JOURNAL OF CLINICAL MICROBIOLOGY, Oct. 2004, p. 4419–4431 Vol. 42, No. 10
0095-1137/04/$08.00+0 DOI: 10.1128/JCM.42.10.4419–4431.2004

MINIREVIEW

Rare and Emerging Opportunistic Fungal Pathogens: Concern for Resistance beyond *Candida albicans* and *Aspergillus fumigatus*

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The frequency of invasive mycoses due to opportunistic fungal pathogens has increased significantly over the past two decades (35, 74, 83, 88, 89, 101, 106). This increase in infections is associated with excessive morbidity and mortality (33, 50, 108) and is directly related to increasing patient populations at risk for the development of serious fungal infections, which includes individuals undergoing solid-organ transplantation, blood and marrow transplantation (BMT), and major surgery and those with AIDS, neoplastic disease, immunosuppressive therapy, advanced age, and premature birth (5, 35, 89, 106). Serious life-threatening infections are being reported with an ever increasing array of pathogens, including the well-known opportunists *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus* (35, 63, 88). New and emerging fungal pathogens include species of *Candida* and *Aspergillus* other than *C. albicans* and *A. fumigatus*: opportunistic yeast-like fungi such as *Trichosporon* spp., *Rhodotorula* spp., and *Geotrichum capitatum* (*Blastoschizomyces capitatus*); the zygomycetes; hyaline molds, such as *Fusarium*, *Acremonium*, *Scedosporium*, *Paecilomyces*, and *Trichoderma* species; and a wide variety of dematiaceous fungi (Table 1) (6, 57, 71, 83, 90, 94, 106, 113). The field of medical mycology has become an extremely challenging study of infections caused by a wide and taxonomically diverse array of opportunistic fungi. The message to both clinicians and clinical microbiologists is that there are no uniformly nonpathogenic fungi: any fungus can cause a lethal infection in a sufficiently immunocompromised host and should never be dismissed out of hand as a contaminant.

Given the complexity of the patients at risk for infection and the diverse and increasing array of fungal pathogens, opportunistic mycoses pose considerable diagnostic and therapeutic challenges (79, 106). Diagnosis depends upon clinical suspicion and the retrieval of appropriate material for culture and histopathology. Isolation and identification of the infecting organisms are extremely important for the proper management of infections due to the less common opportunistic fungi (106). Some of these organisms are inherently nonsusceptible to standard azole or polyene therapy and may require the use of alternative antifungal agents, in addition to surgical management and reversal of the underlying impairment of host defenses (106).

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In this article we review selected emerging agents (e.g., *C. glabrata*) and less common agents of opportunistic mycoses with an emphasis on what is known of their susceptibility and resistance to both new and established antifungal agents. Although we now have available several exciting new antifungal agents with improved spectra of activity and potencies, it is useful to keep in mind that broad and injudicious use of any anti-infective agent in a severely immunocompromised host may result in superinfections due to organisms that are both unusual and drug resistant (94, 106).

EMERGING AND RARE *CANDIDA* SPECIES: BEYOND *C. ALBICANS*

More than 17 different species of *Candida* have been identified as etiologic agents of bloodstream infections (BSIs). Approximately 95% of all *Candida* BSIs are caused by four species: *C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis* (35, 74, 88). The excellent activities of new and established systemic antifungal agents against *C. albicans*, *C. parapsilosis*, and *C. tropicalis* are well documented (35, 74, 85). Among these common species, only *C. glabrata* can be said to be truly emerging as a cause of BSIs, due in part to its intrinsic and acquired resistance to azoles and other commonly used antifungal agents (88, 101). The remaining 5% of *Candida* BSIs are caused by 12 to 14 different species, including *C. krusei*, *C. lusitaniae*, *C. guilliermondii*, *C. dubliniensis*, and *C. rugosa*, among others (83). Although these species must be considered rare causes of BSIs, several have been observed to occur in nosocomial clusters and/or to exhibit innate or acquired resistance to one or more established antifungal agents (13, 19, 22, 36, 98, 111). Given that these uncommon species may emerge as important opportunistic pathogens in the future, it is useful to describe the activities of both new and established antifungal agents as potential therapeutic options for infections due to these species (83, 84). The in vitro activities, determined by National Committee for Clinical Laboratory Standards (NCCLS) reference methods (67), of seven systemically active antifungal agents against one emerging species (*C. glabrata*) and five of the less common species of *Candida* isolated from blood cultures are shown in Table 2.

***C. glabrata*.** *C. glabrata* has emerged as an important and potentially resistant opportunistic fungal pathogen (84, 88, 101). Trick et al. (101) have demonstrated that among the *Candida* spp. *C. glabrata* alone has increased in incidence as a cause of BSIs in U.S. intensive care units since 1993. Likewise,

TABLE 1. Rare and emerging opportunistic fungal pathogens[a]

Pathogenic fungus
Candida species
C. glabrata
C. krusei
C. lusitaniae
C. dubliniensis
C. guilliermondii
C. rugosa
Opportunistic yeast-like fungi
Trichosporon spp.
Rhodotorula spp.
Geotrichum capitatum
Hyaline molds
Aspergillus terreus
Zygomycetes
Other molds
Fusarium spp.
Acremonium spp.
Scedosporium spp.
Paecilomyces spp.
Trichoderma spp.
Dematiaceous molds
Bipolaris spp.
Exophiala spp.
Phialophora spp.
Wangiella spp.

[a] The list is not all inclusive.

in certain regions of the United States *C. glabrata* both is a common cause of BSI and is also often resistant to fluconazole (35, 88). Surveys from other parts of the world, however, suggest that *C. glabrata* has not increased as a cause of BSIs to the same extent as that seen in the United States and, furthermore, may not be as resistant to fluconazole as U.S. isolates (84, 88, 91, 100).

In a recent study of clinically invasive isolates of *C. glabrata* from four different geographic regions (North America, Europe, Latin America, and the Asia-Pacific region), we confirmed that the azoles were less active against isolates from North America than those from other regions of the world (84). We have also shown that azoles have the greatest activities against *C. glabrata* isolates from the Asia-Pacific region (84, 88).

C. glabrata is innately less susceptible to fluconazole and amphotericin B than most other species of *Candida* (77, 81, 84) and displays the capacity to rapidly develop resistance to all azoles via induction of CgCDR1 and PDH1 efflux pumps (4, 92). Exposure of *C. glabrata* to subtherapeutic concentrations of fluconazole may result in resistance (4), and clinical studies have shown that the frequency of colonization and infection of patients with *C. glabrata* may be increased in populations subjected to fluconazole prophylaxis (52). However, the reason for the emergence of *C. glabrata* as an important cause of BSIs is likely not as simple as selection by drug pressure (e.g., fluconazole) but may be influenced by patient age, underlying diseases, geographic location, or other unknown factors (84, 88).

The data in Table 2 demonstrate the decreased susceptibility of *C. glabrata* to fluconazole (61.9% susceptible [S] at ≤8 μg/ml) and amphotericin B (75.2% S at ≤1 μg/ml). Amphotericin B MICs were >2 μg/ml for 12 of the 601 isolates tested (2%) by the Etest method (84). The activities of the new extended-spectrum triazoles against *C. glabrata* were considerably better than that of fluconazole. This is because the vast majority of isolates for which fluconazole MICs are 16 to 32 μg/ml (susceptible-dose dependent) appear to be susceptible to voriconazole, posaconazole, and ravuconazole (87 to 97% S at MIC ≤1 μg/ml).

It has been suggested that the new triazoles may be active against strains of *C. glabrata* that are resistant to fluconazole (43); however, a strong positive correlation can be seen between voriconazole ($R = 0.9$) and posaconazole ($R = 0.8$) MICs and fluconazole MICs (Fig. 1). We have also noted a similar correlation between ravuconazole MICs and fluconazole MICs, suggesting cross-resistance (86). Isolates resistant to fluconazole are less susceptible to voriconazole, ravuconazole, and posaconazole, with MICs ≥2 μg/ml for 83, 89, and 92% of isolates, respectively. Although the clinical significance of these in vitro data has yet to be determined, cross-resistance among the azoles should not be surprising with *C. glabrata*, given the ability of this species to rapidly upregulate CDR drug efflux pumps and the effectiveness of these pumps against all of the azoles (4).

Caspofungin (MIC at which 90% of isolates are inhibited [MIC_{90}] = 0.06 μg/ml; 100% S at MIC ≤1 μg/ml) and flucytosine (MIC_{90} = 0.12 μg/ml; 99.2% S) were the most active against *C. glabrata* (Table 2). All fluconazole-resistant strains were also susceptible to both of these agents (MICs ≤ 0.25 μg/ml). Although it may not be unexpected that a novel newly introduced agent such as caspofungin would be active against this species, the excellent potency of flucytosine against *C. glabrata* is not widely appreciated (82, 84). Both of these agents may be useful therapeutic options in regions where azole resistance is a concern.

***C. krusei*.** *C. krusei* accounts for 2 to 3% of all *Candida* BSIs (88). This species is best known for its propensity to emerge in settings where fluconazole is used for prophylaxis (110, 111); however, it is worth noting that colonization and infection among those with hematologic malignancies were apparent in certain medical centers well in advance of the use of fluconazole (41, 109). The antifungal susceptibility profile of *C. krusei* is that of a multidrug-resistant (MDR) pathogen with decreased susceptibility to fluconazole (2.9% S; all isolates should be considered resistant), amphotericin B (the MIC was ≤1 μg/ml for 8.0% of isolates), and flucytosine (4.0% S) (Table 2). This MDR pattern is well recognized for *C. krusei* and is the basis for continuing concern regarding this species as a possible emerging pathogen (77). Importantly, this resistance profile does not extend to the newer triazoles or the echinocandins. Cross-resistance among azoles does not appear to be an issue with *C. krusei*, as ≥99% of clinical isolates are susceptible to voriconazole, posaconazole, and ravuconazole (MICs = 1 μg/ml or less). Likewise, caspofungin has excellent activity against this species (MIC_{90} = 0.25 μg/ml; 99% S at ≤1 μg/ml).

***C. lusitaniae*.** *C. lusitaniae* most often causes fungemia in patients with malignancies or other serious comorbid conditions (36). *C. lusitaniae* is often mentioned in the literature as being capable of developing resistance to amphotericin B during the course of therapy (36, 76, 77) and may present as breakthrough fungemia in immunocompromised patients (36).

TABLE 2.. In vitro susceptibilities of rare and emerging species of *Candida* to new and established antifungal agents determined by NCCLS M27-A2 broth dilution MIC methods[a]

Species	Antifungal agent	No. of isolates tested	MIC (μg/ml)			% S[b]
			Range	50%	90%	
C. glabrata	Amphotericin B	601[c]	0.06–16	1	2	75.2
	Flucytosine	601	0.06–8	0.06	0.12	99.2
	Fluconazole	1,966	0.12–>128	8	32	61.9
	Posaconazole	1,929	0.015–>8	0.5	2	86.2
	Ravuconazole	1,869	0.007–>8	0.25	1	90.3
	Voriconazole	1,966	0.007–>8	0.25	1	91.8
	Caspofungin	601[d]	0.007–0.5	0.03	0.06	100
C. krusei	Amphotericin B	234[c]	0.06–16	4	8	8.0
	Flucytosine	234	0.06–>128	16	32	4.0
	Fluconazole	312	4–>128	32	64	2.9
	Posaconazole	306	0.12–2	0.5	1	99.3
	Ravuconazole	302	0.03–2	0.5	0.5	99.0
	Voriconazole	312	0.06–4	0.25	0.5	99.4
	Caspofungin	101[d]	0.03–4	0.12	0.25	99.0
C. lusitaniae	Amphotericin B	103[c]	0.06–16	0.25	1	96.7
	Flucytosine	103	0.06–>128	0.06	8	89.3
	Fluconazole	103	0.12–64	0.5	2	96.1
	Posaconazole	129	0.015–1	0.03	0.12	100
	Ravuconazole	103	0.007–4	0.015	0.06	98.1
	Voriconazole	134	0.007–2	0.007	0.03	99.2
	Caspofungin	24[d]	0.06–0.5	0.12	0.25	100
C. dubliniensis	Amphotericin B	101[c]	0.06–1	0.25	0.5	100
	Flucytosine	101	0.06–0.25	0.06	0.06	100
	Fluconazole	101	0.12–>128	0.25	8	91.1
	Posaconazole	103	0.015–>8	0.03	0.06	98.1
	Ravuconazole	101	0.007–>8	0.007	0.03	98.0
	Voriconazole	103	0.007–>8	0.007	0.03	98.1
	Caspofungin	71[d]	0.03–1	0.25	0.5	100
C. guilliermondii	Amphotericin B	102[c]	0.06–32	0.25	1	98.0
	Flucytosine	102	0.06–4	0.12	0.25	100
	Fluconazole	102	025–>128	4	16	85.3
	Posaconazole	85	0.015–8	0.25	0.5	97.6
	Ravuconazole	102	0.007–>8	0.25	1	97.1
	Voriconazole	92	0.007–>8	0.06	0.5	96.7
	Caspofungin	27[d]	0.06–>8	0.5	1	96.3
C. rugosa	Amphotericin B	13[c]	0.5–32	1	4	54.5
	Flucytosine	13	0.06–32	0.5	16	84.6
	Fluconazole	19	0.5–32	4	16	78.9
	Posaconazole	19	0.015–0.5	0.06	0.25	100
	Ravuconazole	13	0.007–0.25	0.015	0.25	100
	Voriconazole	19	0.015–0.25	0.015	0.12	100
	Caspofungin	3[d]	0.12–0.5	0.25	ND[e]	100

[a] Data compiled from references 83 to 88.
[b] % S, percent susceptible at MICs of ≤8 μg/ml (fluconazole), ≤4 μg/ml (flucytosine), or ≤1 μg/ml (all other agents).
[c] Amphotericin B MICs were determined by Etest (80).
[d] Caspofungin MICs were read as the lowest concentration at which prominent inhibition (≈50%) is observed at 24 h of incubation (87).
[e] ND, not done.

Among the 103 BSI isolates tested for amphotericin B resistance by Etest (Table 2), 96.7% were susceptible at concentrations of ≤1 μg/ml and two appeared to be highly resistant (MICs = 8 and 16 μg/ml, respectively). This level of susceptibility to amphotericin B is comparable to that seen with *C. albicans* (95% S) (81). In contrast to broth microdilution testing, the Etest method has been shown to be both sensitive and specific for the detection of resistance to amphotericin B in isolates of *C. lusitaniae* and other species of *Candida* (80, 107). On the basis of these data, it appears that primary resistance to amphotericin B is uncommon among incident BSI isolates of *C. lusitaniae* (i.e., those from the first positive blood culture); however, if amphotericin B is used to treat infections due to this species, the patient should be monitored closely for the emergence of secondary resistance (77). *C. lusitaniae* may exhibit resistance to flucytosine (89.3% susceptible, 6% resistant) but is highly susceptible to both triazoles (96.1 to 100% susceptible) and caspofungin (100% susceptible).

C. dubliniensis. *C. dubliniensis* is a recently identified opportunistic yeast pathogen that is closely related to, but genetically

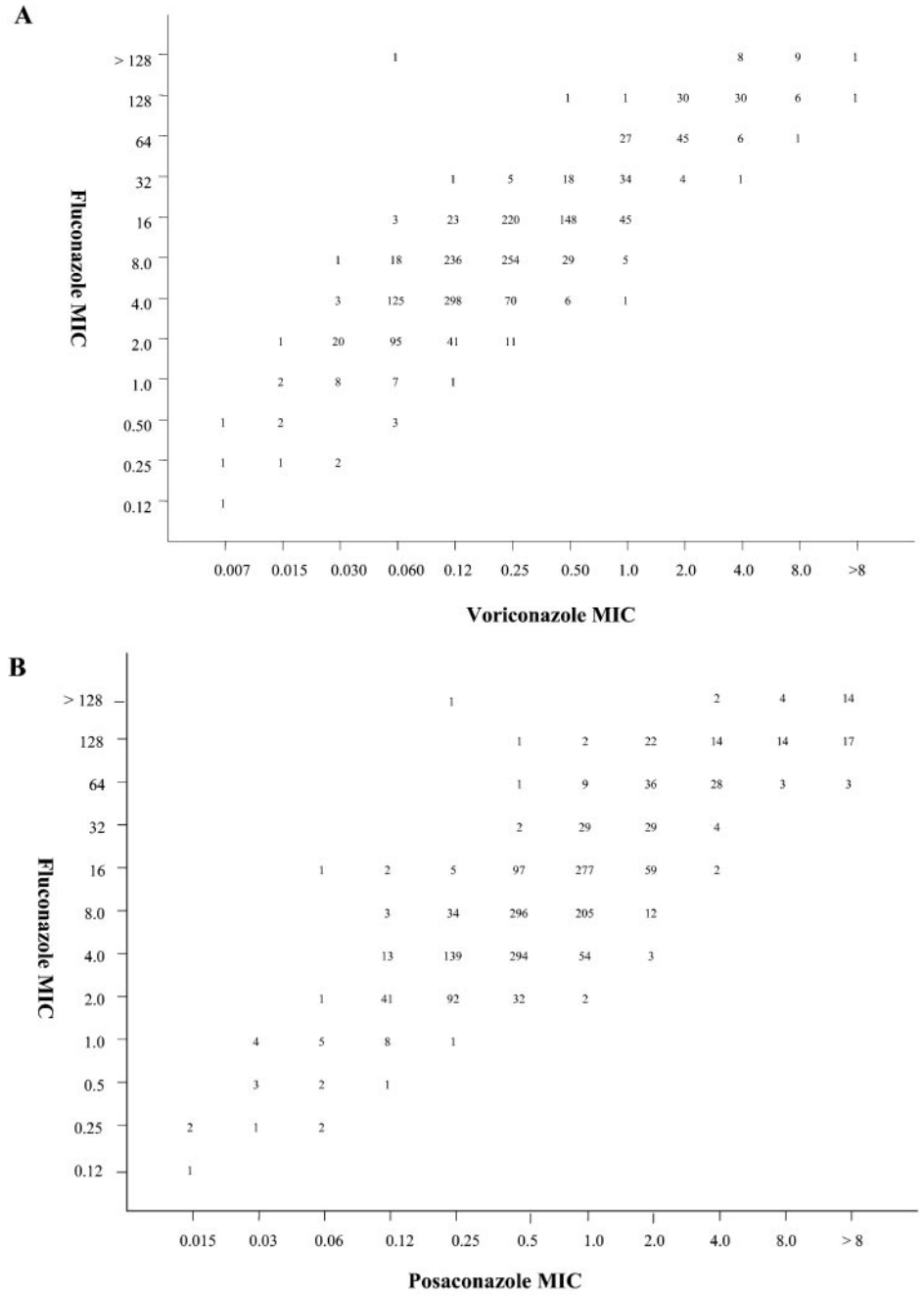

FIG. 1. Scattergram comparing fluconazole and voriconazole MICs ($R = 0.9$) (A) and fluconazole and posaconazole MICs ($R = 0.8$) (B) for *C. glabrata*. The strong correlations suggest considerable cross-resistance.

distinct from, *C. albicans* (12). This species is now recognized as a minor constituent of the normal human oral microbial flora and a cause of oral thrush in human immunodeficiency virus (HIV)-infected individuals (12). With the development of methods to detect and identify this species (29, 44), it has become evident that *C. dubliniensis* may also cause oral and vaginal candidiasis in HIV-negative persons (12). Although the incidence of BSIs due to *C. dubliniensis* is unknown, fungemia due to this species has been reported in North America, Europe, and Australia (7, 54, 59).

Although the majority of *C. dubliniensis* isolates are susceptible to azoles (83), fluconazole resistance has been observed in clinical isolates from AIDS patients with prior exposure to fluconazole (56, 66). In addition, stable fluconazole resistance is rapidly induced following exposure to the drug in vitro (65). Fluconazole-resistant strains of *C. dubliniensis* exhibit increased expression of multidrug transporter genes, especially *CdMDR*1 (66). These findings suggest that antifungal resistance may be a factor in the emergence of *C. dubliniensis* infections.

Despite concerns regarding the ability of *C. dubliniensis* to become resistant to fluconazole, most studies have found clin-

ical isolates to be quite susceptible to this agent (7, 54, 59, 83). Only 3 (2.9%) of 101 isolates tested in our laboratories were resistant to fluconazole, and 98% were highly susceptible to the extended-spectrum triazoles (Table 2). Likewise, 100% of the isolates tested were susceptible to amphotericin B, flucytosine, and caspofungin. Thus, it appears that there are several treatment options should resistance to fluconazole become an issue with *C. dubliniensis*.

***C. guilliermondii*.** Although *C. guilliermondii* is most often associated with onychomycosis, it has been shown to cause osteomyelitis and hematogenously disseminated candidiasis (19, 98). Dick et al. (19) reported on a case of disseminated candidiasis due to *C. guilliermondii* in which the patient died, despite amphotericin B therapy. The organism was subsequently shown by in vitro testing to be resistant to amphotericin B. Aside from this case report, resistance to amphotericin B has not been widely appreciated for this species. Among the 102 isolates of *C. guilliermondii* tested by Etest, only two (MICs = 2 and 32 μg/ml, respectively) appeared to be resistant to amphotericin B. Fluconazole resistance was implicated in a case of osteomyelitis of the finger caused by *C. guilliermondii* (98). The infection failed to respond, despite prolonged administration of fluconazole (400 mg/day), and partial amputation of the infected finger was ultimately required. The isolate of *C. guilliermondii* obtained from cultures of infected bone was resistant to both fluconazole and itraconazole. In support of these observations, *C. guilliermondii* does appear to be less susceptible to fluconazole than the more common BSI isolates of *Candida* (85.3% of *C. guilliermondii* isolates were susceptible [Table 2], whereas 97 to 99% of *C. albicans*, *C. tropicalis*, and *C. parapsilosis* isolates were susceptible) (24, 25, 88). Although the new triazoles appear to be quite active against this species (96.7 to 97.1% susceptibility to voriconazole, ravuconazole, and posaconazole at an MIC ≤1 μg/ml), one isolate was resistant to all three of these agents (MIC > 8 μg/ml) as well as to fluconazole. The MICs of caspofungin tend to be 2- to 16-fold higher for *C. guilliermondii* than for other *Candida* species (87); however, 96.7% of the isolates tested were susceptible at ≤1 μg/ml, and limited experience suggests that this species may respond clinically to treatment with caspofungin (64) (Table 2). All of the isolates tested were susceptible to flucytosine at the NCCLS breakpoint of ≤4 μg/ml (Table 2).

***C. rugosa*.** Decreased susceptibility to amphotericin B, nystatin, and fluconazole has been reported for *C. rugosa* (22, 24). Dube et al. (22) reported on 15 episodes of candidemia due to *C. rugosa* in burn patients receiving topical nystatin treatment. Although the source of the outbreak was not identified, the isolates were all shown to be resistant to nystatin. More recently, a cluster of six episodes of candidemia caused by *C. rugosa* was reported from Brazil (13). Two of the episodes represented breakthrough infections during treatment with amphotericin B, and all four patients receiving this agent died. Thus, resistance to polyenes and nosocomial spread have been reported for *C. rugosa* (13, 22). Amphotericin B is clearly less active in vitro against this species than against most other *Candida* species (Table 2). Similarly, decreased susceptibility to flucytosine (84.6% S) and fluconazole (78.9% S) was observed. This profile resembles that of *C. krusei*, in that resistance to the three established antifungal agents may be seen with *C. rugosa*. As with *C. krusei*, *C. rugosa* is highly susceptible to voriconazole, posaconazole, and ravuconazole as well as caspofungin (100% of the isolates were susceptible to concentrations ≤1 μg/ml).

OPPORTUNISTIC YEAST-LIKE FUNGI

In the same manner that *Candida* species have taken advantage of immunocompromising conditions, indwelling devices, and broad-spectrum antibiotic use, so have a number of non-*Candida* yeast-like fungi found an "opportunity" to colonize and infect immunocompromised patients (26). These organisms may occupy environmental niches or may be found in food and water and can be normal human microbial flora. The list of these opportunistic yeasts is long, but we will limit this discussion to three genera that pose particular problems with respect to antifungal resistance: *Trichosporon* spp., *Rhodotorula* spp., and *Geotrichum capitatum* (formerly *Blastoschizomyces capitatus*; teleomorph, *Dipodascus capitatus*).

***Trichosporon* spp.** The genus *Trichosporon* consists of six species at present: *Trichosporon asahii* and *T. mucoides* are known to cause deep invasive infections, *T. asteroides* and *T. cutaneum* cause superficial skin infections, *T. ovoides* causes white piedra of the scalp, and *T. inkin* causes white piedra of the pubic hair (26). Unfortunately, most of the literature on serious opportunistic trichosporonosis refers to the older nomenclature of *T. beigelii*.

Trichosporon causes catheter-associated fungemia in neutropenic patients but may gain entrance to the bloodstream via the respiratory or gastrointestinal tract as well (103, 104, 106). Widespread hematogenous dissemination may manifest as positive blood cultures and multiple cutaneous lesions. Chronic hepatic trichosporonosis mimics hepatic candidiasis and may be seen upon recovery from neutropenia (26).

Trichosporon has been reported to be the most common cause of noncandidal yeast infection in patients with hematological malignancies, and infection carries a mortality rate in excess of 80% (26, 103, 104, 106). Susceptibility to amphotericin B is variable, and this agent lacks fungicidal activity against *Trichosporon*. Clinical failures with amphotericin B, fluconazole, and combinations of the two have been reported; and the outcome is generally dismal in the absence of neutrophil recovery (26, 103, 104, 106). The multiresistant nature of *T. asahii* makes it a threat for nongranulocytopenic patients as well, as evidenced by a report of apparent nosocomial transmission of a strain resistant to amphotericin B, fluconazole, itraconazole, and flucytosine (112). Notably, the new triazoles appear to be more active than fluconazole against *Trichosporon* (75), and voriconazole has successfully been used to treat disseminated *T. asahii* infection in a patient with acute myeloid leukemia (27).

In vitro susceptibility studies of *Trichosporon* species by NCCLS methods are limited and generally include only a small number of isolates (Table 3). Arikan and Hascelik (2) reported elevated amphotericin B MICs and moderate susceptibility to fluconazole and itraconazole for 43 isolates of *T. asahii* (Table 3). Similar results for these agents were reported by Paphitou et al. (75), whereas good activity was seen with the extended-spectrum triazoles, especially posaconazole (MIC_{50}, 0.12 μg/ml) and voriconazole (MIC_{50}, 0.06 μg/ml). Paphitou et al. (75) found non-*T. asahii* isolates to be more susceptible than *T.*

TABLE 3. In vitro susceptibilities of opportunistic non-*Candida* yeast-like fungi to new and established antifungal agents determined by NCCLS M27-A2 broth dilution MIC methods[a]

Species	Antifungal agent	No. of isolates tested	MIC (μg/ml)			Reference
			Range	50%	90%	
T. asahii	Amphotericin B	43	1–8	4	4	2
	Fluconazole	43	0.25–16	2	8	2
	Itraconazole	43	0.06–4	0.5	1	2
	Ravuconazole	24	0.25–>16	0.5	NA[b]	75
	Posaconazole	24	0.06–>16	0.12	NA	75
	Voriconazole	24	0.03–>16	0.25	NA	75
Non-*T. asahii*	Amphotericin B	15	0.06–1	0.25	NA	75
	Fluconazole	15	0.5–4	2	NA	75
	Itraconazole	15	0.03–0.5	0.12	NA	75
	Ravuconazole	15	0.03–>16	0.5	NA	75
	Posaconazole	15	0.03–0.5	0.12	NA	75
	Voriconazole	15	0.03–0.25	0.06	NA	75
T. beigelii	Amphotericin B	5	0.5–2	2	ND[c]	25
	Fluconazole	5	1–2	2	ND	25
	Itraconazole	5	0.06–0.25	0.25	ND	25
	Posaconazole	5	0.12–1	1	ND	24
	Voriconazole	5	<0.03–0.12	<0.03	ND	25
	Caspofungin	5	16–>16	>16	ND	24
	Anidulafungin	5	>16	>16	ND	24
Rhodotorula spp.	Amphotericin B	35	0.12–0.5	0.25	0.5	28
	Flucytosine	35	0.06–0.25	0.12	0.25	28
	Fluconazole	35	32–256	256	256	28
	Itraconazole	35	0.25–1	1	1	28
	Posaconazole	54	0.25–>8	2	4	21
	Ravuconazole	56	0.015–2	0.25	1	21
	Voriconazole	55	0.25–>8	2	4	21
	Caspofungin	55	8–>8	>8	>8	21
	Micafungin	10	>64	>64	>64	113
Geotrichum capitatum	Amphotericin B	23	0.06–0.25	0.12	0.12	30
	Flucytosine	23	0.12–16	0.12	4	30
	Fluconazole	23	1–32	8	8	30
	Itraconazole	23	0.03–0.5	0.12	0.25	30
	Voriconazole	23	0.03–0.5	0.25	0.25	30
	Anidulafungin	4	1–4	4	ND	6

[a] Testing was performed as described in reference 67.
[b] NA, not available.
[c] ND, not done.

asahii isolates to amphotericin B, fluconazole, and itraconazole, whereas the new triazoles gave activity comparable to that seen against *T. asahii* (Table 3). Espinel-Ingroff (24, 25) reported results for *T. beigelii* that were similar to those reported by Arikan and Hascelik (2) and Paphitou et al. (75) for amphotericin B and the azoles and, in addition, showed the lack of activity of the echinocandins, caspofungin, and anidulafungin (Table 3). On the basis of the results of these in vitro studies, it appears that the azoles in general, and voriconazole and posaconazole in particular, have activities superior to that of amphotericin B. Similar to flucytosine, the echinocandins lack any useful activity against this organism. On the basis of the limited amount of data available at present, treatment of disseminated trichosporonosis in a persistently neutropenic patient should include an azole in conjunction with granulocyte-macrophage colony-stimulating factor (26).

***Rhodotorula* spp.** Species of *Rhodotorula* include *Rhodotorula glutinis*, *R. mucilaginosa*, *R. rubra*, and *R. minuta*. These yeast-like fungi are found as commensals in skin, nails, and mucous membranes as well as in cheese and milk products and environmental sources, including air, soil, shower curtains, bathtub grouts, and toothbrushes. *Rhodotorula* species are emerging as important human pathogens in immunocompromised patients and those with indwelling devices (8, 23, 40, 46). *Rhodotorula* has been implicated as a cause of central venous catheter infection and fungemia (40, 113), ocular infections (34), peritonitis (23), and meningitis (46).

There are very few studies in the literature dealing with the in vitro susceptibility of *Rhodotorula* to systemically active antifungal agents (21, 28, 113). When clinical isolates of *Rhodotorula* are tested by NCCLS methods (67), the isolates are the most susceptible to amphotericin B (MIC_{90} = 0.5 μg/ml, 100% of isolates S at ≤1 μg/ml) and flucytosine (MIC_{90} = 0.25 μg/ml, 100% S at ≤4 μg/ml) (Table 3). The MICs of fluconazole (MIC_{90} = 256 μg/ml), caspofungin (MIC_{90} > 8 μg/ml), and micafungin (MIC_{90} > 64 μg/ml) were all high, representing resistance to these agents. Both itraconazole and ravuconazole were moderately active (MIC_{90} = 1 μg/ml). The MICs of

posaconazole and voriconazole were fourfold higher than those of ravuconazole and itraconazole.

Amphotericin B has excellent activity against *Rhodotorula* and, coupled with catheter removal, is an optimal therapeutic approach to infections with this organism (8, 113). Flucytosine has excellent in vitro activity but should not be considered for monotherapy. Neither fluconazole nor the echinocandins should be used to treat infections due to *Rhodotorula* species, and the role of the extended-spectrum triazoles is uncertain pending additional clinical data. Of the extended-spectrum triazoles, ravuconazole is the most potent.

***G. capitatum*.** Among the emerging opportunistic yeast pathogens, *Geotrichum capitatum* (formerly *Blastoschizomyces capitatus*; teleomorph, *Dipodascus capitatus*) is a rarely described yeast-like fungus that produces severe systemic infection in immunocompromised patients, especially those with hematological malignancies (6, 9, 17, 57). It is widely distributed in nature and may be found as part of the normal skin flora. Infection with *G. capitatum* presents similarly to that with *Trichosporon* in neutropenic patients, with breakthrough infection (36% of episodes), frequent fungemia with multiorgan (including brain) dissemination, and a mortality rate of 60 to 80% (57). Blood cultures are usually positive. As with *Trichosporon*, a chronic disseminated form of *G. capitatum* infection, similar to chronic disseminated candidiasis, may be seen upon resolution of neutropenia.

Data on the antifungal susceptibilities of *G. capitatum* are quite limited; however, resistance to fluconazole and decreased susceptibility to amphotericin B have been described (6, 9, 30). In vitro susceptibilities determined by NCCLS methods (Table 3) indicate high levels of susceptibility to amphotericin B, itraconazole, and voriconazole. Most isolates were susceptible to flucytosine (MIC_{90} = 4 μg/ml) and fluconazole (MIC_{90} = 8 μg/ml), although isolates with decreased susceptibilities to both of these agents were observed. Anidulafungin showed only modest activity against the few strains tested.

The optimal approach to therapy is not yet defined. Some investigators believe that *G. capitatum* has decreased susceptibility to amphotericin B (102); however, the strains tested generally appear to be susceptible (Table 3), and recent clinical experience with patients with leukemia was favorable for treatment with amphotericin B (57). The excellent activity of voriconazole suggests that it may be a useful agent for the treatment of *G. capitatum* infections. Rapid removal of central venous catheters, adjuvant immunotherapy, and novel antifungal therapies (e.g., either voriconazole or high-dose fluconazole plus amphotericin B) are recommended for treatment of this rare but devastating infection (57).

FILAMENTOUS FUNGI: BEYOND *A. FUMIGATUS*

Invasive infections due to *Aspergillus* spp. and other hyaline and dematiaceous fungi have emerged as prominent causes of morbidity and mortality worldwide (18, 50, 53). Although *A. fumigatus* heads the list of these opportunistic molds (18, 20, 50), infections due to less common but antifungal-resistant species such as *A. terreus*, an expanding array of zygomycetes, and previously uncommon hyaline (e.g., *Fusarium*, *Acremonium*, *Scedosporium*, *Paecilomyces*, and *Trichoderma*) and dematiaceous (e.g., *Bipolaris*, *Cladophialophora*, and *Alternaria*) filamentous fungi are being reported with greater frequency (3, 26, 42, 106). Infections due to these opportunistic molds are usually marked by a poor response to antifungal therapy, resistance in vitro to most available antifungal agents (Fig. 2), and an overall poor outcome with excessive mortality (26, 47, 106).

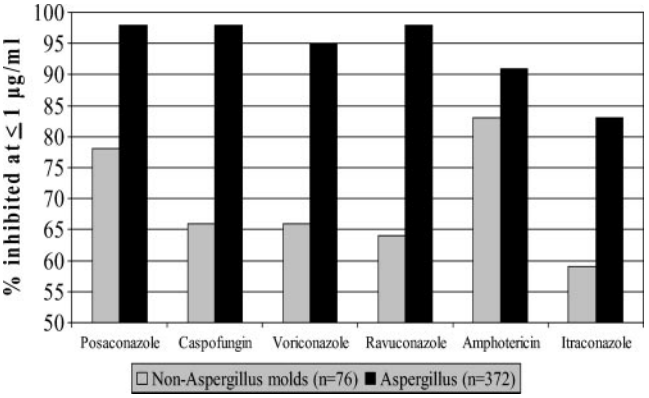

FIG. 2. Antifungal susceptibilities of *Aspergillus* spp. and non-*Aspergillus* molds to six systemically active antifungal agents, as determined by NCCLS M38-A broth dilution. Data are compiled from reference 20.

***A. terreus*.** The frequency of *Aspergillus terreus* as a cause of invasive aspergillosis varies from 3 to 12.5% (42, 78). Infections due to this species appear to be increasing in recent years and are of concern given its apparent resistance in vitro to amphotericin B and poor clinical response to treatment with this agent (3, 14, 42, 47, 96). Environmental studies have found *A. terreus* in showerheads, hospital water storage tanks, and potted plants (1, 48).

Invasive aspergillosis caused by *A. fumigatus* is rarely documented by positive blood cultures (45, 78). In fact, most bloodstream isolates of *Aspergillus* species have been shown to represent pseudofungemia or terminal events at autopsy (45). Importantly, among all species of *Aspergillus*, *A. terreus* has been shown to cause true aspergillemia (45, 78, 93, 105). Similar to other angioinvasive filamentous fungi (e.g., *Fusarium* spp., *Paecilomyces lilacinus*, *Scedosporium* spp., and *Acremonium* spp.), *A. terreus* is capable of adventitious sporulation in which yeast-like spores, or aleurioconidia, are formed in tissue and blood and are more likely to be detected in blood collected for culture (78, 105). Recognition of these aleurioconidia on microscopic examination of tissue, fine needle aspirates, or bronchoscopy specimens can allow a rapid presumptive identification of *A. terreus* (105).

In contrast to *A. fumigatus*, *A. terreus* is resistant in vitro and in vivo to the fungicidal effects of amphotericin B (Table 4) (14, 20, 47, 96, 105). Of note, the new triazoles and echinocandins all have excellent activities in vitro against *A. terreus* (Table 4). Although clinical experience is limited, both voriconazole and caspofungin have successfully been used to treat invasive aspergillosis due to this species.

Zygomycetes. Infections due to the zygomycetes are rare, occurring at an annual rate of 1.7 infections per million population in the United States (89). Unfortunately, when they do occur, infections due to these agents are generally acute and rapidly progressive, with mortality rates of 70 to 100% (31).

TABLE 4. In vitro susceptibilities of opportunistic filamentous fungi to new and established antifungal agents determined by NCCLS M38-A broth dilution MIC methods[a]

Species	Antifungal agent	No. of isolates tested	MIC (μg/ml)			Reference
			Range	50%	90%	
Aspergillus terreus	Amphotericin B	101	1–16	4	4	96
	Itraconazole	16	0.25–1	0.5	0.5	20
	Posaconazole	16	0.06–0.25	0.12	0.25	20
	Ravuconazole	16	0.03–0.5	0.25	0.5	20
	Voriconazole	101	0.06–16	0.25	0.25	96
	Caspofungin	16	0.015–0.12	0.03	0.06	20
	Anidulafungin	2	≤0.03	≤0.03	ND[b]	24
Rhizopus spp.	Amphotericin B	15	0.06–1	0.5	1	16
	Itraconazole	15	0.25–32	0.5	4	16
	Posaconazole	15	0.12–1	0.25	0.5	16
	Ravuconazole	5	0.5–>8	>8	ND	20
	Voriconazole	15	4–64	8	16	16
	Caspofungin	5	>8	>8	ND	20
Absidia spp.	Amphotericin B	10	0.06–0.12	0.12	0.12	16
	Itraconazole	10	0.03–0.25	0.06	0.25	16
	Posaconazole	10	0.06–0.25	0.06	0.12	16
	Ravuconazole	8	1–8	2	ND	62
	Voriconazole	10	2–16	16	16	16
Mucor spp.	Amphotericin B	7	0.5–1	1	ND	62
	Itraconazole	7	0.5–>16	>16	ND	62
	Posaconazole	6	0.5–2	1	ND	16
	Ravuconazole	7	1–>16	>16	ND	62
	Voriconazole	7	16–>16	>16	ND	62
	Caspofungin	3	>8	>8	ND	20
Fusarium spp.	Amphotericin B	11	1–2	1	2	20
	Itraconazole	11	2–>8	>8	>8	20
	Posaconazole	11	0.5–>8	>8	>8	20
	Ravuconazole	11	0.25–>8	8	>8	20
	Voriconazole	11	0.25–>8	4	>8	20
	Caspofungin	11	>8	>8	>8	20
	Anidulafungin	12	16–>16	(>16)[c]	NA[d]	24
Fusarium oxysporum	Amphotericin B	6	2	2	ND	25
	Itraconazole	6	1–>16	(8)[c]	ND	25
	Voriconazole	6	4	4	ND	25
Fusarium solani	Amphotericin B	6	1–2	(1.3)[c]	ND	25
	Itraconazole	6	1–>16	(8)[c]	ND	25
	Voriconazole	6	8–16	(10.5)[c]	ND	25
Scedosporium apiospermum	Amphotericin B	13	1–16	4	16	60
	Itraconazole	13	0.25–8	0.5	4	60
	Posaconazole	13	0.25–2	1	2	60
	Ravuconazole	3	0.25–4	2	ND	62
	Voriconazole	13	0.03–0.5	0.25	0.5	60
	Caspofungin	6	NA	(1.3)[c]	ND	24
	Anidulafungin	5	2–>16	(4)[e]	ND	72
Scedosporium prolificans	Amphotericin B	55	2–>16	>16	>16	60
	Itraconazole	55	>32	>32	>32	60
	Posaconazole	55	>8	>8	>8	60
	Ravuconazole	6	>16	>16	ND	62
	Voriconazole	55	1–8	4	4	60
	Anidulafungin	5	8–16	(8)[e]	ND	72
	Terbinafine	55	2–>32	16	32	60
Acremonium spp.	Amphotericin B	33	NA	1	4	32
	Itraconazole	33	>10	>10	>10	32
	Voriconazole	3	0.25–1	(1)	ND	72
	Anidulafungin	3	1–>16	(>16)[e]	ND	72

Continued on following page

TABLE 4—*Continued*

Species	Antifungal agent	No. of isolates tested	MIC (μg/ml)			Reference
			Range	50%	90%	
Paecilomyces spp.	Amphotericin B	6	0.06–>8	0.5	ND	20
	Itraconazole	6	0.06–2	0.25	ND	20
	Posaconazole	6	0.03–0.5	0.12	ND	20
	Ravuconazole	6	0.03–4	0.25	ND	20
	Voriconazole	6	0.03–2	0.25	ND	20
	Caspofungin	6	0.03–8	0.06	ND	20
	Anidulafungin	5	0.03–>16	(8)[e]	ND	72
Trichoderma spp.	Amphotericin B	NA	1–2	NA	NA	11
	Itraconazole	NA	≥4	NA	NA	11
	Voriconazole	NA	0.25–2	NA	NA	11
Bipolaris spp.	Amphotericin B	6	0.5–1	(0.6)[c]	ND	25
	Itraconazole	6	<0.03–0.12	(0.06)[c]	ND	25
	Posaconazole	6	0.06–0.25	(0.14)[c]	ND	24
	Voriconazole	6	0.12–1	(0.3)[c]	ND	25
	Caspofungin	6	1–2	(1.7)[c]	ND	24
	Anidulafungin	6	1–4	(2.7)[c]	ND	24
Exophiala spp.	Amphotericin B	5	2–16	(2)[e]	ND	72
	Voriconazole	5	0.5–2	(0.5)[e]	ND	72
	Anidulafungin	5	0.12–2	(1)[e]	NA	72
Phialophora spp.	Amphotericin B	5	2–4	(2)[e]	NA	72
	Voriconazole	5	0.12–1	(1)[e]	NA	72
	Anidulafungin	5	0.03–0.25	(0.12)[e]	NA	72
Wangiella spp.	Amphotericin B	5	4–≥16	(4)[e]	NA	72
	Voriconazole	5	0.5–2	(1)[e]	NA	72
	Anidulafungin	5	2–8	(2)[e]	NA	72

[a] Testing was performed as described in reference 68.
[b] ND, not done.
[c] Geometric mean MIC.
[d] NA, not available.
[e] Median MIC.

The most common etiologic agents of zygomycosis include members of the genera *Rhizopus*, *Mucor*, and *Absidia*. These organisms cause infections in immunocompromised individuals, especially those with diabetic ketoacidosis, neutropenia, and corticosteroid therapy (31). Zygomycetes have a marked predilection for blood vessels and produce multiple emboli with concomitant infarction and necrosis of surrounding tissues. The classic clinical presentation of zygomycosis is that of rhinocerebral and pulmonary involvement; however, cutaneous, gastrointestinal, and disseminated infections are well documented (31, 94, 99).

Amphotericin B is the first-line therapy of choice for zygomycosis, often supplemented by surgical debridement and immune reconstitution (31). Most of the zygomycetes appear to be quite susceptible to amphotericin B in vitro and are generally not susceptible to the triazoles or echinocandins (Table 4). Among the extended-spectrum triazoles, however, posaconazole stands apart from both voriconazole and ravuconazole in that it appears to be active against most of the zygomycetes (Table 4) (15, 16, 20, 95). Furthermore, posaconazole has documented efficacy in murine models of zygomycosis (15, 95) and for the treatment of infections in humans, although the experience has been limited (99). In contrast, voriconazole is inactive against these agents (Table 4), and breakthrough zygomycosis has recently been reported in BMT patients receiving voriconazole prophylaxis (58, 94). The latter experience serves to emphasize the fact that in very high risk patients, such as BMT recipients, the organism with the greatest intrinsic resistance to the antifungal agent used will ultimately emerge as a cause of infection (94). Broad usage of any antifungal agent in this population carries a risk of superinfection with an unusual, drug-resistant opportunistic fungus.

Other hyaline molds. The list of hyaline molds that have been shown to cause opportunistic infections is quite long, and it is well beyond the scope of this minireview to discuss them all (26, 106). The taxonomically diverse agents of hyalohyphomycosis do share several characteristics, in that many exhibit decreased susceptibilities to a number of antifungal agents, and when they are present in tissue, they appear as hyaline (nonpigmented), septate, branching filamentous fungi that may be indistinguishable from *Aspergillus* (106). Culture is necessary to identify these agents and may be critical in determining the most appropriate therapy.

Among the vast numbers of hyaline molds that may serve as opportunists, there are a handful that deserve special mention, given that they are relatively more common and/or that they exhibit antifungal resistance profiles that should be recognized. These organisms are *Fusarium* spp., *Acremonium* spp., *Scedosporium* spp., *Paecilomyces* spp., and *Trichoderma* spp. These organisms tend to cause infections in neutropenic patients that

are often disseminated in nature and that are almost uniformly fatal in the absence of immune reconstitution (106). Several of these organisms are capable of adventitious conidiation (generation of spores in tissue) with concomitant hematogenous dissemination, positive blood cultures, and multiple cutaneous lesions (26, 106).

The agents of hyalohyphomycosis as a whole tend to be considerably less susceptible than *Aspergillus* spp. to virtually all of the systemically active antifungal agents (Fig. 2) (20, 24, 25, 72). *Fusarium* spp. often appear to be resistant to amphotericin B in vitro (Table 4), and breakthrough infections occur frequently in patients treated with this agent (71, 106). Among the new triazoles, only modest activity is seen in vitro (Table 4); however, voriconazole has successfully been used in some patients with amphotericin B-refractory fusariosis (79). Primary therapy with either a lipid formulation of amphotericin B or voriconazole plus vigorous efforts at immune reconstitution is recommended at this time (71, 106).

Within the genus *Scedosporium*, *Scedosporium apiospermum* (teleomorph, *Pseudallescheria boydii*) and *S. prolificans* represent two important antifungal-resistant opportunistic pathogens. *S. apiospermum* is a well-known cause of mycetoma and may cause deep-seated infections (e.g., central nervous system [CNS] abscesses) and disseminated infection in BMT recipients and other neutropenic, immunosuppressed individuals (61, 70). This organism is generally considered resistant to amphotericin B, the MICs of which are elevated (Table 4) and to which the clinical response is very poor, despite the use of high doses (106). The extended-spectrum triazoles are active in vitro against *S. apiospermum*, and both posaconazole and voriconazole have successfully been used for the treatment of CNS abscesses (61, 70). In addition to antifungal therapy, restoration of immune competence is essential for survival in these often fatal infections (106).

S. prolificans causes bone and soft tissue infections in immunocompetent individuals and deeply invasive and disseminated infections in immunocompromised patients. *S. prolificans* is considered resistant to virtually all of the systemically active antifungal agents, including the extended-spectrum triazoles and the echinocandins (Table 4). Although terbinafine, an inhibitor of squalene epoxidase, does not appear to be active alone, synergy between triazoles and terbinafine against *S. prolificans* has been demonstrated in vitro (60), and a single patient with disseminated *S. prolificans* infection has successfully been treated with a combination of voriconazole and terbinafine, in addition to aggressive surgical debridement (39). Despite this apparent success, medical therapy for nonresectable or disseminated disease due to *S. prolificans* is virtually always ineffective (106). Surgical resection remains the only definitive therapy for infections caused by *S. prolificans* (106).

Invasive infections due to *Acremonuim* spp. are almost exclusively seen in patients with neutropenia, transplantation, or some other cause of immunodeficiency (32, 106) and present in a manner similar to that of *Fusarium* infections, with hematogenously disseminated skin lesions and positive blood cultures (32, 106). The optimal treatment for invasive infections due to *Acremonium* spp. has not been established. In vitro resistance to amphotericin B, itraconazole, and the echinocandins is seen, whereas the newer triazoles, such as voriconazole, appear to be active in vitro (Table 4). A recent report of successful treatment of a pulmonary infection due to *Acremonium strictum* with posaconazole suggests that the new triazoles may be useful in treatment of *Acremonium* infections (37).

Although they are uncommon, *Paecilomyces* spp. may cause invasive disease in organ and hematopoietic stem cell recipients, individuals with AIDS, and other immunocompromised patients (10, 49, 55, 73). The portal of entry is often breaks in the skin or intravascular catheters; and dissemination, possibly aided by adventitious conidiation in tissue, is common (51, 73). Susceptibility to amphotericin B is variable, with resistance seen in *P. lilacinus* (Table 4). The triazoles and caspofungin demonstrate good activities (Table 4), and voriconazole has successfully been used to treat both severe cutaneous infections (38) and disseminated disease (55). Given the poor responses of disseminated infections to high-dose amphotericin B therapy that have been reported, the use of voriconazole or lipid formulations of amphotericin B may prove more effective and less toxic (106).

Trichoderma spp. are excellent examples of fungi previously labeled as nonpathogenic that have emerged as important opportunistic pathogens in immunocompromised patients and in patients undergoing peritoneal dialysis (11). Fatal disseminated disease due to *Trichoderma longibrachiatum* occurs in patients with hematologic malignancies and following BMT or solid-organ transplantation (11). Most *Trichoderma* spp. show decreased susceptibilities to amphotericin B, itraconazole, fluconazole, and flucytosine (Table 4) (11). Voriconazole appears to be active against the few species tested (Table 4).

Dematiaceous molds. As with the agents of hyalohyphomycosis, the list of dematiaceous fungi is both long and taxonomically diverse. These organisms are characterized by the presence of a pale brown to dark melanin-like pigment in the cell wall. The dematiaceous fungi may cause a variety of cutaneous and subcutaneous infections in immunocompetent individuals and invasive or disseminated infections in both immunocompetent and immunocompromised patients (69, 90, 97).

Infections involving dematiaceous fungi are known as phaeohyphomycoses. The number of dematiaceous molds reported to be etiologic agents of phaeohyphomycosis continues to grow, and several of these organisms appear to be neurotropic (90, 106). Those fungi known to be neurotropic include *Cladophialophora bantiana*, *Bipolaris spicifera*, *Exophiala* spp., *Wangiella dermatitidis*, *Ramichloridium obovoideum*, and *Chaetomium atrobrunneum* (90). Brain abscess is the most common CNS presentation. *Bipolaris* spp. and *Exerohilum rostratum* infections may initially present as sinusitis, which then extends into the CNS (90, 106).

The optimal treatment for disseminated or CNS phaeohyphomycosis has not yet been established, although it most often includes early administration of amphotericin B and complete surgical excision (90, 106). Despite these efforts, phaeohyphomycosis does not respond well to therapy and relapses are common (69, 90).

The in vitro activities of the antifungal triazoles (itraconazole, voriconazole, and posaconazole) are superior to that of amphotericin B against many of the dematiaceous molds (Table 4). Posaconazole has successfully been used to treat disseminated infections due to *Exophiala spinifera* (69). In those patients with brain abscesses, complete excision of the lesion has been associated with improved survival (90). Long-term

triazole (posaconazole or voriconazole) therapy coupled with repeat surgical resection may prevent recurrences (106).

SUMMARY AND CONCLUSIONS

Given the ever increasing number of individuals at risk for fungal infections, it is imperative that physicians "think fungus" when evaluating a potentially infected patient. The list of documented fungal pathogens is extensive, and one can no longer ignore or dismiss fungi as contaminants or clinically insignificant when they are isolated from clinical material. It is also apparent that the prognosis and response to therapy may vary with the type of fungus causing the infection as well as with the immunological status of the host. The extended-spectrum triazoles and the echinocandins clearly expand the coverage available against opportunistic pathogens; however, several of the less common opportunists discussed herein are not susceptible to these newer agents. Thus, fungi with intrinsic resistance to even the very newest antifungal agents already exist in our environment and will surely emerge as opportunistic pathogens as these agents are used broadly in the high-risk patient groups. Both clinicians and microbiologists must become familiar with the various fungi, their epidemiologic and pathogenic features, and the optimal approaches to diagnosis and therapy.

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