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Use of Urine Antigen Testing for *Blastomyces* in an Integrated Health System

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Purpose	Blastomycosis, an endemic fungal infection, mimics many other diseases. We explored the use of <i>Blastomyces</i> urine antigen (BuAg), reportedly the most sensitive noninvasive test, in clinical practice and compared it to other noninvasive tests.
Methods	A total of 836 BuAg tests performed on unique patients (first test only) at one large integrated health system from June 2013 to May 2016 were retrospectively reviewed to examine test characteristics and demographic features. Of these, 100 cases from 2015, a year containing a large local blastomycosis outbreak, were randomly selected for detailed analysis.
Results	Demographics for the BuAg-tested population: mean age 54.9 years, 55.0% male, 78.9% white, 213 zip codes represented. Test results were positive in 49 of 836 (5.9%, across 43 zip codes); 16 of the 49 (32.7%) stemmed from the 2015 outbreak. BuAg-positive patients were younger than those who tested negative, even with outbreak subjects removed (48.1 vs 56.7 years, $P=0.008$); and Asians and males were overrepresented. Sensitivity/specificity/positive predictive value of BuAg test was 87.9%/97.9%/76.3%, respectively, based on 33 culture-positive cases. Only 2 of 20 culture-positive cases were found positive by <i>Blastomyces</i> antibody (Ab) immunodiffusion (ID) test and 0 of the other 18 by Ab complement fixation (CF). Of those with positive BuAg who were co-tested, 16.1% were positive by Ab ID and 3.9% by Ab CF. <i>Histoplasma</i> urine antigen was co-performed with BuAg in 578 patients (69.1%) and positive in 25 (4.3%); 16 of these 25 (64.0%) also were BuAg-positive (ie, known cross-reactivity). Of the 100 patients examined for index illness details, 7 (6 BuAg-positive) were ultimately diagnosed with blastomycosis, 7 other fungal disease, 26 noninfectious lung disease, 22 pneumonia, 5 skin lesions, 6 malignancies, 3 mycobacteria, 11 other, and 1 unknown. Of 100, 12 were tested by BuAg based on symptoms.
Conclusions	<i>Blastomyces</i> urine antigen is commonly used for work-up of broad differential diagnoses or known exposures. Not adding Ab ID/CF diagnostic tests (\$80 each) to the BuAg test saves money without losing sensitivity. (<i>J Patient Cent Res Rev.</i> 2018;5:176-182.)
Keywords	<i>Blastomyces</i> ; blastomycosis; antigens, fungal; <i>Histoplasma</i> ; disease outbreaks

Blastomycosis is a potentially serious systemic and cutaneous fungal infection endemic to eastern North America.¹⁻³ Disease is acquired from the environment by inhalation of spores of the etiologic fungi *Blastomyces dermatitidis*

or *Blastomyces gilchristii*.^{2,4} Incidence rates are particularly high in Wisconsin compared to the rest of the nation.^{2,5} Pulmonary disease, the most common clinical manifestation, has a broad differential diagnosis,^{1,6,7} and proper diagnosis is important to avoid increased morbidity and mortality. Dissemination beyond the lung may occur to most any organ or tissue, particularly skin, bone, genitourinary system and central nervous system.^{1,2,6} Thus, the differential diagnoses of various presentations of blastomycosis may be quite broad.^{1,6}

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Fungal culture is reportedly 86% sensitive in pulmonary cases and may take up to 5 weeks for the organism to grow.⁸ Fungal smears for rapid diagnosis vary from 24% to 55% sensitivity depending on the site sampled.³ Blastomycosis diagnosis by histopathology, compared with culture, was 85%–89% sensitive in two studies.^{9,10} Modern serologic tests approach 80%–90% sensitivity; however, antibody testing by complement fixation (CF) or immunodiffusion (ID) is insensitive.^{1,2}

Urine antigen testing for *Blastomyces* (BuAg) has been described for the past 14 years,¹¹ though it has only been commercially available and more frequently utilized in the past few years. It uses readily available, noninvasive urine samples, and turnaround time is frequently within 48 hours, much sooner than fungal culture. Reported sensitivities range from 76% to 93%,¹¹⁻¹⁵ with specificities of 77%–79%.^{11,15} Specificity improved to 99% by using control subjects who were healthy or had nonfungal infections, and by use of urine antigen detection by quantitative enzyme immunoassay.¹² There is, however, significant cross-reaction in patients with histoplasmosis.^{11,12}

Increased use of BuAg may be leading to more blastomycosis diagnoses in community settings.¹³ However, there have been few studies that have examined the epidemiologic and clinical features of patients on whom this test is ordered and test characteristics in a general patient population.^{13,14} This study explored the demographic and clinical features of patients on whom BuAg is performed, as well as test characteristics, in an eastern Wisconsin integrated health system. Understanding of these features may guide clinicians regarding the usefulness of this test in patients who may have blastomycosis and its ability to supplant older serological tests.

METHODS

Setting and Subject Selection

Subject identifiers for this retrospective electronic medical records (EMR) review were obtained from the affiliated laboratory of a large, integrated health system that included, at the time of the study, 15 hospitals and 159 outpatient clinics throughout eastern Wisconsin and extreme northeastern Illinois. This area contains the majority of Wisconsin's urban and suburban population. Our system houses medical

records of more than 1.2 million unique patients. The geodemographic features of blastomycosis cases in our health system have been previously described.¹⁶ Approvals for the present study were obtained from the local institutional review board.

Subjects included all inpatients and outpatients, regardless of age, who had BuAg processed through our laboratory during the time period June 2013 to May 2016. All BuAg tests within the study period were performed at our reference laboratory, which uses quantitative sandwich enzyme immunoassay technology to detect a galactomannan found in the cell wall.¹² The first BuAg performed during this time period on each unique patient was examined as the “index test.” Subsequent BuAg tests also were recorded. Additional blastomycosis case finding (including diagnosis by culture, histopathology, and/or cytology/smear) over this same time period was obtained from a search of inclusive ICD-9/10 codes by our institution's research analytics department.

These patient lists were used to perform chart review on all subjects for demographic features and to calculate test characteristics of BuAg, including comparison to the other common noninvasive diagnostic tests for *Blastomyces*, CF and ID. For these comparisons, other tests for *Blastomyces* were included if they were obtained during work-up of the same inpatient or outpatient illness episode as the BuAg test. For fungal culture or histo/cytopathology, these tests were generally concurrent but always within 33 days (sometimes awaiting bronchoscopic examination). For CF and ID tests, virtually all were obtained within 8 days of BuAg (a single outlier was within 25 days).

In addition, the records of 100 randomly selected subjects from the laboratory list were further examined for details of the clinical features and related work-up of the illness that led to the ordering of BuAg and the ultimate diagnosis of that illness. All 100 of these selected cases were drawn from 2015, a year that included a large mid-year outbreak of blastomycosis associated with the Little Wolf River in Waupaca County, Wisconsin.¹⁷ This allowed inclusion of outbreak and nonoutbreak-related subjects tested with BuAg (but, of course, only those seen and tested in our health system).

Inpatient and outpatient records from the index illness were reviewed and included admission history; physical examination, clinic, emergency department, or urgent care notes from the time of initial presentation; discharge summaries; notes from key consultants (eg, infectious disease, pulmonary or critical care medicine); key follow-up visit notes; and laboratory and radiologic reports. Clinical features were recorded if the EMR included documentation of either the presence or absence of the sign or symptom.

Statistical Analysis

Categorical data were analyzed using Fisher's exact test. Normality testing utilized the Anderson-Darling method. Continuous variables were compared with two-sample t-tests of means for distributions approximating normal (age), and Mann-Whitney test for non-normal distributions (BuAg quantitative values). P-values less than 0.05 were considered significant.

RESULTS

BuAg was performed on 836 individuals, who represented 213 zip codes; mean age of population was 54.9 ± 18.0 (range: 5–95) years, 55.0% were male, and 78.9% were white. The last 7 months of 2013 yielded 94 BuAg tests (13.4/month), 261 tests were from 2014 (21.8/month), 356 from 2015 (outbreak year, 29.7/month), and 125 were from the first 5 months of 2016 (25.0/month).

BuAg was positive in 49 of 836 (5.9%, representing 42 zip codes). Among positive tests, 16 of 49 (32.7%) were part of the large 2015 outbreak. Among individuals who were tested and had recorded exposure to the outbreak geography (n=49), 16 (32.7%, representing 28 zip codes), were positive. BuAg-positive patients were younger than those testing negative (Table 1), even when outbreak subjects were removed (48.1 ± 17.9 vs 56.7 ± 17.1 years, $P=0.008$); males were overrepresented in testing positive. Those of Asian ancestry, both those of Southeast Asia ($P<0.0001$) and other parts of Asia ($P=0.005$), were overrepresented compared to whites.

The sensitivity of BuAg was 87.9%, specificity 97.9%, and positive predictive value 76.3% (based on 33 culture-positive cases). There were 2 additional cases of blastomycosis diagnosed by positive histopathology

or cytology/smear, 1 of which was BuAg-positive (sensitivity for all 35 cases: 85.7%).

BuAg-Positive Population

Among the 49 BuAg-positive patients, 43 had pulmonary disease (including 4 who additionally had skin disease, 1 each who additionally had bone, prostate, or central nervous system disease, and 2 with widely disseminated involvement); 3 had skin-only disease, and 3 had bone-only disease. The average quantitative titer of all 49 patients was 2.7 ± 3.5 ng/ml; the median titer was 1.4 (range: <0.2 to >14.7). Median titer did not differ between outbreak and nonoutbreak cases (1.2 vs 1.5, $P=0.23$), nor between cases with and without apparent pulmonary disease (1.5 vs 1.2, $P=0.85$) or pulmonary disease only versus disease spread beyond the lungs (1.5 vs 1.3, $P=0.50$).

In the 15 cases (30.6% of the total 49) in which BuAg was the only positive test for *Blastomyces* (in 3 cases it was the only test performed), only 2 of 15 (13.3%) subjects had blastomycosis identified beyond the lungs. In cases where culture and/or histopathology and/or cytology/smear also were positive, 13 of 34 (38.2%) had disease beyond the lungs ($P=0.10$).

Only 2 of 19 (10.5%) culture-positive cases were positive by *Blastomyces* antibody ID test, 0 of 17 by antibody CF. Of those with positive BuAg, 16.1% of those co-tested were positive by ID, 4.0% by CF. All 11 positive ID/CF cases were positive by BuAg. In the Little Wolf River outbreak population, BuAg was the only test performed for *Blastomyces* detection in 19 of 49 (38.8%) cases. Similar to nonoutbreak cases (31 of 34 [91.2%]), 14 of 16 (87.5%) BuAg-positive cases had at least one other test for *Blastomyces* performed. BuAg was the only positive test in 9 of 16 (56.3%) outbreak cases versus 6 of 34 (17.6%, $P=0.009$) nonoutbreak cases (8 of 14 vs 3 of 31, $P=0.001$, if only co-tested cases are considered).

Serial BuAg tests were performed in 17 of 49 (34.7%) positive index tests. A total of two tests were done in 11 cases, three tests in 4 cases, four tests in 1 case and five tests in 1 case. The median time of first repeat test was 45 days (range: 2–300 days), and 7 of 17 (41.2%) second tests were negative (range: 30–300 days later). All serial titers were lower than previous tests except

Table 1. Demographic Features of BuAg-Tested Subjects

Characteristic	Total, N=836	Positive BuAg, n=49	Negative BuAg, n=787	P
Female	376 (45.0%)	15 (4.0%)	361 (96.0%)	
Male	460 (55.0%)	34 (7.4%)	426 (92.6%)	0.039
White	656 (78.5%)	26 (4.0%)	630 (96.0%)	
Black	71 (8.5%)	5 (7.0%)	66 (93.0%)	0.215*
Hispanic	54 (6.5%)	3 (5.6%)	51 (94.4%)	0.478*
Asian	32 (3.8%) [†]	12 (37.5%)	20 (62.5%)	0.0001*
Native American	8 (1.0%)	1 (12.5%)	7 (87.5%)	0.284*
Unknown	10 (1.2%)	2 (20.0%)	8 (80.0%)	0.062*
All nonwhite	175 (20.9%)	23 (13.1%)	152 (86.9%)	0.0001*
Mean age ± SD	54.9 ± 18.0	40.3 ± 19.1	55.8 ± 17.5	0.0001
Mean age (adjusted [‡]) ± SD	56.4 ± 17.2	48.1 ± 17.9	56.7 ± 17.1	0.008

*Compared to white race.

[†]Includes 9 of 23 Southeast Asians ($P<0.0001$, compared to whites) and 3 of 9 other Asians ($P=0.005$).

[‡]Outbreak-related subjects ($n=49$) removed.

BuAg, Blastomyces urine antigen; SD, standard deviation.

for 3 cases (maximum increase of 0.56 ng/ml over index test value). Final serial titers were all lower than the initial test or were negative. A second BuAg was performed in 21 of 787 (2.7%) negative tests; median time of repeat was 14 days (range: 1–510 days). One test was repeated twice; all repeat tests were negative.

Histoplasma urine antigen was co-performed with BuAg in 69.1% of all cases, and was positive in 25 of 578 (4.3%); 16 of these 25 (64.0%) were also BuAg-positive.

Patient Presentation

Of 100 patients who had BuAg testing and were examined for index illness details, 87 presented with pulmonary disease (including 1 patient each with skin or bone involvement). The 13 nonpulmonary presentations included skin ($n=5$), bone ($n=2$), central nervous system ($n=2$), sinusitis ($n=1$), sepsis ($n=1$), fatigue/weight loss ($n=1$), and pretransplant screening ($n=1$). Seven patients were ultimately diagnosed with blastomycosis (6 of which had positive BuAg); 7 had other systemic fungal disease, 26 had noninfectious lung disease, 22 had pneumonia, 5 had skin lesions, 6 had malignancies, 3 had mycobacteria, 11 had other

specific diagnoses, and 1 had unknown etiology. Twelve individuals were tested based on symptoms and/or exposure, without definitive diagnosis, including 9 with cough/viral symptoms (5 of which had outbreak exposure), 2 with fever of unknown source, and 1 exhibiting fatigue and weight loss. None of these 12 patients were BuAg-positive.

In the randomly selected cohort, 59 patients were hospitalized during the illness. Time intervals from onset of the index illness to the BuAg test and from BuAg to final diagnosis are presented in Table 2.

Among the 100 patients tested with BuAg who were examined in detail, 48 patients had at least one fungal culture during the index illness and 19 had histopathologic examination or cytology. Specific testing for *Histoplasma* was performed on 65 patients, and 24 were tested for *Coccidioides*, 18 for *Cryptococcus*, 30 for *Aspergillus*, 50 for mycobacteria and 15 for *Pneumocystis jirovecii*.

Among those with active pulmonary symptoms at the time of presentation ($n=70$) and whose records included information regarding a particular symptom, a majority

Table 2. Time, by Category, From Illness Onset to Test and From Test to Diagnosis

Time category	From onset to BuAg test	From BuAg to diagnosis
<7 days, n	24	76
7–30 days, n	33	13
1–3 months, n	19	6
>3 months, n	8	2
Total N	84	97

BuAg, *Blastomyces urine antigen*.

had the following: dyspnea (44 of 50 [88%]), cough (58 of 67 [87%]), fatigue (32 of 40 [80%]), myalgias/muscle pain (12 of 20 [60%]), night sweats (14 of 24 [58%]), and fever (34 of 61 [56%]). A minority had weight loss (42%), chest discomfort (30%), bone/joint pain (24%), and hemoptysis (20%).

DISCUSSION

BuAg appears to be commonly utilized in this large integrated health system with clinic locations spanning eastern Wisconsin. The ultimate diagnoses (pneumonia, noninfectious pulmonary processes, other systemic fungal disease, malignancies, mycobacterial disease) of the 100 randomly selected BuAg-tested patients for detailed analysis are consistent with the differential diagnosis of blastomycosis as presented in texts and reviews,^{1,6} and with the results of a survey of Wisconsin clinicians who were asked to list their top three diagnoses when presented blindly with various case vignettes of blastomycosis presentations.⁷ Similarly, for active pulmonary disease (while readily acknowledging the limitations of retrospective EMR review), mean age, gender distribution, and presenting symptomatology was quite similar to that recently reported from northern Wisconsin, except that dyspnea was significantly more prevalent in the present report.¹⁸ Thus, BuAg appears to be ordered in clinical settings that indeed would include blastomycosis in the differential diagnosis.

The calculated sensitivity of BuAg in this study, 85.7%, may be compared with the reports of Durkin et al (92.9%, calculated from 42 cases),¹¹ Connolly et al, who used quantitative BuAg (89.9%, 89 cases),¹² and

Bariola et al, who used quantitative BuAg in newly diagnosed patients (85.1%, 27 cases).¹⁵ It is apparently similar to Azar et al (exact figure not reported).¹³ Our figure is higher than that reported by Frost and Novicki (76.3%, 59 cases, mixture of qualitative and quantitative BuAg), despite our study's similarly broad representation of patients from an endemic area of Wisconsin.¹⁴ Our study exclusively included quantitative BuAg, and the proportion of isolated pulmonary cases was greater in their study (88%) than ours (69%); however, such cases had the highest BuAg sensitivity (82.7%) in their study.¹⁴

Ignoring cross-reactivity with *Histoplasma*, our calculated specificity (97.9%) was similar to that of Connolly et al (99.0%).¹² Our cross-reactivity (64%) was lower than that found by others (up to 96%),^{11,12,15} but still substantial. As previously suggested, further tests and relative values of the two positive assays can be considered to differentiate histoplasmosis from blastomycosis.^{12,15} Fortunately, initial treatment of these two mycoses is similar such that therapy may be started while awaiting specific confirmation.^{1,2,19}

The poor sensitivity of antibody testing by the older CF and ID techniques is well known¹⁻³ and was further confirmed by our study. In no instance did these tests contribute to the diagnosis of blastomycosis. The current charge for each of these tests is approximately \$80, which may be saved by not ordering them. Antibody testing for *Blastomyces* surface protein BAD-1 by enzyme immunoassay, in combination with BuAg, shows promise for sensitive and specific blastomycosis diagnosis, as the former has minimal cross-reactivity with *Histoplasma*.²⁰

Based on recorded histories, 49 of 836 BuAg-tested subjects had exposure to the environs of the Little Wolf River during and shortly after the 2015 Waupaca County blastomycosis outbreak,¹⁷ with one-third testing positive for *Blastomyces*. BuAg testing appeared particularly useful in this setting. As of this writing, no summary of the complete outbreak has been published.

Our study revealed that Asians were significantly overrepresented regarding the proportion of those tested with BuAg who were positive (37.5%). Recent

studies have suggested differing susceptibility to blastomycosis among different human genetic and ethnic groups.^{12,21} Roy et al found significantly higher blastomycosis incidence rates among Asians in sporadic and outbreak cases.²² The genesis of these findings is not clear, but the overrepresentation of Asians in outbreak or hyperendemic areas may be due to genetic predisposition and/or socioeconomic reasons.

Finally, BuAg was the only positive test in a significant portion of apparent blastomycosis cases. Such cases may not be reported, as they do not meet the Wisconsin case definition for blastomycosis.²³ Thus, the true incidence of blastomycosis may be underestimated.

Limitations

The limitations of our study include all of those inherent in retrospective EMR reviews. Our study was limited to a single health system in a moderately high endemic area.²⁴ The calculations of test characteristics were based on 33 patients (not unlike other studies).^{11,15} We were unable to provide a comparison group of patients presenting with a similar clinical presentation who were not tested with BuAg. Our strengths included a moderately large, comprehensive study of outpatients and inpatients tested with BuAg (rather than just those who tested positive or who were diagnosed with blastomycosis by some means).

CONCLUSIONS

Blastomyces urine antigen testing appears to be commonly performed in this region for work-up of broad differential diagnoses that appropriately include blastomycosis or for symptomatic patients with known exposure to the fungus. It may be particularly useful in outbreak settings. Fungal culture and BuAg testing (perhaps with the future addition of antibody testing for *Blastomyces* surface protein BAD-1) are the preferred tests for *Blastomyces* in symptomatic patients from an endemic area. Not adding highly insensitive CF and ID tests to BuAg testing for blastomycosis would save money without losing sensitivity.

Patient-Friendly Recap

- There are a number of diagnostic tests used to confirm suspected blastomycosis, a fungal infection of the lungs.
- One such test, referred to as BuAg, uses the patient's urine to look for byproducts of the fungus *Blastomyces*.
- The author found that BuAg is commonly ordered by local physicians and yields test results reasonably comparable to the more time-consuming culture method.
- Also shown was that a pair of alternative antibody tests did not add true diagnostic value, making their use inadvisable.

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Conflicts of Interest

None.

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