MAJOR ARTICLE

Infections Due to *Aspergillus terreus:* A Multicenter Retrospective Analysis of 83 Cases

William J. Steinbach,[1] Daniel K. Benjamin, Jr.,[1,3] Dimitrios P. Kontoyiannis,[4] John R. Perfect,[2] Irja Lutsar,[9] Kieren A. Marr,[6,7] Michail S. Lionakis,[4] Harrys A. Torres,[4] Hasan Jafri,[5] and Thomas J. Walsh[8]

Departments of [1]Pediatrics and [2]Medicine, Duke University Medical Center, and [3]Duke Clinical Research Institute, Durham, North Carolina; [4]M.D. Anderson Cancer Research Center, Houston, and [5]University of Texas—Southwestern Medical Center, Dallas, Texas; [6]Fred Hutchinson Cancer Research Center, and [7]University of Washington, Seattle, Washington; [8]Immunocompromised Host Section, Pediatric Oncology Branch, National Cancer Institute, Bethesda, Maryland; and [9]Pfizer Inc., Sandwich, United Kingdom

Current in vitro and in vivo data indicate that invasive aspergillosis due to *Aspergillus terreus* is resistant to treatment with amphotericin B. Because little clinical data are available to guide therapy, we performed a retrospective cohort study of cases of invasive *A. terreus* infections from 1997–2002 to determine whether the use of voriconazole, compared with use of other antifungal therapies, led to an improved patient outcome. We analyzed a total of 83 cases of proven or probable invasive *A. terreus* infection (47% and 53%, respectively). A total of 66.3% of patients (55 of 83) died during management of IA, with 55.8% mortality (19 of 34 patients) in the voriconazole group and 73.4% mortality (36 of 49) in the group that received therapy with other antifungals. By use of Cox proportional hazards modeling, decreased mortality at 12 weeks was observed in those patients who received voriconazole (hazard ratio, 0.29; 95% CI, 0.15–0.56). Voriconazole is likely to be a better treatment choice for *A. terreus* infection than is a polyene.

Invasive aspergillosis (IA) is the most common filamentous fungal infection observed in immunocompromised patients [1–4]. *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus* are the most common species causing IA [5, 6], but most studies identify *A. fumigatus* or *A. flavus* as the etiological agent in the majority of cases. The frequency of *A. terreus* infections varies from 3%–12.5% [5–9]. Recent in vitro and in vivo studies indicate that *A. terreus* is distinguished from *A. fumigatus*, *A. flavus*, and *A. niger* as being more resistant to amphotericin B therapy [10, 11]. Further laboratory investigations also have demonstrated significantly greater in vitro and in vivo activity of new antifungal triazoles against *A. terreus*, with improved survival in experimental infection [11]. It is unknown whether this laboratory-documented resistance to amphotericin B or increased response to triazoles extends to the therapeutic management of human infections. Limited clinical data suggest that *A. terreus* infection may be associated with greater mortality than is infection with other *Aspergillus* species [9]. Hence, optimal therapy for this emerging mould infection remains important and uncertain.

Previous clinical reports of *A. terreus* infection have been limited to small case-series and case reports [9]. In addition, there are cases aggregated in larger clinical studies in which the outcomes of infection with specific *Aspergillus* species are not analyzed separately. The largest previous review devoted to *A. terreus* invasive infections was a single institution's 12-year retrospective analysis of 13 cases that occurred in 1985–1996 [9]. In the present study, we analyzed 83 recent cases of *A. terreus* infection (1997–2002) from 3 major US medical centers and the Voriconazole Clinical Program Database. To further understand the impact of polyene and extended-spectrum triazole therapy, we compared patient outcomes with voriconazole treatment versus patient outcomes with any other systemic antifungal

Received 19 December 2003; accepted 26 February 2004; electronically published 28 June 2004.

Presented in part: 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, 14–17 September 2003 (abstract M-1753).

Reprints or correspondence: Dr. William J. Steinbach, Div. of Pediatric Infectious Diseases, Box 3499, Duke University Medical Center, Durham, NC 27710 (stein022@mc.duke.edu).

Clinical Infectious Diseases 2004; 39:192–8

1058-4838/2004/3902-0008$15.00

treatment, principally amphotericin B. Based upon in vitro and in vivo data and preliminary clinical data, our hypothesis was that voriconazole treatment would lead to improved patient outcome for *A. terreus* infection, compared with the other antifungal regimens.

METHODS

Inclusion criteria and definitions. These retrospective clinical data were obtained from all cases of IA due to *A. terreus* treated at 3 US medical centers during a 6-year period from 1 January 1997 to 31 December 2002. Institutional review board approval was obtained at all participating institutions. Data on cases were also collected from the Voriconazole Clinical Program Database (Sandwich, United Kingdom), and some of these case data have been published elsewhere [12, 13]. The participating US medical centers were MD Anderson Cancer Center (Houston, TX), Duke University Medical Center (Durham, NC), and the Fred Hutchinson Cancer Research Center (Seattle, WA). All cases from the 3 medical centers and the Voriconazole Clinical Program Database were merged for analysis after the elimination of any duplicate cases.

Cases were determined by searching microbiology records for all cases of IA due to culture-proven *A. terreus* at each medical center. IA was required to be either proven IA or probable IA with culture-proven *A. terreus,* as defined according to the joint guidelines of the European Organization for Research and Treatment of Cancer (EORTC) and the Mycoses Study Group (MSG) of the National Institute of Allergy and Infectious Diseases [14]. Definitions were extrapolated to those patients who did not have malignancy and had not undergone hematopoietic stem cell transplantation (HSCT). Infection characteristics were determined clinically and were supported by autopsy results, if available. Day of diagnosis was defined as the day the specimen was obtained for the culture that yielded *A. terreus.* Primary antifungal therapy was defined as the antifungal therapy received on the day after diagnosis or on the day after the diagnostic procedure was performed, and alternative antifungal therapy was defined as alternative or additional antifungal agents administered after the primary antifungal therapy. Concurrent antifungal therapy was defined as the simultaneous administration of $\geqslant 2$ systemic antifungal agents.

Statistical analyses. The primary outcome in our statistical models was voriconazole use, defined as receipt of voriconazole at any time after the day of diagnosis. Patients were categorized into 1 of 2 groups: those patients who received at least 1 dose of voriconazole after diagnosis, and those patients who received other systemic antifungal agents (excluding voriconazole) for treatment of their *A. terreus* infection. Specifically, the patients who received other triazoles or echinocandins without voriconazole were also categorized in the group that received any other antifungal. The primary outcome variable for therapeutic response was overall mortality 12 weeks after diagnosis, as assessed by multiple author review. In addition, clinical response was categorized as described elsewhere [3]. We did not compare outcomes of proven IA versus probable IA, because of previous reports indicating similar findings [15].

To evaluate graft-versus-host disease (GVHD), we generated a dummy variable. However, only certain patients can experience GVHD—specifically, those patients who have undergone allogeneic transplantation. Thus, we generated a GVHD-transplantation term. The parameter estimate from this term reflects GVHD-transplant interaction. However, the model includes only transplant and transplant-GVHD (rather than the fully saturated transplant; GVHD; and transplant-GVHD), because only those patients who underwent transplantation are eligible to experience the exposure GVHD.

We used the Fisher's exact test to compare data for the patient groups. Our primary interest was survival; thus, we used Cox proportional hazards (PH) modeling to evaluate the impact of potential risk factors on patient outcome. Because patients who received voriconazole did not all start voriconazole therapy simultaneously, this form of analysis is susceptible to bias—specifically, a healthier patient population was selected because patients had sufficient time to receive voriconazole. Therefore, we completed 2 additional analyses. We compared survival rates for patients who received primary antifungal therapy with voriconazole versus rates for those who received the drug later in their treatment course (results are presented in this report). We also repeated the analysis by use of logistic regression. The bivariable logistic regression and Cox PH results did not substantially differ in the point estimate of effect, but differed in the widths of the 95% CIs. The logistic regression and Cox PH multivariable results were similar. The logistic regression results are not presented in this report but are available upon request. We used Stata software, version 8.1 (Stata Corporation), and SAS software, version 8.1 (SAS), for the analyses.

RESULTS

Patient characteristics. We analyzed a total of 83 cases of IA (table 1) from MD Anderson Cancer Center (34 [41%] of 83 cases), Duke University Medical Center (17 [20%] of 83), and the Fred Hutchinson Cancer Research Center (4 [5%] of 83). There were also 28 cases (34%) from the Voriconazole Clinical Program Database. The underlying conditions of the 83 patients included the following: malignancy not treated with HSCT (25 [30.1%] of 83 patients), an underlying disorder treated with HSCT (38 [45.8%] of 83), solid organ transplantation (6 [7.2%] of 83), and other conditions (14 [16.9%] of 83).

There were a total of 38 HSCT recipients, including 37 allogeneic HSCT recipients. The majority of the allogeneic HSCT recipients (30 [81.1%] of 37 recipients) had documented acute

Table 1. Characteristics of 83 patients with invasive aspergillosis due to *Aspergillus terreus* in a multicenter study, 1997– 2002.

Patient characteristic	Voriconazole treatment group (n = 34)	Other antifungal treatment group (n = 49)	All patients	P
Sex				
Male	24	32	56	.64
Female	10	17	27	
Ethnicity				
White	30	42	72	1.0
Other	4	7	11	
Underlying condition				
Malignancy				
Any	19 (55.9)	35 (71.4)	54	.25
Acute lymphoblastic leukemia	4	2	6	
Acute myelogenous leukemia	9	22	31	
Chronic lymphocytic leukemia	2	3	5	
Chronic myelogenous leukemia	4	8	12	
Solid tumor	2 (5.9)	7 (14.3)	9	
Solid organ transplant	2 (5.9)	4 (8.2)	6	
Kidney	0	1	1	
Heart	1	1	2	
Lung	1	2	3	
Other underlying condition	11 (32.4)	3 (6.1)	14	
HSCT	16 (47.1)	22 (44.9)	38	1.0
Autologous	0	1	1	
Allogeneic	16	21	37	
Matched related	4	5	9	
Matched unrelated	4	11	15	
Mismatched related	0	1	1	
Unrelated cord blood	2	2	4	
Unsure of allogeneic type	6	2	8	
ANC				.17
<100 cells/μL	6	7	12	
101–500 cells/μL	7	8	15	
501–1000 cells/μL	3	2	5	
>1000 cells/μL	18	32	50	
Mean duration of neutropenia (ANC <500 cells/μL), days	18.9	11.8	…	.36
Acute GVHD (⩾grade 2) in allogeneic HSCT	14 (41.2)	16 (32.7)	30	.67
No acute GVHD in allogeneic HSCT	2	4	6	

NOTE. Data are no. (%) of patients, unless otherwise indicated. ANC, absolute neutrophil count; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant.

GVHD. Of these, 19 (63.3%) of 30 recipients had active acute GVHD on the day of diagnosis, 9 (30%) of recipients had active acute GVHD within the 14 days prior to the day of diagnosis, and 2 (6.7%) of recipients had active acute GVHD after the day of diagnosis.

A. terreus was isolated as the only pathogen in 55% of cases (table 2), but in the remaining cases, *A. terreus* was isolated along with other fungal pathogens. The most common pathogen isolated with *A. terreus* was *A. fumigatus* (48% of cooccurring isolates), followed by other *Aspergillus* species, such as *A. flavus* (15%), *A. versicolor* (7.5%), and *A. nidulans* (5%). In addition, 37% of the *A. fumigatus* isolates occurred with a third *Aspergillus* species, generally *A. flavus*. Other fungal pathogens isolated with *A. terreus* included with *Rhizopus* species (in cultures for 2 patients), and *Paecilomyces* species, *Penicillium* species, and *Scedosporium apiospermum* (in 1 patient each).

Antifungal therapies. The majority of patients treated with voriconazole (21 [61.7%] of 34 patients) or other antifungals (43 [87.7%] of 49 patients; $P < .01$) received ⩾1 prophylactic or empirical antifungal agent prior to treatment for their in-

Table 2. Characteristics of invasive aspergillosis (IA) due to *A spergillus terreus* in a multicenter cohort of 83 patients.

Characteristic	No. (%) of patients			
	Voriconazole treatment group (n = 34)	Other antifungal treatment group (n = 49)	All patients	P
Diagnosis of IA				<.01
Proven	24	15	39 (47.0)	
Probable	10	34	44 (53.0)	
Fungal culture isolates				.66
A. terreus and other(s)	14	23	37 (44.6)	
A. terreus	20	26	46 (55.4)	
Type of IA				1.0
Initial	33	47	80 (96.4)	
Relapse	1	2	3 (3.6)	
Initial site of IA				.73
Lung	31	43	74 (89.2)	
Bone	3	0	3 (3.6)	
Sinus	0	2	2 (2.4)	
Skin	0	1	1 (1.2)	
Other	0	3	3 (3.6)	

vasive *A. terreus* infection. Antifungal therapy after the day of diagnosis was administered to all but 1 patient (82 [98.7%] of 83 patients) as either primary or alternative antifungal therapy. However, this patient received amphotericin B lipid complex for 15 days, and then therapy was changed to liposomal amphotericin B for 18 days, including concomitant caspofungin for the final 6 days, before dying on the day the diagnosis of culture-proven IA due to *A. terreus* was made.

Only 17 (50%) of 34 patients in the voriconazole treatment group received voriconazole as the first antifungal after diagnosis. Voriconazole was given as alternative therapy for the other patients, either as a second antifungal ($n = 13$) or as a third antifungal ($n = 4$). The group that received other systemic antifungal therapy largely consisted of those who received treatment with an amphotericin B formulation (41 [85.4%] of 48 patients), including those who received an amphotericin B lipid formulation as their primary antifungal therapy (30 [62.5%] of 48 patients). However, 24 (50%) of 48 patients in the group that received any other antifungal therapy received an antifungal other than amphotericin B that also possessed anti-*Aspergillus* activity. This included 16 patients (33.3%) who received itraconazole, 6 (12.5%) who received caspofungin, and 2 (4.2%) who received posaconazole. Therefore, only 24 patients in the group that received other antifungal therapy received only an amphotericin B formulation as treatment for their *A. terreus* infections.

We also investigated the number of patients who received concurrent combination systemic antifungal therapy for ⩾7 days after the day of diagnosis. A total of 17 (20.7%) of 82 patients received 2 concurrent antifungal agents, and 6 (7.3%) of 82 patients received 3 concurrent antifungal agents for treatment. The most-common double-antifungal therapy was an amphotericin B lipid formulation plus caspofungin (received by 7 of 17 patients), and the second most-common combination was voriconazole plus caspofungin (received by 4 of 17). The most-common concurrent triple-antifungal regimen was an amphotericin B lipid formulation plus itraconazole plus caspofungin (received by 3 of 6 patients).

Only 2 of 83 patients received GM-CSF, and slightly more than one-half of the patients (44 of 83) received G-CSF. In addition, only 6 (7.2%) of 83 patients received granulocyte transfusions, and an equal percentage underwent surgery as adjunctive therapy for their IA.

Patient outcome. A total of 55 (66.3%) of 83 patients died (table 3), and all except 1 of those died with active IA. Overall mortality in the voriconazole group was 55.8% (19 of 34 patients), and it was 73.4% (36 of 49 patients) in the group that received other antifungal therapy. Death in the voriconazole group occurred a mean of 100 days after diagnosis (median, 40 days; range, 6–457 days). Death in the group that received other antifungal therapy occurred a mean of 29.9 days after diagnosis (median, 11 days; range, 1–312 days). The 17 patients who received voriconazole as primary therapy had a greater overall survival rate (64.7% [11 of 17]), compared with those patients who received voriconazole as their second or third antifungal (23.5% [3 of 17]; $P = .04$). The patients who received voriconazole as their primary antifungal therapy also had greater overall survival than those patients who received an amphotericin B formulation as their primary therapy (26.2% [11 of 42]; $P = .01$). Finally, the survival rate for those patients

Table 3. Outcomes at 12 weeks of therapy for 83 patients with invasive aspergillosis (IA) treated with voriconazole or other antifungals.

Outcome	Percentage (proportion) of patients[a]	
	Voriconazole treatment group (n = 34)	Other antifungal treatment group (n = 49)
Clinical response		
Complete response	20.6 (7/34)	12.2 (6/49)
Partial response	11.8 (4/34)	10.2 (5/49)
Stable	14.7 (5/34)	10.2 (5/49)
Antifungal treatment failure	52.9 (18/34)	65.3 (32/49)
Other failure	0 (0/34)	2.0 (1/49)
Death, by cause		
IA	47.4 (9/19)	44.4 (16/36)
Underlying disease with IA	31.6 (6/19)	30.6 (11/36)
Other infection with IA	10.5 (2/19)	19.4 (7/36)
Other cause with IA	10.5 (2/19)	2.8 (1/36)
Underlying disease without IA	0 (0/19)	2.8 (1/36)

[a] Percentage of patients (no. of with response or cause of death/no. in group or subgroup).

who received voriconazole as primary therapy was more favorable than it was for those 24 patients who received only an amphotericin B formulation during their entire treatment course, and, therefore, did not receive another triazole or an echinocandin as additional therapy for their *A. terreus* infection (survival rate, 16.7% [4 of 24]; $P < .01$). Regarding combination antifungal therapy, 23.5% of patients (4 of 17) who received 2 concurrent antifungal agents survived, and 33.3% of the patients (2 of 6) who received 3 concurrent antifungal agents survived.

In the bivariable analyses (table 4), decreased mortality was observed for those patients who received voriconazole, and increased mortality was observed for those patients who underwent allogeneic transplantation and in those who experienced GVHD. In the multivariable analyses (table 5), decreased mortality was observed for those patients who received voriconazole (HR, 0.29; 95% CI, 0.15–0.56; $P < .01$). The parameter estimates for voriconazole varied <10% in the multivariable Cox proportional hazards models, regardless of the terms included in the model. We present the full model in table 5, but more parsimonious models are available upon request.

DISCUSSION

Previous studies of *A. terreus* in vitro [10] and in an animal model [11] have demonstrated that *A. terreus* is resistant to amphotericin B but susceptible in vitro and is effectively treated in animal model infections by triazole antifungal compounds. These preclinical studies suggest that amphotericin B therapy might lead to a poor patient outcome in the treatment of *A. terreus* infection. However, there have been little data on management and outcome of *A. terreus* clinical infections. This current study, coupled with prior laboratory data [10, 11], attempts to provide an assessment of the potential use of voriconazole in lieu of amphotericin B for the treatment of *A. terreus* infections.

In the multivariable analysis of 83 patients, overall survival was greater for patients who received voriconazole as a part of their antifungal therapeutic regimen, compared with patients who received other systemic antifungal compounds (largely amphotericin B formulations). Specifically, patients who received voriconazole as their primary therapy also had a greater overall survival than those who received an amphotericin B formulation as their primary antifungal therapy. The increased survival observed for those patients who received voriconazole treatment was also observed for patients who received voriconazole as an alternative antifungal therapy. This reproduces recent findings that use of primary therapy with voriconazole was more successful than initial use of amphotericin B with a later switch to another licensed agent, which demonstrates the importance of effective initial therapy for IA [16].

The largest analysis of invasive *A. terreus* infections prior to our study was a single-center review [9] comparing 13 cases with 19 published reports. That review found that, for all *Aspergillus* species isolated, *A. terreus* was associated with the greatest mortality from IA and the largest percentage of cases of IA not diagnosed until postmortem examination (60%). In a review of 29 patients with IA treated with amphotericin B monotherapy (at a dosage of 1.5 mg/kg/d), all patients with

Table 4. Bivariable analyses in which the primary outcome is mortality in a multicenter cohort of 83 patients

Variable	Hazard ratio	95% CI	P
Antifungal management			
Voriconazole	0.38	0.20–0.72	<.01
No voriconazole	Reference group		
Allogeneic HSCT			
Recipient	2.01	1.12–3.60	.02
Nonrecipient	Reference group		
Acute GVHD[a]			
Present	1.91	1.07–3.41	.03
Absent	Reference group		
Fungal culture isolates			
A. terreus	0.93	0.52–1.66	.80
A. terreus and other(s)	Reference group		
ANC, cells/mL			
>1000	0.92	0.51–1.66	.78
<1000	Reference group		

NOTE. ANC, absolute neutrophil count; HSCT, hematopoietic stem cell transplant; GVHD, graft-versus-host disease.

[a] In allogeneic HSCT recipients only.

Table 5. Multivariable analysis in which the primary outcome is mortality in a multicenter cohort of 83 patients.

Variable	Hazard ratio	95% CI	*P*
Voriconazole treatment	0.29	0.15–0.56	<.01
A. terreus culture isolate only	0.93	0.52–1.67	.82
HSCT	1.94	0.58–6.53	.28
HSCT and acute GVHD	1.46	0.44–4.95	.54
ANC >1000 cells/mL	0.67	0.36–1.24	.20

NOTE. ANC, absolute neutrophil count; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant.

isolates that had an amphotericin B MIC of <2 μg/mL survived, but 22 of 24 patients with isolates that had an amphotericin B MIC of ⩾2 μg/mL died, including all 9 of the patients infected with *A. terreus*. Despite similar patient characteristics for infections with the different *Aspergillus* species, the lethality of the *A. fumigatus* infections (mortality, 63%) was lower than that of *A. terreus* infections (mortality, 100%) [17]. Another comparison between 20 patients with *A. terreus* infection and 23 patients with *A. fumigatus* infection revealed similar risk factors and overall therapeutic responses (15% vs. 17%). For example, only 1 of 6 patients with persistent neutropenia and *A. fumigatus* infection responded to therapy, while 0 of 4 with *A. terreus* infection responded to therapy [18].

A. terreus infection may be a possible marker for poor clinical outcome regardless of treatment, because *A. terreus* infection selects for an extremely immunocompromised host. There have been several outcome analyses of IA [3, 19, 20]; however, no study has stratified outcome according to the particular *Aspergillus* species to determine whether species is a critical factor. In a recent landmark study analyzing voriconazole as primary therapy for 391 patients with IA, there were 6 cases of *A. terreus* infection among the 110 infections in which the species were identified at baseline but were not differentiated by outcome [12].

In our retrospective, uncontrolled study of *A. terreus* infection, the survival rate of patients in the voriconazole group was 47% (16 of 34 patients) compared with only 24% (14 of 49 patients) in the group who received other antifungal compounds. This result is generally lower than the overall rate of survival in the large, randomized, controlled study of patients with IA caused by all *Aspergillus* species, but largely caused by *A. fumigatus* [12], in which survival of patients who received initial therapy with voriconazole was 70.8% (102 of 144 patients), compared with 57.9% (77 of 133) for initial therapy with amphotericin B. Although one cannot directly compare a retrospective analysis with a prospective, randomized, controlled clinical trial, this report offers some insight into the potential consideration that infection with *A. terreus* is a marker for a patient at a higher risk of treatment failure or death from underlying disease.

Our study has the limitations imposed on any retrospective, uncontrolled analysis, including potential patient-selection bias. We attempted to alleviate compatibility problems by combining data from a limited number of sites and a global registry with a standardized data-capture form. Although we did accumulate data from a substantial number of cases of *A. terreus* infection, this number is still a relatively small sample size from only 3 US centers and a centralized database and, thus, limits the power of our analyses. The majority of patients in the voriconazole group also originated from clinical trials, in which selection criteria may have excluded critically ill patients. This analysis is also vulnerable to both residual confouding (e.g., within grade of GVHD) and unmeasured confounding.

Because of the retrospective nature of the analysis and the different centers involved, the antifungal agents were not administered in a standard fashion to every patient, and, therefore, this report does not provide uniformity of treatment assessment. We chose to compare therapy with voriconazole versus therapy with any other systemic antifungal agent in our multivariable model. However, it is possible that our estimate of successful treatment in the group that received treatment with other antifungals is biased, because only 50% of the that group received only an amphotericin B product, and the other 50% received either another triazole or an echinocandin with anti-*Aspergillus* activity.

In addition, only 50% (17 of 34) of the patients who received voriconazole received it as their primary antifungal therapy. One concern would be that those patients who received voriconazole as alternative therapy were actually healthier, because they had survived long enough to receive additional therapy; this concern is similar to longstanding questions about analyzing outcomes in patients who receive oral itraconazole after initially receiving parenteral amphotericin B. However, our figures for individual mortality showed that the survival rate for patients who received voriconazole as primary therapy was greater than that of patients who received it as alternative therapy.

The management of IA today is changing; the epidemiology of IA in HSCT recipients is shifting toward late-onset disease [1], and the treatment options for IA have, fortunately, increased in the past several years [21]. In general, the treatment of choice for IA has shifted from amphotericin B therapy [22] toward voriconazole therapy [12]. The ability to distinguish *A. terreus* from other *Aspergillus* species is important from a prognostic and therapeutic-outcome viewpoint. It is emphasized from in vitro and animal model data and previous clinical data that amphotericin B may not be a consistently effective treatment for invasive *A. terreus* disease. This large cohort review of 83 cases of IA caused by *A. terreus* is consistent with previous experimental data, because *A. terreus* displays some evidence of amphotericin B resistance in humans. In summary, our mul-

tivariable regression analyses suggest a potential preferential treatment role for voriconazole compared with amphotericin B for this emerging deadly non-*fumigatus* species of *Aspergillus*.

Acknowledgments

Financial support. W.J.S. is an NICHD Fellow of the Pediatric Scientist Development Program (NICHD K12-HD00850). D.K.B. received support from NICHD 1 R03 HD42940-02, and J.R.P. received support from P01-AI-449175 (Duke University Mycology Research Unit).

Conflict of interest. K.A.M.: Consultant for Pfizer; D.P.K.: Speakers' bureau and grant support: Pfizer, Merck, Fujisawa, and Grizon; I.L.: Employee of Pfizer. All other authors: No conflict.

References

1. 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.
2. Denning DW. Invasive aspergillosis in immunocompromised patients. Curr Opin Infect Dis **1994**; 7:456–62.
3. Patterson TF, Kirkpatrick WR, White M, et al. Invasive aspergillosis: disease spectrum, treatment practices, and outcomes. Medicine **2000**; 79:250–60.
4. Groll AH, Shah PM, Mentzel C, et al. Trends in postmortem epidemiology of invasive fungal infections at a university hospital. J Infect **1996**; 33:23–32.
5. Wald A, Leisenring W, van Burik JAH, Bowden RA. Epidemiology of *Aspergillus* infection in a large cohort of patients undergoing bone marrow transplantation. J Infect Dis **1997**; 175:1459–66.
6. Perfect JR, Cox GM, Lee JY, et al. The impact of culture isolation of *Aspergillus* species: a hospital-based survey of aspergillosis. Clin Infect Dis **2001**; 33:1824–33.
7. Walmsley S, Devi S, King S, et al. Invasive *Aspergillus* infections in a pediatric hospital: a ten year review. Pediatr Infect Dis J **1993**; 12: 673–82.
8. Khoo SH, Denning DW. Invasive aspergillosis in patients with AIDS. Clin Infect Dis **1994**; 19:S41–8.
9. Iwen PC, Rupp ME, Langnas AN, Reed EC, Hinrichs SH. Invasive pulmonary aspergillosis due to *Aspergillus terreus:* 12-year experience and review of the literature. Clin Infect Dis **1998**; 26:1092–7.
10. Sutton DA, Sanchie SE, Revankar SG, Fothergill AW, Rinaldi MG. In vitro amphotericin B resistance in clinical isolates of *Aspergillus terreus,* with a head-to-head comparison to voriconazole. J Clin Microbiol **1999**; 37:2343–5.
11. Walsh TJ, Petraitis V, Petraitiene R, et al. Experimental pulmonary aspergillosis due to *Aspergillus terreus:* pathogenesis and treatment of an emerging fungal pathogen resistant to amphotericin B. J Infect Dis **2003**; 188:305–19.
12. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med **2002**; 347:408–15.
13. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. Clin Infect Dis **2003**; 36:1122–31.
14. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis **2002**; 34:7–14.
15. Denning DW, Lee JY, Hostetler JS, et al. NIAID Mycoses Study Group multicenter trial of oral itraconazole therapy for invasive aspergillosis. Am J Med **1994**; 97:135–44.
16. Boucher HW, Herbrecht R, Bennett JE, et al. The strategy of following voriconazole vs. amphotericin B with other licensed antifungal therapy for primary therapy of invasive aspergillosis [abstract M-964]. In: Program and abstracts of the 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy (Chicago). Washington, DC: ASM Press, **2003**.
17. Lass-Florl C, Kofler G, Kropshofer G, et al. In vitro testing of susceptibility to amphotericin B is a reliable predictor of clinical outcome in invasive aspergillosis. J Antimicrob Chemother **1998**; 42:497–502.
18. Hachem R, Kontoyiannis D, Boktour M, et al. Invasive aspergillosis with *Aspergillus terreus* and *Aspergillus fumigatus:* a comparative analysis of risk factors and outcome in cancer patients [abstract 338]. In: Program and abstracts of the 40th Annual Meeting of the Infectious Diseases Society of America (IDSA) (Chicago). Alexandria, VA: IDSA, **2002**.
19. Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin Infect Dis **1998**; 26:1383–96.
20. Denning DW, Marinus A, Cohen J, et al. An EORTC multicentre prospective survey of invasive aspergillosis in haematological patients: diagnosis and therapeutic outcome. J Infect **1998**; 37:173–80.
21. Steinbach WJ, Stevens DA. Review of newer antifungal and immunomodulatory strategies for invasive aspergillosis. Clin Infect Dis **2003**; 37(Suppl 3):S157–87.
22. Stevens DA, Kan VL, Judson MA, et al. Practice guidelines for diseases caused by *Aspergillus.* Clin Infect Dis **2000**; 30:696–709.