Brief Report

Blastomycosis in Children: A Study of 14 Cases

Evan J. Anderson,[1,2,a] Paul B. Ahn,[3] Ram Yogev,[1] Preeti Jaggi,[4] Deanna B. Shippee,[1] and Stanford T. Shulman[1]
Departments of [1]Pediatrics and [2]Medicine, Northwestern University Feinberg School of Medicine, Chicago, Ilinois; [3]Greater Roslindale Medical & Dental Center, Roslindale, Massachusetts; and [4]Department of Pediatrics, Nationwide Children's Hospital, Columbus, Ohio

Corresponding Author: Evan J. Anderson, MD, Emory University School of Medicine, Departments of Pediatrics and Medicine, 2015 Uppergate Dr, Atlanta, GA 30323. E-mail: evanderson@emory.edu.

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[a]**Present Affiliation:** Departments of Pediatrics and Medicine, Emory University School of Medicine.

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We retrospectively reviewed 14 children with active blastomycosis. Pulmonary disease occurred in 86% of the cohort and extrapulmonary dissemination was noted in 46%. Urine blastomycosis or histoplasmosis antigens were positive in all tested patients. Acute kidney injury was common in patients who were treated with amphotericin. Mortality tended to be associated with a delay in diagnosis.

Key words. Blastomycosis; Pediatric; Amphotericin; Itraconazole

Blastomycosis most commonly occurs in the Midwest, South Central, and Southeastern United States, and Manitoba and northwestern Ontario in Canada [1–4]. Blastomycosis can cause a life-threatening pneumonia and disseminate to other organs, particularly skin and bone. Limited data suggest that the infection disseminates more frequently in children than in adults [5]. Because pediatric data are limited, we reviewed our experience with blastomycosis in an endemic region.

MATERIALS AND METHODS

An institutional review board-approved retrospective chart review was conducted at our tertiary care pediatric hospital [Children's Memorial Hospital (CMH)] in Chicago, IL. Cases of blastomycosis occurring in children ≤18 years of age between 1987 and 2011 were identified by inpatient and outpatient databases of International Classification of Diseases, Ninth Revision, Clinical Modification code 116.0. Infectious disease clinic and microbiology records were reviewed and cross referenced to identify additional cases. A case was defined as identification of blastomycosis from culture or identification of broad-based budding yeast from a pathological specimen if no culture from the surgical specimen was obtained and the patient did not have an alternative diagnosis. Demographic, epidemiology, clinical information, treatment, and outcomes were collected. Acute kidney injury was defined as creatinine increase of >0.3 mg/dL from baseline.

Continuous variables were analyzed using the unpaired *t* test, whereas dichotomous variables were analyzed with the Fischer exact test. A Grubbs' test was performed to identify outliers. A 2-tailed *P* value of ≤.05 was considered significant.

RESULTS

Patient Demographics

Over the 25-year study period, 14 patients with blastomycosis were identified at CMH (Table). Two of these patients have been reported previously (patient nos. 8 and 11) [6, 7]. The median age was 11.5 years, 57% were female, and 43% were black. Underlying cardiac disease was present in 21%. More patients had onset of illness during the fall and winter (October–March, 79%) compared with the spring and summer (April–September, 21%, $P = .03$ for the difference).

Clinical Signs and Symptoms and Laboratory Findings

Common symptoms among those with blastomycosis included cough in 79%, fever in 71%, and weight loss in 50% (Table). The median white blood cell count in the 12 patients for whom it was available was 16.6×10^9 cells/L (range, $8.6–30.4 \times 10^9$ cells/L). The erythrocyte

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sedimentation rate was elevated in all 9 patients in whom it was available (median, 67 mm/h; range, 40–111 mm/h). Sputum fungal culture ultimately identified blastomycosis in 3 of 7 subjects from whom it was sent, whereas the yield from culture of endotracheal secretions or bronchoalveolar lavage was higher (6 of 7 subjects). Serology was infrequently positive (1 of 7), whereas the urine blastomycosis or urine histoplasmosis antigen tests were positive in all tested patients (7 of 7 tests sent) (Table). Pneumonia was present in 86%, and 1 additional patient had isolated laryngeal blastomycosis. This patient was excluded from calculations regarding the burden of extrapulmonary disease due to uncertainty regarding the pathophysiology of laryngeal involvement. Extrapulmonary disease occurred in 46%, with skin disease and bone involvement each occurring in 31%. The classic triad of lung, bone, and skin disease was observed in only 2 patients (15%).

Treatment and Outcomes

In total, 86% were hospitalized, and one-third of those were admitted to the intensive care unit and were mechanically ventilated (Table). The median hospital stay was 12.5 days. One patient with refractory dilated cardiomyopathy was only identified as having blastomycosis post mortem and did not receive antifungal therapy (patient no. 2). Of the 13 patients who were treated, 7 of 8 patients (87.5%) who were treated with liposomal or deoxycholate amphotericin for >1 day had acute kidney injury, whereas 0 of 5 patients who were treated initially with itraconazole had kidney toxicity ($P = .005$). Three patients died. Patient no. 2 (mentioned above) developed refractory hypotension and respiratory failure, but an infectious etiology was not considered. Patient no. 3 had acute respiratory distress syndrome (ARDS) and required extracorporeal membrane oxygenation that was complicated by a cerebral hemorrhage, and patient no. 8 had ARDS and empyema that was complicated by pneumothorax and cardiopulmonary arrest. Three of the 4 subjects with bone disease had residual orthopedic issues. The subject with laryngeal blastomycosis was identified as an outlier by Grubbs' test (540 days from onset of symptoms to diagnosis) and was excluded. Mortality tended to be associated with a delay from onset of symptoms to treatment (mean of 114 days for those who died vs 57 days for those who survived, $P = .09$).

DISCUSSION

Most recent series suggest that children comprise ≥5% of all blastomycosis cases [1, 5, 7, 8]. Although our limited data did not show an increased rate of blastomycosis in recent years, a number of studies, including some Illinois data, describes increasing numbers of patients with blastomycosis [7, 8]. Corresponding with previous reports, most blastomycosis cases occurred during the cold-weather months [1, 3, 7, 8]. Although pediatric studies with small numbers of subjects have reported extrapulmonary rates of 50%–100% [1], our data and that of Fanella et al [3] suggest that the rate is <50% and closer to the rate reported in adults. Laryngeal blastomycosis, like that observed in our subject no. 12, has been described, but the pathophysiology (hematogenous vs airborne) has not been definitively determined [9]. A recent study noted approximately 15% of infected children had evidence of central nervous system disease [3], which was not observed in our patients.

Schutze et al [1] reported that the diagnosis of pulmonary blastomycosis may be particularly challenging and that 4 of 5 children with pulmonary disease required a lung biopsy. The higher yield of sputum and endotracheal cultures observed in our study and reported by others [3, 10] compared with that reported by Schutze et al [1] may be due to technical limitations of specimen collection as noted in their study. The blastomycosis urinary antigen test performed well in diagnosing blastomycosis, although the number of patients in which it was performed was small [6]. Cross-reaction between blastomycosis and histoplasma urinary antigens is well known [6, 11], and we also found that the histoplasmosis urinary antigen test was falsely positive in 4 of 4 patients who had it performed. In contrast, complement fixation or immunodiffusion tests performed poorly (1 of 7 subjects) in our study and that of others [1, 10].

Although children generally tolerate amphotericin B deoxycholate better than adults [12], almost all of the children in our study developed acute kidney injury. Notably, some children with kidney injury related to amphotericin B deoxycholate were successfully switched to liposomal amphotericin without additional toxicity. However, even children treated exclusively with liposomal amphotericin developed kidney injury.

Based on limited data (primarily from a retrospective study of 10 patients), it has been suggested that children respond less satisfactorily to oral azoles [1, 12]. It should be noted that almost all of the azole treatment "failures" in that study were due to nonadherence, to treatment with ketoconazole or fluconazole (which are considered inferior to itraconazole in the treatment of blastomycosis [12]), or to concomitant medications known to increase hepatic clearance of itraconazole [1]. In adults, serum itraconazole levels are known to be variable with serum concentrations ~30% higher with

Table. Demographics, Presentation, Diagnosis, Treatment, and Outcomes of 14 Children With Blastomycosis

	Demographics and Clinical Presentation						Diagnosis		
Subject Number	Age (y), Gender, Race	Past Medical History	Additional Contact With Other Known Endemic Areas	Date of Clinical Presentation Resulting in Diagnosis	Days of Illness Prior to Presentation	Organs Involved	Serology	Sputum Fungal Culture	Fungal Culture of BAL or ETT Aspirate
1	11.9, F, W	Prior pneumonia x 2	Wisconsin summer home	December-87	45	Lung	Negative	ND	ND
2	4.8, F, B	Dilated cardiomyopathy, prior pneumonia, left atrial clot	None	July-94	180	Lung	ND	ND	ETT Positive
3	15.6, F, NA	None	Lived in a Northern Wisconsin Native American Reservation	February-96	90	Lung	Negative	Positive	ETT Positive
4	10.9, F, B	None	None	May-96	90	Lung, Bone, Kidney	Negative	ND	ND
5	15.6. M, B	None	None	April-97	120	Lung, Skin, Bone	Positive	Positive	BAL Positive
6	10.7, F, A	None	Wisconsin travel 2 months before	November-97	21	Lung	Negative	Negative	BAL Negative
7	11.1, F, H	None	None	July-98	90	Lung, Skin, Bone	Negative	Negative	ND
8	9.3, M, B	None	None	February-03	42	Lung, Skin	ND	ND	ETT Positive
9	18.7, M, B	Tetrology of Fallot partially surgically corrected by a right ventricular outflow tract patch, VSD closure, and placement of a right ventricle to pulmonary artery conduit	None	October-04	14	Lung	Negative	Negative	BAL Positive
10	14.2, M, A	None	Visited Wisconsin several times per year	November-04	28	Skin	ND	ND	ND
11	10.7, F, B	None	None	March-05	10	Lung	ND	Positive	ND
12	13.8, F, H	None	None	December-07	540	Larynx	ND	ND	ND
13	15.8, M, H	None	None	January-08	60	Lung, Bone	ND	Negative	ND
14	5.5, M, W	Dilated cardiomyopathy	None	January-11	60	Lung	ND	ND	BAL Positive

Abbreviations: M, Male; F, Female; W, White; H, Hispanic; B, Black; NA, Native American; A, Asian; ND, Not Done; BAL, Bronchoalveolar lavage; ETT, Endotracheal injury; Serology, Either complement fixation or immunodiffusion; Blasto, Blastomycosis; Histo, Histoplasmosis; Both, Both blastomycosis and histoplasmosis.

		Treatment and Outcomes						
Urinary Antigen Result	Results of Other Diagnostic Procedures	Approximate Days of Illness Before Antifungal Therapy	Total Days Each Antifungal	Toxicity	Hospital Days	Intensive Care Unit and Mechanical Ventilation	Orthopedic Complications	Survival
ND	Thoracotomy - positive pathology, no culture sent, thoracentesis negative, bone marrow negative	45	AmBD 5 days, Ketoconzole 5.5 months	AKI on AmBD	6	No	None	Yes
ND	ND	199	0	NA	19	Yes	None	No
ND	Thoracentesis negative	98	AmBD 10 days, L-AmB 7 days	AKI on AmBD	24	Yes	None	No
ND	Biopsy of soft tissue mass and first metatarsal - pathology positive, no culture sent	92	AmBD 90 days, L-AmB 42 days	AKI on AmBD, switched to L-AmB	13	No	Partial resection of the base of first metatarsal with persistent defect	Yes
ND	Biopsy of lip pathology positive, but no culture sent, I + D of wrist abscess pathology and culture positive	122	AmBD 10 days, L-AmB 56 days, itraconazole 2 months	AKI on AmBD, switched to L-AmB	15	No	Destruction of distal radius joint and distal radial/ulnar joint, application of an external fixator with wrist fusion, continued weakness	Yes
ND	CT-guided lung biopsy - pathology and culture positive	31	Itraconazole 6 months	None	12	No	None	Yes
ND	Ultrasound-guided lung biopsy - pathology and culture positive, Skin biopsy pathology and culture positive	91	AmBD 5 days; L-AmB 30 days; itraconazole 8 months	AKI on AmBD, switched to L-AmB	11	No	None	Yes
ND	Thoracentesis smear and culture positive	46	AmBD 2 days, L-AmB 1 day	None	6	Yes	None	No
Blasto ND, Histo positive	ND	21	Diflucan 3 days, L-AmB 22 days, itraconazole 6 months	AKI on L-AmB	44	Yes	None	Yes
ND	Skin biopsy pathology and culture positive	28	Itraconazole 9 months	None	0	No	None	Yes
Both positive	ND	19	Itraconazole 6 days; Amphotericin one day; Intraconazole 6 months	Intolerance of amphotericin B due to rigors, vomiting with itraconazole initially	20	No	None	Yes
ND	Biopsy of laryngeal lesion pathology and culture positive	540	Itraconzole 6 months	None	0	No	None	Yes
Both positive	Biopsy of paraspinal muscle collection with stain consistent with blastomycosis, no culture sent	60	L-AmB 8 weeks, Itraconazole 10 months	AKI on L-AmB	7	No	Kyphosis (29 degrees at T5)	Yes
Both positive	ND	64	Itraconazole >6 months	None	4	No	None	Yes

tube aspirate; NA, Not Applicable; AmBD, Amphotericin B Deoxycholate; L-AmB, Liposomal amphotericin; pk, peak; Cr, Creatinine; AKI, Acute kidney

solution than with capsules [12]. In the current study, both solution and capsules were used. We and others have not monitored itraconazole levels routinely and have not observed increased frequency of treatment failures [3]. Thus, we agree with the recommendation of others that itraconazole level monitoring may not be necessary in otherwise healthy children tolerating itraconazole solution at recommended doses who are clinically responding [3]. Our data and that of others [3] provide reassurance that itraconazole is effective in the treatment of children with mild-to-moderate blastomycosis and was better tolerated than amphotericin. In severe cases of blastomycosis, lipid formulation of amphotericin B should be the drug of choice [12] with careful monitoring of kidney function.

Among the 500 blastomycosis cases reported to the Illinois Department of Public Health from 1993 to 2003, a $\geq$120 day delay in the time from onset of illness to diagnosis was associated with an increased risk of death [7]. Our study also noted a trend towards increased mortality in those for whom a diagnosis of blastomycosis was delayed, underscoring the importance of a having a high index of suspicion of blastomycosis. Similar to previous reports, we observed a higher mortality rate among blacks (2 of 6, 33%) [7]. The mortality noted in our study (21%) was higher than that described in most other studies ($\leq$10%) [1, 2, 4, 5, 7]. This discrepancy may be explained by our institution being a tertiary referral hospital where more severely affected patients are seen.

Limitations of this study include its retrospective, single-center design. The data regarding the toxicity of amphotericin B are likely impacted by the extended (25 year) study period, because the kidney toxicity of liposomal amphotericin is less than that of amphotericin B deoxycholate, which was administered in earlier years of the study.

In summary, our study suggests that urinary antigen testing is superior to serological testing for blastomycosis diagnosis. Kidney toxicity was common with amphotericin. A prolonged delay between onset of symptoms and diagnosis of blastomycosis trended toward higher mortality.

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