

Epidemiology of Blastomycosis in a Region of High Endemicity in North Central Wisconsin

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The clinical and epidemiologic features of 73 patients with laboratory-confirmed blastomycosis who were identified over an 11-year period in North Central Wisconsin are presented. Pulmonary disease was the sole manifestation in 77% of patients. More than one-half of all patients had symptoms that included fever, cough, weight loss, night sweats, and pleuritic chest pain. Virtually all were previously healthy, and most did not have an outdoor occupation. However, 82% of these patients lived or had visited within 500 m of rivers or associated waterways. The majority experienced the onset of symptoms between December and April. The estimated mean annual incidence rate of infection for Vilas County was 40.4 cases per 100,000 persons, and that for the largest city in the county was 101.3 cases per 100,000 persons. Several areas with an exceptionally high incidence of the infection were observed. We suggest that, in regions where blastomycosis is hyperendemic, clinical disease is most often pulmonary and occurs in immunocompetent individuals and that residence near an ecological focus may be a greater risk factor for acquisition of blastomycosis than is occupation.

Blastomycosis, a disease of humans, canines, and other animals, is caused by the dimorphic fungus *Blastomyces dermatitidis*. With the exception of inoculation disease [1, 2], blastomycosis is a systemic process. Primary infection occurs after spores from the environment are inhaled; transition to the yeast form occurs in the lungs [3, 4]. The incubation period for clinical disease is 21–106 days following exposure to the organism [5]. Acute pulmonary infection may be asymptomatic or mild and self-limited [5–7]. Conversely, severe acute pneumonia or chronic pulmonary disease may occur. Dissemination may result in single or multiple lesions of the skin, bone, joints, genitourinary tract, CNS, or other organs [3, 4]. Endogenous reactivation is occasionally seen, sometimes many years after primary exposure [8].

In North America blastomycosis is endemic in the southeastern United States (with the exception of Florida), the states comprising the Ohio and Mississippi River basins, and around the Great Lakes [9, 10]. The precise ecological niche(s) within areas of endemicity have not been defined but appear to be characterized by an acidic pH, high organic content (due to rotting or decayed wood or vegetation and animal or bird droppings), abundant moisture, and proximity to waterways [4, 11].

In a previous report Vilas County, located in North Central Wisconsin, was shown to have the highest incidence of blastomycosis in the state on the basis of laboratory data [12]. The waterways of southeastern Vilas County have been associated with clusters of canine cases [13] and have been the site of two large outbreaks of blastomycosis [5, 7].

We report the clinical presentations and epidemiologic features of 73 cases of laboratory-confirmed blastomycosis in residents of and visitors to the Vilas County area over an 11-year period.

Background

Vilas County, which is 867 square miles in size, is located in North Central Wisconsin and borders Upper Michigan at a latitude of 46° north and a longitude of 89°–90° west. It is bordered by the Wisconsin counties of Iron to the west, Oneida to the south, and Forest to the east. According to census figures, the population of the county was 17,707 persons in 1990. The only incorporated city, Eagle River, serves as the county seat; it is located in southeastern Vilas County and has a population of 1,374 persons. The elevation ranges from approximately 1,600 to 1,845 feet above sea level [14, 15].

Approximately 73% of Vilas County is forest and the balance is composed of waterways. The combined shorelines of all lakes and streams total ~2,300 miles. The soil primarily consists of sandy loams; however, 79,446 of the 648,130 acres are classified as deep organic soils; 10,637 acres are classified as level, wet bogland with acid peat; and 1,551 acres are classified as floodplain soils. The average tempera-

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ture in Vilas County is 39°F. The growing season is ~105 days. The average annual rainfall is 65 in (including 50–60 in of snow per year). Snow covers the ground ~120 days of the year [14, 15].

Methods

Patients with blastomycosis who resided in or visited Vilas County and adjacent portions of Oneida and Iron Counties were identified for the period November 1979 through December 1990. Names, ages, genders, addresses, phone numbers, and clinical data on patients with confirmed or suspected cases of blastomycosis were obtained from the following sources: (1) case reports at the Vilas County Health Department, where countywide records based on mandatory physician and laboratory reports have been compiled since 1984; (2) inpatient and outpatient case records from the 41-bed community hospital in Eagle River, from an affiliated 99-bed secondary referral hospital located in Woodruff, Wisconsin (1 mile south of the southwestern portion of Vilas County), and from the only other hospital in Vilas County, a 19-bed community hospital located in Phelps, Wisconsin; and (3) individuals who had suspected cases of blastomycosis (as ascertained during interviews of patients with blastomycosis).

Only cases confirmed by culture or histology were included in the study. These were documented by examination of medical records, examination of Vilas County Health Department records, or both.

All patients for whom current addresses or telephone numbers were available were contacted for a personal or telephone interview. For information on deceased persons or children, spouses or parents were interviewed.

Available subjects were questioned in detail with regard to major medical illnesses (diabetes, hypertension, heart disease, lung disease, cancer, or other chronic illnesses), smoking, prescription medications, and treatment and outcome of the case of blastomycosis. The date of onset of illness and details with regard to presentation were sought. Subjects were specifically questioned about signs and symptoms, including elevation in temperature, cough, weight loss, night sweats, myalgias, pleuritic chest pain, and hemoptysis. Residential and occupational histories and a description of homesteads and places frequented were obtained. Subjects were posed open-ended questions about their activities over a 6-month period before the onset of symptoms of blastomycosis and were prompted, if necessary, to include outdoor and recreational activities (digging, exposure to rotten wood, gardening, purchase of soil or other lawn and garden material, excavation or exposure to excavation sites, and travel). They were similarly queried with regard to involvement in and location of hunting, fishing, or other hobbies; exposure to beaver dams or lodges; and contact with other persons or animals with blastomycosis or similar symptoms. Informa-

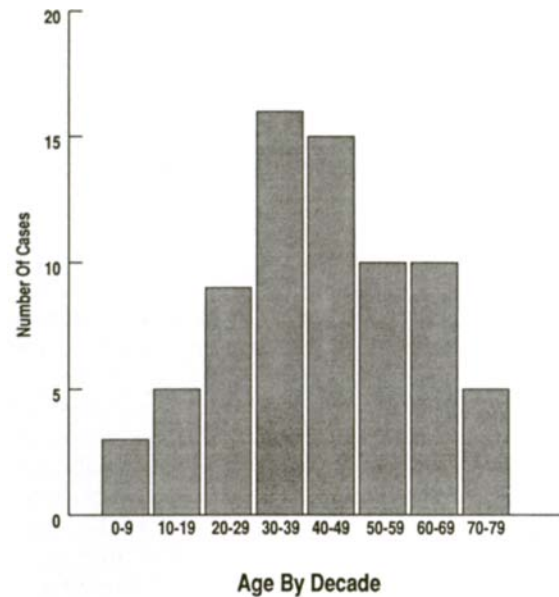


Figure 1. Age distribution in 73 cases of laboratory-confirmed blastomycosis by decade.

tion on pet ownership and cases of blastomycosis in pets was included.

For each case we attempted to identify one or more activities that may have led to exposure to *B. dermatitidis*; historical factors that were examined included timing, location, unusual exposure to soil, and contact with canines or other humans with blastomycosis.

Mean annual incidence rates were calculated with use of 1990 census data on permanent residents of Vilas County and the Eagle River area (Cloverland, Lincoln and Washington Townships, and the City of Eagle River); these data included the home addresses of the residents at the time of diagnosis (visitors were excluded) in these areas for the years 1984 through 1990 (there was mandatory reporting of blastomycosis during these years).

Categorical data were analyzed using the χ^2 test with Yates' correction. *P* values <.05 were considered significant.

Results

Seventy-three laboratory-confirmed cases of blastomycosis were identified in the Vilas County area from November 1979 through calendar year 1990. Reports of 48 cases were on file at the Vilas County Health Department; 19 additional cases were identified at the three local hospitals; and six other cases were identified following interviews of patients with blastomycosis. Sixty-four cases occurred in residents, and nine occurred in visitors to the area; these 64 of 73 cases occurred in residents of or visitors to Vilas County, seven cases were related to northern Oneida County, and two were related to Iron County.

The distribution of ages, by decade, for all 73 patients is shown in figure 1. The average age was 42.4 years, and the

Table 1. Symptoms in patients with pulmonary blastomycosis.

Symptom	No. of patients (%)*
Cough	41/48 (85)
Fever	31/48 (65)
Night sweats	28/46 (61)
Pleuritic chest pain	29/50 (58)
Weight loss	29/50 (58)
Myalgias	15/44 (34)
Hemoptysis	8/48 (17)

* Denominator indicates number of interviewed patients who recalled details of symptoms.

median age, 42.0 years. Forty-five patients (62%) were male, and 28 (38%) were female.

Sixty-one patients (84%) submitted to interviews by one of the authors. Eleven patients or their relatives could not be contacted, and one patient would not return our calls. Available demographic data for these 12 patients are included in the results.

Clinical features. For 56 (77%) of our 73 patients, pulmonary disease was recorded as the only manifestation of blastomycosis. Three patients (4%) had skin lesions only, and two patients (3%) had osseous blastomycosis only. Eleven patients (15%) had disseminated blastomycosis, which was defined as involvement of two or more organ systems. One of these patients had CNS involvement (the brain). One patient had cholangitis due to blastomycosis, and her case has been previously reported [16].

The frequency of presenting symptoms in the 50 patients with pulmonary blastomycosis who were interviewed is shown in table 1. Weight loss was 10 lb or greater in 19 (68%) of 28 patients who could quantify their loss. Fever persisted 2 weeks or more in 20 (71%) of 28 febrile patients who could precisely date this symptom. Thirty-five percent, however, had not been aware of any fever. Three of our 61 patients who were interviewed had incidental pulmonary blastomycosis that was initially discovered on routine chest roentgenography, and they remained asymptomatic.

Two elderly patients with pulmonary blastomycosis suffered from worsening diabetes mellitus and congestive heart failure before the onset of symptoms of blastomycosis, had ceased most of their previously extensive outdoor activity for several years before the onset of symptoms, and may have had reactivation of previously asymptomatic infection. All four interviewed patients who had bone disease as the presenting complaint recalled having sustained a prior injury or having chronic pain in the affected joint before onset of the symptoms of blastomycosis.

The treatment history of the disease was available for 62 patients and is summarized in table 2. One patient, who had severe diabetes mellitus and congestive heart failure, died of pulmonary blastomycosis despite having received therapy

Table 2. Treatment history of 62 patients with blastomycosis.

Initial treatment (no. of patients treated)	No. of patients whose treatment failed or who had recurrence of infection	Subsequent treatment (no. of patients treated)*
Ketoconazole (30) [†]	5	Amphotericin B (4); itraconazole (1)
Amphotericin B (28) [‡]	2 [§]	Itraconazole (1)
No treatment (3)	0	
Fluconazole (1)	0	

* No patient who received subsequent treatment experienced recurrence of infection.

[†] Seven patients were observed <2 years.

[‡] Six patients were observed <2 years.

[§] One patient died.

with amphotericin B. The only other known death attributed, in part, to blastomycosis in our 73 cases occurred in a patient with a prior history of bone blastomycosis. Pulmonary blastomycosis and lung cancer were both documented at autopsy for this patient.

Table 3 contains data on 59 of our patients who provided information with regard to underlying disease at the time of onset of blastomycosis. Fifty-six of these patients were also questioned about smoking. The majority of patients had no underlying disease and were nonsmokers.

Epidemiologic features. One patient experienced the onset of symptoms in November 1979; two patients developed symptoms in calendar year 1982; and three developed symptoms in 1983. The distribution of the remaining 67 cases, by year, from the start of recording of mandatory reports in 1984 through 1990, varied between seven (1984 and 1986) and 16 (1990). The month of onset of symptoms was determined from hospital records or personal interviews in 69 cases and is illustrated in figure 2.

Table 3. Underlying medical conditions in patients with blastomycosis.

Condition	No. of patients (%)*
Smoking	17/56 (30)
Diabetes mellitus	8/59 (13)
Hypertension	6/59 (10)
Coronary artery disease	5/59 (8)
Remote history of cancer	4/59 (7)
Congestive heart failure	3/59 (5)
Active cancer (lung)	2/59 (3)
Alcoholism	2/59 (3)
Cerebrovascular accident	2/59 (3)
Chronic lung disease	1/59 (2)
Oral steroid use	1/59 (2)

* Denominator indicates number of interviewed patients who recalled details of conditions.

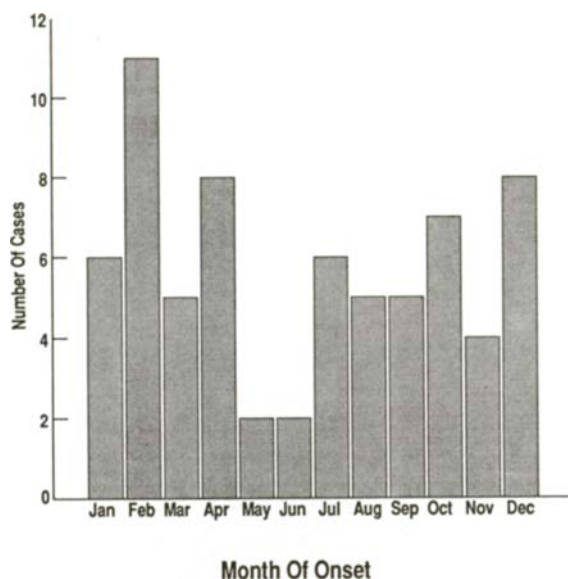


Figure 2. Distribution of 69 cases of blastomycosis, by month of onset, in which definitive onset of symptoms could be determined.

On the basis of data from the 50 Vilas County residents who developed blastomycosis between 1984 and 1990, it was determined that the mean annual incidence rate for blastomycosis in Vilas County was 40.4 cases per 100,000 persons. The mean annual incidence rate during this same period for the Eagle River area was 101.3 cases per 100,000 persons. Within Vilas County, the Eagle River area (the City of Eagle River and three adjacent townships) contained 32% of the population of Vilas County in 1990 yet accounted for 46 (82%) of 56 cases of blastomycosis that occurred in County residents during the duration of this study.

Figure 3 illustrates the distribution throughout Vilas County of 64 of the 65 patients with blastomycosis for whom addresses were available. For visitors the postulated site of likely exposure is indicated; in seven of nine of these cases, the area about the dwelling that was visited was implicated. One visitor had significant lowland exposure east of the city of Eagle River (location used for our analysis) but also had a permanent residence on the Fox River near Kaukauna, Wisconsin, an area associated with clusters of canine cases [13]. The majority of residents were considered to have been exposed near their place of residence; dots on figure 3 represent home addresses for all Vilas County residents with blastomycosis.

Overall, specific potential, nonresidence sites of exposure were identified in eight cases. These include the Wisconsin River near the area of the beaver pond outbreak [5], a popular fishing spot (six persons); a workplace near the Wisconsin River in Rhinelander, Wisconsin, where significant excavation had taken place; and an area of tornado-damaged timber near St. Germain. In addition, 12 persons had outdoor occu-

pations that resulted in widespread exposure in Vilas and Oneida Counties.

A great majority of exposures speculatively occurred along the Eagle River chain of lakes and the Eagle and Wisconsin Rivers, particularly near State Highway 70, west of Eagle River, near and below the confluence of the Eagle and Wisconsin Rivers (figure 3). Thirty-one (44%) of 70 patients for whom proximity to waterways could be determined lived or had visited within 500 m of the Wisconsin or Eagle Rivers, their confluence, or tributary creeks; four patients lived or had visited within 500 m of the associated chain of lakes. Sixteen others lived or visited within 500 m of other rural lakes; two, near swamps; three, near a creek; and one, near a pond. Only 13 (18%) of these 70 patients resided or visited >500 m from a body of water.

We noted that the areas of greatest concentration of blastomycosis cases, or sites of outbreaks, are characterized by dense growths of conifers. State Highway 70 on the western portion of the City of Eagle River is populated primarily by red pine (*Pinus resinosa*), eastern white pine (*Pinus strobus*), and other mature conifers. The areas of the beaver pond outbreak [5], the Watersmeet Lake outbreak [7], and the Lost Lake outbreak detailed below are characterized by coniferous forests and also include significant proportions of scrub pine, particularly balsam fir (*Abies balsamea*).

Six sets of common-source or same-household exposure occurred during the period of this study. The large beaver pond outbreak has been previously reported by Klein et al. [5], and those patients (all visitors) were not included in this study. Four individuals were associated with a previously reported outbreak of human and canine blastomycosis [7] and are included in this study. Three sets of same-household exposure were identified.

The sixth set, which is reminiscent of an excavation-associated outbreak in Eagle River in 1988 [7], occurred between June and October 1990 on a lakeshore near St. Germain.

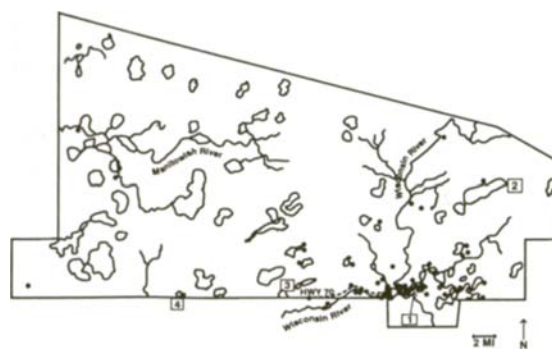


Figure 3. Geographic distribution of 64 cases of blastomycosis in Vilas County, Wisconsin, between November 1979 and December 1990. Each dot represents one case. 1, Eagle River; 2, Phelps; 3, St. Germain; and 4, Woodruff. Smaller lakes and streams are not shown.

Table 4. Mode of exposure of patients with blastomycosis.

Epidemiologic feature	No. of patients (%)*
Fishing	30/60 (50)
Hunting	19/58 (33)
Gardening	15/45 (33)
Outdoor occupations	13/39† (33)
Associated excavation	17/60 (28)
Exposure to beaver structures	16/59 (27)

* Denominator indicates number of interviewed patients who recalled details.

† Number of patients employed at the time of exposure.

This involved two tourists and one canine who were staying two houses from an excavation site that was associated with three canine cases of blastomycosis that occurred during that same period.

Canine and human cases of blastomycosis were frequently associated in this study. Of 31 patients who had owned or kept dogs at the address of likely exposure, 10 (32%) reported that at least one of their dogs had been diagnosed with blastomycosis by their veterinarian. For seven of the 10 owners, blastomycosis occurred in their dogs at least 6 months before or after the owners' onset of symptoms.

Table 4 summarizes additional epidemiologic data (mode of exposure) specifically sought from patients who were interviewed. One-half (26/52) of these patients were visitors to the area or had resided in the area for ≤ 3 years at the time of exposure.

In this study 38 (55%) of 69 patients experienced the onset of their symptoms during the months December through April. There were, however, no significant differences between the proportion of interviewed residents with defined onset of pulmonary blastomycosis who admitted to hunting ($\chi^2 = 0.01$), fishing ($\chi^2 = 0.16$), or either activity ($\chi^2 = 0.002$) when those with December–April onset were compared with those whose illness began in the other 7 months.

Nearly one-third of patients had speculatively associated excavation with the acquisition of blastomycosis; 14 implicated nearby excavation sites, including basements, garages, and roads, and five had occupations as excavators and/or bulldozers. In addition, digging in the yard or gardening (four patients), raking of leaves or pine needles (five patients), and working with rotten wood (five patients) were implicated as likely mechanisms of exposure.

Thirty-nine patients were employed at the time of presumed exposure; of these, 33% were engaged in outdoor occupations. Besides the five persons who were excavators, three were employees of public utilities and recalled removing rotten utility poles, sometimes near riverbanks; two were landscapers; and one was a logger. Of these 11 patients who had significant occupational exposure to soil, seven had worked at these jobs in the Vilas County area for >2 years

(range 4–35 years). Seven patients recalled no significant outdoor activities or exposure to soil or excavation sites in the 6 months before the onset of symptoms, although five of these individuals lived in the area of concentrated cases along the Eagle/Wisconsin Rivers.

Discussion

This data demonstrates that blastomycosis in the Vilas County, Wisconsin area is highly endemic, with an estimated annual incidence rate of 40.4 cases per 100,000 population for the County and 101.3 cases per 100,000 persons for the Eagle River area. These figures are substantially higher than the highest previously reported incidence rate for a population in North America, i.e., 6.8 cases per 100,000 population in Washington Parish, Louisiana [17].

Findings on median age (42 years), age distribution, and ratio of males to females (1.6:1) in our study are similar to those in other recent reports from Louisiana [17], Arkansas [18], and Wisconsin [12]. Findings on the distribution of organ system involvement in this study, however, are dissimilar from those in other reports. Pulmonary disease accounted for 77% of our cases, compared with 27%–59% in other studies [17–19]. The low rate of extrapulmonary disease may be explained by the hypothesis that physicians in this area of high endemicity diagnose pulmonary blastomycosis quickly, even in early and mildly symptomatic cases. Thus, potentially self-limited pulmonary infections were identified that in other areas may not have been detected and reported. Similarly, early diagnosis and treatment of pulmonary disease may have led to fewer patients developing extrapulmonary manifestations.

Cough was reported by 85% of patients with pulmonary blastomycosis, but a significant proportion had no history of fever. Clinical criteria which include both cough and fever for the presumptive diagnosis of blastomycosis are likely insensitive. Early diagnosis requires a high index of suspicion and appropriate laboratory testing.

The treatment histories in our series reflect the recent popularity and relative success of oral imidazole therapy for blastomycosis. Overall, the prognosis is favorable with prompt diagnosis and treatment. Only two of 73 patients have thus far suffered death attributable, in part, to blastomycosis, and both had significant concurrent illnesses. Mild or asymptomatic disease, which is now well recognized [5–7], was also evident in our study.

Lowry et al. [17] in their case-control study in Louisiana found no association among factors including smoking, alcohol intake, diabetes mellitus, chronic lung disease, or steroid use with blastomycosis. Similarly, smoking and underlying medical disease were present in a minority of our patients. Most commonly, blastomycosis affected patients with apparently normal immune systems, a concept previously suggested [11, 20].

The abundant forests and waterways that typify Vilas County are characteristic of other areas of high endemicity for blastomycosis [3, 17, 19], although the altitude of the County (487–561 m above sea level) is higher than that of high-prevalence areas of Arkansas (59–114 m above sea level) [21] and Louisiana (30–105 m above sea level) [17].

High endemicity has been associated with the loblolly (*Pinus taeda*) and shortleaf (*Pinus echinata*) pine forests in the southeastern United States [17, 21]. In Vilas County, a similar association with scrub and mature pine has also been suggested. Whether this association reflects the fact that by-products of the growth and decay of such conifers encourages growth of *B. dermatitidis* or rather that the composition and acidity of the soil favors the growth of *B. dermatitidis* (and is also optimal for certain species of pine) is unclear.

The findings of this study also suggest an association between habitation along waterways and acquisition of blastomycosis, as has been previously observed for human [12] and canine [13] disease. Lakes and streams have also been implicated by study of outbreaks [5, 7, 22, 23]. It is again unclear whether the association with riverbanks reflects conditions favorable to the organism such as optimum soil types, abundant moisture (perhaps with changing water levels), and frequent animal waste deposits, or rather the fact that exposure is increased because of the popularity and accessibility of waterways as places to hunt, fish, and recreate [11, 20].

In our study a nonrandom distribution of cases within the County was observed. A significant cluster was demonstrated surrounding the confluence of the Eagle and Wisconsin Rivers near the City of Eagle River, the site of previously reported large outbreaks of blastomycosis [5, 7] and clusters of canine cases [13]. This clustering of cases could not be explained on the basis of population distribution, as other populated waterways of the County were relatively spared, including the area of the Manitowish River. One would presume that soil and other environmental factors are less favorable for the growth of *B. dermatitidis* in these other regions.

Vaaler et al. [9] studied forestry workers in northern Minnesota and North Central Wisconsin, including the Vilas County area. Using an antigen-specific lymphocyte stimulation assay, they demonstrated a 30% incidence of presumed remote subclinical blastomycosis among these individuals who had sustained intense outdoor exposure. The fact that a higher level of previous exposure to *B. dermatitidis* was not demonstrated for an occupational group thought to be at high risk and that some of the excavators and landscapers in our study had performed these tasks in the region for several years before infection suggests that the organism may not be commonly encountered, even in areas of high endemicity.

All of this evidence supports the concept of scattered, perhaps fluctuating, microfoci of *B. dermatitidis* within macrofoci of high endemicity, as suggested by Sarosi and Davies [20]. Some of these microfoci, however, may be relatively persistent or recurrent within the macrofoci. This is sug-

gested by the clustered cases (including same-household contacts) and the commonly associated canine disease observed in this study and the demonstration, albeit rare, of periodic isolations from the same site in nature [24, 25].

The association between canine and human disease has been previously recognized [7, 13, 26, 27] and presumably reflects similar environmental exposures rather than the pet acting as a fomite. This is supported in our study by the lack of close temporal association between most related human and canine cases.

In our study over one-half of patients experienced the onset of disease during the months December–April. As summarized by Klein et al. [11], in most prior studies a peak incidence of human disease has been observed in the winter, although Lowry et al. [17] found no seasonality in Louisiana. The onset of disease in winter would suggest a peak human exposure in the fall and early winter. One might hypothesize that activities, such as hunting, during this season lead to greater exposure to the natural, scattered, riparian habitat of *B. dermatitidis* [20]; however, neither hunting nor fishing was a more prevalent activity among the patients in our study who were exposed from December through April. This particular season may instead afford environmental and climatic conditions favorable to the fungus.

The presence of rotten wood and animal droppings has been associated with successful isolations of *B. dermatitidis* from natural sources [5, 24, 28], and the banks of waterways may be common places for human contact with animal excreta. With the coming of fall and the unavailability of green plants, a shift in diet to include stems and bark occurs among some animals that are native to North Central Wisconsin. Such animals include beaver (*Castor canadensis*, whose scats are largely deposited in water); white-tailed Deer (*Odocoileus virginianus*); the eastern cottontail (*Sylvilagus floridanus*); snowshoe hares (*Lepus americanus*, whose scats are deposited on the ground); and porcupines (*Erethizon dorsatum*, whose scats are deposited about bases of trees, burrows, and hollow logs). The cottontail, snowshoe hare, and beaver also engage in coprophagy and produce excreta of highly digested wood by-products [29, 30]. Thus, the potential contribution of such excreta to acquisition of disease in the fall must be considered.

In conclusion, the results of our study do not indicate that blastomycosis is restricted to persons who have experienced intense outdoor exposure to *B. dermatitidis*. Similarly, a case-control study of Washington Parish, Louisiana by Lowry et al. found no association between cases of blastomycosis and outdoor occupations, hunting, gardening, or camping [17]. Place of residence or visitation was not a controlled variable in our study, but the majority of patients with blastomycosis lived or visited near waterways. Thus, it may be speculated that in areas hyperendemic for blastomycosis such as North Central Wisconsin, place of residence may be

a greater risk factor for acquisition of blastomycosis than is the degree of outdoor exposure.

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