

MINIREVIEW

In Vitro Analyses, Animal Models, and 60 Clinical Cases of Invasive *Aspergillus terreus* Infection

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Invasive aspergillosis (IA) is the most common filamentous fungal infection in immunocompromised patients (16, 51). However, not all *Aspergillus* species possess the same biologic attributes or even the same antifungal susceptibility patterns. *Aspergillus fumigatus* and *A. flavus* are the species most commonly associated with IA (67, 99), and the frequency of IA caused by *A. terreus* varies from 3 to 12.5% (40, 67, 99, 100). Present data from in vitro studies (90) and in vivo studies (101) and a retrospective analysis of contemporary clinical data (86) indicate that IA due to *A. terreus* may be resistant to amphotericin B and associated with a high rate of mortality. However, the optimal therapy for infections caused by this emerging pathogen is uncertain.

Our clinical understanding of this historically difficult to treat pathogen is meager. There are various individual reports of invasive *A. terreus* disease, but most appear as isolated clinical cases. Additionally, there are cases aggregated in larger clinical studies for which the details of the specific *Aspergillus* species were not reported. The only review devoted to invasive *A. terreus* infection was a 12-year retrospective analysis of 13 cases confined to a single medical center from 1985 to 1996 (36). We present a review of 60 clinical cases of invasive *A. terreus* infection, as well as 28 in vitro studies and 9 reports of animal models of *A. terreus* infection, that occurred or that were published from 1966 to 2003 to better understand the characteristics and therapy for this emerging non-*A. fumigatus* *Aspergillus* species.

We searched the English-language literature through the MEDLINE database from 1966 to December 2003 for in vitro and in vivo studies of *A. terreus* as well as clinical case reports using the keywords “*Aspergillus terreus*” and cross-references. Additionally, we also reviewed abstracts from worldwide infectious diseases conferences held from 1999 to 2003 (Inter-science Conference on Antimicrobial Agents and Chemotherapy, annual meetings of the Infectious Diseases Society of America, Focus on Fungal Infections) for studies in which *A. terreus* was specifically analyzed. We excluded articles and abstracts in which *A. terreus* was one of several *Aspergillus* species tested yet in which the specific results or outcomes were not

stratified by species to allow comparison. Inclusion criteria for the review of in vitro studies included antifungal susceptibility testing of *A. terreus*, including a specific stratification of results if multiple *Aspergillus* species were tested. Inclusion criteria for the review of clinical studies consisted of proven or probable IA caused by *A. terreus*, as proven by culture and as defined according to the joint guidelines of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group of the National Institute of Allergy and Infectious Diseases (4).

EPIDEMIOLOGY OF *A. TERREUS*

The previously largest review of *A. terreus* infections examined the microbiology records of one center from 1985 to 1996 and discovered 11 cases of primary invasive pulmonary aspergillosis and 2 cases of primary *Aspergillus* peritonitis (36). The authors compared the 11 cases of invasive pulmonary aspergillosis with the findings from 19 published studies from that 12-year time period. At the authors' institution *A. terreus* was the third most common *Aspergillus* species and accounted for 13 of 133 (9.8%) of cases of IA. *A. terreus* was the most frequent cause of invasive pulmonary aspergillosis in patients with leukemia (54.5%) and the most common species in patients with neutropenia (63.6%) and patients with neutropenia for the longest duration (median, 27 days). *A. terreus* caused the greatest mortality from invasive pulmonary aspergillosis (10 of 11 patients died) and the largest percentage of cases of aspergillosis not diagnosed until postmortem examination (60%).

A review of 1,477 separate *Aspergillus*-positive cultures from 24 medical centers found that *A. fumigatus* was the most frequently isolated *Aspergillus* species, causing 67% of cases of IA (67). *A. flavus* accounted for 16% of the strains causing IA, followed by *A. niger* (5%) and *A. terreus* (3%). When presentations were stratified by disease distributions, although *A. fumigatus* was the leading pathogen causing IA, *A. fumigatus* was also the predominant cause of chronic necrotizing aspergillosis, aspergilloma, allergic bronchopulmonary aspergillosis, colonization, and contamination. In fact, only 19% of *A. fumigatus* isolates were involved in IA. In contrast, although *A. terreus* is an uncommon isolate, it was strongly associated with IA (8 of 8 positive cultures), while *A. flavus* was predominantly associated with IA (41 of 49 positive cultures [83%]).

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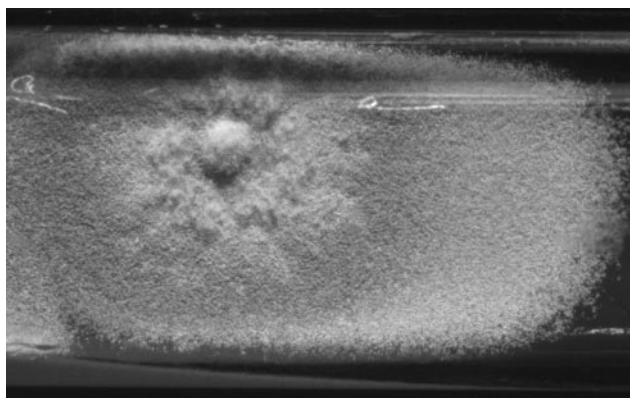


FIG. 1. *A. terreus* from a 3-week-old primary culture of a lung biopsy specimen on inhibitory mold agar.

One study used randomly amplified polymorphic DNA analysis-PCR to analyze 43 clinical *A. terreus* isolates from 28 patients from 1996 to 2001 at a major medical center and found great strain diversity (5). Another study used the same molecular biology-based techniques and concluded that patients with cystic fibrosis are likely colonized with *A. terreus* from the soil and air prior to hospitalization (12). A 3-year prospective study that sampled the air, environmental surfaces, and hospital water of a major medical center found *A. terreus* present in patient showerheads with the same frequency as *A. fumigatus*, and half of the hospital water storage tanks contained *A. terreus* or *A. fumigatus* (1). Volumetric air sampling of one military medical center revealed that *A. niger* was the most commonly found *Aspergillus* species (38%), followed by *A. terreus* (26%). However, only *A. terreus* was recovered from each of four sampling sites, and only *A. terreus* and *A. niger* were consistently recovered throughout the 4-month sampling period (44).

BIOLOGY AND PATHOPHYSIOLOGY OF *A. TERREUS*

A. terreus is widespread in warm arable soils, especially in the southern and southwestern United States. It is generally less common in the forest than cultivated soils and is rarely found in the acidic forest soils from the colder temperate zone (75). *A. terreus* is distinguished from the more common *Aspergillus* species by its compactly columnar, cinnamon to tan (sometimes yellowish to orange-brown) conidial heads, and tan to yellow coloration on the colony reverse (Fig. 1) (75). *A. terreus*, *A. carneus*, *A. flavipes*, and *A. niveus* are unique among *Aspergillus* species, as they produce morphologically distinct lateral conidia (aleurioconidia) in infected tissue (71, 72). These conidia are usually attached directly to a very short lateral extension of the hyphae and are generally borne singly, although multiple conidia can be formed from a single locus (64, 95). In one study the metabolic and growth rates of a human *A. terreus* isolate were double those of two soil isolates when the isolates were grown at 37°C, and the human isolate was more than 1,000-fold more virulent than the soil isolates in a murine model (76), confirming earlier work on relative virulence in studies with animals (72).

The diagnosis of aspergillosis by blood culture is rare, and one recent review concluded that only 32 cases of true *Aspergil-*

lus fungemia have been correctly documented in patients with hematological disease (27). Disease caused by *A. fumigatus* is rarely documented by blood culture (19, 67). In general, the *Aspergillus* hyphal mass that develops in the lumen during angioinvasion remains in place until the force of blood flow causes hyphal breakage, which then allows the mass to circulate. The likelihood that a blood culture would capture these irregularly and infrequently discharged units is small. This difficulty in detection of *A. fumigatus* in blood cultures stands in contrast to the ease of detection of other angioinvasive filamentous fungi (e.g., *Fusarium* species, *Paecilomyces lilacinus*, *Scedosporium prolificans*, and *Acremonium* species) that have the ability to discharge a steady series of unicellular spores into the bloodstream, which are more likely to be captured in a blood sample. This ability to sporulate in tissue and blood has been termed adventitious sporulation (80). As *A. terreus* also displays adventitious sporulation, histopathology and KOH examination of these spores also can allow the rapid, presumptive identification of *A. terreus* (Fig. 2) (49, 72). Therefore, a blood culture positive for *A. terreus* or another fungus that demonstrates adventitious sporulation should not be ignored (81).

IN VITRO ANTIFUNGAL SUSCEPTIBILITY DATA

A total of 28 in vitro analyses testing 418 *A. terreus* isolates met our inclusion criteria (Table 1). In the largest in vitro study of 101 *A. terreus* clinical isolates (90), the 48-h amphotericin B MICs were ≤ 1 $\mu\text{g/ml}$ for less than 2% of the isolates, and the mean MIC was 3.37 $\mu\text{g/ml}$. The minimum fungicidal concentrations (MFCs) were elevated beyond the levels of amphotericin B deoxycholate achievable in serum, with a mean 24-h MFC of 7.03 $\mu\text{g/ml}$ and a mean 48-h MFC of 13.4 $\mu\text{g/ml}$. The 48-h MIC at which 90% of the isolates were inhibited (MIC₉₀) was 4 $\mu\text{g/ml}$ for amphotericin B, with an MFC at which 90% of isolates were inhibited of 16 $\mu\text{g/ml}$, implying that *A. terreus* was resistant to the fungicidal properties of amphotericin B in vitro. In one study (69) only 25% of *A. terreus* isolates were inhibited by amphotericin B (MIC ≤ 1 $\mu\text{g/ml}$), whereas 92% of other *Aspergillus* species isolates were inhibited by amphoter-

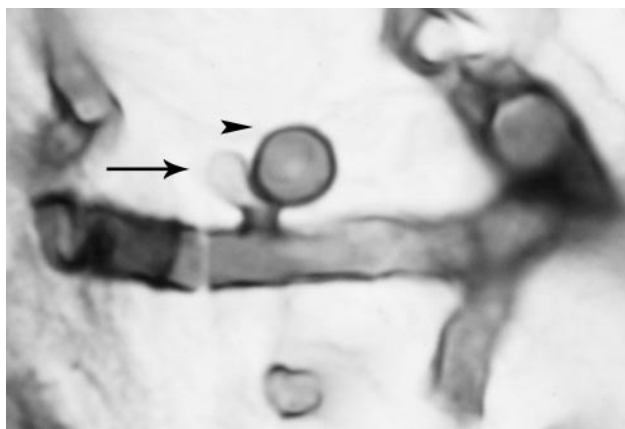


FIG. 2. A mature conidium (arrowhead) displaced by the formation of a second conidium (arrow). The organism was grown from a biopsy specimen from a lip lesion from a neutropenic patient and stained with silver.

TABLE 1. Mean 48-h MIC₉₀s and MFCs for *A. terreus* from in vitro studies^a

Reference	No. of isolates	Analysis method	MIC ₉₀ (µg/ml [MFC {µg/ml}])							
			AMB	ABL/C	ABCD	L-AMB	L-Nys	ITZ	VCZ	PCZ
61	7	Other ^b	8.8 (>16)					0.07		
22	2	M27-A ^b								0.05
45	9	M27-P	≥2							ND (1.0)
90	101	M27-A ^b	3.37 (13.4)						0.22 (17.4 ^c)	
14	20	M38-P	2					1		
91	10	M27-A	2					0.25		
60	8	Other ^b	5.7 (32)	32 (32)	20.7 (32)	32 (32)	8.7 (32)	0.1 (14.7)		
70	1	M38-P						0.5		
Flatley et al. ^e	3	M38-T ^b	4					0.06		
Gavaldà et al. ^f	3	M38-P	>8					0.25 (2)	1.0 (>8)	20.2 (0.2)
24	29	M38-P	4 (>8)							
Sutton et al. ^g	50	M38-P								32
47	5	M27-P						(1)	(0.5)	
53	1	M38-P	2-4					0.5-1		
56	12	Other	4					0.5		0.25
2	9	M38-P ^b								
Troke et al. ^h	14	M38-P	4					0.25	1.0	0.5
3	3	M38-P1	0.06-0.125							1->16
58	2	Other	2-4 (32)					0.125 (2)		0.062-0.125
46	7	Other	1.25		0.78	0.39				
66	10	M38-P							0.5-1	
69	8	M38-P ^d	2					0.5	0.25	0.12
Cuenca-Estrella et al. ⁱ	20	M38-P ^b							0.25	0.25
Espinel-Ingroff et al. ^j	42	M38-P	4.0					0.25		0.90
23	15	M38-A	1.4 ^b					0.14 ^b	0.50	
68	19	M38-A						0.5	0.5	0.27 ^b
Lewis et al. ^k	7	M38-P	0.5-1							0.25-0.5
	1	M38-A	1 (2)					1 (8)	0.25 (4)	

^a Abbreviations: AMB, Amphotericin B; ABL/C, amphotericin B lipid complex; ABCD, amphotericin B colloidal dispersion; L-AMB, liposomal amphotericin B; L-Nys, liposomal nystatin; ITZ, itraconazole; VCZ, voriconazole; PCZ, posaconazole; RCZ, ravuconazole; ALB, albendazole; CAS, caspofungin; AND, anidulafungin; TER, terbinafine; ND, not determined; M27-A, M27-P, M38-P, M38-T, and M38-A, standard methods of the NCCLS.

^b Values are geometric means.

^c The voriconazole MICs for only 51 isolates were tested.

^d Values are MIC₅₀s.

^e A. M. Flatley, P. S. Hicks, A. Wilcox, and H. Rosen, Abstr. 40th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 936, 2000.

^f J. Gavaldà, M. Martín, P. López, M. Cuenca-Estrella, X. Gomis, J. Ramírez, J. Ramírez-Tudela, and A. Pahisa, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. J-107, 2001.

^g D. A. Sutton, M. G. Rinaldi, and A. W. Fothergill, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. J-113, 2001.

^h P. F. Troke, A. Espinel-Ingroff, E. M. Johnson, and H. Schlamm, Abstr. 41st Intersci. Conf. Antimicrob. Agents Chemother., abstr. J-820, 2001.

ⁱ M. Cuenca-Estrella, E. Meliádo, A. Gómez-López, A. Monzon, and J. L. Rodríguez-Tudela, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. M-1514, 2002.

^j A. Espinel-Ingroff, A., E. Johnson, and P. Troke, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. M-1518, 2002.

^k R. E. Lewis, N. P. Wiederhold, and M. E. Klepser, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. M-1255, 2003.

icin B. In another study (24) the largest difference in MICs and MFCs seen for all *Aspergillus* species tested was for *A. terreus*, for which only 34% (10 of 29 pairs) of the MICs and MFCs were within 2 dilutions. An additional study (52) investigated the activity of amphotericin B against *A. terreus* suspended in tissue culture medium and showed that only the highest concentration tested (80 µg/ml) was fungistatic against *A. terreus*.

In another study (101), amphotericin B activity was assessed in vitro by MIC determination, a microbicidal time-kill assay, a colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay of hyphal damage, and sterol composition analysis of the fungal cell membrane. Additionally, the monocyte-macrophage host response to two different *Aspergillus* species was analyzed. This in vitro work revealed a loss of concentration-dependent killing of *A. terreus* by amphotericin B in a time-kill assay, while killing continued for *A. fumigatus*. The MTT assay also showed that *A. terreus* is resistant to amphotericin B-induced hyphal damage after 6 h (101).

The newer agents showed greater in vitro activity than amphotericin B. For instance, in one study of 16 *A. terreus* isolates (17), voriconazole, posaconazole, ravuconazole, and caspofungin inhibited all isolates at ≤0.5 µg/ml. Of all *Aspergillus* species tested, *A. terreus* was the most susceptible to posaconazole, with an MIC range of 0.03 to 0.125 µg/ml. *A. terreus* was also the species most susceptible to itraconazole, with an MIC range of 0.06 to 0.125 µg/ml (61). In another study (22), the MICs for two *A. terreus* isolates were <0.03 to 0.5 µg/ml for posaconazole, 0.5 µg/ml for caspofungin, and <0.03 µg/ml for anidulafungin. In another study (90), the voriconazole 48-h mean MIC for *A. terreus* was within levels achievable in serum (0.22 µg/ml) and the 48-h MIC₉₀ was 0.25 µg/ml. The mean MFCs at 24 and 48 h were 5.39 and 17.4 µg/ml, respectively (90), and thus, voriconazole was shown to be fungistatic only for this *Aspergillus* species, despite reports of fungicidal activity against other *Aspergillus* species. One large review (25) of the in vitro spectrum of activity of voriconazole included a compilation of 139 *A. terreus* isolates from previously published reports and reported that the drug had excellent antifungal activity.

Testing of the activities of antifungal combinations against *A. terreus* in vitro has shown some positive interactions. One in vitro study (66) showed that voriconazole and caspofungin have synergistic activity against *Aspergillus* spp., including 10 clinical isolates of *A. terreus*. Another study (58) revealed that terbinafine and itraconazole as well as terbinafine and fluconazole had synergistic activities against two isolates of *A. terreus* and that amphotericin B and caspofungin had indifferent or slightly additive interactions against three isolates of *A. terreus* (3). The activity of the combination of amphotericin B and anidulafungin against *A. terreus* was indifferent, and that of the combination of amphotericin B and micafungin was slightly additive (L. Ostrosky-Zeichner, M. Matar, V. L. Paetznick, J. R. Rodriguez, E. Chen, and J. H. Rex, Abstr. 42nd Intersci. Conf. Antimicrob. Agents Chemother., abstr. M-1816, 2002). While synergy was observed with nikkomycin Z-micafungin against *A. fumigatus*, this combination showed indifference against *A. terreus* (11).

In summary, in vitro studies of the susceptibility of *A. terreus* to amphotericin B generally reveal high MICs without the potential for fungicidal activity at concentrations safely achiev-

able in plasma. On the basis of these in vitro data, one would hypothesize that the polyene would also demonstrate failure in vivo (45). The limited testing with echinocandin antifungals, generally caspofungin (Table 1), and azole antifungals show that they clearly possess MICs lower than those of amphotericin B. Unfortunately, data with which to specifically compare the activities of the individual azoles against *A. terreus* on a larger scale were limited.

ANIMAL MODELS

There have been few animal models of *A. terreus* infections. An intracheal instillation model of murine and rabbit pulmonary aspergillosis showed the ability of *A. terreus* to produce disease (62). One murine aspergillosis model was used to study 14 different *Aspergillus* species and reported that the pathogenicity of *A. terreus* was average among those of the *Aspergillus* species tested (26). The aleurioconidia of *A. terreus* have been demonstrated in murine brain tissue after intravenous inoculation, demonstrating endogenous sporulation in nonnecrotic host tissue and its blood vessels. This finding is potentially clinically relevant, as in cases of human disseminated disease the aleurioconidia are not able to gain access to vessels in large numbers, but aleurioconidia were observed in blood vessels in this animal model. In fact, in one isolate the aleurioconidial preparation was approximately 10 times as infective as the conidial suspension (72).

In a model of disseminated *A. terreus* infection in immunocompetent mice, the mice were treated with amphotericin B (4.5 mg/kg of body weight once daily intraperitoneally) or itraconazole (50 or 100 mg/kg/day in two oral daily doses), and each drug was continued for 10 days beginning 2 h after infection. The MICs, according to the NCCLS M27-A standards, for the infecting *A. terreus* clinical isolate were 2 µg/ml for amphotericin B and 1 µg/ml for itraconazole. Treatment with itraconazole at 50 and 100 mg/kg/day resulted in survival rates of 70% (7 of 10) and 90% (9 of 10), respectively. All mice (10 of 10) receiving amphotericin B died within 12 days, which was the same as the death rate for controls receiving glucose injections. Itraconazole significantly reduced the fungal burdens in the kidneys and the brain in a dose-dependent fashion, but amphotericin B treatment was no better than no treatment at reducing the tissue fungal burden. Sterol analysis of the infecting isolate showed an ergosterol content of 85%, which is similar to what has been described for *A. fumigatus* isolates that are susceptible to amphotericin B in vivo. This finding suggests that the amphotericin B resistance observed in this murine model was not related to a lack of the ergosterol target in the cell membranes (13).

A model of *A. terreus* infection in temporarily neutropenic mice showed that treatment with either amphotericin B deoxycholate or liposomal amphotericin B was ineffective (102). However, treatment with itraconazole or micafungin prolonged the length of survival over that for the untreated controls. The colony counts in the lungs and livers of mice with this *A. terreus* infection were >100-fold higher than the colony counts in the lungs and livers of mice with *A. fumigatus* infections evaluated in parallel with identical treatment arms, highlighting the differences in the treatments for infections caused by the two species. Another model of systemic *A. terreus* infec-

tion in mice showed that the survival rate for mice treated with saperconazole was superior to that for the untreated controls, but this azole did not reduce the kidney fungal burden compared to that in the controls (32).

A model of systemic *A. terreus* infection in neutropenic mice compared therapy with posaconazole, caspofungin, or amphotericin B at various doses (J. R. Graybill, A. W. Fothergill, S. Hernandez, L. K. Najvar, and R. Bocanegra, Focus Fungal Infect. 13, abstr. P-62, 2003). In three studies amphotericin B was not effective when it was administered at 6 mg/kg intraperitoneally daily, and amphotericin B reduced the semiquantitative fungal burdens in the spleens to levels lower than those in the controls only when it was administered at 10 mg/kg every other day. Caspofungin (15 mg/kg/day) inconsistently prolonged survival and reduced the counts in the spleens to levels lower than those in the controls, but lower doses of caspofungin (0.5, 5, and 10 mg/kg daily) were completely ineffective. Posaconazole at 20 mg/kg, but not at 10 mg/kg, prolonged survival, while both doses reduced the fungal burdens in the lungs but not in the spleens. Another murine model with DBA2/J mice and a range of caspofungin doses showed that the drug achieved a 50% effective reduction in the fungal burden in the kidneys when it was administered at 0.05 mg/kg/day, a value higher than that required to achieve the same result against *A. flavus* or *A. nidulans* (E. J. Simmons, G. Abruzzo, J. Bowman, C. Douglas, A. M. Flattery, C. Gill, M. Hsu, A. Misura, B. Pikounis, and J. Kahn, Abstr. 43rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. M-1251, 2003).

The in vivo analysis with the most number of endpoints compared *A. fumigatus* and *A. terreus* invasive pulmonary aspergillosis in a persistently neutropenic rabbit model (101). Rabbits received amphotericin B deoxycholate (0.5 mg/kg/day), liposomal amphotericin B (5 mg/kg/day), itraconazole (6 or 20 mg/kg/day), or posaconazole (6 or 20 mg/kg/day). The histology of the lung tissues of rabbits infected with *A. terreus* and treated with amphotericin B were indistinguishable from that of the lung tissues of untreated controls; however, aleurioconidia were seen along the lateral walls of hyphal elements invading the lung tissue infected with *A. terreus*. There was also no difference in the galactomannan levels in the amphotericin B-treated rabbits compared to those in the controls. Survival was statistically improved by treatment with posaconazole or itraconazole at 20 mg/kg/day, while the rate of survival of rabbits treated with amphotericin B was similar to that of the untreated controls. The study observed that while *A. terreus* was more resistant to amphotericin B in vivo, it appeared to be less virulent than *A. fumigatus* in vivo, such that untreated rabbits infected with *A. terreus* survived longer than those infected with *A. fumigatus*. Sterol analysis demonstrated decreasing levels of membrane ergosterol content with increasing MICs for *A. terreus* isolates.

This collection of data from studies that have used animal models are concordant with the in vitro observations that amphotericin B is an ineffective clinical antifungal option. The limited testing of echinocandins in vivo reveals that this group of drugs has inconsistent activity in terms of decreasing mortality or fungal burden. However, the azoles appear to be the most active group of drugs against this particular *Aspergillus* species in experimental animal models, and this finding mirrors the data from in vitro studies.

CLINICAL REPORTS

A. terreus has been recognized as a cause of allergic bronchopulmonary aspergillosis (43, 98), aspergilloma (38, 39, 43), onychomycosis (63, 103), aural cavity disease (20, 31, 73, 89, 93), subcutaneous abscesses (9, 88), and keratitis (78, 84). Many factors influence the overall clinical efficacy of treatment for IA, including the pharmacokinetics and pharmacodynamics of the antifungal agent used, the host's immune status, the site of infection, and the virulence of the pathogen. For example, a comparison of 20 patients with *A. terreus* infections and 23 patients with *A. fumigatus* infections revealed similar risk factors and overall responses (complete or partial) to antifungal therapy (15 and 17%, respectively). Only one of six patients reported to have persistent neutropenia and *A. fumigatus* infections responded to treatment, while none of four patients reported to have *A. terreus* infections responded to treatment (R. Hachem, D. Kontoyiannis, M. Boktour, C. Afif, C. Cooksley, I. Chatzinikolaou, and I. Raad, Program Abstr. 40th Annu. Meet. Infect. Dis. Soc. Am., abstr. 338, 2002).

We reviewed a total of 60 previously published clinical invasive *A. terreus* infections described in 39 reports published from 1968 to 2003 (Table 2). Interestingly, 75% (45 of 60) of those clinical cases were reported in the last 14 years (1990 to 2003). The ages of the patients ranged from 1 month to 80 years, and 23% (14 of 60) of the patients were reported to be neutropenic (absolute neutrophil counts, <500 cells/ μ l) at the time of diagnosis. While pulmonary disease makes up the vast majority of clinical presentations in other studies, only 45% (27 of 60) of these patients with *A. terreus* infections had pulmonary infections, while 18% (11 of 60) had endocarditis and 17% (10 of 60) had a bone or joint infection.

Consistent with the overall reports of the treatments for IA, amphotericin B monotherapy was used to treat 52% (31 of 60) of cases; this was followed by 17% (10 of 60) of cases in which amphotericin B was administered concurrently with another antifungal and 10% (6 of 60) of cases in which amphotericin B treatment was followed by sequential therapy with another antifungal agent. No therapy was given to 12% (7 of 60) of cases due to postmortem diagnoses, and 10% (6 of 60) were treated with another antifungal agent. In 82% (49 of 60) of cases of *A. terreus* infection reported, the patient died. Of the 11 reported patients with clinical improvement, only 2 were treated with amphotericin B monotherapy. Eight of the remaining nine reported patients were treated with an azole; one was treated with ketoconazole, one was treated with itraconazole, three were treated with amphotericin-itraconazole, one was treated with amphotericin-miconazole, and two were treated with amphotericin B followed by treatment with itraconazole.

In another review (45) of 29 patients with hematological malignancies who developed IA and who were treated with amphotericin B monotherapy (1.5 mg/kg/day), 31% (9 of 29) had *A. terreus* infections. The overall rate of mortality from IA was 76% (22 of 29 patients), and all patients infected with isolates for which the amphotericin B MIC was <2 μ g/ml survived, while 22 of 24 patients infected with isolates for which the amphotericin B MIC was $\geq$ 2 μ g/ml died, including all *A. terreus*-infected patients. The rate of lethality from the *A. fumigatus* infections (63%) was lower than that from the *A.*

TABLE 2. Previously published clinical reports of invasive *A. terreus* infection^a

Reference	Yr	Age (yr)/sex	Underlying disease, condition, or characteristic	Neutropenic at diagnosis	Type of IA	Source of culture	Antifungal treatment	Patient outcome
54	1968	15/M	Mitral valve regurgitation	No	Endocarditis	Autopsy specimen	None	Death
50	1969	40/M	Immunocompetent	No	Disseminated	Cervical lymph node biopsy specimen	None	Death
82	1977	42/F	Portal hepatofibrosis, IVDA	No	Vertebral osteomyelitis	Biopsy specimen	AMB	Improvement
18	1980	65/M	Porcine valve replacement	No	Endocarditis	Surgical specimen	AMB + 5FC	Death
28	1982	71/M	Aortofemoral bypass	No	Vertebral osteomyelitis, pseudoaneurysm	Biopsy specimen	AMB, surgery	Death
85	1982	24/F	Heroin addiction	No	Meningitis	CSF culture	AMB	Death
43	1982	53/F	Rheumatic heart disease, valve replacement	No	Endocarditis	Autopsy	None	Death
95	1983	23/M	AML	No	Disseminated	Lung biopsy specimen	AMB + 5FC	Death
92	1983	24/F	VSD, right aortic sinus aneurysm rupture	No	Endocarditis	Surgical specimen	AMB + 5FC, surgery	Death
8	1986	60/M	AML	Yes	Pulmonary	Transbronchial biopsy specimen	AMB	Death
57	1988	70/F	Lymphoma	No	Pulmonary	Transbronchial biopsy specimen	AMB	Death
33	1989	80/F	Immune thrombocytopenia	No	Pulmonary	BAL specimen	AMB	Death
33	1989	28/M	Myelodysplastic syndrome, BMT	Yes	Disseminated	Sputum, pericardial fluid, urine	AMB + ketoconazole	Death
33	1989	65/F	CLL	Yes	Disseminated	NR	NR	Death
7	1989	0/F	Truncus arteriosus	No	Endocarditis	Autopsy	None	Death
41	1990	37/F	SLE	No	Pulmonary	Autopsy	None	Death
79	1990	58/F	Aortic stenosis, valve replacement	No	Disseminated	Autopsy	AMB	Death
37	1991	65/F	CLL	No	Disseminated	BAL specimen, skin specimen	AMB	Death
55	1992	46/M	AIDS	No	Pulmonary	Autopsy	None	Death
74	1992	41/M	AIDS, lymphoma	No	Pulmonary	Sputum, autopsy	AMB	Death
64	1992	72/M	NIDDM	No	Septic bursitis	Joint fluid	Surgery	Improvement
15	1993	50/M	Cataract extraction	No	Endophthalmitis	Vitreotomy biopsy specimen	Ketoconazole, intravitreal AMB	Improvement
100	1993	2/F	Aplastic anemia, BMT	NR	Pulmonary, skin	Clinical evidence	AMB, Rifampin, surgery	Death
100	1993	18/F	Aplastic anemia, BMT	NR	Skin	Clinical evidence	AMB, 5FC, surgery	Death
100	1993	2/F	T-cell deficiency	NR	Liver	Autopsy	AMB, 5FC	Death
29	1993	21/M	ALL, allogeneic BMT	No	Pulmonary	Biopsy	AMB + miconazole and then itraconazole	Improvement
96	1993	36/M	Non-Hodgkin's lymphoma, autologous BMT	No	Pulmonary	Transbronchial biopsy specimen	AMB + 5FC + aerosolized AMB	Death
96	1993	23/M	ALL, allogeneic BMT	Yes	Disseminated	Autopsy	AMB	Death
96	1993	27/M	CML, allogeneic BMT	No	Disseminated	BAL specimen	AMB	Death
96	1993	41/M	AML, allogeneic BMT	No	Disseminated	Cerebral biopsy specimen, autopsy	AMB	Death
35	1993	NR	Non-Hodgkin's lymphoma	No	Pulmonary	NR	AMB	Death
35	1993	NR	Non-Hodgkin's lymphoma	No	Disseminated	Blood culture, BAL specimen	AMB	Death
59	1994	5/F	Aplastic anemia	Yes	Pulmonary, sinus	Maxillary sinus puncture	AMB	Death
42	1995	15/F	Aortic stenosis and valvotomy	No	Aortic abscess and pseudoaneurysm	Surgical specimen	AMB	Death
77	1995	40/F	CML, allogeneic BMT	Yes	Pulmonary	Surgical specimen	AMB, itraconazole, surgery	Death
77	1995	57/M	Cirrhosis, liver transplant	No	Pulmonary	Surgical specimen	AMB, itraconazole, surgery	Improvement
87	1997	51/M	Hepatic cirrhosis	No	Septic arthritis	Joint fluid	Itraconazole, surgery	Improvement
10	1998	33/M	CML, PSCT	No	Endocarditis, disseminated	Autopsy specimens	AMB	Death
81	1998	60/F	ALL	No	Endocarditis, aortic embolization	Multiple blood cultures	AMB, surgery	Death
36	1998	34/F	Non-Hodgkin's lymphoma, autologous PSCT	Yes	Pulmonary	Autopsy	AMB	Death
36	1998	72/M	AML	Yes	Pulmonary	Autopsy	None	Death
36	1998	46/F	Chronic hepatitis B, liver transplant	No	Pulmonary	Autopsy	Fluconazole	Death
36	1998	76/M	AML	Yes	Pulmonary, cutaneous	Skin specimen culture	AMB	Death
36	1998	1/M	Liver-small bowel transplant	No	Disseminated	Multiple cultures	Fluconazole	Death
13	2000	54/M	AML	Yes	Pulmonary	BAL specimen	AMB + itraconazole	Improvement
48	2000	NR	AML	No	Pulmonary	Lung biopsy specimen	AMB	Death

48	2000	NR	CLL	No	Disseminated	Tracheal secretion	AMB	Death
48	2000	NR	CLL	No	Pulmonary	Lung biopsy specimen	AMB	Death
48	2000	NR	AML	Yes	Pulmonary	BAL specimen	AMB	Death
48	2000	NR	CLL	No	Disseminated	Tracheal secretion, brain biopsy specimen	AMB	Death
48	2000	NR	AML	Yes	Pulmonary	BAL specimen	AMB	Death
48	2000	NR	Multiple myeloma	Yes	Pulmonary	Lung biopsy specimen	AMB	Death
48	2000	NR	Aplastic anemia	No	Pulmonary	BAL specimen	AMB	Death
48	2000	NR	ALL	Yes	Pulmonary	Lung biopsy specimen	AMB	Death
36	2000	40/M	AML	No	Pulmonary, vertebral osteomyelitis	BAL and biopsy specimens	AMB + itraconazole, surgery	Improvement
83	2000	11/M	AML	No	Pulmonary, mycotic aneurysm	BAL and biopsy specimens	ABLC + rifampin + aerosolized AMB and then itraconazole, surgery	Improvement
65	2000	37/M	ALL	No	Vertebral osteomyelitis	Biopsy specimen	AMB, surgery	Improvement
97	2001	33/M	History of pulmonary aspergillosis	No	Sclerosing mediastinitis	Biopsy specimen	AMB	Death
94	2001	13/M	Common variable immunodeficiency	No	Hepatic abscess	Biopsy	Liposomal AMB + GM-CSF + itraconazole	Improvement
21	2002	19/F	Biliary atresia	No	Cholangitis	Biliary drainage	ABCD, then itraconazole, and then ABCD	Death

^a Abbreviations: M, male; F, female; IVDA, intravenous drug abuser; CSF, cerebrospinal fluid; AML, acute myelogenous leukemia; VSD, ventricular septal defect; BMT, bone marrow transplant; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; SLE, systemic lupus erythematosus; PSCT, peripheral blood stem cell transplant; NIDDM, non-insulin-dependent diabetes mellitus; NR, not reported; BAL, bronchoalveolar lavage; AMB, amphotericin B; 5FC, flucytosine; ABLC, amphotericin B lipid complex; ABCD, amphotericin B colloidal dispersion.

terreus infections (100%). The characteristics of the patients infected with different *Aspergillus* species were similar; four of nine *A. terreus*-infected patients were neutropenic at the time of diagnosis, and the neutropenia resolved in two of four patients.

In a recent study analyzing voriconazole as primary therapy for IA (34), 6 cases of *A. terreus* infection were identified among the 110 infections in which the species were identified at the baseline. Of the total of 391 patients from 95 centers in 19 countries, successful outcomes were achieved for 31.6% of patients who received amphotericin B as primary therapy, whereas the rate of successful outcomes was 52.8% among the patients who received voriconazole as the initial therapy. Unfortunately, the outcomes for those six cases were not stratified, so there are no specific data on *A. terreus* therapy from the largest aspergillosis treatment trial ever completed. In a contemporary retrospective review (85) of 83 cases of *A. terreus* infection conducted from 1997 to 2002, patients who were treated with voriconazole at any time during therapy had a significantly lower overall mortality rate at 12 weeks (odds ratio, 0.38; 95% confidence interval, 0.14 to 0.99; $P = 0.049$) than patients who received other antifungals (chiefly amphotericin B). The patients who received voriconazole as their primary antifungal therapy also had a greater overall survival rate (64.7% [11 of 17 patients]; $P = 0.008$) than the patients who received amphotericin B.

With the advent of new therapeutic options, the ability to distinguish *A. terreus* from other *Aspergillus* species may be important in the development of an effective therapeutic strategy. The synthesis of data from in vitro and animal model studies as well as clinical observations suggests that amphotericin B therapy may not be effective against IA due to *A. terreus*. This review also describes the largest collection of previously reported *A. terreus* clinical cases and extends the concept of amphotericin B resistance into the clinical realm, as 7 of the 11 patients reported to have survived received an azole. While no randomized clinical trials specifically analyzing the outcomes of treatments for *A. terreus* infections have been conducted and only one cohort study has been able to offer conclusions, this review suggests that amphotericin B may not be effective against *A. terreus* infections and that clinicians should strongly consider using a triazole antifungal against this emerging non-*A. fumigatus* *Aspergillus* species.

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