcare providers and public health experts is needed to facilitate earlier diagnosis and treatment of blastomycosis and develop effective methods for prevention.

Disclaimer The findings and conclusions of this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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