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Blastomycosis in Missouri: epidemiology and risk factors for endemic disease

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SUMMARY

Between 1992 and 1999, 93 cases of blastomycosis, including 25 laboratory confirmed cases, were identified in Missouri (annual incidence, 0·2/100 000 population). Mississippi County in southeastern Missouri had the highest incidence (12/100 000) with a much higher rate among blacks than whites in this county (43·2/100 000). The mortality rate, 44% was also higher among blacks. To determine risk factors for endemic blastomycosis, a case-control study was conducted among southeastern Missouri residents. Independent risk factors for blastomycosis were black race and a prior history of pneumonia. No environmental exposures or socioeconomic factors were significantly associated with increased risk. The increased risk among blacks may possibly be related to genetic factors, but further studies are needed to clarify this. However, heightened awareness of the disease and a better understanding of the risk factors are important and may lead to earlier diagnosis and start of treatment, possibly improving outcome.

INTRODUCTION

Blastomycosis is an uncommonly diagnosed fungal infection caused by the dimorphic fungus, *Blastomyces dermatitidis* and is primarily acquired by inhalation. The clinical presentation can range from asymptomatic infection to subacute pneumonia and dissemination to a variety of extrapulmonary sites.

Most cases of blastomycosis in the United States occur in areas around the Mississippi River basin, the Great Lakes and the Southeast [1]. Although it is reportable in some states where it is endemic, information on the incidence of disease is limited. Outbreaks of blastomycosis have provided us with important information on epidemiologic features of the disease [2]. However, these outbreaks are rare, and risk factors for endemic disease are still not well understood. From 1992 to 1999, 36 cases of culture-confirmed blastomycosis were reported to the Missouri State Reference Laboratory. Twenty of these cases occurred in five counties in the southeastern part of the state, and of those, 12 (60%) were in

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Mississippi County. Of those 12 cases, nine, including four deaths, occurred in blacks. Although blacks account for a small proportion of the population in Mississippi County (12%), a large proportion (44%) of deaths due to blastomycosis occurred among blacks. Although it was previously noted that blacks were more frequently infected with blastomycosis than whites [3], race has not been documented as an independent risk factor for blastomycosis.

To estimate the incidence of blastomycosis in Missouri and to describe the demographic and clinical features of persons with the disease, we retrospectively reviewed hospital-based and laboratory-based records to identify confirmed cases between 1992 and 1999. We also performed a case-control study to identify risk factors for blastomycosis and to determine possible preventive measures.

METHODS

Case definition

A 'laboratory-confirmed' case of blastomycosis was defined as a positive culture or histopathology for *Blastomyces dermatitidis* from any body site in a resident of Missouri during the study period from 1 January 1992 to 31 December 1999. A 'surveillance' case of blastomycosis was defined by the presence of a discharge diagnosis of blastomycosis, upon review of the hospital discharge database, but without laboratory confirmation.

Case finding

To identify potential cases of blastomycosis, we reviewed the following: (1) microbiology records with positive cultures and/or histopathological findings of *B. dermatitidis* from the Missouri State Reference Laboratory and hospital and pathology laboratories, and (2) the Missouri hospital discharge database listing ICD-9 Codes. All records that had blastomycosis ICD-9 Code (116·0) were identified. However, for practical purposes, we only reviewed individual medical records of patients in the hospitals included in the study area, which consisted of eight southeastern counties (Mississippi, New Madrid, Pemiscot, Scott, Stoddard, Dunklin, Butler and Cape Girardeau). Information was collected on demographic and clinical characteristics, social history, medical history and outcome of blastomycosis.

Case-control study

A case-control study was performed to determine risk factors for endemic blastomycosis. A case-patient was defined as a patient with a positive culture of histopathological findings consistent with blastomycosis in a Southeastern Missouri resident in the study area during 1992–1999 ('laboratory-confirmed' case). Four controls were enrolled for each case-patient and were matched by sex, age group (18–34, 35–64 and $\geqslant 65$ years) and city or county. Controls were randomly selected from the city or township personal property tax list. A list of controls was generated using random digit table (Epi-Info version 6.04b, CDC, Atlanta, GA).

Using a standardized questionnaire, we interviewed case-patients and controls by telephone, and approximately three attempts were made to contact subjects who were initially unavailable to participate in the interview. The following information was collected: demographics; proximity of residence and work place to a body of water, farm or wooded area; occupational and recreational activities with exposures to soil and water, pets and other animals; social history; medical history; and access to health care. Information on activities and exposures was collected for the year prior to the interview for control subjects and during the year before the diagnosis of blastomycosis for case-patients. Additional information was obtained from case-patients regarding the medical course of their illness and hospitalization. Surrogates were interviewed when patients were unable to respond to the questionnaire because of impaired mental status or death.

Statistical analysis

Population denominators were obtained from the 1992 to 1999 intercensus data for Missouri. The mean annual incidence rates of blastomycosis from 1992 to 1999 were calculated for the state, for each county and for regions within the state. Data on blastomycosis cases before 1992 were unavailable for comparison.

Data were analyzed using Epi-Info version 6.04b (CDC, Atlanta, GA) and SAS version 6.12 (SAS Institute, Cary, NC). Categorical variables were compared with the Fischer's exact test, while continuous variables were compared with the Wilcoxon two-sample text. Epi-Info was used for matched univariate analysis in the case-control study. Factors found to be statistically significant ($P \leqslant 0{\cdot}15$) in the matched univariate analysis and all potential

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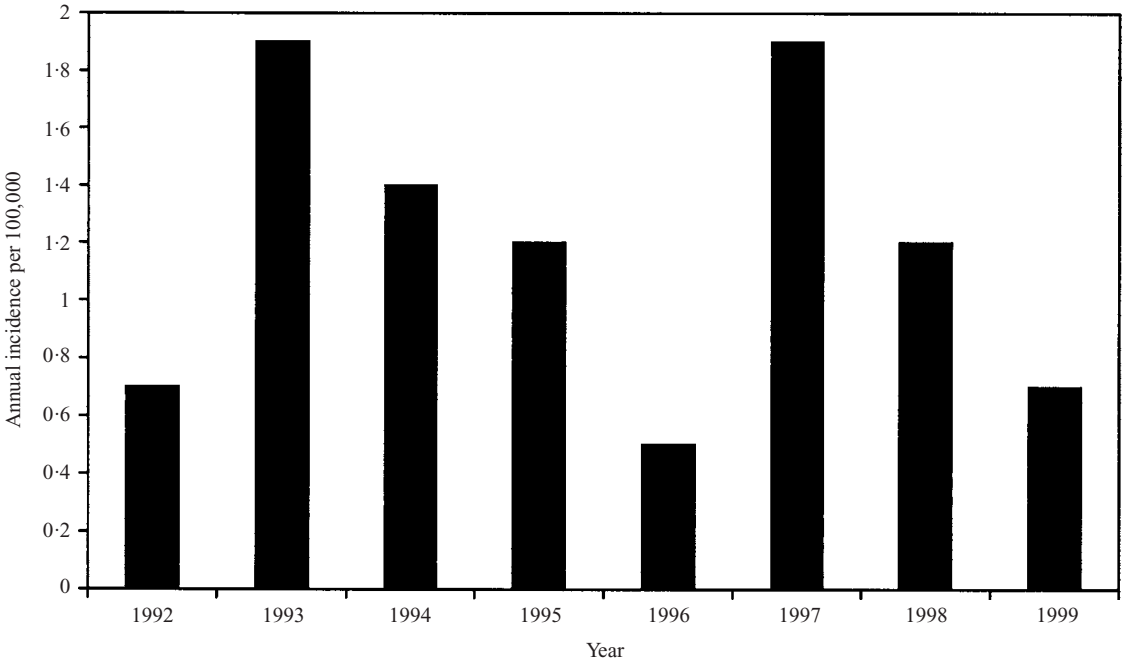

Fig. 1. Annual incidence rate of blastomycosis in southeastern Missouri, 1992–1999.

Table 1. *Distribution of blastomycosis cases (laboratory-confirmed and surveillance) by region in Missouri, 1992–1999*

Region	No. of cases	Average annual incidence (per 1 000 000 population)
Central	4	0·8
East	14	0·9
Northeast	2	1
Northwest	9	0·9
Southeast*	42	10
Southwest	22	4
Total	93	2

* The study area included eight counties within the region.

confounders were included in the multivariable model. Multivariable analysis was performed using backward elimination conditional logistic regression (PHREG procedure). Odds ratios (OR) and 95% confidence intervals (CI) were calculated.

RESULTS

Surveillance

A total of 93 cases of blastomycosis from 1992 to 1999 were identified, including 25 laboratory-confirmed and 68 surveillance cases, representing a statewide mean annual incidence of 2 cases per 1 000 000 population. Of the 25 laboratory-confirmed cases (positive culture or histopathology for *B. dermatitidis*), only nine were also identified in the hospital discharge database, indicating a low sensitivity (36%) of hospital discharge review for detection of blastomycosis. Although 36 cases of culture-confirmed blastomycosis were initially reported by the state reference laboratory, nine were in non-Missouri residents and were excluded from the study.

Missouri is divided into six regions, and the mean annual incidence rate for each region is shown in Table 1. The highest incidence was in southeastern Missouri, where 42 (45%) cases were identified. Figure 1 shows the annual incidence rate for southeastern Missouri during the study period. A total of 34 cases were identified in the study area, which included the following counties: Mississippi, New Madrid, Pemiscot, Scott, Stoddard, Dunklin, Butler and Cape Girardeau. Mississippi County had a total of 13 cases from 1992 to 1999, with the highest average annual incidence rate (12 per 100 000 population). Almost all the laboratory-confirmed cases (24/25) were identified in the study area.

Demographic characteristics

Medical records for 28 of 34 patients identified through the hospital discharge database and

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Table 2. *Average annual sex-, race- and age-specific rates of blastomycosis in the study area* in southeastern Missouri, 1992–1999*

Characteristic	*n* (%)	Annual incidence rate (per 100 000 population)	*P*
Sex			
Male	19 (68)	1·9	0·03
Female	9 (32)	0·8	
Race			
White	12 (43)	0·6	0·0002
Black	16 (57)	2·8	
Age			
<18	1 (4)	0·2	
18–34	8 (30)	1·7	
35–64	11 (41)	1·4	
⩾65	7 (26)	2·4	0·067

* Eight counties.

Table 3. *Clinical characteristics of patients with blastomycosis in the study area in southeastern Missouri, 1992–1999*

Characteristic	*n* (%)
Medical history (*n*=27)	
Chronic obstructive pulmonary disease	6 (22)
Diabetes	8 (30)
Anemia	10 (37)
Hypertension	9 (33)
Stroke	7 (25)
Cancer	3 (11)
HIV	1 (4)
Pneumonia	13 (48)
Symptoms (*n*=25)	
Cough	21 (84)
Fever	15 (60)
Dyspnea	13 (53)
Weight loss	11 (44)
Skin lesion	6 (24)
Headache	5 (20)

microbiology records from the study area were available for review. The case-patients were from the following southeastern Missouri counties: Mississippi (12), New Madrid (4), Pemiscot (3), Scott (2), Stoddard (1), Dunklin (1), Butler (3), and Cape Girardeau (2). Information on age, sex and race is summarized in Table 2. The mean age was 46·7 ± 18·3 years (range 17–78 years). Although blacks account for a small proportion of the population (13% in Southeastern Missouri), the incidence rate among blacks was five times higher than for whites in the study area. In Mississippi County, the annual incidence rate for blacks was 43·2/100 000 population compared with 3·4/100 000 for whites.

Of 27 case-patients from whom information about occupation was available, seven (26%) had outdoor occupations (e.g., farming, construction, truck driving).

Clinical characteristics

Selected clinical characteristics of the case-patients are shown in Table 3. The median time from onset of symptoms to diagnosis of blastomycosis was 49 days (range 6–200 days). Of 22 patients for whom information was available, 17 (77%) presented with a history of ⩾4 weeks of symptoms. Unilobar infiltrates were the most common finding on chest radiographs. Disseminated disease occurred in 21 patients: four (19%) had dissemination to the skin, two (10%) to the brain and one (5%) to the liver. No bone involvement or genitourinary disease occurred in any of the patients.

Twenty three case-patients had a positive culture for blastomycosis: 12 (52%) from sputum, 8 (35%) from bronchoalveolar lavage fluid, 2 (9%) from skin lesion and 1 (4%) from lung tissue. Information on histopathology was available for seven patients; four (57%) were positive.

Information on therapeutic interventions was available for 20 (71%) patients. Sixteen (80%) patients received antifungal therapy: amphotericin B alone (8), amphotericin followed by itraconazole (2), amphotericin B followed by ketoconazole (1), itraconazole alone (4) and ketoconazole alone (1). No further information was available on the four patients who did not receive therapy.

Nineteen (68%) patients were hospitalized for a median of 7 days (range 2–155 days); of those, five were admitted to the intensive care unit. Six (22%) patients died as a result of blastomycosis, of whom four were males, five were blacks, and four were <40 years old. The time from the onset of symptoms to the time of death varied considerably, ranging from 16 to 360 days (median of 76 days). The median number of days from the time of onset of symptoms to the time of diagnosis for those who died was not statistically significant ($P>0·05$) to that for those who survived (40 *vs.* 49, respectively). Patients who died were no more likely than those who survived to have an

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Table 4. *Risk factors for blastomycosis in southeastern Missouri, 1992–1999, univariate and multivariate analysis*

Characteristic	Patients	Controls	Matched OR (95% CI)	*P*
Univariate analysis				
Black race	12 (45)	11 (14)	12·3 (2·66–121·0)	0·0002
Diabetes	8 (33)	8 (8·5)	5·80 (1·51–21·5)	0·004
Anemia	8 (33)	4 (4·3)	10·2 (2·30–57·1)	0·00005
Cardiovascular disease	7 (29)	8 (8·5)	5·94 (1·24–24·8)	0·006
History of pneumonia	14 (58)	5 (5·3)	17·8 (4·58–90·5)	0·0000003
Family with blastomycosis	2 (8·3)	0	Undefined	0·05
Non-family members with blastomycosis	6 (25)	3 (3·2)	7·92 (1·85–107·7)	0·002
Swimming	2 (9·0)	34 (36)	0·22 (0·02–0·88)	0·039
Live or work <1 mile of				
River	5 (22)	26 (27)	0·70 (0·18–2·40)	0·74
Ditch	17 (71)	54 (58)	1·96 (0·63–6·41)	0·33
Boating	6 (25)	26 (28)	0·88 (0·25–2·81)	0·98
Hunting	8 (33)	29 (31)	1·16 (0·33–3·96)	0·98
Construction	4 (17)	13 (14)	1·33 (0·26–5·95)	0·94
Farming	5 (21)	15 (16)	1·43 (0·35–5·04)	0·56
Gardening	14 (58)	48 (52)	1·31 (0·48–3·80)	0·73
Multivariate analysis				
Black race			28·0 (2·79–280·8)	
History of pneumonia			31·6 (3·74–266·2)	

Case and control data are no. (%).

underlying medical illness (e.g., diabetes, malignancy, chronic pulmonary disease).

From the surveillance data, there were no statistically significant differences between black and white case-patients by age, sex, occupation, medical history, underlying illnesses, medications, complications of blastomycosis, treatment, type of health insurance, hospitalizations and outcome.

Case-control study

A total of 24 laboratory-confirmed cases and 94 matched controls were enrolled in the case-control study. For two cases, only three controls were enrolled. In the univariate analysis, blastomycosis was significantly associated with black race, diabetes, anemia, cardiovascular disease, history of pneumonia, having a family member with a history of blastomycosis and knowing persons who had blastomycosis (Table 4). Persons who participated in swimming as a recreation activity were at decreased risk for blastomycosis. No other recreational and occupational exposures (e.g., living or working less than 1 mile of a body of water, engaging in boating, hunting, farming and earth-moving projects during the specified year) were found to be significantly associated with blastomycosis. Tobacco or alcohol consumption and steroid use were also not significantly associated with increased risk for blastomycosis. On multivariable analysis, being black and having a history of pneumonia remained the only factors that were independently associated with increased risk of disease.

DISCUSSION

This study, initially started because of public concern that there was a large proportion of deaths due to blastomycosis, resulted in defining the burden of blastomycosis in Missouri, particularly in southeastern Missouri, and provided relevant clinical and epidemiological information on blastomycosis in an endemic area. It is also one of only a few studies that has attempted to determine risk factors for endemic blastomycosis.

The mean annual incidence rate of blastomycosis in southeastern Missouri is comparable to rates that have been reported in other states with endemic disease [3, 7–9]. For example, in Wisconsin and Mississippi, the statewide annual incidence rates were 1·4 and 1·3 per 100 000 population, respectively. As noted in other studies [3, 8], we identified counties or areas with unusually high rates of blastomycosis (e.g., 12

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cases per 100 000 in Mississippi County). Average annual incidence rates of 5·1–41·9 per 100 000 have been reported in certain areas of other states, such as Wisconsin [9, 10]. These findings are consistent with the hypothesis that *B. dermatitidis* exists in nature in reservoirs that are geographically restricted. The incidence of blastomycosis in Missouri overall most likely represents a marked underestimated of the burden of disease, since as this study suggests, it is often missed as a diagnosis or not documented as a diagnosis in the medical records. Although we could not determine rates of disease before 1992, annual incidence rates did not vary significantly during the study period, suggesting that the recent concern in the community was due to increased awareness rather than a true increase in occurrence of blastomycosis.

For our incidence rate calculations and overall description of the cases, we included both laboratory-confirmed cases and surveillance cases. Although we did not assess the specificity of the ICD-9 code for blastomycosis, it is quiet unlikely to use such a discharge diagnosis unless the patient has a laboratory evidence of infection with *B. dermatitidis*. The reason for this is that the clinical presentation of patients with blastomycosis is quite non-specific, therefore a diagnosis needs to be well documented, before specific, and usually prolonged, antifungal therapy is initiated. Finally, it is not clear why almost all of the laboratory-confirmed cases (24/25) were identified in the study area; since we mostly relied on the State microbiology laboratory records to identify such cases, it is possible that we could have missed cases from hospitals in other parts of the state that do not send their specimens to the State laboratory.

Although the number of blastomycosis infections in humans documented during 1993 was not significantly greater compared with other years, the increase during that year may be related to environmental changes that occurred in the southeastern part of the state. Yearly floods are common in the areas bordering the Mississippi River, but in 1993, the Southeastern Missouri counties along the Mississippi River had a drought and then late flooding that lasted for several months. In particular, the amount of rainfall reported during 1993 in Mississippi County (median of 4·0 inches) was the higher than in other years [11]. During that year, river stages for the Ohio and Mississippi River were also the highest [11]. Higher incidence rates of endemic blastomycosis, as well as outbreaks, had been previously associated with regions of low elevation containing acidic soil and bodies of water [3, 5, 8]. Growth of the fungus is facilitated by higher soil temperatures, and aerosolization of the organism may be increased by rain and by other disturbance of an area with contaminated soil [5]. Mississippi County, which has the highest annual incidence rate in Missouri, has several environmental features (sandy, acidic soil, low elevation and multiple bodies of water) that may be conducive to the growth of the fungus. Similar climactic and environmental factors have also been associated with areas of hyperendemic blastomycosis in Wisconsin [10], Louisiana and Arkansas [8].

The predominance of males with blastomycosis, as noted in our study and in previous studies of sporadic cases [2, 3, 7, 8], most likely reflects the increased environmental exposure to the fungus associated with more males engaging in outdoor occupations (e.g., construction, farming) and recreational activities (e.g., hunting, fishing, boating). However, because we matched for sex in the case-control study, its association with increased risk of disease cannot be determined. The age and sex distribution of patients in our study was similar to other studies [2, 3]. The increased incidence rate of blastomycosis with age may represent increased susceptibility to infection as immunity wanes with age. Furcolow and Chapman have reported a large number of cases in older patients; 43% of patients were older than 50 years [3, 4].

The clinical presentation of the patients in our study was typical of findings described by others [2, 3, 7, 8]. Pulmonary symptoms were the most common, and most patients had an indolent onset and progressive disease. As in previous studies, the skin was the predominant extrapulmonary site to be involved [3]. Disseminated disease was noted in 32% of the cases, a result similar to those in studies from Mississippi, Arkansas and Wisconsin, in which 23% to 41% of the patients had extrapulmonary disease [3]. Interestingly, the majority of the patients were symptomatic for $\geqslant$4 weeks, and a number of these patients with persistent symptoms had been evaluated by more than one physician and were believed to have poorly responding pneumonia or tuberculosis or malignancy. The delay in diagnosis was frequently a result of the health care provider not considering the possibility of blastomycosis infection rather than the time needed to perform an appropriate diagnostic procedure or laboratory test.

The mortality rate in our study was higher than that reported in other studies, 22%, *vs.* 2·4–17% [3].

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This result may be attributed to delay in diagnosis, especially for younger patients, who present with nonspecific symptoms that can mimic influenza, bacterial infection, chronic pneumonia or tuberculosis and for whom progression of any disease would be least suspected. Patients saw an average of three health care providers for their symptoms before they were ultimately diagnosed with blastomycosis. Although Missouri is in an area of endemic disease, only a limited number of health care providers may be aware of the problem. Finally, underdiagnosis of blastomycosis may lead to overestimating the case-fatality rate, since physicians tend to perform more diagnostic procedures on patients with more severe disease.

Therapeutic interventions in our study varied from lobectomy to amphotericin B and/or ketoconazole or itraconazole. Although there have been no comparative trials of antifungal agents for the treatment of blastomycosis, amphotericin B, ketoconazole, itraconazole and fluconazole have all been shown to be effective [3]. However, for widely disseminated disease, particularly with central nervous system involvement, amphotericin B remains the treatment of choice. Itraconazole appears to be the first-line therapy for non-life-threatening blastomycosis because of fewer side effects [13].

Our case-control study did not reveal common occupational or recreational exposures that would increase the risk of blastomycosis, a finding that has been noted by others [8]. Our inability to detect common-source exposures among the patients may be due to various factors. The exposures we evaluated are quite common in endemic-disease areas and would require larger numbers of cases to detect differences in the exposures between patients and controls. Likewise, exposures that were noted to be sources of infection in outbreak settings may not be important risk factors in endemic blastomycosis. The finding that only 26% of case-patients were involved in outdoor activities that can increase their environmental exposure to *B. dermatitidis*, would support the suggestion that other factors are important for infection. The relatively small sample size also reduced the power to identify potential risk factors. Recall of activities that occurred several years before the interview for the case-patients also limited our findings. To minimize recall bias regarding specific exposures, since many of our case-patients had developed blastomycosis many years earlier, we asked patients and controls about their routine activities throughout the year. Therefore, we could have missed particular exposures occurring before illness. The nonspecific symptoms of blastomycosis and delay in diagnosis also make it difficult to relate activities or exposures to the period of acquisition of the infection. Nevertheless, the role of environmental exposures could be better assessed using a prospective case-control study design where these limitations could be minimized.

History of pneumonia and underlying illnesses was significantly associated with blastomycosis in this study. These factors are possibly markers for poor health status and decreased immunity, resulting in increased susceptibility to respiratory infections in general, and in particular, to *B. dermatitidis*. Decreased risk for blastomycosis among persons who participated in swimming may represent better health in these individuals.

The association of black race as an independent risk factor for blastomycosis also supports the suggestion that genetic factors may possibly be involved. Our finding that blacks have a higher incidence of infection than do whites is in agreement with other surveillance studies [3, 8]. Average annual incidence rates for blacks have been reported to be 1·5–3 times higher than rates for whites. Lowry et al. reported an incidence rate of 9·0 per 100 000, compared to 5·9 for whites in Washington Parish, Lousiana [8]. However, to our knowledge, the incidence rate of 43·2 for blacks compared with 3·4 for whites in Mississippi County is the highest average annual incidence rate ever reported for blacks. A study in Canada had noted that rates specific for ethnicity showed significantly higher incidence of blastomycosis among aboriginal persons [14]. Results of an ongoing genetic study by researchers at the National Institute of Health may help clarify the significance of genetic and immunologic factors that influence the risk of blastomycosis in certain racial groups.

This study has identified a group of persons at high risk for blastomycosis who may benefit from preventive measures or at least early diagnosis of the disease. Since the ecological niche of blastomycosis is not well defined, and diagnostic tests still show poor sensitivity and specificity, controlling blastomycosis by decreasing the risk of exposure to the fungus in the environment will be difficult. However, heightened awareness of the disease and a better understanding of the risk factors continue to be important and will lead to earlier diagnosis and treatment, possibly preventing a poor outcome for this disease.

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