MAJOR ARTICLE

Infections Due to *Scedosporium apiospermum* and *Scedosporium prolificans* in Transplant Recipients: Clinical Characteristics and Impact of Antifungal Agent Therapy on Outcome

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Background. Unique characteristics, impact of therapy with antifungal agents, and outcome of infections with *Scedosporium* species were assessed in transplant recipients.

Methods. The patients comprised a total of 80 transplant recipients with *Scedosporium* infections, including 13 patients from our institutions (University of Pittsburgh Medical Center [Pittsburgh, PA], University of Maryland [Baltimore], Duke University Medical Center [Durham, NC], Emory University [Atlanta, GA], and Hospital Gregorio Marañón [Madrid, Spain]) and 67 reported in the literature. The transplant recipients were compared with 190 non–transplant recipients with scedosporiosis who were described in the literature.

Results. Overall, 69% of the infections in hematopoietic stem cell transplant (HSCT) recipients and 53% of the infections in organ transplant recipients were disseminated. HSCT recipients, compared with organ transplant recipients, were more likely to have infections caused by *Scedosporium prolificans* ($P = .045$), to have an earlier onset of infection ($P = .007$), to be neutropenic ($P < .0001$), and to have fungemia ($P = .04$). Time elapsed from transplantation to *Scedosporium* infection in transplant recipients has increased in recent years ($P = .002$). The mortality rate among transplant recipients with scedosporiosis was 58%. In a logistic regression model using amphotericin B as comparison treatment, voriconazole was associated with a trend towards better survival (odds ratio [OR], 10.40; $P = .08$). Presence of disseminated infection (OR, 0.20; $P = .03$) predicted lower survival, and receipt of adjunctive surgery as treatment (OR, 5.52; $P = .02$) independently predicted a better survival in this model.

Conclusions. *Scedosporium* infections in transplant recipients were associated with a high rate of dissemination and a poor outcome overall. The use of newer triazole agents warrants consideration as a therapeutic modality for these infections.

Scedosporium apiospermum, an anamorph or asexual form of *Pseudallescheria boydii,* is a ubiquitous saprophytic mold that can be readily isolated from a variety of environmental sources (e.g., soil, sewage, polluted water, and decaying vegetation) [1–3]. Described as a human pathogen and as an agent of mycetoma in 1911, *S. apiospermum* has since been shown to be associated with disseminated infections, including those involving the CNS [2, 4–8]. The natural habitat of a related species—*Scedosporium prolificans,* considered to be a dematiaceous fungus [9]—is less well characterized, although the latter is also a soil saprophyte. The spectrum of infections with *S. prolificans* ranges from localized infections involving the bone and joints (usually in immunocompetent individuals) to disseminated infections (most commonly found in neutropenic patients) [10–12].

Scedosporium species are increasingly recognized as significant pathogens, particularly in immunocompromised hosts. These fungi now account for ~25% of all non-*Aspergillus* mold infections in organ transplant recipients [13]. *Scedosporium* species are generally resis-

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tant to amphotericin B. *S. prolificans,* in particular, is also resistant to most currently available antifungal agents [11, 14, 15].

We report 13 cases of scedosporiosis in organ transplant recipients that have occurred at our institutions (University of Pittsburgh Medical Center [Pittsburgh, PA], University of Maryland [Baltimore], Duke University Medical Center [Durham, NC], Emory University [Atlanta, GA], and Hospital Gregorio Marañón [Madrid, Spain]) since 1999. In addition, data for 44 organ transplant recipients and 23 hematopoietic stem cell transplant (HSCT) recipients with *Scedosporium* infections reported in the literature since 1985 were reviewed. Our goals were to assess the unique clinical characteristics of, impact of therapy with antifungal agents on, and variables influencing the outcome of *Scedosporium* infections in transplant recipients.

METHODS

The present study includes 13 cases of *Scedosporium* infection in transplant recipients at our institution (table 1) and cases of scedosporiosis in the literature in patients who had undergone transplantation and patients who had not. For cases in the literature, the MEDLINE database was searched for articles published during 1985–2003 that used the terms "*Scedosporium apiospermum*" and "*Scedosporium prolificans.*" Additional search terms included "*Pseudallescheria boydii,*" "*Allescheria boydii,*" "*Monosporium apiospermum,*" "*Petriellidium boydii,*" and "*Scedosporium inflatum.*" The latter terms refer to prior or other nomenclature for the 2 *Scedosporium* species. Additional cases were identified by review of the bibliographies of the original articles.

The search was limited to articles published in 1985 or after to accurately reflect the current trends in immunosuppressive regimens and clinical practices and to include cases involving traditional antifungal therapy (e.g., amphotericin B therapy) for comparison with those cases involving receipt of newer drugs (e.g., the triazole agents). Furthermore, although *S. apiospermum* has been known to be a pathogen since the early 1900s, most early case descriptions have been descriptions of mycetoma. Finally, *S. prolificans* was not recognized as a human pathogen until 1984.

Two of the authors (S.H. and N.S.) independently extracted the data for cases in the literature. Cases were included if mycologic identification of the fungus was confirmed by culture and evidence of invasive infection was documented. Dissemination was defined as isolation of the fungus from blood cultures, CNS involvement, or infection of $\geqslant 2$ noncontiguous sites. Determination of the time to onset after receipt of transplant was made on the basis of individually detailed cases; summarized data, in which only a mean or a range for a cohort of patients was provided, were excluded from this analysis. Time to onset of infection for patients who received a transplant after 1999 was compared with that for those who received a transplant in 1999 or thereafter. Changes in the epidemiologic characteristics of invasive aspergillosis in organ transplant recipients have previously been documented using similar intervals as a cut-off [16].

Statistical analysis. Categorical variables were compared using Fisher's exact test or χ^2 test. Continuous variables were compared using Student's *t* test (e.g., for age) or the Mann-Whitney *U* test (e.g., for time to onset of infection). A logistic model was developed to assess the effect of primary antifungal

Table 1. Clinical characteristics of 13 organ transplant recipients with *Scedosporium* infections from our institutions.

Patient	Age, years	Sex	Type of transplant	Primary ISA	Time to onset, months after transplantation	Involvement	*Scedosporium* species	Antifungal therapy	Outcome
1	55	M	Small bowel	Tacrolimus	1	Peritoneum	*S. prolificans*	Amphotericin B	Died
2	40	M	Kidney/pancreas	Tacrolimus	17	CNS, pulmonary	*S. prolificans*	Voriconazole	Survived
3	67	M	Kidney	Tacrolimus	36	Skin	*S. apiospermum*	Amphotericin B	Survived
4	51	F	Small bowel	Tacrolimus	4	Aneurysm	*S. prolificans*	Amphotericin B, voriconazole, caspofungin	Died
5	67	M	Heart	Tacrolimus	158	Pulmonary, skin	*S. apiospermum*	Voriconazole	Died
6	17	M	Liver	Tacrolimus	4.7	Pulmonary	*S. prolificans*	Voriconazole	Died
7	64	M	Liver	CsA	1.3	CNS	*S. apiospermum*	None[a]	Died
8	45	M	Heart	CsA	4.4	Pulmonary, skin	*S. apiospermem*	Itraconazole	Died
9	56	M	Liver	CsA	0.8	CNS	*S. apiospermum*	Voriconazole	Died
10	44	F	Heart	CsA	2.8	Pulmonary, skin, sinus	*S. prolificans*	Amphotericin B	Died
11	68	M	Kidney[b]	Tacrolimus	10.4	Skin	*S. prolificans*	Voriconazole	Survived
12	52	M	Small bowel	Tacrolimus	3	Pulmonary	*S. apiospermum*	Amphotericin B, voriconazole, caspofungin	Survived
13	62	M	Kidney/pancreas	Tacrolimus	5	Pulmonary	*S. apiospermum*	Voriconazole	Survived

NOTE. CsA, cyclosporine A; ISA, immunosuppressive agent.

[a] The patient died before therapy could be initiated.

[b] The patient had undergone liver transplantation 9 years before undergoing kidney transplantation.

Table 2. Demographic and clinical characteristics of hematopoietic stem cell transplant (HSCT) and organ transplant recipients with *Scedosporium* infections.

Characteristic	HSCT recipients (n = 23)	Organ transplant recipients (n = 57)	All transplant recipients (n = 80)
Age,[a] mean years ± SD	32.9 ± 3.3	49.5 ± 1.7	44.9 ± 1.7
Time to onset			
Median months[b] (range)	1.3 (0.1–10.8)	4.2 (0.5–158)	4.0 (0.1–158)
⩽6 months after transplantation	75.0 (12/16)	60.7 (34/36)	63.9 (46/72)
Male sex	55.0 (11/20)	73.7 (42/57)	68.8 (53/77)
Immunosuppressive regimen			
CsA	87.5 (7/8)	19.6 (10/51)	28.8 (17/59)
CsA/azathioprine	12.5 (1/8)	39.2 (20/51)	35.6 (21/59)
Tacrolimus	0	25.5 (13/51)	22.0 (13/59)
Tacrolimus/azathioprine	0	7.8 (4/51)	6.8 (4/59)
Azathioprine	0	7.8 (4/51)	6.8 (4/59)
Receipt of corticosteroids	87.5 (14/16)	98.1 (51/52)	95.6 (65/68)
Cytomegalovirus infection	15.0 (3/20)	20.4 (10/49)	18.8 (13/69)
Prior rejection episode	33.3 (7/21)	49.0 (25/51)	44.4 (32/72)
Antifungal prophylaxis[c]	63.6 (14/22)	20.0 (9/45)	34.3 (23/67)
Clinical presentation			
Fever	85.7 (18/21)	47.2 (17/36)	61.4 (35/57)
Pulmonary involvement	40.9 (9/22)	42.0 (21/50)	41.7 (30/72)
Skin involvement	36.4 (8/22)	32 (16/50)	33.3 (24/72)
CNS involvement	36.4 (8/22)	30.0 (15/50)	31.9 (23/72)
Fungemia[d]	33.3 (7/21)	10.7 (6/56)	16.9 (13/77)
Disseminated infection	69.0 (16/23)	46.0 (23/50)	54.0 (46/85)
Neutropenia[e]	66.7 (12/18)	8.5 (4/47)	24.6 (16/65)
Renal failure	18.2 (2/11)	32.7 (17/52)	30.1 (19/63)
Species isolated[f]			
Scedosporium prolificans	39.1 (9/23)	16.9 (9/53)	23.7 (18/76)
Scedosporium apiospermum	60.8 (14/23)	83.0 (44/53)	76.3 (58/76)

NOTE. Data are percent (ratio) of patients with the specified characteristic, unless otherwise indicated. CsA, cyclosporine A.

[a] $P = .0001$.
[b] $P = .007$.
[c] $P = .001$.
[d] $P = .04$.
[e] $P < .0001$.
[f] $P = .045$.

therapy on mortality. Factors significantly associated with outcome (i.e., presence of disseminated infection and receipt of adjunctive surgery) were added to the model. Treatment was added to the model as an indicator variable set, with amphotericin B as the comparison group. Patients who did not receive antifungal therapy were excluded from the model. Stata software, version 7.0 (Stata), was used for all statistical analysis.

RESULTS

A total of 80 cases of *Scedosporium* infection in transplant recipients were identified; these comprised 57 cases involving organ transplant recipients (including 13 cases at our institutions) and 23 cases involving HSCT recipients [1, 2, 5, 12, 15, 17–59]. An additional 190 cases in non–transplant recipients were identified using similar search criteria [3–9, 11, 12, 15, 21, 29, 37, 39, 40, 47, 52, 56, 59–154], and these cases are discussed primarily to discern the unique characteristics of scedosporiosis in transplant recipients, compared with other hosts.

Epidemiologic and demographic characteristics. Of 57 organ transplant recipients, 20 (35%) were renal transplant recipients (including 3 kidney-pancreas transplant recipients), 16 (28%) were heart transplant recipients (including 5 heart-lung transplant recipients), 10 (18%) were liver transplant recipients, 8 (14%) were lung transplant recipients, and 3 (5%) were small bowel transplant recipients. Fifty-five percent of the patients had received cyclosporine A, 36% had received tacrolimus, and

Table 3. Clinical variables in patients with *Scedosporium* infections stratified by the underlying host condition.

Variable	HIV-infected patients (n = 14)	Organ transplant recipients (n = 57)	HSCT recipients (n = 23)	Patients with hematologic malignancies (n = 69)	Other IS patients (n = 51)	IC patients (n = 56)
Age,[a] mean years	37	50	33	44	51	36
Prior receipt of antifungal prophylaxis[b]	46.0 (6/13)	20.0 (9/45)	64.0 (14/22)	34.0 (21/62)	4.0 (2/51)	0.0 (0/56)
Clinical presentation						
CNS involvement	15.4 (2/13)	25.0 (13/53)	36.0 (8/22)	28.0 (19/67)	22.0 (11/49)	17.0 (10/56)
Pulmonary involvement[b]	50.0 (7/14)	46.0 (24/52)	40.0 (8/20)	62.0 (41/66)	33.0 (16/49)	15.0 (8/53)
Skin involvement[c]	7.0 (1/14)	32.0 (17/53)	38.0 (8/21)	40.0 (27/67)	31.0 (15/49)	7.0 (4/56)
Fungemia[b]	23.0 (3/13)	16.0 (7/45)	25.0 (5/20)	66.0 (40/61)	6.0 (2/35)	8.0 (2/26)
Disseminated infection[b]	57.0 (8/14)	55.0 (29/53)	69.0 (16/23)	86.0 (59/69)	42.0 (21/50)	20.0 (11/55)
Species isolated						
Scedosporium apiospermum	71.0 (10/14)	83.0 (44/53)	60.9 (14/23)	24.6 (17/69)	82.4 (42/51)	62.5 (35/56)
Scedosporium prolificans	28.6 (4/14)	17.0 (9/53)	39.1 (9/23)	75.4 (52/69)	17.6 (9/51)	37.5 (21/56)
Neutropenia[b]	39.0 (5/13)	13.0 (4/32)	67.0 (12/18)	90.0 (62/69)	4.0 (2/45)	0.0 (0/54)
Renal failure[b]	0.0 (0/4)	56.0 (19/34)	18.0 (2/11)	28.0 (12/43)	20.0 (6/30)	0.0 (0/30)
Mortality	61.5 (8/13)	57.0 (31/57)	68.0 (15/22)	76.8 (53/69)	40.0 (20/50)	6.7 (9/54)

NOTE. Data are percent (ratio) of patients with the specified characteristic, unless otherwise indicated. HSCT, hematopoietic stem cell transplant; IC, immunocompetent; IS, immunosuppressed.

[a] $P = .01$.
[b] $P < .001$.
[c] $P = .001$.

9% were receiving azathioprine without a calcineurin-inhibitor agent (table 1). All but one of the organ transplant recipients were receiving corticosteroids at the onset of infection. Forty-nine percent had previously experienced rejection episodes, and 18% had received prior antifungal prophylaxis (table 2). In all, 44 (83%) of the 53 infections in organ transplant recipients were due to *S. apiospermum,* and 10 (19%) were due to *S. prolificans* (in 4 cases, the *Scedosporium* isolate was not speciated). The median time from transplantation to onset of infection among organ transplant recipients was 4 months (range, 0.5–158 months) for patients with *S. apiospermum* infection and 2.6 months (range, 1–17 months) for patients with *S. prolificans* infection (table 2).

Of 23 HSCT recipients, the type of stem cell transplantation was not specified for 2 patients; among the remaining 21 HSCT recipients, 15 (71%) received allogeneic and 6 (29%) received autologous transplants. Sixty-seven percent of the HSCT recipients were neutropenic, and 52% had previously had graft-versus-host disease. HSCT recipients, compared with organ transplant recipients, were significantly more likely to have received prior antifungal prophylaxis (64% vs.17%; $P = .001$), to be neutropenic (67% vs. 9%; $P < .0001$), and to have infections due to *S. prolificans* (39% vs. 17%; $P = .045$) (table 2). *Scedosporium* infections occurred significantly earlier after transplantation in HSCT recipients, compared with organ transplant recipients (median time to onset, 1.3 vs. 4 months; $P = .007$). This difference may be related to the fact that neutropenia occurred in HSCT recipients at the same time interval. Overall, 75% of the infections in HSCT recipients and 61% of the infections in organ transplant recipients occurred within 6 months after transplantation.

Patients who received transplants after 1999 (the current cohort) were associated with a significantly longer time to onset of *Scedosporium* infections after transplantation (median time to onset, 6 months), compared with those who received transplants in 1999 or earlier (the earlier cohort; median time to onset, 1.2 months; $P = .002$). Eighty-two percent of all *Scedosporium* infections in the earlier cohort occurred within 6 months after transplantation, but in the current cohort, only 51% of *Scedosporium* infections occurred within 6 months ($P = .02$). For *S. apiospermum* infections, the median time to onset after transplantation was 5 months in the current cohort, compared with 2.6 months in the earlier cohort ($P = .07$). For *S. prolificans* infections, the median time to onset was 4.3 months in the current cohort and 1.0 month in the earlier cohort ($P = .04$).

Clinical manifestations. In all, 23 (46%) of 50 *Scedosporium* infections in organ transplant recipients were disseminated. CNS, pulmonary, and cutaneous involvement were present in 29%, 43%, and 31% of the organ transplant recipients, respectively. Other infections included those of the eye (4 patients), those of the peritoneum/abdomen (3), cardiac infections (2), mycotic aneurysm infections (2), and a sinus infection (1). Organ transplant recipients with *S. prolificans* infection were more likely to have fungemia (4 [40%] of 10), compared with those with *S. apiospermum* infection (2 [4.7%] of 43)

Table 4. Variables associated with mortality in transplant recipients with scedosporiosis.

Characteristic	Patients who died (n = 46)	Patients who survived (n = 33)	P
Age, mean years ± SD	42.9 ± 2.2	47.8 ± 2.8	NS[a]
Time to onset			
Median months	2.6	5.0	NS (.07)
≤6 months after transplantation	72.5 (29/40)	54.8 (17/31)	NS
Male sex	69.8 (30/43)	69.7 (23/33)	NS
Cytomegalovirus infection	15.4 (6/39)	20.7 (6/29)	NS
Prior rejection episode	39.0 (16/41)	53.3 (16/30)	NS
Prior antifungal prophylaxis	45.4 (15/33)	23.5 (7/17)	NS
Clinical presentation			
Pulmonary involvment	44.4 (20/45)	38.5 (10/26)	NS
CNS involvment	41.3 (19/46)	12.0 (3/25)	.015
Skin involvment	28.3 (13/46)	44.0 (11/25)	NS
Disseminated infection	71.7 (33/46)	19.2 (5/26)	<.0001
Fungemia	26.7 (12/45)	3.2 (1/31)	.011
Neutropenia	34.3 (12/35)	13.3 (4/30)	NS (.08)
Renal failure	41.7 (15/36)	14.8 (4/27)	.028
Adjunctive surgery	20.0 (7/35)	56.2 (15/23)	.0008
Species isolated			
Scedosporium prolificans	30.4 (14/46)	13.8 (4/29)	NS
Scedosporium apiospermum	69.6 (32/46)	86.2 (25/29)	
Type of transplant			
HSCT	32.6 (15/46)	21.2 (7/33)	NS
Organ	67.4 (31/46)	78.8 (26/33)	
Primary therapy			
AmB	43.5 (20/46)	15.1 (5/33)	.008
Itraconazole	19.6 (9/46)	48.5 (16/33)	.006
Voriconazole	6.5 (3/46)	24.3 (8/33)	.03
AmB and another antifungal agent[a]	13.0 (6/46)	3.3 (1/33)	NS
None	10.9 (5/46)	0.0 (0/33)	NS

NOTE. Data are percent (ratio) of patients with the specified characteristic, unless otherwise indicated. AmB, amphotericin B; HSCT, hematopoietic stem cell transplant; NS, not significant ($P > .05$; exact P value is presented for variables with $P < .10$).

[a] In patients who died, other antifungal agents included miconazole (4 patients), fluconazole (1), and itraconazole (1); one patient who survived received miconazole.

($P = .009$). Disseminated infection and CNS, pulmonary, and cutaneous involvement were present in 69%, 36%, 41%, and 36% of HSCT recipients, respectively. Endocarditis, mycotic aneurysm, eye infection, and joint infection were documented in 1 patient each. Fungemia was present in 7 (33%) of 21 HSCT recipients, compared with 6 (11%) of 56 organ transplant recipients ($P = .04$).

When stratified by underlying host disease, transplant recipients differed significantly from other immunosuppressed hosts with respect to the frequency of disseminated infection, fungemia, and pulmonary and skin involvement, but not with respect to CNS infection (table 3). CNS involvement was present in 15% of the HIV-infected patients, 17% of the immunocompetent patients, 20% of the patients with hematologic malignanies, 25% of organ transplant recipients, and 30% of HSCT recipients ($P > .05$). Sepsis-like syndrome with hypotension was documented exclusively in patients with hematologic malignancy and in HSCT recipients (in 17% and 5%, respectively); it was not documented in other immunosuppressed hosts (table 3). Thirteen percent of all neutropenic patients were hypotensive, compared with 2.4% of the nonneutropenic patients ($P = .005$).

Outcome. The mortality rate among all transplant recipients with scedosporiosis was 58% (46 of 79). The mortality rate among organ transplant recipients was 54% (31 of 57) (77.8% for patients with *S. prolificans* infection, and 54.5% for patients with *S. apiospermum* infections). Amongst HSCT recipients, the overall mortality rate was 68% (15 of 22) (61.5%

for patients with *S. apiospermum* infection, and 77.8% for patients with *S. prolificans* infection).

When variables associated with mortality in transplant recipients were analyzed, disseminated infection ($P < .0001$), CNS involvement ($P = .015$), fungemia ($P = .011$), and renal failure ($P = .028$) were significantly associated with a higher mortality rate in univariate analysis. Surgery as adjunctive treatment ($P = .008$) portended lower mortality (table 4). Of patients with pulmonary lesions, 5 of 5 who underwent adjuvant surgery survived, compared with 4 of 18 who did not receive surgery ($P = .004$). Among patients with CNS lesions, 1 of 2 who underwent surgery survived, compared with 1 of 15 without surgery ($P = .22$).

All transplant recipients—except for 5 who died either shortly after diagnosis or in whom the diagnosis was established at autopsy—had received antifungal treatment. Primary antifungal therapy employed is outlined in table 4 and consisted of amphotericin B in 25 transplant recipients, itraconazole in 25, and voriconazole in 11. In all cases, the aforementioned antifungal agents were employed initially or within 7 days after use of another agent and were continued as primary therapy for the treatment of scedosporiosis. The mortality rates differed significantly between the patients treated with amphotericin B, itraconazole, or voriconazole (table 4). In the logistic regression model, which considered amphotericin B to be the comparison treatment, receipt of voriconazole was associated with a strong trend towards better survival (OR, 0.15; 95% CI, 0.91–30.5; $P = .06$). Itraconazole therapy (OR, 2.42; 95% CI, 0.60–9.68; $P = .215$) was not significantly different from amphotericin B therapy with respect to survival. Disseminated infection was the only variable associated with lower survival (OR, 0.15; 95% CI, 0.04–0.53; $P = .004$) in this model. When adjunctive surgery was added to the model, disseminated infection (OR, 0.20; 95% CI, 0.04–0.85; $P = .03$) and surgery (OR, 5.52; 95% CI, 1.32–23.7; $P = .02$) independently influenced the outcome. The use of voriconazole, when controlled for these 2 variables, continued to be associated with a trend towards better survival ($P = .08$).

When mortality was analyzed for transplant recipients with *S. apiospermum* infections only, disseminated infection ($P < .001$) and CNS involvement ($P = .013$) were significantly associated with greater mortality. In a logistic regression model, using those receiving amphotericin B treatment as the comparison group, survival was greater among those receiving voriconazole, but this difference did not attain statistical significance (OR, 4.7; 95% CI, 0.54–40.9; $P = .15$). Only disseminated infection (OR, 0.10; 95% CI, 0.20–0.47; $P = .003$) independently predicted lower survival.

Of 18 transplant recipients with *S. prolificans* infection, 14 died. Fungemia ($P = .023$) and earlier onset of infection after transplantation ($P = .053$) correlated with a higher mortality rate. Of 13 patients treated with amphotericin B, 11 died. Three patients, 1 of whom died, had received voriconazole. These numbers, however, were too small for logistical modeling.

DISCUSSION

There are several observations that can be made from our study with regard to *Scedosporium* infections in immunocompromised hosts in general and in transplant recipients in particular. Patients with hematologic malignancy and with neutropenia were more susceptible to infections due to *S. prolificans* than to infections due to *S. apiospermum*. Indeed, 49% of *S. prolificans* infections in all hosts and 62% of such infections in immunocompromised patients were in patients with hematologic malignancy (table 3). Innate immune defenses comprising phagocytic responses play a critical role in host defense against *S. prolificans*. In one study [155], mononuclear cell–mediated hyphal damage did not differ among strains of *S. prolificans* and *Aspergillus fumigatus;* however, polymorphonuclear cells tended to induce more damage to *S. prolificans* hyphae than to *A. fumigatus*. Furthermore, hyphal damage mediated by the triazole antifungal agents against *S. prolificans* was synergistically enhanced by polymorphonuclear leukocytes [156]. On the other hand, of immunosuppressed hosts, organ transplant recipients and patients receiving corticosteroids had the highest frequency of *S. apiospermum* infections.

Mold infections are frequently disseminated, particularly in immunosuppressed hosts. The risk for dissemination, however, varies for different mycelial fungi and with the type of transplant. In cases of *Aspergillus* infection, dissemination occurs in 10%–34% of HSCT recipients and in 9%–35% of organ transplant recipients [16, 157]. Higher rates, approaching 50%, have been reported in liver transplant recipients [16]. We show that 69% of the *Scedosporium* infections in HSCT recipients and 46% of such infections in organ transplant recipients were disseminated. *Scedosporium* species, unlike *Aspergillus* species, have adventitial forms capable of in vivo sporulation, which may facilitate hematogenous spread [30].

Fungemia was significantly more likely with *S. prolificans* infection; 57% of *S. prolificans* infections but only 8% of the *S. apiospermum* infections in transplant recipients were associated with fungemia ($P < .0001$). Fungemia occurred more frequently in HSCT recipients, compared with organ transplant recipients ($P = .04$). That HSCT recipients were more likely to have *S. prolificans* infections—a species more likely to be associated with fungemia—may account for this observation. It is also plausible that host defense defects that occur in HSCT recipients as a result of neutropenia have a more profound impact on the susceptibility and severity of scedosporiosis than do the immune deficits in organ transplant recipients.

Scedosporium infections may occasionally present with shock and sepsis-like syndrome [10]. Such a presentation was ob-

served exclusively in patients with hematologic malignancy or in HSCT recipients and was more common in patients with *S. prolificans* infections than in those with *S. apiospermum* infections (13% vs. 1%; $P < .0001$). In an animal model, *S. prolificans* strains have been shown to be more virulent than *S. apiospermum* strains [158, 159]. Whereas mortality associated with *S. prolificans* infections was significantly higher in mice that were immunosuppressed with hydrocortisone than in immunocompetent mice, no difference in mortality associated with *S. apiospermum* infection was observed in the 2 groups of animals [158].

We show that the time elapsed from transplantation to onset of *Scedosporium* infection in transplant recipients has increased in recent years. These trends largely parallel those reported for invasive aspergillosis in HSCT recipients and organ transplant recipients [16, 160]. It is possible that more frequent use in recent years of antifungal prophylaxis with amphotericin B or itraconazole after transplantation could have delayed the onset of these infections. Antifungal prophylaxis could also have selected for *Scedosporium* species, because these fungi have been known to emerge as pathogens in patients receiving amphotericin B, fluconazole, or itraconazole [43, 57, 100]. Our data show that, although transplant recipients receiving antifungal prophylaxis tended to have later onset of *Scedosporium* infections, compared with those who did not receive antifungal prophylaxis (median time to onset, 4 vs. 2.3 months), the proportion of patients who had received antifungal prophylaxis in the current cohort (38%) did not differ significantly from that in the earlier cohort of patients (40%). Whether prolonged survival of transplant patients, delayed occurrence of other risk-factors (e.g., graft-versus-host disease), or as-yet poorly defined factors account for the increase in time before onset of *Scedosporium* infection after transplantation remains to be determined.

Scedosporium species are resistant or have erratic susceptibility to the polyene antifungal agents, such as amphotericin B. The newer triazoles agents, however, have demonstrated superior activity against *S. apiospermum* [14, 161–164]. Voriconazole was more potent than amphotericin B, fluconazole, 5 flucytosine, itraconazole, and ketoconazole [161, 163, 164]. The MIC of voriconazole for *S. apiospermum* isolates has ranged from 0.12–0.5 μg/mL [162, 163, 165]. The newer triazoles (ravuconazole, posaconazole, and voriconazole) were all active against *S. apiospermum,* with geometric mean MICs of 0.125, 0.08, and 0.06 μg/mL, respectively; none of these agents had an MIC >0.25 μg/mL for any strain [164]. Cross-resistance was found among all azoles except posaconazole, suggesting that, for *S. apiospermum,* the mechanism of action for (or resistance to) posaconazole might be different than that for the other azoles [163]. The echinocandins also have some activity against *S. apiospermum,* with MICs ranging from 0.25–4 μg/mL [166, 167]. *S. prolificans,* on the other hand, is largely resistant to currently available antifungal agents. Voriconazole has shown some in vitro activity, however, and the investigational triazole UR-9825 (Uriach Laboratories) has had good activity against *S. prolificans* [163, 164]. A combination of terbinafine and voriconazole was synergistic in vitro [168].

Profound and often irreversible immunosuppression in the host, frequent occurrence of disseminated infection, and lack of an effective antifungal therapy render *Scedosporium* infections among the most difficult invasive mycoses to treat. Overall, the mortality rate for transplant recipients with *Scedosporium* infections was 58% in our study. When adjusted for disseminated infection, therapy with voriconazole, compared with amphotericin B therapy, was associated with a lower mortality rate, a difference that approached statistical significance ($P = .06$). The mortality rates associated with treatments with itraconazole and other antifungal agents, however, were not significantly different from those associated with treatment with amphotericin B. When included in the logistic regression model, receipt of adjunctive surgery independently portended a better survival rate among transplant recipients with scedosporiosis (table 4). A potential bias may nonetheless have existed in the selection of patients to undergo surgical debridement (e.g., they may have been selected because of better performance status or because they had a removable focus of infection). However, the use of voriconazole therapy, compared with amphotericin B therapy, continued to be associated with a trend towards lower mortality, even when controlled for surgery and disseminated infection.

In summary, *Scedosporium* infections in transplant recipients were associated with a high rate of dissemination; were associated with a later onset in patients who received a transplant in recent years, compared with those who received a transplant earlier; and were associated with an overall dismal outcome. HSCT recipients, compared with organ transplant recipients, were more likely to have *S. prolificans* infections and fungemia. The use of voriconazole therapy appeared to portend a better outcome. We caution, however, that these data are based on a small number of patients and are limited by bias inherent to anecdotal reporting of cases in the literature. Nevertheless, given the in vitro activity of the newer triazole agents, these drugs warrant consideration as a preferred therapeutic modality for *Scedosporium* infections.

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References

1. Tadros TS, Workowski KA, Siegel RJ, Hunter S, Schwartz DA. Pathology of hyalohyphomycosis caused by *Scedosporium apiospermum (Pseudallescheria boydii)*: an emerging mycosis. Hum Pathol **1998**; 29: 1266–7.
2. Nesky MA, McDougal EC, Peacock JE Jr. *Pseudallescheria boydii* brain abscess successfully treated with voriconazole and surgical drainage: case report and literature review of central nervous system pseudallescheriasis. Clin Infect Dis **2000**; 31:673–7.
3. Tirado-Miranda R, Solera-Santos J, Brasero JC, Haro-Estarriol M, Cascales-Sánchez P, Igualada JB. Septic arthritis due to *Scedosporium apiospermum:* case report and review. J Infect **2001**; 43:210–6.
4. Munoz P, Marin M, Tornero P, Martin P, Rodriguez-Creixems RM, Bouza E. Successful outcome of *Scedosporium apiospermum* disseminated infection treated with voriconazole in a patient receiving conticosteroid therapy. Clin Infect Dis **2000**; 31:499–501.
5. Horton CK, Huang L, Goozé L. *Pseudallescheria boydii* infection in AIDS. J Acquir Immune Defic Syndr Hum Retrovirol **1999**; 20:209–11.
6. Kershaw P, Freeman R, Templeton D, et al. *Pseudallescheria boydii* infection of the central nervous system. Arch Neurol **1990**; 47:468–72.
7. O'Bryan TA, Browne FA, Schonder JF. *Scedosporium apiospermum (Pseudallescheria boydii)* endocarditis. J Infect **2002**; 44:189–92.
8. Pfeifer JD, Grand MG, Thomas MA, Berger AR, Lucarelli MJ, Smith ME. Endogenous *Pseudallescheria boydii* endophalthalmitis: clinicopathologic findings in two cases. Arch Ophthalmol **1991**; 109:1714–7.
9. Revankar SG, Patterson JE, Sutton DA, Pullen R, Rinaldi MG. Dessiminated phaeohyphomycosis: review of an emerging mycosis. Clin Infect Dis **2002**; 34:467–76.
10. Berenguer J, Diaz-Mediavilla J, Urra D, Munoz P. Central nervous system infection caused by *Pseudallescheria boydii:* case report and review. Rev Infect Dis **1989**; 11:890–6.
11. Idigoras P, Perez-Trallero E, Pineiro L, et al. Disseminated infection and colonization by *Scedosporium prolificans:* a review of 18 cases, 1990–1999. Clin Infect Dis **2001**; 32:e158–65.
12. Steinbach WJ, Schell WA, Miller JL, Perfect JR. *Scedosporium prolificans* osteomyelitis in an immunocompetent child treated with voriconazole and caspofungin, as well as locally applied polyhexamethylene biguanide. J Clin Microbiol **2003**; 41:3981–5.
13. Husain S, Alexander B, Munoz P, et al. Oportunistic mycelial fungi in organ transplant recipients: emerging importance of non-*Aspergillus* mycelial infections. Clin Infect Dis **2003**; 37:221–9.
14. Steinbach WJ, Perfect JR. *Scedosporium* species infections and treatments. J Chemother **2003**; 15:16–27.
15. Berenguer J, Rodriguez-Tudela JL, Carlos R, et al. Deep infections caused by *Scedosporium prolificans:* a report on 16 cases in Spain and a review of the literature. Medicine **1997**; 76:256–65.
16. Singh N, Avery RK, Munoz P, et al. Trends in risk profiles for and mortality associated with invasive aspergillosis among liver transplant recipients. Clin Infect Dis **2003**; 36:46–52.
17. Al Refai M, Duhamel C, Le Rochais JP, Icard P. Lung scedosporiosis: a differential diagnosis of aspergillosis. Eur J Cardiothorac Surg **2002**; 21:938–9.
18. Patterson TF, Andriole VT, Zervos MJ, Therasse D, Kauffman CA. The epidemiology of pseudallescheriasis complicating transplantation: nosocomial and community-acquired infection. Mycoses **1990**; 33: 297–302.
19. Rabodonirina M, Paulus S, Thevenet F, et al. Disseminated *Scedosporium prolificans (S. inflatum)* infection after single-lung transplantation. Clin Infect Dis 1994; 19:138–42.
20. Castiglioni B, Sutton DA, Rinaldi MG, Fung J, Kusne S. *Pseudallescheria boydii* (Anamorph *Scedosporium apiospermum)* infection in solid organ transplant recipients in a teritary medical center and review of the literature. Medicine **2002**; 81:333–44.
21. Caya JG, Farmer SG, Williams GA, Franson TR, Komorowski RA, Kies JC. Bilateral *Pseudallescheria boydii* endophthalmitis in an immunocompromised patient. Wisconsin Med J **1988**; 57:11–4.
22. Rishi R, Frost AE. *Scedosporium apiospermum* fungemia in a lung transplant recipient. Chest **2002**; 121:1714–6.
23. Alsip SG, Cobb CG. *Pseudallescheria boydii* infection of the central nervous system in a cardiac transplant recipient. South Med J **1986**;79: 383–4.
24. Lopes JO, Alves JP, Benevenga A, Salla A, Khmohan C, Silva CB. Subcutaneous *Pseudallescheriasis* in a renal transplant recipient. Mycopathologia **1994**; 125:153–6.
25. Lopez FA, Crowley RS, Wastila L, Valantine HA, Remington JS. *Scedosporium apiospermum (Pseudallescheria boydii)* infection in a heart transplant recipient: a case of mistaken identity. J Heart Lung Transplant **1998**; 17:321–4.
26. Miele PS, Levy CS, Smith MA, et al. Primary cutaneous fungal infections in solid organ transplantation: a case series. Am J Transplant **2002**; 2:678–83.
27. Safdar A, Papadopoulos EB, Young JW. Breakthrough *Scedosporium apiospermum (Pseudallescheria boydii)* brain abscess during therapy for invasive pulmonary aspergillosis following high-risk allogeneic hematopoietic stem cell transplantation: scedosporiasis and recent advances in antifungal therapy. Transpl Infect Dis **2002**; 4:212–7.
28. Hofman P, Saint-Paul MC, Gari-Toussaint M, et al. Infection disseminee a *Scedosporium apiospermum* chez un transplante hepatique. Ann Pathol **1993**; 13:332–5.
29. Bosma F, Voss A, van Hamersvelt HW, et al. Two cases of subcutaneous *Scedosporium apiospermum* infection treated with voriconazole. Clin Microbiol Infect **2003**; 9:750–3.
30. Campagnaro EL, Woodside KJ, Early MG, et al. Disseminated *Pseudallescheria boydii (Scedosporium apiospermum)* infection in a renal transplant patient. Transpl Infect Dis **2002**; 4:207–11.
31. Fortun J, Martin-Davila P, Sanchez MA, et al. Voriconazole in the treatment of invasive mold infections in transplant recipients. Eur J Clin Microbiol Infect Dis **2003**; 22:408–13.
32. Ginter G, de Hoog GS, Pschaid A, et al. Arthritis without grains caused by *Pseudallescheria boydii*. Mycoses **1995**; 38:369–75.
33. Hamida MB, Bedrossian J, Pruna A, Fougueray B, Metvier F, Idatte JM. Fungal mycotic aneurysms and visceral infection due to *Scedosporium apiospermum* in a kidney transplant patient. Transplant Proc **1993**; 25:2290–1.
34. Kusne S, Ariyanayagam-Baksh S, Strollo DC, Abernethy J. Invasive *Scedosporium apiospermum* infection in a heart transplant recipient presenting with multiple skin nodules and a pulmonary consolidation. Transpl Infect Dis **2000**; 2:194–6.
35. Montejo M, Muniz ML, Zarraga S, et al. Case reports. Infection due to *Scedosporium apiospermum* in renal transplant recipients: a report of two cases and literature review of central nervous system and cutaneous infections by *Pseudallescheria boydii/Sc. apiospermum*. Mycoses **2002**; 45:418–27.
36. Wise KA, Speed BR, Ellis DH, Andrews JH. Two fatal infections in immunocompromised patients caused by *Scedosporium inflatum*. Pathology **1993**; 25:187–9.
37. Wood GM, McCormack JG, Muir DB, et al. Clinical features of human infection with *Scedosporium inflatum.* Clin Infect Dis **1992**; 14: 1027–33.
38. Talbot TR, Hatcher J, Davis SF, Pierson IRN, Barton R, Dummer S. *Scedosporium apiospermum* pneumonia and sternal wound infection in a transplant recipient. Transplantation **2002**; 74:1645–7.
39. Barbaric D, Shaw PJ. *Scedosporium* infection in immunocompromised patients: successful use of liposomal amphotericin B and itraconazole. Med Pediatr Oncol **2001**; 37:122–5.
40. Toy EC, Savitch CB. Endocarditis and hip arthritis associated with *Scedosporium inflatum.* South Med J **1990**; 83:957–60.
41. Syndor MK, Kaushik S, Knight TE, Bridges CL, McCarty JM. Mycotic osteomyelitis due to *Scedosporium apiospermum:* MR imaging-pathologic correlation. Skeletal Radiology **2003**; 32:656–60.
42. Bernstein RF, Schuster MG, Stieritz DD, Cheuman PC, Bitto AJ. Disseminated cutaneous *Pseudallescheria boydii*. Br J Dermatol **1995**; 132: 456–60.

43. Tamm M, Malouf M, Glanville A. Pumonary scedosporium infection following lung transplantation. Transpl Infect Dis **2001**; 3:189–94.
44. Welty FK, McLeod GX, Ezratty C, Healy RW, Karchmer AW. *Pseudallescheria boydii* endocarditis of the pulmonic valve in a liver transplant recipient. Clin Infect Dis **1992**; 15:858–60.
45. Walsh TJ, Peter J, McGough DA, Fothergill AW, Rinaldi MG, Pizzo PA. Activities of amphotericin B and antifungal azoles alone and in combination against *Pseudallescheria boydii*. Antimicrob Agents Chemother **1995**; 39:1361–4.
46. Hangensee ME, Bauwens JE, Kjos B, Bowden RA. Brain abscess following marrow transplantation: experience at the Fred Hutchinson Cancer Research Center. Clin Infect Dis **1994**; 19:402–8.
47. Tapia M, Richard C, Baro J, et al. *Scedosporium inflatum* infection. Br J Haematol **1994**; 87:212–4.
48. Baddley JW, Stroud TP, Salzman D, Pappas PG. Invasive mold infections in allogeneic bone marrow transplant recipients. Clin Infect Dis **2001**; 32:1319–24.
49. Albermaz V, Huston B, Castillo M, Mukherji S, Bouldin TW. *Pseudallescheria boydii* infection of the brain: imaging with pathologic confirmation. AJNR Am J Neuroradiol **1996**; 17:589–92.
50. Guyotat D, Piens MA, Bouvier R, Fiere D. A case of disseminated *Scedosporium apiospermum* infection after bone marrow transplantation. Mykosen **1987**; 30:151–4.
51. Bonduel M, Santos P, Figueroa C, Turienzo G, Chantada G, Paganini H. Atypical skin lesions caused by *Curvularia* sp. and *Pseudallescheria boydii* in two patients after allogeneic bone marrow transplantation. Bone Marrow Transplant **2001**; 27:1311–3.
52. Breton Ph, Germaud P, Moren O, Audouin AF, Milpied N, Harousseau JL. Mycoses pulmonaires rares chez le patient d'hematologie. Rev Pneumol Clin **1998**; 54:253–7.
53. Carreter de Granda ME, Richard C, Conde C, et al. Endocarditis caused by *Scedosporium prolificans* after autologous peripheral blood stem cell transplantation. Eur J Clin Microbiol Infect Dis **2001**; 20: 215–7.
54. Howden BP, Slavin MA, Schwarer AP, Mijeh AM. Successful control of disseminated *Scedosporium prolificans* infection with a combination of voriconazole and terbinafine. Eur J Clin Microbiol Infect Dis **2003**; 22:111–3.
55. Machado CM, Martins MA, Heins-Vaccari EM, et al. *Scedosporium apiospermum* sinusitis afater bone marrow transplantation: report of a case. Rev Inst Med Trop S Paulo **1998**; 40:321–3.
56. McKelvie PA, Wong EY, Chow LP, Hall AJ. *Scedosporium endophthalmitis:* two fatal disseminated cases of *Scedosporium* infection presenting with endophthalmitis. Clin Exp Ophthal **2001**; 29:330–4.
57. Oliveira JSR, Kerbauy FR, Colombo AL, et al. Fungal infections in marrow transplant recipients under antifungal prophylaxis with fluconazole. Braz J Med Biol Res **2002**; 35:789–98.
58. Salesa R, Burgos A, Ondiviela R, Richard C, Quindos G, Ponton J. Fatal disseminated infection by *Scedosporium inflatum* after bone marrow transplantation. Scand J Infect Dis **1993**; 25:389–93.
59. Chikhani L, Dupont B, Guilbert E, Improvisi L, Corre A, Bertrand JCh. Une sinusite maxillaire fongique exceptionnelle d'origine dentaire á *Scedosporium prolificans*. Rev Stomatol Chir maxillofac **1995**; 96:66–9.
60. Rusin TA, Steck WD, Helm TN, Bergfeld WF, Bolwell BJ. *Pseudallescheria boydii* in an immunocompromised host: successful treatment with debridement and itraconazole. Arch Dermatol **1996**; 132:382–4.
61. Saracli MA, Erdem U, Gonlum A, Yildiran ST. *Scedosporium apiospermum* keratitis treated with itraconazole. Med Mycol **2003**; 41: 111–4.
62. Taylor A, Wiffen SJ, Kennedy CJ. Post-traumatic *Scedosporium inflatum* endophthalmitis. Clin Experiment Ophthalmol **2002**; 30:47–8.
63. Yao M, Messner AH. Fungal malignant otitis externa due to *Scedosporium apiospermum*. Ann Otol Rhinol Laryngol **2001**; 110:377–80.
64. Tekavec J, Milinaric-Missoni E, Babic-Vazic V. Pulmonary tuberculosis associated with invasive pseudallescheriasis. Chest **1997**; 111:508–11.
65. Sawada M, Isogai S, Miyake S, Kubota T, Yoshizawa Y. Pulmonary pseudallescherioma associated with systemic lupus erythematosus. Intern Med **1998**; 37:1046–9.
66. Scherr GR, Evans SG, Kiyabu MT, Klatt EC. *Pseudallescheria boydii* infection in the acquired immunodeficiency syndrome. Arch Pathol Lab Med **1992**; 116:535–6.
67. Alvarez M, Ponga BL, Rayon C, et al. Nosocomial outbreak caused by *Scedosporium prolificans (inflatum)*: four fatal cases in leukemic patients. J Clin Microbiol **1995**; 33:3290–5.
68. de Batlle J, Motjè M, Balanza R, Guardia R, Oritz R. Disseminated infection caused by *Scedosporium prolificans* in a patient with acute multilineal leukemia. J Clin Microbiol **2000**; 38:1694–5.
69. Slack CL, Watson DW, Abzug MJ, Shaw C, Chan KH. Fungal mastoiditis in immunocompromised children. Arch Otolaryngol Head Neck Surg **1999**; 125:73–5.
70. Yano S, Sishido S, Toritani T, Yoshida K, Nakano H. Intrabronchial pseudallescheriasis in an immunocompetent woman. Clin Infect Dis **1997**; 24:735–6.
71. Sobottka I, Deneke J, Pothmann W, Heinemann A, Mack D. Fatal native valve endocrditis due to *Scedosporum apiospermum (Pseudallescheria boydii)* following trauma. Eur J Clin Microbiol Infect Dis **1999**; 18:387–9.
72. Westerman DA, Speed BR, Prince HM. Fatal disseminated infection by *Scedosporium prolificans* during induction therapy for acute leukemia: a case report and literature review. Pathology **1999**; 31:393–4.
73. Bhermi G, Gillespie I, Mathalone B. *Scedosporium (Pseudallescheria)* fungal infection of a sponge explant. Eye **2000**; 14:247–9.
74. Sridhar MS, Garg P, Bansal AK. Fungal keratitis after laser in situ keratomileusis. J Cataract Refract Surg **2000**; 26:613–5.
75. Stolk-Engelaar MVM, Cox NJM. Successful treatment of pulmonary pseudallescheriasis with itraconazole. Eur J Clin Microbiol Infect Dis **1993**; 12:142.
76. Studahl M, Backteman T, Stalhammar F, Chryssanthou E, Petrini B. Bone and joint infection after traumatic implantation of *Scedosporium prolificans* treated with voriconazole and surgery. Acta Paediatr **2003**; 92:980–2.
77. Bouza E, Munoz P, Vega L, Rodriguez-Creixems M, Berenguer J, Escudero A. Clinical resolution of *Scedosporium prolificans* fungemia associated with reversal of neutropenia following administration of granulocyte colony-stimulating factor. Clin Infect Dis **1996**; 23:192–3.
78. Sullivan LJ, Snibson G, Joseph C, Taylor HR. *Scedosporium prolificans* sclerokeratitis. Aust N Z J Ophthalmol **1994**; 22:207–9.
79. Torok L, Simon G, Csornal A, Tapai M, Torok I. *Scedosporium apiospermum* infection imitating lymphocutaneous sporotrichosis in a patient with myeloblastic-monocytic leukaemia. Br J Dermatol **1995**; 133:805–9.
80. Arthur S, Steed LL, Apple DJ, Peng Q, Howard G, Escobar-Gomez M. *Scedosporium prolificans* keratouveitis in association with a contact lens retained intraocularly over a long term. J Clin Microbiol **2001**; 39:4579–82.
81. Watson JC, Myseros JS, Bullock MR. True fungal mycotic aneurysm of the basilar artery: a clinical and surgical dilemma. Cerebrovasc Dis **1999**; 9:50–3.
82. Wilson CM, O'Rourke EJ, McGinnis MR, Salkin IF. *Scedosporium inflatum:* clinical spectrum of a newly recognized pathogen. J Infect Dis **1990**; 161:102–7.
83. Wu Z, Ying H, Yiu S, Irvine J, Smith R. Fungal keratitis caused by *Scedosporium apiospermum:* report of two cases and review of treatment. Cornea **2002**; 21:519–23.
84. Zaas D. Images of Osler: cases from the Osler Medical Service at Johns Hopkins University. Am J Med **2002**; 113:760–1.
85. Grigg AP, Phillips P, Durham S, Shepherd JD. Recurrent *Pseudallescheria boydii* sinusitis in acute leukemia. Scand J Infect Dis **1993**; 25: 263–7.
86. Bower CPR, Oxley JD, Campbell CK, Archer CB. Cutaneous *Scedosporium apiospermum* infection in an immunocompromised patient. J Clin Pathol **1999**; 52:846–8.
87. Farag SS, Firkin FC, Andrew JH, Lee CS, Ellis DH. Fatal disseminated

Scedosporium inflatum infection in a neutropenic immunocompromised patient. J Infect **1992**; 25:201–4.
88. Canet JJ, Pagerols X, Sanchez C, Vives P, Garau J. Lymphocutaneous syndrome due to *Scedosporium apiospermum.* Clin Microbiol Infect **2001**; 7:648–9.
89. Chaveiro MJ, Vieira R, Cardoso J, Afonso A. Cutaneous infection due to *Scedosporium apiospermum* in an immunosuppressed patient. J Eur Acad Dermatol Venereol **2003**; 17:47–9.
90. Guez S, Calas V, Couprie B, Stoll D, Cabanieu G. Apropos of two cases of *Scedosporium apiospermum* nasosinal infection [in French]. Rev Med Interne **1992**; 13:145–8.
91. Hopwood V, Evans EGV, Matthews J, Denning DW. *Scedsporium prolificans,* a multi-resistant fungus, from a UK AIDS patient. J Infect **1995**; 30:153–5.
92. del Palacio A, Perez-Blazquez E, Cuetara MS, et al. Keratomycosis due to *Scedosporium apiospermum.* Mycoses **1991**; 34:483–7.
93. Dellestable F, Kures L, Mainard D, Pere P, Gaucher A. Fungal arthritis due to *Pseudallescheria boydii (Scedosporium apiospermum).* J Rheumatol **1994**; 21:766–8.
94. D'Hondt K, Parys-Van Ginderdeuren R, Foets B. Fungal keratitis caused by *Pseudallescheria boydii (Scedosporium apiospermum).* Bull Soc Belge Ophtalmol **2000**; 277:53–6.
95. Guerrero A, Torres P, Duran MT, Ruiz-Diez B, Rosales M, Rodiguez-Tudela JL. Airborne outbreak of nosocomial *Scedosporium prolificans* infection. Lancet **2001**; 357:1267–8.
96. Diaz-Valle D, Benitez del Castillo JM, Amor E, Toledano N, Carretero MM, Diaz-Valle T. Severe keratomycosis secondary to *Scedosporium apiospermum.* Cornea **2002**; 21:516–8.
97. Klopfenstein K, Rosselet R, Termuhlen A. Successful treatment of *Scedosporium* pneumonia with voriconazole during AML therapy and bone marrow transplantation. Int J Dermatol **2003**; 36:677–99.
98. Ksiazek SM, Morris DA, Mandelbaum S, Rosenaum PS. Fungal panophthalmitis secondary to *Scedosporium apiospermum (Pseudallescheria boydii)* keratitis. Am J Ophthalmol **1994**; 118:531–3.
99. Durieu J, Parent M, Ajana F, et al. *Monosporium apiospermum* meningoencephalitis: a clinico-pathological case. J Neurol Neurosurg Psychiatr **1991**; 54:731–3.
100. Jabado N, Cassanova J-L, Haddad E. Invasive pulmonary infection due to *Scedosporium apiospermum* in two children with chronic granulomatous disease. Clin Infect Dis **1998**; 27:1437–41.
101. Khurshid A, Baruett VT, Sckkosau M, Gluzburg AS, Onal E. Disseminated *Pseudallescheria boydii* infection in a nonimmunocompromised host. Chest **1999**; 116:572–4.
102. Eckburg PB, Zolopa AR, Montoya JG. Invasive fungal sinusitis due to *Scedosporium apiospermum* in a patient with AIDS. Clin Infect Dis **1999**; 29:212–3.
103. Farina C, Arosio M, Marchesi G, Amer M. *Scedosporium apiospermum* post-traumatic cranial infection. Brain Injury **2002**; 16:627–31.
104. Fays S, Di Cesare M-P, Antunes A, Truchetet F. Infection cutanee et osteoarticulaire a *Scedosporium apiospermum.* Ann Med Intern Fenn **2002**; 153:537–9.
105. Levine NB, Kurokawa R, Fichtenbaum CJU, Howington JA, Kuntz C IV. An immunocompetent patient with primary *Scedosporium apiospermum* vertebral osteomyelitis. J Spinal Disord Tech **2002**; 15: 425–30.
106. Liu YF, Zhao X, Ma CL, Li CX, Zhang TS, Liao WJ. Cutaneous infection by *Scedosporium apiospermum* and its successful treatment with itraconazole. Clin Exp Dermatol **1997**; 22:198–200.
107. Madrigal V, Alonso J, Bureo J, Figols FJ, Salesa R. Fatal meningoencephalitis caused by *Scedosporium inflatum (Scedosporium prolificans)* in a child with lymphoblastic leukemia. Eur J Clin Microbiol Infect Dis **1995**; 14:601–3.
108. Mellinghoff IK, Winston BJ, Mukwaya G, Schiller GJ. Treatment of *Scedosporium apiospermum* brain abscesses with posaconazole. Clin Infect Dis **2002**; 34:1648–50.
109. Mesnard R, Lamy T, Dauriac C, Le Prise P-Y. Lung abscess due to *Pseudallescheria boydii* in the course of acute leukaemia. Acta Haematol **1992**; 87:78–82.
110. Huang H, Zhu J, Zhang Y. The first case of *Pseudallescheria boydii* meningitis in China: electron microscopic study and antigenicity analysis of the agent. J Tongji Med Univ **1990**; 10:218–21.
111. Breton JR, Salavert M, Orero A, et al. Infeccion torpida sobre pulmon poliquistico. Enferm Infecc Microbiol Clin **2001**; 19:130–2.
112. Feltkamp MCW, Kersten MJ, van der Lelie J, Burggraaf JD, de Hoog GS, Kuijper EJ. Fatal *Scedosporium prolificans* infection in a leukemic patient. Eur J Clin Microbiol Infect Dis **1997**; 16:460–4.
113. Fessler RG, Brown FD. Superior sagittal sinus infection with *Petriellidium boydii:* case report. Neurosurgery **1989**; 24:604–7.
114. Fietz T, Knauf W, Schwartz S, Thiel E. Intramedullary abscess in a patient with disseminated *Scedosporium apiospermum* infection. Br J Haematol **2003**; 120:724.
115. Garcia JA, Ingram CW, Granger D. Persistent neutropilic meningitis due to *Pseudallescheria boydii.* Rev Infect Dis **1990**; 12:959–60.
116. Kumar B, Crawford GJ, Morlet GC. *Scedosporium prolificans* corneoscleritis: a successful outcome. Aust N Z J Ophthalmol **1997**; 25: 169–71.
117. Kusuhara M, Hachisuka H. Lymphocutaneous infection due to *Scedosporium.* Int J Dermatol **1997**; 36:677–99.
118. Gillum PS, Gurswami A, Taira JW. Localized cutaneous infection by *Scedosporium prolificans (inflatum).* Int J Dermatol **1997**; 36:276.
119. Piper JP, Golden J, Brown D, Broestler J. Successful treatment of *Scedosporium apiospermum* suppurative arthritis with itraconazole. Pediatr Infect Dis J **1990**; 9:674–5.
120. Pistono PG, Rapetti I, Stacchini E, Guasco C. Segnalazione di un caso clinico di micetoma da *Scedosporium apiospermum.* G Batteriol Virol Immunol **1989**; 82:88–91.
121. Nenoff P, Gutz U, Tintelnot K, et al. Disseminated mycosis due to *Scedosporium prolificans* in an AIDS patient with Burkitt lymphoma. Mycoses **1996**; 39:461–5.
122. Nielsen K, Lang H, Shum AC, Woodruff K, Cherry JD. Disseminated *Scedosporium prolificans* infection in an immunocompromised adolescent. Pediatr Infect Dis J **1993**; 12:882–4.
123. Girmenia C, Luzi G, Monaco M, Martino P. Use of voriconazole in treatment of *Scedospsorium apiospermum* infection: case report. J Clin Microbiol **1998**; 36:1436–8.
124. Gompels MM, Bethune CA, Jackson G, Spickett GP. *Scedosporium apiospermum* in chronic granulomatous disease treated with an HLA matched bone marrow transplant. J Clin Pathol **2002**; 55:784–6.
125. Horre R, Feil E, Stangel AP, et al. Scedosporiose des Gehirns mit letalem Ausgang nach Fuβverletzung. Fallbericht. Mycoses **2000**; 43(Suppl 2):33–6.
126. Horré R, Jovanik B, Marklein G, et al. Fatal pulmonary scedosporiosis. Mycoses **2003**; 46:418–21.
127. Roberts SA, Franklin JC, Mijch A, Speiman D. *Nocardia* infection in heart-lung transplant recipients at Alfred Hospital, Melbourne, Australia, 1989–1998. Clin Infect Dis **2000**; 31:968–72.
128. Hung CC, Chang SC, Yang PC, Hsieh WC. Invasive pulmonary pseudallescheriasis with direct invasion of the thoracic spine in an immunocompetent patient. Eur J Clin Microbiol Infect Dis **1994**; 13: 749–51.
129. Ichikawa T, Saiki M, Tokunaga S, Saida T. *Scedosporium apiospermum* skin infection in a patient with nephrotic syndrome. Acta Derm Venerol **1997**; 77:172–3.
130. Idigoras P, Lopez Lopategui C, et al. Infecion diseminada por *Scedosporium inflatum.* Enferm Infecc Microbiol Clin **1993**; 11:285.
131. Kim HU, Kim SC, Lee HS. Localized skin infection due to *Scedosporium apiospermum:* report of two cases. Br J Dermatol **1999**; 141: 605–6.
132. Kiraz N, Gubas Z, Akgun Y, Uzun P. Lymphadenitis caused by *Scedosporium apiospermum* in an immunocompetent patient. Clin Infect Dis **2001**; 32:e59–61.
133. Lai TF, Malhotra R, Esmail-Zaden R, Galanopoulas A, Chehade M,

Selva D. Use of voriconazole in *Scedosporium apiospermum* keratitis. Cornea **2003**; 22:391–2.
134. Leck A, Matheson M, Tuft S, Waheed K, Lagonowski H. *Scedosporium apiospermum* keratomycosis with secondary endophthalmitis. Eye **2003**; 17:841–3.
135. Lemerle E, Bastien M, Demolliens-Dreux G, et al. Scedosporoise cutanee revelee par un purpura bullo-necrotique. Ann Dermatol Venereol **1998**; 125:711–4.
136. Maertens J, Lagrou K, Deweerdt H, et al. Disseminated infection by *Scedosporium prolificans:* an emerging fatality among haematology patients. Ann Hematol **2000**; 79:340–4.
137. Malekzadeh M, Overtruf GD, Auerbach SB, Wong L, Hirsch M. Chronic, recurrent osteomyelitis caused by *Scedosporium inflatum.* Pediatr Infect Dis J **1990**; 9:357–9.
138. Marin J, Sanz MA, Sanz GF, et al. Disseminated *Scedosporium inflatum* infection in a patient with acute myeloblastic leukemia. Eur J Clin Microbiol Infect Dis **1991**; 10:759–61.
139. Meyer RD, Gaultier CR, Yamashita JT, Babapour R, Pitchon HE, Wolfe PR. Fungal sinusitis in patients with AIDS: report of 4 cases and review of the literature. Medicine **1994**; 73:69–78.
140. Miyamoto T, Sasaoka R, Kawaguchi M, et al. *Scedosporium apiospermum* skin infection: a case report and review of the literature. J Am Acad Dermatol **1998**; 39:498–500.
141. Murayama T, Amintani R, Tsuyuguchi K, et al. Polypoid bronchial lesions due to *Scedosporium apiospermum* in a patient with *Mycobacterium avium* complex pulmonary disease. Eur Respir J **1998**; 12: 745–7.
142. Nulens E, Eggink C, Rijs AJM, Wesseling P, Verweij PE. Keratitis caused by *Scedosporium apiospermum* successfully treated with cornea transplant and voriconazole. J Clin Microbiol **2003**; 41:2261–4.
143. Rollot F, Blanche P, Richaud-Thiriez B, et al. Pneumonia due to *Scedosporium apiospermum* in a patient with HIV infection. Scand J Infect Dis **2000**; 32:439.
144. Ruchel R, Willichowski E. Cerebral pseudallescheria mycosis after near-drowning. Mycoses **1995**; 38:473–5.
145. Ochia N, Shimazaki C, Uchida R, et al. Disseminated infection due to *Scedosporium apiospermum* in a patient with acute myelogenous leukemia. Leuk Lymphoma **2003**; 44:369–72.
146. Perez R, Smith M, McClendon J, Kim J, Eugenio N. *Pseudallescheria boydii* brain abscess: complication of an intravenous catheter. Am J Med **1988**; 84:359–62.
147. Pickles RW, Pacey DE, Muir DB, Merrell WH. Experience with infection by *Scedosporium prolificans* including apparent cure with fluconaozle therapy. J Infect **1996**; 33:193–7.
148. Poza G, Montoya J, Redondo C, et al. Meningitis caused by *Pseudallescheria boydii* treated with voriconazole. Clin Infect Dis **2000**; 30: 981–2.
149. Raffanti SP, Fyfe B, Carreiro S, Sharp SE, Hyma BA, Ratzan KR. Native valve endocarditis due to *Pseudallescheria boydii* in a patient with AIDS: case report and review. Rev Infect Dis **1990**; 12:993–6.
150. Severo LC, Oliveira FD, Londero AT. Subcutaneous scedosporiosis: report of two cases and review of the literature. Rev Inst Med Trop S Paulo **1997**; 39:227–30.
151. Severo LC, Porto ND, Londero AT. Pulmonary scedosporiosis. Rev Inst Med Trop S Paulo **1998**; 40:241–3.
152. Severo LC, Oliveira FD, Garcia CD, Uhlmann A, Londero AT. Peritonitis by *Scedosporium apiospermum* in a patient undergoing continuous ambulatory peritneal dialysis. Rev Inst Med Trop S Paulo **1999**; 41:263–4.
153. Lavigne C, Maillot F, de Muret A, Therizol-Ferly M, Lamisse F, Machet L. Cutaneous infection with *Scedosporium apiospermum* in a patient trated with corticosteroids. Acta Derm Venereol **1999**; 79:402–3.
154. Gatto J, Paterson D, Davis L, Lockwood L, Allworth A. Vetebral osteomyelitis due to *Pseudallescheria boydii.* Pathology **1997**; 29: 238–40.
155. Gil-Lamaignere C, Rodriguez-Tudela JL, Roilides E. Human phagocytic cell responses to *Scedosporium prolificans* hyphae [abstract 1617]. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, 1999. Washington, DC: American Society for Microbiology, **1999**:390.
156. Gil-Lamaignere C, Roilides E, Mosquera J, Maloukou A, Walsh TJ. Antifungal triazoles and polymorphonuclear leukocytes synergize to cause increased hyphal damage to *Scedosporium prolificans* and *Scedosporium apiospermum.* Antimicrob Agents Chemother **2002**; 46: 2234–7.
157. Paterson DL, Singh N. Invasive aspergillosis in transplant recipients. Medicine **1999**; 78:123–38.
158. Cano J, Guarro J, Mayayo E, Fernandez-Ballart J. Experimental infection with *Scedosporium inflatum.* J Med Vet Mycol **1992**; 30:413–20.
159. Ortoneda M, Capilla J, Pujol I, et al. Liposomal amphotericin B and granulocytic colony-stimulating factor therapy in a murine model of invasive infection by *Sceodporium prolificans.* J Antimicrob Chemother **2002**; 49:525–9.
160. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis **2002**; 34:909–17.
161. Cuenca-Estrella M, Rodriguez-Tudela JL. Present status of detection of antifungal resistance: the perspective from both sides of the ocean. Clin Microbiol Infect **2001**; 7:46–53.
162. Radford SA, Johnson LM, Warnock DW. In vitro studies of activity of voriconazole (UK-109,496), a new trizole antifungal agent, against emerging and less-common mold pathogens. Antimicrob Agents Chemother **1997**; 41:841–3.
163. Meletiadis J, Meis JF, Mouton JW, et al. In vitro activities of new and conventional antifungal agents against clinical *Scedosporium* isolates. Antimicrob Agents Chemother **2002**; 46:62–8.
164. Carillo AJ, Guarro J. In vitro activities of four novel triazoles against *Scedosporium* spp. Antimicrob Agents Chemother **2001**; 45:2151–5.
165. Espinel-Ingroff A. In vitro fungicidal activities of voriconazole, itraconazole, and amphotericin B against opportunistic moniliaceous and dermatiaceous fungi. J Clin Microbiol **2001**; 39:954–8.
166. Pfaller MA, Marco F, Messer SA, Jones RN. In vitro activity of two echinocandin derivatives, LY303366 and MK-0991 (L-743,792), against clinical isolates of *Aspergillus, Fusarium, Rhizopus,* and other filamentous fungi. Diagn Microbiol Infect Dis **1998**; 30:251–5.
167. Espinel-Ingroff A. Comparison of in vitro activities of the new triazole SCH56592 and echinocandins MK-0992 (L-743,872) and LY303366 against opportunistic filamentous and dimorphic fungi and yeasts. J Clin Microbiol **1998**; 36:2950–6.
168. Meletiades J, Mouton JW, Meis JF, Verweij PE. In vitro drug interaction modeling of combinations of azoles with terbinafine against clinical *Scedosporiium prolificans* isolates. Antimicrob Agents Chemother **2003**; 47:106–17.