

Histoplasmosis in Solid Organ Transplant Recipients: 10 Years of Experience at a Large Transplant Center in an Endemic Area

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Background. Many clinical scenarios have been encountered by patients who developed histoplasmosis after receiving a solid organ transplant at a large transplant center in an endemic area.

Methods. Cases of posttransplantation histoplasmosis were identified by use of multiple methods, including reviews of microbiology test results, transplant databases, and billing codes. Data were obtained retrospectively. Descriptive statistics were used.

Results. During the 1997–2007 study period, 3436 patients received a solid organ transplant, and 38 patients were identified as having posttransplantation histoplasmosis. Of these 38 patients, 9 were excluded from our study because the diagnosis was solely clinical. Of the remaining 29 patients, 14 had posttransplantation histoplasmosis (incidence, 1 case per 1000 person-years); 14 showed histologic evidence of histoplasmosis in the recipient or donor tissue, which was encountered unexpectedly at the time of transplantation; and 1 had histoplasmosis before receiving the transplant. Of the 14 patients who developed histoplasmosis after transplantation, 5 were heart transplant recipients, 3 were lung transplant recipients, 3 were kidney transplant recipients, 1 was a liver transplant recipient, 1 was a pancreas transplant recipient, and 1 was a kidney-pancreas transplant recipient. The median time from transplantation to diagnosis was 17 months (interquartile range, 8.1–46 months), and the median time from onset of symptoms to diagnosis 3 weeks (interquartile range, 1.9–6.5 weeks). All recipients had disseminated disease. The most common treatment was amphotericin B and itraconazole. All were cured, or still on treatment, but symptom-free. Of the 14 patients who had an explanted organ or donor tissue that showed histologic evidence of histoplasmosis, 13 (93%) were lung transplant recipients, and 1 (7%) was a liver transplant recipient. None of these patients developed active histoplasmosis, but all received prophylactic treatment. Finally, 1 patient had histoplasmosis before transplantation; he was treated with itraconazole 3 months before and after transplantation, and he did well.

Conclusions. In conclusion, posttransplantation histoplasmosis is rare (1 case per 1000 transplant-person-years; 95% confidence interval, 0.6–1.7), even in endemic areas. Prognosis is good but requires protracted therapy. Patients with latent infection did not develop posttransplantation histoplasmosis when prophylaxis was used.

Histoplasmosis and disseminated disease were first described at the beginning of the 20th century by Samuel T. Darling [1]. These types of infection have been reported worldwide but are more prevalent in certain parts of North and Central America [2]. The Ohio and

Mississippi River Valleys are known to be endemic for histoplasmosis since 1945 [3].

The incidence of disseminated histoplasmosis is greatest among immunocompromised individuals, especially patients with human immunodeficiency virus (HIV) infection. For solid organ transplant (SOT) recipients, the incidence of histoplasmosis is estimated to be low, with only a few case series, mostly among renal and liver transplant recipients [4–7]. There are only isolated case reports of histoplasmosis among lung or heart transplant recipients [8–10]. For SOT recipients, disseminated disease may occur as primary infection, as a reactivation of latent infection, or as a donor-

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transmitted infection [11]. Given the scarcity of studies on which to make evidence-based recommendations, the 2007 update of the clinical practice guidelines for the management of patients with histoplasmosis, endorsed by the Infectious Diseases Society of America, provides no specific recommendations on the ideal treatment of histoplasmosis among SOT recipients [12].

The Cleveland Clinic is a large tertiary care referral hospital that admits patients from regions known to be highly endemic for histoplasmosis. We describe the different clinical scenarios encountered by SOT recipients with histoplasmosis at this institution over the course of a decade, including their treatment and outcome. These scenarios include active infection with *Histoplasma capsulatum* either before or after transplantation and histopathologic evidence of histoplasmosis encountered unexpectedly in either the explanted tissue of the donor or recipient at the time of the transplantation.

MATERIALS AND METHODS

Our study period was from 1997 through 2007. Cases were identified and cross-referenced by use of several methods, including a review of all microbiology test results (from sterile body sites) positive for *H. capsulatum* and a review of all billing code data. Data on donor and recipient tissue for all cases of lung transplantation were reviewed, to detect histoplasmosis. An active SOT database tracks infectious disease complications and patient outcomes. All SOT recipients who met one of the clinical scenarios described below were included in our study. Patients were excluded from our study if their histoplasmosis was diagnosed on the basis of clinical symptoms only. Study data were collected retrospectively from medical and microbiology records.

Case Definitions of Clinical Scenarios

Active histoplasmosis. Proven cases of active infection required that the patient have compatible clinical manifestations as well as show histologic (yeast forms compatible with *H. capsulatum*) and/or microbiologic (growth of *H. capsulatum* in culture) evidence of histoplasmosis. Possible cases of active infection required that the patient have compatible clinical manifestations plus a positive *Histoplasma* urine antigen test result and/or a positive serology test result (which was previously negative or had a 4-fold increase in titers).

Type of infection (disseminated vs. localized histoplasmosis). A diagnosis of disseminated disease was based on radiographic, histologic, or microbiologic evidence of involvement of at least 2 organs or a blood or bone marrow sample that tested positive for *H. capsulatum* on culture; otherwise, patients were considered to have localized disease.

Testing. Histologic testing revealed yeast forms compatible with *H. capsulatum* in the explanted organ of the recipient or

in the tissue of the donor that were identified at the time of transplantation. For patients who were awaiting kidney-liver transplantation and had new respiratory symptoms, consistent radiological findings, new serology testing done, and granulomata, the *Histoplasma* urine antigen test (MiraVista Diagnostics) was used, and *Histoplasma* antibody testing (by immunodiffusion and by complement fixation) was performed in the laboratory of the Cleveland Clinic.

Statistical Analysis

Descriptive statistics were used. To determine the incidence rate, we identified the population at risk, as defined by person-years; the data were obtained by reviewing the Cleveland Clinic Transplant Center database. For patients with ≥ 1 transplant, the organ group and follow-up time for each SOT recipient was calculated starting with their first transplant. Analyses were conducted with SAS, version 9.1 (SAS).

RESULTS

During the 10-year period from 1997 through 2007, a total of 3572 solid organ transplantations were performed for 3436 patients (829 heart, 499 lung, 746 liver, 1222 kidney, 38 pancreas, and 102 kidney-pancreas transplants). Thirty-eight patients were identified as having posttransplantation histoplasmosis, and 29 patients met the inclusion criteria. Patients were classified according to their first transplantation. The initiation of immunosuppressive medication during the first transplantation specifically increased the risk of infection [5]. Of the 29 patients who were included in the analysis, 14 had proven active histoplasmosis after transplantation (scenario 1), 10 had an explanted organ that showed evidence of histoplasmosis, 4 received donor tissue that showed evidence of histoplasmosis (scenario 2), and 1 had active histoplasmosis before transplantation (scenario 3).

Scenario 1: Active Histoplasmosis after Solid Organ Transplantation

Of the 3436 SOT recipients, 14 developed proven active histoplasmosis (table 1). The overall attack rate of histoplasmosis in the posttransplantation period per 1000 solid organ transplantations was 4.1 cases (95% confidence interval [CI], 2.2–6.8 cases). Rates were highest in pancreas transplant recipients at 26.3 cases (95% CI, 0.7–138.1 cases), followed by kidney-pancreas, heart, lung, kidney, and liver transplant recipients. The global incidence of posttransplantation active histoplasmosis was 1 case per 1000 person-years. By type of transplant, the incidence was again highest in the pancreas transplant group, with 10.7 cases per 1000 person-years (95% CI, 0.3–59.9 cases), followed by kidney-pancreas, lung, heart, kidney, and liver transplant recipients.

Patient characteristics. The demographic and clinical char-

Table 1. Attack and Incidence Rates of Histoplasmosis at the Cleveland Clinic, by Type of Organ Transplanted, 1997–2007

Type of organ transplanted	No. of SOT recipients	No. of SOT recipients with active histoplasmosis	Attack rate, cases per 1000 transplantations (95% CI)	Follow-up, ^a person-years	Incidence rate, cases per 1000 person-years (95% CI)
Heart	829	5	6.0 (2.0–14.0)	4073	1.2 (0.4–2.9)
Lung	499	3	6.0 (1.2–17.5)	1505	2 (0.4–5.8)
Kidney	1222	3	2.5 (0.5–7.2)	4985	0.6 (0.1–1.8)
Liver	746	1	1.3 (0–7.4)	2579	0.4 (0.0–2.2)
Pancreas	38	1	26.3 (0.7–138.1)	93	10.7 (0.3–59.9)
Kidney-pancreas	102	1	9.8 (0.2–53.4)	389	2.6 (0.0–14.3)
All	3436	14	4.1 (2.2–6.8)	13,624	1.0 (0.6–1.7)

NOTE. Patients were classified according to the first solid organ transplant (SOT) received. CI, confidence interval.

^a The first SOT a patient received was used in calculating follow-up period in person-years.

acteristics of the 14 patients with posttransplantation histoplasmosis are displayed in table 2. Of these 14 patients, 9 (64%) were male. The median age was 45.5 years (interquartile range [IQR], 38–56.5 years); 13 (93%) were white, and 1 (7%) was African American. Thirteen patients resided in Ohio, and one lived in Buffalo, New York. The most common immunosuppressive regimen at the time of presentation (ie, for 9 [64%] of the 14 patients) was prednisone, tacrolimus, and mycophenolate mofetil. The median time from transplantation to infection was 17 months (IQR, 8.1–46 months).

Clinical presentation. The median duration of symptoms before the diagnosis of active histoplasmosis was 3 weeks (IQR, 1.9–6.5 weeks). Clinical manifestations varied and were non-specific. Fever (13 [93%] of 14 patients) and shortness of breath (8 [57%] patients) were the most common clinical manifestations, followed by diarrhea (6 patients [43%]), cough (6 patients [43%]), diaphoresis (5 patients [36%]), and headache (4 patients [29%]). Surprisingly, weight loss was not as frequent (3 patients [21%]). All patients had lung involvement as evidenced by radiologic studies, culture, and/or histopathology. In this group, all patients had disseminated infection (11 patients had at least 2 compatible biopsies and/or positive culture results from different organs; the remaining 3 had a compatible lung biopsy and radiographic evidence of involvement of another organ). Notable findings at presentation included hoarseness in a patient with a tonsillar abscess due to *H. capsulatum* infection and blurry vision in a patient with central nervous system involvement (patients 5 and 1 in table 2, respectively).

Imaging. Only 7 (50%) of the 14 patients with active histoplasmosis after transplantation had an abnormal chest radiograph, yet all 13 patients had chest computed tomography (CT) scans that revealed new abnormalities consistent with acute histoplasmosis (figure 1A). The most common abnormalities revealed on a chest CT scan were multiple nodular lesions and diffuse bilateral infiltrates. Five (50%) of 10 patients who had abdominal CT scans had abnormalities suggestive of

H. capsulatum infection, including splenomegaly (with and without focal lesions) and lymphadenopathy.

Laboratory results. The most common laboratory abnormalities were anemia and leukopenia (12 [86%] of 14 patients). The median white blood cell count was 3.84×10^3 cells/ μ L (IQR, 2.07–6.85 $\times 10^3$ cells/ μ L), and the median hemoglobin level was 9.9 (IQR, 9–11.4 g/dL). In contrast to HIV-infected patients with disseminated disease, only 2 patients had mildly elevated liver transaminase levels, and none had an increased alkaline phosphatase or total bilirubin level. For 8 patients, data on lactate dehydrogenase level were available; of these 8 patients, 5 had elevated levels, with a median lactate dehydrogenase level of 287 U/L (range, 205.3–474.5 U/L; normal range, 100–220 U/L). Ferritin levels were determined for 6 patients, and in all 6 patients, the levels were elevated, with a median ferritin level of 1007 ng/mL (IQR, 543.5–9703.3 ng/mL; normal range, 9–300 ng/mL). The median immunoglobulin G level at the time of diagnosis was 645 mg/dL (IQR, 445.5–829.3 mg/dL; normal range, 717–1411 mg/dL). For 5 patients, an adenosine triphosphate immune function assay (ImmuKnow; Cylex) was performed at the time of diagnosis, with a median of 254 ng/mL (IQR, 201–290 ng/mL; normal range, 225–525 ng/mL).

Diagnosis. All 14 patients had proven histoplasmosis (table 2). Seven (50%) had both positive culture results and positive diagnostic histopathology test results (figure 1B), and the remaining 7 patients (50%) had ≥ 2 body sites where *H. capsulatum* was isolated. For 13 patients, a *Histoplasma* urine antigen test was performed; of these 13 patients, 9 (69%) tested positive. For 12 patient, *Histoplasma* serology testing, by complement fixation and immunodiffusion, was performed; of these 12 patients, 4 (33%) tested positive.

Treatment and outcomes. The most common type of initial antifungal therapy was the administration amphotericin B products (11 [79%] of 14 patients); the median duration of treatment with amphotericin B was 23.5 days (IQR, 5.75–42.5

Table 2. Demographic and Relevant Clinical Characteristics of Patients with Posttransplantation Histoplasmosis at the Cleveland Clinic, 1997–2007

Patient	Age, years	Sex	Type of organ transplanted	Time to infection after transplantation, months	Immunosuppression therapy	Method of diagnosis		Urine antigen test (result), ELISA unit	Serological test	Treatment	Duration of treatment, months	Outcome ^b
						Histopathology	Culture ^a					
1	24	F	Kidney	16	Data incomplete	Brain	...	6.76 (+)	–	AmB, Itr	38.9 ^c	Recurred, controlled
2	45	M	Kidney	43.9	Tacro, Myco, Pred	Lung, BM	BAL, BM	<1.0 (–)	–	AmB, Itr	4.5	Cured
3	64	F	Kidney-pancreas	18.7	Tacro, Myco, Pred	Lung	BAL	40.61 (+)	–	Itr	6.8	Cured
4	42	M	Heart	55	Tacro, Myco, Pred	...	Blood, BAL	<1.0 (–)	+	Itr	51.43	Cured
5	26	F	Liver	18	Tacro, Pred	Liver, tonsillar, BM	Blood, BM	NA	NA	AmB, Itr	6.7	Cured
6	47	M	Heart	7.9	Tacro, Myco, Pred	Lung, BM	BAL, BM	<1.0 (–)	+	AmB, Itr	41.4	Cured
7	41	M	Lung	9.8	Tacro, Myco, Pred	Lung	...	0.61 (+)	–	AmB, Vor	6.7	Cured
8	52	M	Lung	46.6	Myco, Pred, Siro	Lung	...	0.49 (–)	N/A	AmB, Itr	15.2 ^c	Cured
9	36	M	Heart	47.4	Myco, Tacro	...	Blood	1.79 (+)	–	AmB, Itr	6.6	Cured
10	37	F	Pancreas	8.8	Myco, Tacro	Lung	Blood, BAL	>39 (+)	–	AmB, Itr	6.3 ^c	Cured
11	46	F	Heart	3.1	Cysp A, Myco, Pred	Lung	Blood, BAL	17.08 (+)	–	AmB, Itr	6.8 ^c	Cured
12	58	M	Kidney	1.8	Tacro, Myco, Pred	BM	...	14.06 (+)	+	Itr, Vor	3.3 ^c	Persistently elevated level of urine antigen
13	64	M	Lung	83.1	Tacro, Aza, Pred	Lung, BM	BAL	3.77 (+)	+	AmB, Vor	4.4 ^c	Cured
14	65	M	Heart	4.8	Tacro, Myco, Pred	...	Blood, BAL	33.83 (+)	–	AmB, Itr	2.5 ^c	Cured

NOTE. AmB, amphotericin B (colloidal dispersion or lipid formulations); Aza, azathioprine; BAL, bronchoalveolar lavage; BM, bone marrow; Cysp A, cyclosporine A; ELISA, enzyme-linked immunosorbent assay; Itr, itraconazole; Myco, mycophenolate mofetil; NA, not available; Pred, prednisone; Siro, sirolimus; Tacro, tacrolimus; Vor, voriconazole.

^a Blood samples were obtained from all patients for culture; however, BM samples were obtained only from patients 1, 2, 4, 5, 6, 12, and 13.

^b All patients were alive at the end of our study.

^c Patient was still receiving treatment or suppressive therapy.

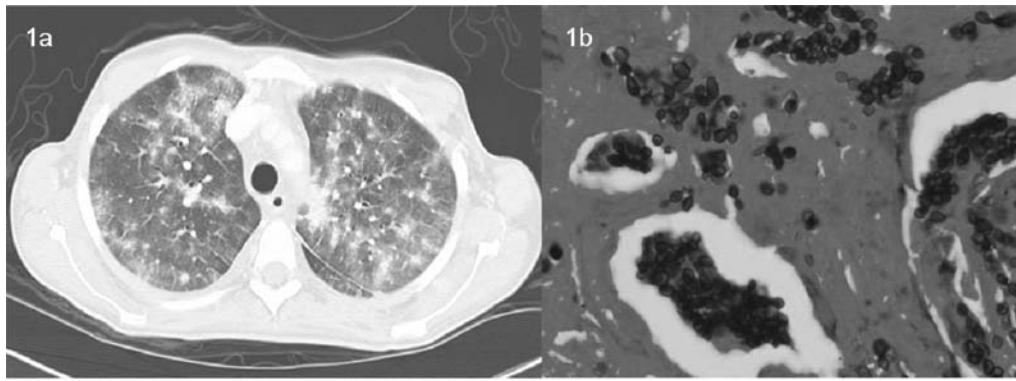


Figure 1. A, Computed tomography of the chest with multiple bilateral nodular patchy infiltrates. B, Lung biopsy. Gomori methenamine silver stain highlights yeast forms compatible with *Histoplasma capsulatum* (original magnification, $\times 1000$).

days). Of these 11 patients, 9 switched to itraconazole. The other 2 patients switched to voriconazole, as a result of physician preference in 1 case and symptomatic disease onset during itraconazole prophylaxis in the other (ie, patients 13 and 7 in table 2, respectively). Two patients with milder symptoms were treated with itraconazole alone. Finally, 1 kidney transplant recipient (patient 12) with severe renal impairment was started on itraconazole but was switched to voriconazole because of progressive disease. He eventually returned to itraconazole, remains free of symptoms, but has a persistently elevated level of urine antigen. The overall median duration of treatment was 6.7 months (IQR, 4.9–13.1 months).

The median follow-up period from the time of diagnosis was 19 months (IQR, 6.9–49.6 months). All patients were alive at the end of our study. Overall, 7 (50%) of the 14 patients were cured, and antifungal treatment was stopped; another 6 patients (43%) were still on treatment but asymptomatic. One patient (patient 1) showed evidence of recurrence 3 months after treatment was stopped, at which point central nervous system involvement was diagnosed. These 7 remaining patients received a course of amphotericin B and itraconazole. They were restarted on amphotericin B and switched to lifelong suppressive itraconazole after 6 months.

Scenario 2: Evidence of Histoplasmosis in the Explanted Organ of the Recipient or in Donor Tissue

In addition to the patients described above, we also encountered 14 patients who showed evidence of *H. capsulatum* infection in the explanted organ of the recipient or donor tissue. Of these 14 patients, 10 showed evidence of histoplasmosis in their explanted organs, and 4 had donor tissue that showed evidence of histoplasmosis. The overall incidence of *H. capsulatum* infection in the explanted organ of transplant recipients was 2.9 cases per 1000 transplantations. Of the 10 recipients, 9 were lung transplant recipients (for which donor and/or recipient lung and lymph node tissue were routinely evaluated), and 1

was a liver transplant recipient who had splenectomy due to massive splenomegaly. *H. capsulatum* was found in the explanted spleen. The incidence of unexpected histoplasmosis in the explanted organ in lung recipients was 18 cases per 1000 transplantations, and most had lung parenchyma and lymph node involvement. Also, lung transplant recipients comprised the 4 cases in which evidence of histoplasmosis was found in donor tissue. In these cases, evidence of histoplasmosis was found in donor lymph node tissue.

Pretransplantation imaging. The pretransplantation radiology reports of the 10 explanted organs positive for *H. capsulatum* were reviewed. All 9 lung transplant recipients had abnormal chest CT scans; 4 (44%) of the 9 lung transplant recipient showed indirect evidence of histoplasmosis (calcified lymph nodes and granulomata). The liver transplant recipient had splenomegaly on the abdominal CT scans but no calcifications. No information is available on the donors' radiologic findings.

Management and outcome. Antifungal prophylaxis for all lung transplant recipients at the Cleveland Clinic consists of 18 months of oral itraconazole (liquid formulation usually preferred) and a short course of inhaled amphotericin B, until oral treatment results in detectable levels. All lung transplant recipients with evidence of histoplasmosis in their explanted organs or in the donor tissue received this regimen. The liver transplant recipient received 2 weeks of amphotericin B lipid complex and then completed 6 months of fluconazole as a result of significant itraconazole intolerance. Patients were not managed with a lesser degree of immunosuppression on account of their preexisting histoplasmosis. No patient in this group, with a median follow-up period of 13.5 months (IQR, 9.5–45.7 months), developed posttransplantation histoplasmosis.

Scenario 3: Pretransplantation Histoplasmosis

One patient had possible active histoplasmosis while on the waiting list for a kidney-liver transplant. The patient had new

onset of shortness of breath; evaluation revealed a new lung nodule and a positive *Histoplasma* antibody (M band). Lung biopsy revealed loosely formed granulomata. He received itraconazole for 3 months before the transplantation and continued treatment for 3 months after the transplantation. Symptoms had subsided before he received the transplant. The posttransplantation clinical course has been uneventful, with no evidence of recurrent histoplasmosis during 9 months of follow-up.

DISCUSSION

Symptomatic or asymptomatic *H. capsulatum* infection is usually accompanied by hematogenous dissemination, which, in the normal host, is usually controlled by T cell-mediated immunity [13, 14]. Immunocompromised patients are unable to mount adequate immune responses and frequently become symptomatic during the period of acute dissemination [14, 15]. Although histoplasmosis is the most common endemic mycosis among immunocompromised patients in general, the frequency of histoplasmosis among SOT recipients appears to be low. In a study performed in an area hyperendemic for histoplasmosis, no cases were observed after a mean follow-up period of 16 months for 586 SOT recipients [4]. In our study, the incidence of posttransplantation histoplasmosis was 1 case per 1000 person-years. To our knowledge, this is the largest single-center series of its kind.

Differences between SOT groups are striking and should be explored more thoroughly in a multicenter study. Of note, the attack rate and incidence of histoplasmosis among pancreas transplant recipients appear to be higher than they are among other SOT populations, although the small numbers are reflected in wide CIs. Contrary to a report by Freifeld et al [16], in which it was reported that histoplasmosis was more common in liver transplant recipients, with no cases in heart or lung transplant recipients, we observed higher incidences in heart and lung transplant recipients than in liver transplant recipients. Although differences in antifungal prophylaxis could account for differences in the attack rate and incidence of disease, lung transplant recipients in our study were at the median for both measures.

The median time interval from transplantation to histoplasmosis was ~17 months, similar to that previously reported by Wheat et al [7], with a broad range from 2 months to 7 years. The clinical features of disseminated histoplasmosis in SOT recipients are nonspecific and similar to many other disseminated infections. The most common symptoms are fever and shortness of breath, but mild symptoms may also be present, and disseminated disease may not be apparent from the initial evaluation. Eventually all patients in this series had lung involvement documented by radiologic studies, culture, and/or histopathology. For 7 (50%) of 14 patients in our series, the

chest CT outperformed the chest radiograph. The chest CT scan was abnormal in each case for which it was performed.

A diagnosis of proven posttransplantation histoplasmosis is established with culture or histopathology, but other tests, such as the *Histoplasma* urine antigen test or the *Histoplasma* serological test, may provide more rapid results and may aid in the diagnosis. According to a previous published study [15], the sensitivity of the *Histoplasma* urine antigen test for the diagnosis of disseminated disease is 90% for patients with AIDS and 82% for other immunocompromised patients. These sensitivities reflect the performance of the previous generation assay and not the one currently in use. In our study, 69% of patients had a positive *Histoplasma* urine antigen test result; moreover, the negative test results were of the earlier cases, for which the older, less sensitive assay was used. As suggested by Kauffman [15], a serological diagnosis of disseminated histoplasmosis appears to be of limited value for immunosuppressed patients, with only one-third of the patients in our series testing positive. However, seroconversion or a 4-fold increase in titers strongly suggests a diagnosis of histoplasmosis.

According to the Infectious Diseases Society of America guidelines for the management of histoplasmosis, the recommended treatment for acute or disseminated histoplasmosis of moderate to severe disease is liposomal amphotericin B products followed by itraconazole; itraconazole alone is recommended in less severe cases of acute disease [12, 17]. Recommendations for the duration of treatment vary from 12 weeks for acute disease to ≥ 12 months for progressive disseminated disease [12]. Treatment should be individualized on the basis of diagnosis, net state of immunosuppression, and potential consequences of location of disease (eg, central nervous system) [12]. In our experience, this approach, when applied to SOT recipients, is effective, as evidenced by the good clinical response, despite continued immunosuppression. However, clinicians must keep in mind the drug-drug interactions between the calcineurin inhibitors frequently used in the immunosuppressive regimens of these patients and itraconazole. Itraconazole is a potent inhibitor of the cytochrome P450 3A4 isoenzyme system and can result in significant increases in blood levels of calcineurin inhibitors. Levels of the latter should be closely monitored [18].

Another clinical scenario encountered in histoplasmosis-endemic areas is the unexpected evidence of histoplasmosis in either the explanted tissue from the recipient or the donor tissue. This situation is encountered almost exclusively in lung transplant recipients (18 cases per 1000 lung transplantations), and to our knowledge, this is the first series to report on the management of these patients. Whether these patients would have developed active histoplasmosis after transplantation without prophylaxis is uncertain, but the probability of reactivation after solid organ transplantation exists. Histoplasmosis was seen

in a series of SOT recipients who migrated from areas of endemicity to areas of nonendemicity [19]. Cases of reactivation in other immunocompromised individuals have also been reported [20]. The aggressive antifungal prophylaxis used in this center's lung transplant program seems to be effective in preventing reactivation.

In summary, posttransplant histoplasmosis is a potentially lethal event but is relatively uncommon, even in endemic areas. Because of the nonspecific symptoms of histoplasmosis and because its time to onset varies, continued clinical suspicion for and vigorous diagnostic pursuit of histoplasmosis result in its timely diagnosis and treatment. Although invasive diagnostic methods (eg, histopathology exam and culture) have been successful at determining a diagnosis of histoplasmosis, less invasive urine and blood tests can aid in establishing the diagnosis. Although disseminated disease is common among SOT recipients, the prognosis appears to be good. The unexpected finding of histoplasmosis in the explanted tissue of either a donor or the recipient is a scenario mostly found in the lung transplant recipients. In our case series, none of the lung transplant recipients who received aggressive antifungal prophylaxis developed active histoplasmosis. As antifungal prophylaxis evolves over time, to reduce infectious complications after transplantation, we must continue to pay attention to the regional epidemiology of histoplasmosis.

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References

1. Darling ST. A protozoan general infection producing pseudotubercles in the lungs and focal necrosis in the liver, spleen, and lymph nodes. *JAMA* **1906**; 46:1283–5.
2. Cano M, Hajjeh RA. The epidemiology of histoplasmosis: a review. *Semin Respir Infect* **2001**; 16:109–18.
3. Christie A, Peterson JC. Pulmonary calcification in negative reactors to tuberculin. *Am J Public Health Nations Health*. **1945**; 35:1131–47.
4. Vail GM, Young RS, Wheat LJ, Filo RS, Cornetta K, Goldman M. Incidence of histoplasmosis following allogeneic bone marrow transplant or solid organ transplant in a hyperendemic area. *Transpl Infect Dis* **2002**; 4:148–51.
5. Freifeld AG, Iwen PC, Lesiak BL, Gilroy RK, Stevens RB, Kalil AC. Histoplasmosis in solid organ transplant recipients at a large midwestern university transplant center. *Transpl Infect Dis* **2005**; 7:109–15.
6. Peddi VR, Hariharan S, First MR. Disseminated Histoplasmosis in renal allograft recipients. *Clin Transplant* **1996**; 10:160–5.
7. Wheat LJ, Smith EJ, Sathapatayavongs B, et al. Histoplasmosis in renal allograft recipients: two large urban outbreaks. *Arch Intern Med* **1983**; 143:703–7.
8. Oh YS, Lisker-Melman M, Korenblat KM, Zuckerman GR, Crippin JS. Disseminated histoplasmosis in a liver transplant recipient. *Liver Transpl* **2006**; 12:677–81.
9. Koo HL, Hamill RJ, Gentry LO. Disseminated histoplasmosis manifesting as a soft-tissue chest wall mass in a heart transplant recipient. *Transpl Infect Dis* **2008**; 10:351–3.
10. Shah SS, Karnak D, Shah SN, et al. Broncholith caused by donor-acquired histoplasmosis in a lung transplant recipient. *J Heart Lung Transplant* **2007**; 26:407–10.
11. Limaye AP, Conolly PA, Sagar M, et al. Transmission of *Histoplasma capsulatum* by organ transplantation. *N Engl J Med* **2000**; 343:1163–6.
12. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for management of histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis* **2007**; 45:807–25.
13. Porta A, Maresca B. Host response and *Histoplasma capsulatum*/macrophage molecular interactions. *Med Mycol* **2000**; 38:399–406.
14. Kauffman CA. Histoplasmosis: a clinical and laboratory update. *Clin Microbiol Rev* **2007**; 20:115–32.
15. Kauffman CA. Diagnosis of histoplasmosis in immunosuppressed patients. *Curr Opin Infect Dis* **2008**; 21:421–5.
16. Freifeld A, Kauffman CA, Pappas P, et al. Endemic fungal infections among solid organ transplant recipients [abstract 737]. In: Program and abstracts of the 43rd Annual Meeting of the Infectious Disease Society of America (San Francisco). Alexandria, VA: Infectious Diseases Society of America, **2005**.
17. Wheat J, Sarosi G, Mc Kinsey D, et al. Practice guidelines for the management of patients with histoplasmosis. *Clin Infect Dis* **2000**; 30:688–95.
18. Leather H, Bovette RM, Tian L, Wingard JR. Pharmacokinetic evaluation of the drug interaction between intravenous itraconazole and intravenous tacrolimus or intravenous cyclosporin A in allogeneic hematopoietic stem cell transplant recipients. *Biol Blood Marrow Transplant* **2006**; 12:325–34.
19. Davies SE, Sarosi GA, Peterson PK, et al. Disseminated histoplasmosis in renal transplant recipients. *Am J Surg* **1979**; 137:686–91.
20. Jain VV, Evans T, Peterson MW. Reactivation histoplasmosis after treatment with anti-tumor necrosis factor alpha in a patient from a non-endemic area. *Respir Med* **2006**; 100:1291–3.