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Histoplasmosis After Solid Organ Transplantation

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ABSTRACT

Background. In order to improve our understanding of risk factors, management, diagnosis and outcomes associated with histoplasmosis after solid organ transplantation (SOT), we report a large series of histoplasmosis occurring after SOT.

Methods. All cases of histoplasmosis in SOT recipients diagnosed between January 1st, 2003 and December 31, 2010 at 24 institutions were identified. Demographic, clinical, and laboratory data were collected.

Results. 152 cases were identified- kidney (51%), liver (16%), kidney/pancreas (14%), heart (9%), lung (5%), pancreas (2%), other (2%). The median time from transplantation to diagnosis was 27 months, but 34% were diagnosed in the first post-transplant year. Twenty-eighty percent of patients had severe disease (requiring intensive care unit admission); 81% had disseminated disease. Urine *Histoplasma* antigen detection was the most sensitive diagnostic method, positive in 132/142 (93%). An amphotericin formulation was administered initially to 73% of patients for a median duration of 2 weeks; step down therapy with an azole was continued for a median duration of 12 months. Ten percent of patients died due to histoplasmosis with 72% of deaths occurring in the first month after diagnosis; older age and severe disease were risk factors for death from histoplasmosis. Relapse occurred in 6% of patients.

Conclusions. While late cases occur, the first year after SOT is the period of highest risk for histoplasmosis. In those who survive the first month after diagnosis, treatment with an amphotericin formulation followed by an azole for 12 months is usually successful with only rare relapse.

INTRODUCTION

The dimorphic fungus, *Histoplasma capsulatum,* is most common in the United States in the Ohio and Mississippi River valleys. Sensitivity to *Histoplasma* antigens among individuals living in these river valleys may exceed 80% [1]. Infection is often asymptomatic or subclinical. Because of the relationship between an individual's underlying immune function and histoplasmosis severity, the early years of the acquired immune deficiency syndrome (AIDS) epidemic resulted in an increase in the incidence of symptomatic and severe *Histoplasma* infection [2]. Clinicians thus gained experience regarding the diagnosis, treatment and outcomes of this life-threatening infection in immunosuppressed populations.

In the field of solid organ transplantation (SOT), T cell immune dysfunction can also be significant, although the incidence of clinical histoplasmosis is < 0.5% in most studies [3-8]. Infection can be difficult to predict with variable clinical presentation, response to therapy, and risk for complications. Symptomatic infection among SOT recipients could occur via primary infection, secondary infection in patients with prior exposure who come in contact with a large inoculum in a now immunosuppressed state, and reactivation of previous latent infection. Rarely, transmission from the allograft itself has been reported [9, 10].

Much of our present knowledge of histoplasmosis after SOT comes from single center studies from areas of variable endemic rates [3, 5]. Specific data regarding diagnosis, incidence, treatment and outcomes of this infection are needed. The present study attempts to improve our understanding by performing a large multicenter evaluation of histoplasmosis after SOT.

METHODS

All cases of histoplasmosis in SOT recipients diagnosed between January 1st, 2003 and December 31, 2010 at 24 participating institutions were retrospectively identified. Multiple transplant centers in the United States were approached and data was collected by those interested in participating. Diagnosis of histoplasmosis required positive culture, positive serum or urine *Histoplasma* antigen (Miravista Diagnostics, Indianapolis, Indiana), histopathology demonstrating yeast-like structures characteristic of *H.capsulatum*, the presence of H or M precipitin bands by immunodiffusion, or complement fixation titers ≥ 1:8. Progressive disseminated histoplasmosis (PDH) was defined as clinical, laboratory, or imaging evidence of extrapulmonary involvement as previously suggested [11]. The site of extrapulmonary involvement was determined based on clinical signs or laboratory evidence. Pulmonary histoplasmosis was defined as respiratory symptoms and chest imaging (radiograph or computed tomography) with infiltrates and/or mediastinal lymphadenopathy in the absence of PDH. As has been done in previous studies, disease was characterized as mild, moderate or severe [12]. Mild disease was treated with outpatient therapy, moderate disease required hospitalization but not critical care, and severe disease was treated in an intensive care unit. Suppressive therapy was defined as treatment continued more than 12 months after diagnosis except if given for relapse. Death was directly attributed to histoplasmosis if the patient had findings of active histoplasmosis and no other cause of death was identified. Evidence of active histoplasmosis included one or more of the following: treatment for less than 6 weeks, persistent signs and symptoms, failure of antigen to decline, demonstration of organisms by

cytology or pathology, or positive culture. Histoplasmosis was considered to have contributed to the death if a patient died of another condition but the investigator felt that the patient had evidence for active histoplasmosis. Clinical and demographic data was collected from investigators. Patient management decisions were made by treating clinicians. Institutional Review Board approval was obtained by the investigator at each site. At some centers, patients included in this series had been included in previously published series [3, 5, 6, 13]. All patient data was collected independently for this study; no data was extracted from previous publications.

Baseline characteristics were compared using the 2 sample independent t test for continuous variables and chi square test for categorical variables. For variables with expected cell count of less than 5, Fisher's exact test was used. For variables that are not normally distributed, Mann Whitney and Wilcoxon rank-sum tests were used. To determine risk factors for death and relapse, a multivariate analysis was used. Initially univariate analysis was conducted based on clinical grounds and available variables. Variables included age, disease severity, fungemia, urine antigen results, immunosuppression reduction, amphotericin treatment, type of transplant, and organ involvement. Variables that were statistically significant (p value ≤ 0.05) were then entered into the multivariate analysis. Appropriateness of the model was assessed using Hosmer and Lemeshow goodness-of-fit test. Two way interactions were tested when appropriate. Case-wise diagnostics were performed to detect any outliers. SPSS software version 19 was used.

RESULTS

Patient and Center Characteristics

From 24 solid organ transplant centers, we identified 152 cases of post-transplant histoplasmosis. One center contributed 22 cases, 5 centers 10-20 cases, and the remaining centers had ≤ 10 cases. The location of the centers and the rates of histoplasmin reactivity are in **(table 1).** Baseline characteristics are described in **(table 2)**. Most patients were on maintenance immunosuppression with a calcineurin inhibitor, mycophenolate mofetil, and a corticosteroid. Ten percent of patients were treated for rejection in the 3 months preceding the diagnosis of histoplasmosis.

Clinical Characteristics

The median time from transplantation to diagnosis with histoplasmosis was 27 months, but 34% presented in the first year with 2% presenting within one month of transplantation. The longest interval from transplantation to diagnosis was 20 years **(figure 1)**. Most patients had disseminated disease (81%). **Table 3** describes specific organ involvement. Fungemia was present in 63%. Twenty-seven percent had severe disease, 63% moderate disease, and 8% mild disease. In multivariate analysis, use of mycophenolate preparation, and the presence of fungemia were risk factors for severe disease **(table 3)**.

Diagnosis

Table 4 describes the overall yield of the diagnostic tests used. Antigen detection provided the highest sensitivity for diagnosis, 93% for antigenuria and 86% for antigenemia. Detection of antibody was the least sensitive diagnostic method, positive in 36% of cases.

While more than one diagnostic test was positive in 116 (76%), a single test was positive in 36 (24%). These included antigenuria in 27 (18%), pathology or cytology in 6 (4%), culture in 3 (2%), and antibody detection in 1 (1%). Combined visualization of the organism and detection of antigen was the basis for diagnosis in 69 (45%), while antigen was positive but pathology was negative in 20 (13%) and pathology was positive but antigen was negative in 9 patients (6%). Culture provided the sole basis for diagnosis in 3 patients (2%) and antibody detection by complement fixation in 1 patient (1%). In this case a patient with meningitis demonstrated complement fixation titer of 1:32 in serum and 1:8 in CSF; antigen was negative in serum using a less sensitive version of the antigen assay as existed in 2003 [14]; urine antigen, cultures, cytology and pathology were not performed. Antigen detection was more sensitive in patients with disseminated disease as compared to those with pulmonary disease alone.

Organisms were visualized in the bone marrow in 12 of 17 patients (71%). In 5 patients all diagnosed between 7-12 months after transplantation, granuloma was observed on biopsy of tissue in the transplanted organ.

Treatment and Outcome

The most common management strategy was an amphotericin formulation followed by therapy with an azole **(table 5)**. For patients with severe disease, 42 (98%) initially received an amphotericin formulation and one (2%) initially received an azole. Moderate disease was initially treated with amphotericin in 69% of cases with 31% receiving initial therapy with an azole. Ninety-two percent of patients with mild disease initially received azole therapy. Seventeen patients (11%) died prior to receiving step down therapy. In the remaining cases, an

azole was given as step down therapy for a median duration of 12 months **(table 5)**. Twenty-one percent of patients continued chronic suppressive therapy. Immunosuppression was held or decreased in the majority of patients **(table 5)**.

Nineteen percent of the patients in the cohort died; histoplasmosis was the cause of death in 10% and 72% of deaths occurred within the first month after diagnosis resulting in a median interval to death of 2 weeks. No histoplasmosis related deaths occurred within 2 months of transplantation. In univariate analysis, older age, severe disease, fungemia, and higher urine antigen were associated with death from histoplasmosis. In multivariate analysis, age and severe disease remained statistically significant risk factors **(table 6)**.

Relapse occurred in 9 (6%) patients. Six occurred in the first 2 years following the original diagnosis; one patient relapsed 9 years later. Follow-up for more than one year after discontinuation of therapy was available for 57 patients; 6 relapsed and 3 received 7 months or less of initial therapy and 3 were treated for at least one year. The other 3 relapses occurred among the 38 patients on chronic maintenance therapy who were followed for at least one year on chronic maintenance therapy (medium 34 months, range 12-74 months). Relapse occurred at 5, 14, and 48 months of chronic maintenance antifungal therapy. Relapse occurred in 3 of 38 (8%) while receiving therapy, and 6 of 57 (10%) that stopped therapy (p=0.67). Information on drug levels was not available. Of the 9 relapsed patients, 2 died of histoplasmosis post-relapse. One died one month and the other 4 months after beginning treatment for relapse. The only risk factor significantly associated with relapse was failure to reduce calcineurin inhibitor dosage (75% versus 95%; p=0.043).

DISCUSSION

This paper describes the largest series (152 cases) of histoplasmosis after SOT. *Histoplasma* related mortality was 10%, with most deaths occurring soon after diagnosis. One-third of the cases occurred within one year of transplantation, and almost half occurred in the first two years after transplantation. The very early development of disease and presence of granuloma in the transplanted organ suggests that some of these cases were donor-derived. Antigenuria was the most sensitive diagnostic test. Patients were typically treated with polyenes followed by azoles for a median of one year, and relapse was rare suggesting that chronic suppressive treatment is unnecessary in most cases. Nonetheless, two deaths occurred after relapse and clinical and laboratory monitoring after discontinuation of therapy is prudent.

Previous single center studies have demonstrated an incidence of 0.48% of histoplasmosis among SOT recipients [3-8], with a significant proportion (34%) of cases occurring during the first year after transplantation. A recent, large prospective multicenter study of invasive fungal infection after SOT reported 48 cases of histoplasmosis with 43% occurring within 6 months of transplantation [13]. These rates are disproportionate compared to the proportion of living transplant patients who were transplanted within the last year. For example, of all living patients in the UNOS registry as of December 31, 2011, 9.3% were transplanted that year and 89.7% in preceding years (personal communication, Sarah Taranto, OPTN/UNOS). Thus, about one-third of cases occur in approximately 10% of the patients at risk. More intense immunosuppression likely plays a major factor in the increased first year risk as could donor-derived infection.

Donor-derived histoplasmosis is rare, but confirmed transmission has been reported [9, 15]. We noted eight cases that exhibited features suggestive of donor-derived histoplasmosis based either on diagnosis in the first month after transplantation or the finding of granuloma in the transplanted organ combined with diagnosis during the first year after transplantation. Other possible explanations for early disease include "smoldering" infection in the recipient prior to transplantation, and newly acquired disease in the recipient. In either of these circumstances, granuloma might be observed in the transplanted organ. As we do not have clinical information on the donor or other recipients, donor–derived infection cannot be proven. Our study supports continued attention to the possibility of donor-derived histoplasmosis when assessing donors in endemic areas [16].

The significant mortality associated with post-transplant histoplasmosis and the non-specific clinical presentation emphasizes the importance of maintaining a low threshold for consideration of histoplasmosis, and raises the question whether screening before or during the first year following transplantation could identify cases earlier, perhaps reducing mortality. The role of routine screening for antigenuria following transplantation has not been studied, but this approach was addressed in patients receiving treatment with tumor necrosis factor inhibitors in which results of a pilot project did not support screening [17]. More information is needed to determine the benefit of screening.

Detection of antigenuria was the most sensitive diagnostic method. Antigenuria was present in all of the cases in two other reports [5, 6]. In another study, only 69% of patients exhibited antigenuria, which was attributed to use of older, less sensitive assays [3]. Sensitivity of antigen testing is lower in patients who do not have disseminated disease [12]. Although

not demonstrated in this study, other studies and clinical experience show that the highest sensitivity for diagnosis is achieved by testing both urine and serum [18, 19]. Serologic tests for antibodies to *H. capsulatum* were not sensitive, positive in about one-third of patients, and the sole basis for diagnosis in only one patient.

As the majority of patients presented with disseminated disease, treatment usually consisted of a lipid formulation of amphotericin B followed by itraconazole, combined with a reduction in immunosuppression. Despite aggressive treatment, 10% of the patients died of histoplasmosis with most deaths occurring within the first 3 weeks following diagnosis, including 2 that died prior to treatment. In the literature, death during the first few weeks following diagnosis was reported in the 2 other fatal cases for which information was provided [4, 5]. Higher antigen concentration as well as older age and fungemia were associated with higher death rates in univariate analysis. While most patients with disseminated disease should initially be treated with an amphotericin formulation, patients with these risk factors are particularly likely to require polyene therapy even if renal function is impaired. Although it is common practice and makes intuitive sense to reduce maintenance immunosuppression in SOT recipients with severe infections, we did not find a correlation between reduction of immunosuppression and risk of death. Any benefit of reducing immunosuppression, however, may have been masked by the fact that immunosuppression was reduced in > 90% of cases and most deaths occurred soon after diagnosis.

The optimal duration of treatment for histoplasmosis after solid organ transplantation is unknown. In two other reports suppressive therapy was administered in 23% [6] and 50% [3] of patients; in a third report none received suppressive therapy with no relapses noted in patients

treated for 12 months [5]. Combining the four series, 14 of 197 patients (7.1%) relapsed, nine (64.3%) within the first two years, 12 (85.7%) within the first four years and one patient each at 6 and 9 years following the original episode. Thus, the greatest risk is during the first two years, but 36% occurred later, up to at least nine years following the original episode. Overall, our findings support the safety of discontinuing antifungal therapy following a 12 month course of treatment. Heightened awareness of findings consistent with relapse should be maintained during the first two years following the initial episode, and continued awareness of the risk of relapse for the remainder of the patient's life.

Sequential antigen testing might be useful in determining if a subset of patients is at risk for relapse if azole therapy is discontinued. The IDSA guidelines suggests that antigen concentration should be less than 2 ng/mL prior to stopping therapy and monitored for at least 12 months after treatment is stopped [20]. As patients in our study did not all have antigenuria monitored at routine intervals, our conclusions regarding the utility of this practice are incomplete. However, some observations can be made. Antigenuria progressively declined during therapy. Relapse occurred in 2 of the 7 patients (29%) with antigenuria above 2 ng/mL and 1 of 32 patients (3%) with antigen concentrations of 1.9 ng/mL or less (undetectable in 17 of 32). One of the 2 patients that discontinued therapy before antigen concentration fell below 2 ng/mL died following a relapse of histoplasmosis: the concentration at discontinuation of therapy was 5.9 ng/mL in that patient. In another report antigenuria persisted in 3 of 9 patients at the time treatment was stopped, and relapse did not occur [5]. Antigen levels in the urine and serum had declined from peak at the time treatment was stopped and the authors concluded that antigen testing and clinical follow-up should be performed for at least 18-24

months. A significant increase in antigen should prompt very careful clinical monitoring or reinstitution of treatment.

Our study has several important limitations. Data was not collected prospectively and diagnostic and treatment strategies varied over time and from center to center. The scope of the study and the multicenter nature made a case-control series impractical. Thus, risk factors for the development of histoplasmosis could not be determined. Further, since data from each center providing the number of surviving post-transplant patients stratified by time from transplant was not available, precise incidence rates could not be calculated. A standardized diagnostic protocol was not used at each center and comparison of performance of diagnostic methods was thus imperfect. Determination of the cause of death by retrospective review of medical records is difficult and impacts the analysis of risk factors. Finally, conclusions regarding the safety of discontinuing chronic maintenance therapy must be tempered by the variable duration of follow-up.

This study describes a large, multicenter cohort of patients with histoplasmosis after SOT. While a significant number of late cases occur, the first year after transplant is the period of greatest risk. Some of these cases likely represent donor-derived infection. Antigen detection in the serum or urine is the most sensitive diagnostic test. As is true of many infections post-transplantation, serological tests are of limited sensitivity. While early deaths occur, treatment with a polyene followed by 12 months of azole therapy is successful in most cases with only rare relapses. Conducting prospective studies to refine the optimal treatment of histoplasmosis would be very challenging. Future prospective studies, however, could focus

on universal serological or antigen based screening of donors and recipients in endemic areas to better inform practices to reduce the incidence of early donor or recipient derived disease.

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DISCLAIMER

The views and opinions expressed in this article/presentation are those of the authors and do not reflect official policy or position of the United States Air Force, Department of Defense, or US Government.

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Table 1: Participating Centers and Rates of Histoplasmin Skin Test Reactivity

City, State	Institution	Skin Test Positive (%)[21]	TransNet Center
Omaha, Nebraska	University of Nebraska	10.7%	yes
Indianapolis, Indiana	Indiana University	55.1%	no
Birmingham, Alabama	University of Alabama	13.2%	yes
Cleveland, Ohio	Cleveland Clinic	4.9%	no
Columbus, Ohio	Ohio State University	44.0%	no
Iowa city, IA	University of Iowa	26.6%	yes
Madison, Wisconsin	University of Wisconsin	10.60%	yes
Minneapolis, Minnesota	University of Minnesota	9.70%	yes
Rochester, Minnesota	Mayo Clinic	6.40%	yes
Kansas City, Missouri	University of Kansas	36.00%	no
Ann Arbor, Michigan	University of Michigan	11.80%	yes
Kansas City, Missouri	Infectious Disease Associates of Kansas City	36.00%	no
Lexington, Kentucky	University of Kentucky	96.90%	no
New York City, New York	Mount Sinai	1.40%	no
Wichita, Kansas	University of Kansas	19.10%	no
Chicago, Illinois	University of Chicago	6.80%	no
Dayton, Ohio	Wright-Patterson Medical Center	67.10%	no
Dayton, Ohio	Wright State University	67.10%	no
Joplin, Missouri	St. John's Regional Medical Center	53.60%	no
Baltimore, Maryland	Johns Hopkins	11.10%	yes

New Orleans, Louisiana	Ochsner Medical Foundation	5.20%	no
Pittsburgh, Pennsylvania	University of Pittsburgh	3.90%	no
Fontana, California	Kaiser Permanente	3.60%	no
Miami, Florida	University of Miami	2.80%	no

Table 2: Demographic characteristics of 152 cases

Characteristic	Percentage
Age (median)	48.5 (3 - 80)
Male	66% (100/152)
Race	
Caucasian	80% (121/152)
African American	15% (23/152)
Latino	2% (3/152)
Asian	1% (1/152)
Diabetes	34% (51/152)
Cancer	1% (1/152)
Organ transplant	
Kidney	51% (78/152)
Liver	16% (24/152)
Kidney/pancreas	14% (22/152)
Heart	9% (14/152)
Lung	5% (8/152)
Pancreas	2% (3/152)
Lung/kidney	1% (1/152)
Small bowel	1% (1/152)
Kidney/heart	1% (1/152)
Immunosuppression	
Calcineurin inhibitor	91% (138/152)
Mycophenolate preparation	82% (124/152)
Corticosteroid	76% (115/152)
Azathioprine	3% (4/152)
Sirolimus	1% (1/152)
Rejection within 3 months before diagnosis	10% (15/152)

Table 3: Selected risk factors for severe disease

Risk Factor	Mild-Moderate[1]	Severe	Univariate OR (95% CI)	p value	Multivariate OR (95% CI)	P value
Transplant Type[2]						
Heart	11/105; 10%	3/43; 7%	0.71 (0.18-2.72)	0.76		
Liver	15/105; 14%	9/43; 21%	1.59 (0.63-3.90)	0.32		
Renal	56/105; 53%	21/43; 49%	0.84 (0.41-1.70)	0.62		
Pancreas	1/105; 1%	2/43; 5%	5.07 (0.56-45.9)	0.20		
Renal/pancreas	17/105; 16%	5/43; 12%	0.68 (0.23-1.98)	0.48		
Lung	5/105; 5%	3/43; 7%	1.50 (0.34-6.55)	0.59		
Immunosuppression						
Calcineurin inhibitor	99/108; 92%	40/43; 93%	1.21 (0.28-7.30)	1.00		
Mycophenolate	83/108; 76%	39/43; 92%	2.94 (1.00-8.71)	*0.05*	9.41 (1.27-66.1)	*0.028*
Corticosteroid	86/108; 80%	28/43; 65%	0.48 (0.22-1.04)	0.06		
Organ involvement						
Pulmonary	85/108; 79%	37/43; 86%	2.94 (0.99-8.71)	0.07		
Disseminated	83/108; 77%	39/43; 91%	0.37 (0.13-1.05)	0.06		
Bone marrow	23/108; 21%	16/43; 37%	2.20 (1.02-4.70)	*0.04*	2.62 (0.81-12.2)	0.098
Liver	19/108; 18%	8/43; 19%	1.07 (0.43-2.68)	0.89		
Spleen	10/108; 9%	9/43; 21%	2.50 (0.99-6.78)	0.06		
Skin	4/108; 4%	1/43; 2%	0.62 (0.07-5.63)	0.56		
Gastrointestinal	13/108; 12%	3/43; 7%	0.50 (0.15-2.00)	0.56		
Central nervous system	6/108; 6%	4/43; 9%	1.74 (0.47-6.45)	0.76		
Fungemia	28/57; 49%	27/30; 90%	9.32 (2.72-32.1)	*0.001*	5.40 (1.24-23.4)	*0.024*
Median urine antigen ng/ml (number sent, range)	10.8 (101[3]; 0->19)	19 (40[3]; 0->19)	1.11 (1.05-1.18)	*0.001*	1.029 (0.87-1.22)	0.73
Urine antigen >19 ng/ml	31%	56%	2.9 (1.30-6.20)	*0.01*	5.86 (0.62-55.7)	0.124
Median serum antigen ng/ml (number sent, range)	11.6 (37[3]; 3.5->19)	10.2 (13[3]; 0->19)	1.016 (0.97-1.07)	0.40		

OR= odds ratio; CI=confidence interval; ng=nanograms;

(1) Severity of one case could not be classified

(2) one small bowel and two multiorgan non-renal/pancreas transplants not included

(3) number of patients in whom results of the respective test was available

Table 4: Results of diagnostic test

Test	Pulmonary	Disseminated	Total (%)	P value
Culture	17/29 (59%)	87/118 (74%)	104/147 (71%)	0.11
Lung, respiratory culture	15/25 (60%)	56/73 (77%)	71/98 (72%)	0.11
Pathology or cytology	20/24 (83%)	65/83 (78%)	85/107 (79%)	0.58
Lung, respiratory pathology or cytology	18/21 (86%)	36/49 (74%)	54/70 (77	0.26
Culture, pathology, or cytology	25/29 (86%)	100/107 (93%)	125/146 (86%)	0.20
Lung, repiratory culture, pathology or cytology	22/26 (85%)	60/74 (81%)	82/100 (82%)	0.68
Antigenuria	19/26 (73%)	113/116 (97%)	132/142 (93%)	0.01
Antigenemia	2/4 (59%)	41/46 (89%)	43/50 (86%)	0.03
Antibody	5/8 (62%)	11/36 (28%)	16/44 (36%)	0.08

Table 5: Treatment and immunosuppression management

Initial Treatment	
Amphotericin product	72% (110/152)
ABLC	39% (60/152)
Liposomal amphotericin	26% (40/152)
Amphotericin B deoxycholate	7% (10/152)
Azole	26% (39/152)
Itraconazole	25% (38/152)
Voriconazole/fluconazole/unknown	1% (1/152)
Subsequent Treatment	
Itraconazole	74% (113/152)
Voriconazole	6% (9/152)
Itraconazole/voriconazole	9% (14/152)
Fluconazole	1% (1/152)
Early death	10% (15/152)
Decrease or stop immunosuppression	
Calcineurin inhibitor	95% (144/152)
Mycophenolate preparation	91% (138/152)
Corticosteroid	71% (108/152)

ABLC=Amphotericin B lipid complex

Table 6: Risk factors for death due to histoplasmosis

	Death due to *histoplasmosis* (15)	Survival (128)	Univariate OR (95% CI)	P value	Multivariate OR (95% CI)	*p* value
Median age (range)	54 (43-68)	47 (3-80)	1.058 (1.009-1.111)	0.02	1.104 (1.002-1.150)	*0.046*
Severe disease	94%	37%	40 (5-333)	<0.001	5-333 (0.004-0.485)	*0.011*
Fungemia	92%	63%	7.67 (1.0-62.6)	0.048	3.294 (0.156-69.38)	0.44
Median urine antigen ng/ml (range)	>19 (2.1-19.0)	12 (0->19.0)	1.112 (1.0-1.26)	0.039	1.12 (0.79-1.59)	0.52
Urine antigen > 19 ng/mL	61%	38%	3.4 (0.9-12)	0.06		0.64
Reduced calcineurin inhibitor	100%	75%	*	1.0	*	
Amphotericin treatment	87%	70%	2.75 (0.59-12.7)	0.23		

OR=odds ratio; CI=confidence interval; ng=nanograms; *=cannot be calculated with zero count cells

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Figure Legends:

Figure 1: Time in years from transplantation to diagnosis with histoplasmosis