MAJOR ARTICLE

Opportunistic Mycelial Fungal Infections in Organ Transplant Recipients: Emerging Importance of Non-*Aspergillus* Mycelial Fungi

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To determine the spectrum and impact of mycelial fungal infections, particularly those due to non-*Aspergillus* molds, 53 liver and heart transplant recipients with invasive mycelial infections were prospectively identified in a multicenter study. Invasive mycelial infections were due to *Aspergillus* species in 69.8% of patients, to non-*Aspergillus* hyalohyphomycetes in 9.4%, to phaeohyphomycetes in 9.4%, to zygomycetes in 5.7%, and to other causes in 5.7%. Infections due to mycelial fungi other than *Aspergillus* species were significantly more likely to be associated with disseminated ($P = .005$) and central nervous system ($P = .07$) infection than were those due to *Aspergillus* species. Overall mortality at 90 days was 54.7%. The associated mortality rate was 100% for zygomycosis, 80% for non-*Aspergillus* hyalohyphomycosis, 54% for aspergillosis, and 20% for phaeohyphomycosis. Thus, non-*Aspergillus* molds have emerged as significant pathogens in organ transplant recipients. These molds are more likely to be associated with disseminated infections and to be associated with poorer outcomes than is aspergillosis.

Invasive fungal infections have long been recognized as a significant complication in organ transplant recipients. A vast majority of infections in these patients are due to either *Candida* (35%–91%) or *Aspergillus* species (9%–52%), with other opportunistic fungi accounting for 1%–2% of the fungal infections [1–10]. Within the past decade, however, infections due to infrequently encountered fungi (e.g., hyaline molds, dematiaceous filamentous fungi, and zygomycetes) have become increasingly common in immunocompromised hosts, most notably, hematopoeitic stem cell transplant recipients [11, 12]. These trends are worrisome, given that the opportunistic molds are often refractory to conventional antifungal agents. Innate resistance or erratic susceptibility to amphotericin B is characteristic of certain fungi (e.g., *Aspergillus terreus, Scedosporium apiospermum,* and *Scedosporium prolificans*) [13–16]. The advent of novel antifungal agents represents an advance in the management of invasive mycoses. However, fungi such as *S. prolificans* and the zygomycetes are also resistant to the currently available triazoles and the echinocandins [13–16].

The spectrum and overall impact of these emerging fungal pathogens has not been fully defined in solid-organ transplant recipients. In a prospective, multicenter study, we sought to determine the types of mycelial fungi associated with infections in liver and heart trans-

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plant recipients, to define the characteristics of patients developing these infections, and to discern the outcome of the infections.

METHODS

The study population comprised 53 consecutive, prospectively identified liver and heart transplant recipients with invasive mold infections who were admitted to the participating sites from December 1998 through July 2002. The following data were collected: age; underlying illness; United Network of Organ Sharing status; type of primary immunosuppressive agent; comorbid conditions (e.g., diabetes mellitus and dialysis); history of intensive care unit (ICU) stay, intubation at the onset of infection, retransplantation, episodes of transplant rejection, and prior cytomegalovirus (CMV) infection; laboratory variables (e.g., results of liver and renal function tests at diagnosis); antifungal prophylaxis received; type of mold infection; time of infection onset; sites involved; antifungal agent used for therapy; duration of therapy; and infection outcome. Data for a subset of liver transplant recipients with invasive aspergillosis in this study were previously reported in context of comparison with a cohort from 1990–1995 [17].

The clinical care of the patients and the immunosuppressive regimens used were in accordance with the standard of care at each participating institution. Invasive fungal infections were defined in accordance with the criteria for proven and probable infections proposed by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group [18]. Proven mold infection was defined as a histopathologic examination that revealed tissue invasion and a culture result positive for the mold, or as a positive culture result for a sample obtained by sterile procedure from normally sterile and clinically or radiologically abnormal site consistent with infection [18]. The criteria for probable invasive fungal infection [18] were used for the diagnosis of pulmonary infections only. Involvement of $\geq$2 noncontiguous organ sites or the CNS was considered to indicate disseminated infection. The antifungal regimen used and the duration of therapy were at the discretion of health care providers at individual institutions. Infection was considered early if it occurred <90 days and late if it occurred $\geq$90 days after transplantation.

Detection of *Aspergillus* species in cultures of respiratory tract specimens is common, and differentiation of colonization from invasive infection is difficult in lung transplant recipients. Therefore, given that the diagnosis of probable invasive aspergillosis can be unreliable in lung transplant recipients, and given the overall lower prevalence of invasive mycelial infections in renal transplant recipients, the study was limited to liver and heart transplant recipients. Institutional review board approval was obtained in accordance with local requirements.

Statistical analysis was performed using Prophet statistical software, version 6.0 (AbTech). Categorical variables were compared using the χ^2 test or Fisher's exact test, and continuous variables were compared using Student's t test or the Mann-Whitney U test. A logistic model was used to evaluate the effects of multiple risk factors on outcome. A χ^2 analysis for trend was used to estimate a dose response for the risk for mortality in an individual patient.

RESULTS

Patient characteristics. Of 53 patients with invasive mold infections, 36 were liver transplant recipients (including 2 recipients of liver/kidney transplants and 1 recipient of a liver/small-bowel transplant), and 17 were heart transplant recipients (including 1 heart/lung transplant recipient). The median age

Table 1. Types of invasive mycelial fungal infections in the 53 organ transplant recipients.

Fungus	No. (%) of patients (n = 53)
Aspergillus species	
All	37 (69.8)
A. fumigatus	29
A. flavus	5
A. terreus	2
A. niger	1
Non-*Aspergillus* hyalohyphomycetes	
All	5 (9.4)
Scedosporium apiospermum	3
Fusarium species	2
Phaeohyphomycetes	
All	5 (9.4)
Cladophialophora bantiana	1
Scedosporium prolificans	1
Exophiala jeanselmei	1
Pyrenochaeta romeroi	1
Cladosporium species	1
Zygomycetes	
All	3 (5.7)
Rhizopus species	2
Mucor species	1
Other	
All	3 (5.7)
Trichophyton rubrum	1[a]
Unidentified	2

[a] This case was previously reported in the context of posttransplantation hypogammaglobulinemia [19].

Table 2. Site classifications for mycelial fungus infection in 53 organ transplant recipients.

Site classification	No. (%) of patients				
	Aspergillosis (n = 37)	Non-*Aspergillus* hyalohyphomycoses (n = 5)	Zygomycoses (n = 3)	Phaeohyphomycoses (n = 5)	P
Disseminated	4 (10.8)	3 (60)	3 (100)	1 (20)	.003
Pulmonary only	26 (70.3)	1 (20)	0 (0)	2 (40)	.02
Cutaneous only	0 (0)	0 (0)	0 (0)	2 (40)	.02
Any pulmonary involvement	29 (78.4)	3 (60)	3 (100)	2 (40)	NS
Any CNS involvement	2 (5.4)	1 (20)	1 (33.3)	1 (20)	NS
Any cutaneous involvement	0 (0)	2 (40)	0 (0)	2 (40)	.002

NOTE. NS, not significant ($P > .05$).

of the patients was 51 years (range, 17–70 years). The indications for transplantation in liver transplant recipients were hepatitis C virus infection in 33.3% of patients; primary sclerosing cholangitis in 19.4%; alcohol use–related cirrhosis in 16.7%; postnecrotic cirrhosis in 8.3%; Wilson disease, shortgut syndrome, and hepatocellular carcinoma in 5.6% each; and hemochromatosis, α-1 antitrypsin deficiency, and autoimmune liver disease in 2.8% each (some patients had >1 underlying liver disease). Underlying cardiac diseases in heart transplant recipients were idiopathic cardiomyopathy in 41% of patients, ischemic cardiomyopathy in 35.3%, myocarditis in 11.7%, and Eisenmenger complex and pulmonary hypertension in 5.9% each. Overall, 28 (52.8%) of the 53 patients were in the ICU, 25 (47.2%) had undergone intubation, 21 (39.6%) required dialysis, and 12 (22.6%) had undergone retransplantation at the time of onset of infection.

Spectrum and characteristics of fungal infections. Etiologic pathogens were as follows: *Aspergillus* species, in 37 (69.8%) of the 53 patients; non-*Aspergillus* hyalohyphomycetes (*S. apiospermum* and *Fusarium* species), in 5 (9.4%); phaeohyphomycetes (dematiaceous fungi), in 5 (9.4%); zygomycetes (*Rhizopus* and *Mucor* species), in 3 (5.7%); and *Trichophyton rubrum,* in 1 (1.8%). The types of specific pathogens recovered from the patients are outlined in table 1. In 2 patients, mycelial fungal hyphae were documented histopathologically (by lung nodule biopsy in one patient and in CNS blood vessels on autopsy in another). However, cultures were not performed for these patients; they were considered to have had an unidentified mycelial fungal infection.

A total of 30 (56.6%) of the 53 patients had pulmonary infections only, and 12 (22.6%) had disseminated infection. Any pulmonary, CNS, or cutaneous site involvement was documented in 37 (69.8%), 5 (9.4%), and 5 (9.4%) of the 53 patients, respectively (the 2 unidentified mold infections were excluded here). Of the 34 patients with lung involvement in whom the diagnosis was established antemortem, the type of the infiltrate was nodular in 32%, focal consolidation in 32%, diffuse or bilateral alveolar in 18%, cavitary in 6%, and unspecified in 12%.

The risk of disseminated infection differed significantly between specific types of mycelial fungal infections. Infections due to mycelial fungi other than *Aspergillus* species were more likely to be disseminated than were infections due to *Aspergillus* species (7 [50%] of 14 infections vs. 4 [10.8%] of 37 infections; $P = .005$). Disseminated infection was present in 3 (100%) of the 3 patients infected with zygomycetes, 3 (60%) of the 5 patients infected with non-*Aspergillus* hyalohyphomycetes, 1 (20%) of the 5 patients infected with phaeohyphomycetes, and

Table 3. Time of onset of invasive mycelial infections in 53 organ transplant recipients.

Time of onset after transplantation	Aspergillosis (n = 37)	Non-Aspergillus hyalohyphomycosis (n = 5)	Zygomycosis (n = 3)	Phaeohyphomycosis (n = 5)
At specific times, no. (%) of patients				
<30 days	7 (18.9)	1 (20)	1 (33.3)	0 (0)
31–90 days	13 (35.1)	1 (20)	1 (33.3)	0 (0)
91–180 days	3 (8.1)	1 (20)	0 (0)	3 (60)
181 days–1 year	4 (10.8)	0 (0)	0 (0)	0 (0)
1–2 years	3 (8.1)	0 (0)	1 (33.3)	0 (0)
>2 years	7 (18.9)	2 (40)	0 (0)	2 (40)
Median, months	2.7	4.5	1.7	4.7

Table 4. Variables associated with early-onset (<90 days after transplantation) and late-onset (≥90 days after transplantation) fungal infection in 53 organ transplant recipients.

Variable	Early-onset infection (n = 26)	Late-onset infection (n = 27)
Age, mean years	51.2	48.8
Female sex	7 (26.9)	12 (44.4)
Type of transplant		
Liver	18 (69.2)	18 (66.7)
Heart	8 (30.8)	9 (33.3)
Retransplantation	8 (30.8)	4 (14.8)
Transplant rejection		
≤1 month after infection	6 (23.1)	6 (22.2)
Any	9 (34.6)	14 (51.9)
Primary immunosuppressive therapy		
Tacrolimus	18 (69.2)	16 (59.3)
Cyclosporine A	8 (30.8)	11 (40.7)
CMV infection	11 (42.3)	8 (29.6)
CMV disease	4 (15.4)	4 (14.8)
Dialysis	12 (46.2)	9 (33.3)
Infection site classification		
Disseminated	6 (23.1)	6 (22.2)
Pulmonary (any)	19 (73.1)	19 (70.4)
Cutaneous (any)	0 (0)	5 (18.5)
Death	14 (53.8)	15 (55.6)

NOTE. Data are no. (%) of patients, unless otherwise indicated. None of the variables differed significantly between the two groups except cutaneous involvement tended to be higher (P = .051) in late-onset infections. CMV, cytomegalovirus.

4 (10.8%) of the 37 patients with *Aspergillus* infections (table 2). Infections limited to the lungs were significantly more likely to be due to *Aspergillus* species, compared with other molds (26 [70.3%] of 37 infections vs. 3 [21.4%] of 14 infections; P = .003). Infections limited to the CNS were less likely to be observed with infections due to *Aspergillus* species (0 [0%] of 37), compared with infections with other mycelial fungi (3 [21.4%] of 14; P = .017). Cutaneous involvement was present in none of the patients infected with *Aspergillus* species or zygomycetes, in 33% of the patients infected with non-*Aspergillus* hyalohyphomycetes, and in 60% of those infected with phaeohyphomycetes (P = .002; table 2).

The median time to onset of infection was 1.7 months after transplantation for infection with zygomycetes, 2.7 months for *Aspergillus* infection, 4.5 months for infection with other hyalohyphomycetes, and 4.7 months for infection with phaeohyphomycetes (table 3). Twenty-six (49.1%) of all 53 mycelial infections occurred <3 months after transplantation. Overall, 20 (54.1%) of the 37 *Aspergillus* infections, and 2 (66.6%) of the 3 infections with zygomycomycetes, 2 (40%) of the 5 infections with non-*Aspergillus* hyalohyphomycetes, and none of the infections with phaeohyphomycetes occurred <90 days after transplantation.

When mycelial fungal infections occurred <90 days after transplantation were compared with those that occurred ≥90 days after transplantation, a lower proportion of the patients with early-onset infections had cutaneous involvement (0 [0%] of 26 vs. 5 [18.5%] of 27; P = .051). The rate of retransplantation (14.8% vs. 30.8%) tended to be higher, and the rate of

Table 5. Variables associated with *Aspergillus* infection and infections with other molds in 53 organ transplant recipients.

Variable	Aspergillus infection (n = 37)	Other mold infections[a] (n = 14)
Type of transplant		
Liver	26 (70.3)	9 (64.3)
Heart	11 (29.7)	6 (42.9)
Immunosuppressive therapy		
Tacrolimus	24 (64.9)	8 (57.1)
Cyclosporine A	13 (35.1)	6 (42.9)
Time of infection onset after transplantation		
<30 days	7 (18.9)	2 (14.3)
31–90 days	13 (35.1)	2 (14.3)
91–180 days	3 (8.1)	5 (35.7)
181–365 days	4 (10.8)	0
1–2 years	3 (8.1)	1 (7.1)
>2 years	7 (18.9)	4 (28.6)
Retransplantation	9 (24.3)	2 (14.3)
Dialysis	16 (43.2)	4 (28.6)
Renal failure[b]	17 (45.9)	6 (42.9)
Prior transplant rejection	8 (21.6)	4 (28.6)
ICU stay	21 (56.8)	6 (42.9)
Intubation	19 (51.4)	5 (35.7)
CMV infection	10 (27.0)	8 (57.1)
CMV disease	5 (13.5)	3 (21.4)
Bilirubin level, median mg/dL	1.4	1.2
WBC count		
Mean, cells/mm^3	10,800	10,600
<3000 cells/mm^3	5 (14.3)[c]	0 (0)
Infection site classification		
Disseminated[d]	4 (10.8)	7 (50)
Pulmonary only[e]	70.3 (26/37)	3 (21.4)
Cutaneous only[f]	0 (0)	3 (21.4)

NOTE. Data are no. (%) of patients, unless otherwise indicated. CMV, cytomegalovirus; ICU, intensive care unit.

[a] Two patients with unidentified mold infections were excluded from this analysis.

[b] Creatinine level, >2 mg/dL.

[c] Data are for 35 patients.

[d] P = .005.

[e] P = .003.

[f] P = .017.

transplant rejection preceding infection tended to be lower (34.6% vs. 51.9%) in the patients with early-onset infection, compared with those who had late-onset infection (table 4). The risk of dissemination, CNS infection, and risk factors (e.g., the incidence of dialysis preceding infection) did not differ significantly between patients with infections that occurred in the early as opposed to the late posttransplantation period (table 4).

Antifungal prophylaxis had been administered to 8% of the patients with aspergillosis and to 21.4% of those with other mold infections (P = NS). Antifungal agents for prophylaxis consisted of fluconazole (in 1 patient) and low-dose amphotericin B (in 2 patients) with aspergillosis, low-dose amphotericin B (in 1 patient) with the non-*Aspergillus* hyalohyphomycoses, fluconazole (in 1 patient) with zygomycoses, and itraconazole (in 1 patient) with phaeohyphomycoses.

Patients with *Aspergillus* infection tended to have a lower rate of preceding CMV infection than did patients with other mycelial fungal infections (27% vs. 57.1%; $P = .057$; table 5). Other factors (e.g., immunosuppressive regimen, retransplantation, renal failure, and dialysis) did not differ for patients with *Aspergillus* infection compared with those who infected with other mycelial fungi (table 5). Three patients had received sirolimus (rapamycin); all had *Aspergillus* infections, and none had CNS involvement. Patients requiring dialysis had a greater risk of disseminated infection (6 [28.6%] of 21 patients) than did those who were did not require dialysis (3 [9.4%] of 32 patients); however, the difference was not statistically significant ($P = .13$).

Mortality. Mortality at 90 days for all patients was 54.7% (29 of 53 patients died). Retransplantation ($P = .024$), CMV infection ($P = .038$), requirement of dialysis ($P = .003$), intubation ($P = .005$), and disseminated infection ($P = .003$) correlated significantly with mortality in univariate analysis (table 6). The mortality rate was higher among liver transplant recipients than among heart transplant recipients with invasive mycelial fungal infections, with the difference approaching statistical significance ($P = .051$; table 6). Trend analysis for the risk of mortality (with retransplantation, dialysis, CMV infection, and disseminated fungal infection as the factors) showed that the mortality rate was 11.8% when none of the above factors were present (OR, 1.0); 58.8%, when 1 factor was present (OR, 10.71; 95% CI, 1.4–83.8); 81.8%, when 2 factors were present (OR, 33.75; 95% CI, 1.6–702); and 100%, when $\geqslant 3$ factors were present (OR, undefined; $P = .0004$, by χ^2 test for trend). Because 80% of the intubated patients also had undergone retransplantation, required dialysis, and had CMV infection, intubation was excluded from this analysis.

In multivariate analysis (with retransplantation, dialysis, and CMV infection in the model), only dialysis (OR, 5.81; 95% CI, 1.39–24.27; $P = .016$) and CMV infection (OR, 4.78; 95% CI, 1.21–19.64; $P = .026$) were independently significant predictors of mortality in patients with mold infections. Addition of disseminated infection to the logistic regression model was not feasible because all patients with disseminated infection died, which yielded infinite odds. When intubation was added to the model, only CMV infection was significantly associated with outcome ($P = .02$); retransplantation ($P = .11$), dialysis ($P = .09$), and intubation ($P = .10$) were not.

A trend towards a higher mortality rate was observed in patients with zygomycosis (3 [100%] of 3) and non-*Aspergillus* hyalohyphomycoses (4 [80%] of 5), compared with patients who had aspergillosis (20 [54.1%] of 37) or phaeohyphomycoses (1 [20%] of 5). The difference, however, was not statistically significant (figure 1). The overall mortality rate (14 [53.8%] of 26 vs. 15 [55.6%] of 21) and mortality associated with aspergillosis (9 [45%] of 20 vs. 11 [65%] of 17), non-*Aspergillus* hyalohyphomycoses (2 [100%] of 2 vs. 2 [66.6%] of 3), and zygomycoses (2 [100%] of 2 vs. 1 [100%] of 1) in the early posttransplantation did not differ from those for the late posttransplantation period, respectively. The antifungal therapy administered to the patients is presented in tables 7 and 8.

Table 6. Factors associated on univariate analysis with 90-day mortality for 53 organ transplant recipients.

Factor	Died (n = 29)	Lived (n = 24)
Age, mean years	48.9	51.2
Type of transplant		
Liver	23 (79.3)	13 (54.2)
Heart	6 (20.7)	11 (45.8)
Retransplantation[a]	10 (34.5)	2 (8.3)
CMV infection[b]	14 (48.3)	5 (20.8)
CMV disease	7 (24.1)	1 (4.2)
Transplant rejection	9 (31.0)	3 (12.5)
Immunosuppressive therapy		
Tacrolimus	21 (72.4)	13 (54.2)
Cyclosporine A	8 (27.6)	11 (45.8)
Dialysis[c]	17 (58.6)	4 (16.7)
Diabetes	9 (31.0)	7 (29.2)
Intubation[d]	19 (65.5)	6 (25)
Infection site classification		
Disseminated[e]	9 (31.0)	0 (0)
CNS only	3 (10.3)	0 (0)
Pulmonary only[e]	10 (34.5)	19 (79.2)
Cutaneous only	0 (0)	3 (12.5)

NOTE. Data are no. (%) of patients, unless otherwise indicated. Other variables did not differ significantly between the 2 groups.

[a] $P = .024$.
[b] $P = .038$.
[c] $P = .002$.
[d] $P = .005$.
[e] $P = .003$.

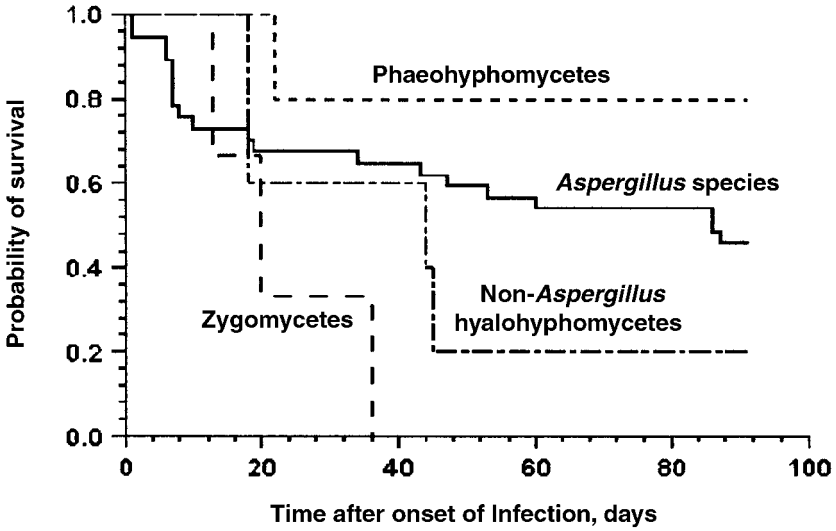

Figure 1. Kaplan-Meier curve showing probability of survival for 53 transplant recipients with various types of mold infections ($P = .153$, by the Mantel-Cox test).

DISCUSSION

The opportunistic molds include a diverse group of fungi that are classified as having either nonseptate (e.g., zygomycetes) or septate hyphae. Although this classification may be considered mycologically oversimplistic, the septate molds further include fungi that have either hyaline hyphae (i.e., without pigment in the cell wall; e.g., hyalohyphomycoses) or phaeohyphomycoses that have dematiaceous or pigmented cell walls containing melanin. For the purpose of this report, *Aspergillus* species (hyaline mold) are discussed separately from the non-*Aspergillus* hyalohyphomycoses. Our study documents the growing importance of these mycelial fungi in organ transplant recipients. A body of work involving organ transplant recipients through the early 1990s has documented that only 2% of all mycelial infections in these patients were due to fungi other than *Aspergillus* species [1–9, 20]. We show that non-*Aspergillus* mycelial fungi now account for 27% of mold infections. Our data also document important differences in the characteristics and outcome of specific types of mycelial fungal infections.

A total of 50%–60% of liver and 20%–35% of heart transplant recipients with invasive aspergillosis have been shown to have disseminated infection [21–23]. Disseminated infection has been documented in 13% of organ transplant recipients with zygomycosis [24]. In addition, 39% of zygomycotic infections that occur after transplantation have been of the rhinoorbitocerebral form [24]. Thus, disseminated or CNS involvement may occur in up to 52% of transplant recipients with zygomycosis. Disseminated infections have been reported in 30%–35% of patients with *Scedosporium* infections [25–27]. A vast majority of the phaeohyphomycotic infections in transplant recipients comprise skin and soft-tissue infections (79%), with systemic invasive infections occurring in 21% [28, 29]. Most *Fusarium* infections in organ transplant recipients are localized, which is not the case in bone marrow transplant recipients [30]. To our knowledge, a total of 6 cases of fusariosis have been reported in organ transplant recipients, of which only 1 (16.6%) was a disseminated infection [30].

Our data show that mold infections other than aspergillosis were significantly more likely to be associated with disseminated infections: 4 (10.8%) of the 37 *Aspergillus* infections were disseminated, compared with 7 (50%) of the 14 other mold infections ($P = .005$). CNS involvement was present in 5% of the patients with *Aspergillus* infection, compared with 14.3% of those with other mold infections ($P = .07$). Patients with aspergillosis, on the other hand, were more likely to have infection that was limited to the lungs. Therefore, it appears that, although the risk of dissemination of *Aspergillus* infection in our cohort of patients is lower [17], the risk of dissemination of infections due to the other molds has remained unchanged (or is higher) than has traditionally been documented in transplant recipients.

Precise reasons for a lower risk of disseminated infection with *Aspergillus* species than for other mold infections are not clear. It is unlikely that aspergillosis as opposed to the other mold infections was diagnosed earlier during the course of illness and that delayed diagnosis occurred selectively for the non-*Aspergillus* molds and accounted for a higher frequency of disseminated infection due to these molds. Although surveillance tests using the Platelia galactomannan antigen can lead to an earlier diagnosis of invasive aspergillosis, our patients were not monitored in this manner. Antifungal prophylaxis with the azoles (fluconazole) for candidiasis was shown to cor-

Table 7. Antifungal therapy used by and outcomes for transplant recipients with non-*Aspergillus* mold infections.

Infectious agent, patient	Antifungal therapy (duration)	Outcome at 90 days
Scedosporium apiospermum		
1	Itraconazole (19 days)	Died
2	Voriconazole (16 days)	Died
3	None[a]	Died
Scedosporium prolificans: 1 patient	Voriconazole (128 days)	Alive
Fusarium species		
1	Lipid-based AmB (50 days)	Died
2	Lipid-based AmB (48 days), followed by itraconazole (10 months)	Alive
Exophiala jeanselmei: 1 patient	Itraconazole (6 months)	Alive
Pyrenochaeta romeroi: 1 patient	Itraconazole (12 months)	Alive
Cladophialophora bantiana: 1 patient	Lipid-based AmB (22 days)	Died
Cladosporium species: 1 patient	Voriconazole (3 days), followed by lipid-based AmB (113 days)	Alive
Rhizopus species		
1	Lipid-based AmB (3 days)	Died
2	Lipid-based AmB (19 days)	Died
Mucor species: 1 patient	None[b]	Died

NOTE. AmB, amphotericin B.

[a] The patient died 1 day after diagnosis.

[b] Patient received diagnosis at autopsy.

relate with a higher risk of developing invasive mycelial infections that were innately resistant to this agent [31]. However, in our study, patients with *Aspergillus* infection did not differ from those with other mold infections with regard to the proportion who received prophylaxis and the type of antifungal agents used.

Patients infected with non-*Aspergillus* molds, however, were more likely to have prior CMV infection, indicating more-profound immunosuppression, which may explain the higher rate of dissemination. In addition, calcineurin and target of rapamycin (TOR) pathways have been shown to affect a variety of cellular physiological processes, including cell cycle progression, morphogenesis, cation homeostasis, and virulence, in a number of pathogenic yeasts and molds, including *Aspergillus* species [32–34]. Calcineurin regulates hyphal growth and has been shown to be essential for cell cycle progression in *Aspergillus nidulans* [35, 36]. Inhibitors of calcineurin/TOR pathway are toxic in vitro against *Aspergillus* species [32]. Furthermore, calcineurin/TOR inhibitors—in particular, tacrolimus and sirolimus—were found to enhance the activity of antifungal agents in vitro and attenuate the growth of all *Aspergillus* species tested [37]. Although invasive aspergillosis continues to be observed in organ transplant recipients, currently used calcineurin/TOR inhibitors may have specific effects on clinical manifestations, tissue tropism or the risk of dissemination associated with this fungus as has been shown for *Cryptococcus neoformans* [38]. Data from animal studies corroborate this clinical observation. In a mouse model of invasive aspergillosis, the immunosuppressive agents had no impact on survival [39]. However, histopathologic examination documented widely disseminated hy-

Table 8. Antifungal therapy used by and outcomes for *Aspergillus*-infected transplant recipients.

Treatment regimen (duration)	Total no. of patients	No. of patients who died
AmB regimens		
AmB (median, 29 days)	4	4
AmB (60 days), then itraconazole	1	0
Lipid-based AmB formulations		
Formulation alone (median, 14 days)	14	9
Formulation (median, 32 days), then itraconazole	7	1
Formulation plus itraconazole (20 days)	1	1
Formulation (median, 5 days), then voriconazole or posaconazole	4	1
Other		
Caspofungin (median, 83 days), then itraconazole	2	0
No therapy[a]	3	3

NOTE. AmB, amphotericin B.

[a] Patients received diagnosis at autopsy or died shortly after diagnosis.

phae in the brains of cyclosporine A–treated mice, whereas the brains of tacrolimus- and sirolimus-treated mice showed a nearly complete absence of *Aspergillus* hyphae [39].

The outcome for patients with disseminated mycelial fungal infection has been poor. Disseminated infections due to zygomycetes in organ transplant recipients have been uniformly fatal [24]. The mortality rate for the rhinocerebral form of zyomycosis in transplant recipients whose cases were diagnosed antemortem was found to be 50% [24]. Of organ transplant recipients with *S. apiospermum* infection, 73% died; all patients with disseminated infection and 91% of those with CNS infection died [25]. Phaeohyphomycotic fungi belonging to the genera *Dactylaria, Ochroconis,* and *Scolecobasidium* are noteworthy for their neurotropic potential and predilection to cause brain abscesses. The reported mortality rate for patients with systemic invasive phaeohyphomycosis is 57% [29]. The mortality rate for our patients with invasive mycelial infection, particularly infection due to zygomycetes and the non-*Aspergillus* hyalohyphomycetes, exceeded the mortality rate for *Aspergillus* infection; all patients infected with zygomycetes and 80% of those infected with non-*Aspergillus* hyalohyphomycetes died. A higher rate of disseminated infection and currently available antifungal therapy that is largely ineffective against these fungi likely accounted for the dismal outcome for these patients.

The recent development of the echinocandins and the third-generation triazoles has contributed towards an expanded armamentarium of antifungal drugs, particularly for treatment of *Aspergillus* infection. However, the echinocandins have limited in vitro activity against phaeohyphomycoses, *Fusarium* species, and the zygomycetes [14]. However, the new triazole agent voriconazole is a potentially promising drug for the treatment of *S. apiospermum* and phaeophyhomycotic fungal infections. Reports documenting the efficacy of voriconazole for *S. apiospermum* infections, including CNS infection, have been reported [25, 40–43]. In pediatric patients with *S. apiospermum* infection who were treated with voriconazole, 83% had a successful outcome [44]. The triazoles, including voriconazole, are now regarded as the drugs of choice for treatment of dematiaceous fungal infection [45]. For infections due to other opportunistic molds (most notably, *S. prolificans* and the zygomycetes), the existing therapies remain suboptimal. Two investigational triazole compounds, posaconazole and ravuconazole, appear to be more active against *Rhizopus* species with a MIC_{50} of 1–2 μg/mL, compared with >8 μg/mL for voriconazole [46]. A study involving an animal model has also suggested a potential role of posaconazole for this infection [47]. The efficacy of these novel antifungal agents or that of combination therapies for these molds, however, remains to be determined.

In summary, our study documents that non-*Aspergillus* mycelial fungi have emerged as significant and increasingly commonly occurring pathogens in transplant recipients. The non-*Aspergillus* mycelial fungal infections were more likely to be disseminated and tended to be associated with poorer outcome, compared with aspergillosis. In this context, devising novel therapeutic approaches (e.g., combination antifungal or immunomodulatory therapies) and discerning the role of diagnostic strategies (including non–culture based assays) that may facilitate early diagnosis of these infections have now become an important consideration and a challenge.

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