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In Vitro Activity of Seven Systemically Active Antifungal Agents against a Large Global Collection of Rare *Candida* Species as Determined by CLSI Broth Microdilution Methods▽

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Five *Candida* species (*C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*) account for over 95% of invasive candidiasis cases. Some less common *Candida* species have emerged as causes of nosocomial candidiasis, but there is little information about their in vitro susceptibilities to antifungals. We determined the in vitro activities of fluconazole, voriconazole, posaconazole, amphotericin B, anidulafungin, caspofungin, and micafungin against invasive, unique patient isolates of *Candida* collected from 100 centers worldwide between January 2001 and December 2007. Antifungal susceptibility testing was performed by the CLSI M27–A3 method. CLSI breakpoints for susceptibility were used for fluconazole, voriconazole, anidulafungin, caspofungin, and micafungin, while a provisional susceptibility breakpoint of ≤1 μg/ml was used for amphotericin and posaconazole. Of 14,007 *Candida* isolates tested, 658 (4.7%) were among the less common species. Against all 658 isolates combined, the activity of each agent, expressed as the MIC_{50}/MIC_{90} ratio (and the percentage of susceptible isolates) was as follows: fluconazole, 1/4 (94.8%); voriconazole, 0.03/0.12 (98.6%); posaconazole, 0.12/0.5 (95.9%); amphotericin, 0.5/2 (88.3%); anidulafungin, 0.5/2 (97.4%); caspofungin, 0.12/0.5 (98.0%); and micafungin, 0.25/1 (99.2%). Among the isolates not susceptible to one or more of the echinocandins, most (68%) were *C. guilliermondii*. All isolates of the less common species within the *C. parapsilosis* complex (*C. orthopsilosis* and *C. metapsilosis*) were susceptible to voriconazole, posaconazole, anidulafungin, caspofungin, and micafungin. Over 95% of clinical isolates of the rare *Candida* species were susceptible to the available antifungals. However, activity did vary by drug-species combination, with some species (e.g., *C. rugosa* and *C. guilliermondii*) demonstrating reduced susceptibilities to commonly used agents such as fluconazole and echinocandins.

More than 95% of *Candida* bloodstream infections (BSI) are caused by five species: *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* (83). The in vitro activities of available antifungal agents against these five species have been documented extensively (21, 25, 64, 83, 91), whereas very little is known regarding the susceptibility profiles of the less frequently isolated *Candida* species (8, 40, 75–77, 94).

Among the *Candida* strains reported to cause BSI, more than 17 different species have been identified (31, 32, 84). Aside from the five most common species noted above, the remaining species include *C. lusitaniae*, *C. guilliermondii*, *C. kefyr*, *C. pelliculosa*, *C. famata*, *C. lipolytica*, and *C. rugosa* (Table 1) (31, 77, 84). Many of these species have been observed to occur in nosocomial clusters and/or to exhibit innate or acquired resistance to one or more established antifungal agents (6, 9, 23, 27, 36, 48, 49, 79, 80, 87, 88, 106). In addition, the use of molecular identification methods has resulted in the identification of new species within larger species complexes (e.g., *C. dubliniensis* within the *C. albicans* complex and *C. orthopsilosis* and *C. metapsilosis* within the *C. parapsilosis* complex) (43–46, 100). In vitro susceptibility data specific to those newly described species groups are also lacking.

These less common species may emerge as important opportunistic pathogens in the future, so it is important to describe the activities of both new and established antifungal agents as potential therapeutic options (63, 95). In this study, we report the in vitro activities, determined by the Clinical and Laboratory Standards Institute (CLSI) broth microdilution (BMD) reference method (15, 16), of amphotericin B, fluconazole, posaconazole, voriconazole, anidulafungin, caspofungin, and micafungin against 658 clinical isolates of the less common species of *Candida* isolated from hospitalized patients with invasive infections in North America, Latin America, Europe, and the Asia-Pacific region.

MATERIALS AND METHODS

Organisms. A total of 658 clinical isolates obtained from 100 medical centers worldwide between January 2001 and December 2007 were tested. The collection included the following numbers of isolates (Table 1): 171 isolates of *C. lusitaniae*, 175 isolates of *C. guilliermondii*, 102 isolates of *C. orthopsilosis*, 74 isolates of *C. kefyr*, 40 isolates of *C. pelliculosa*, 16 isolates of *C. famata*, 30 isolates of *C. metapsilosis*, 18 isolates of *C. dubliniensis*, 16 isolates of *C. lipolytica*, and 16 isolates of *C. rugosa*. The isolates were obtained from 658 different patients with invasive candidiasis, and all were incident isolates from blood samples or specimens from normally sterile sites. Isolates were identified using Vitek and API yeast identification systems (bioMérieux, Dunham, NC) supplemented by conventional methods as needed (32). The identification of *C. guilliermondii*, *C.*

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TABLE 1. Distribution of 14,007 isolates of *Candida* spp. from blood and other normally sterile sites, 2001 to 2007

Species	No. tested	% of total
C. albicans	7,412	52.9
C. glabrata	1,993	14.2
C. parapsilosis	1,895	13.5
C. tropicalis	1,614	11.5
C. krusei	435	3.1
C. guilliermondii	175	1.2
C. lusitaniae	171	1.2
C. orthopsilosis	102	0.7
C. kefyr	74	0.5
C. pelliculosa	40	0.3
C. metapsilosis	30	0.2
C. famata	16	0.1
C. dubliniensis	18	0.1
C. lipolytica	16	0.1
C. rugosa	16	0.1

orthopsilosis, *C. metapsilosis*, and *C. dubliniensis* was confirmed by molecular methods as described previously (43–45, 100). Isolates were stored as water suspensions until they were used. Prior to testing, isolates were plated onto potato dextrose agar (Remel, Lenexa, KS) and CHROMagar *Candida* medium (Becton Dickinson, Sparks, MD) to ensure purity and viability.

Antifungal susceptibility testing. Reference antifungal susceptibility testing of all isolates was performed by BMD exactly as described in CLSI document M27–A3 (15). Antifungal reference powders of posaconazole (Schering), voriconazole (Pfizer), fluconazole (Pfizer), anidulafungin (Pfizer), caspofungin (Merck), and micafungin (Astellas) were obtained from their respective manufacturers. BMD panels containing serial twofold dilutions of each antifungal agent (ranges, 0.007 to 128 μg/ml for fluconazole and 0.007 to 8 μg/ml for all other agents) in RPMI 1640 medium buffered to pH 7.0 with 0.165 M morpholinepropanesulfonic acid buffer, frozen in 96-well plates at −70°C for no more than 3 months, were thawed and inoculated with an organism suspension adjusted to attain a final inoculum concentration of $1.5 \times 10^3 \pm 1.0 \times 10^3$ cells/ml. The panels were incubated in air at 35°C and observed for the presence and absence of growth at 24 h (for echinocandins) and 48 h (for azoles). Both azole and echinocandin MICs were read as the lowest concentration that produced a prominent decrease in turbidity (ca. 50% reduction in growth) relative to that of the drug-free control (15). The susceptibilities of *Candida* isolates to amphotericin B were determined by using Etest (AB Biodisk, Solna, Sweden) and by using RPMI 1620 medium agar with 2% glucose (Remel) as described previously (73). Quality control was ensured by testing the CLSI-recommended strains *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 (16).

The interpretive criteria for susceptibility to fluconazole, voriconazole, and the echinocandins were those published by Pfaller et al. (81, 82, 86) and the CLSI (15, 16). Interpretive criteria for amphotericin B or posaconazole have not yet been defined. For purposes of comparison in this study, we have classified the isolates inhibited by ≤1 μg/ml of amphotericin B as susceptible and those inhibited by >1 μg/ml as resistant. Likewise, for posaconazole, we have elected to use the voriconazole breakpoints of ≤1 μg/ml (susceptible), 2 μg/ml (susceptible, dose dependent), and ≥ 4 μg/ml (resistant).

RESULTS AND DISCUSSION

Table 1 demonstrates the rank-order of *Candida* species among 14,007 isolates from blood samples and specimens from normally sterile sites submitted for testing between 2001 and 2007. The rare species of *Candida* comprised 4.7% of the total and included 10 different species.

Most of these uncommon species have been described previously as causing serious infections in individuals with severe underlying disease and often with vascular and/or peritoneal catheters (1, 6, 11, 12, 23, 24, 26–28, 30, 49, 79, 80, 87, 88, 92, 97, 98, 99, 106). Several species, such as *C. lusitaniae* (6, 28, 30, 65, 72), *C. guilliermondii* (24, 27, 36, 48, 49, 70, 79), *C. kefyr* (8, 88, 92), *C. famata* (106), *C. dubliniensis* (17, 74, 99), and *C. rugosa* (20, 26, 80, 98), have been reported to express resistance to one or more antifungal agents and have occurred in nosocomial clusters, either in association with the selective pressure of an antifungal agent or in relation to intravascular catheters and breaks in infection control procedures (31, 77). Thus, although rare, these species of *Candida* must be considered to be opportunistic pathogens that may pose resistance problems for the currently licensed antifungal agents.

C. lusitaniae (teleomorph, *Clavispora lusitaniae*) most often causes fungemia in patients with malignancies and other comorbid conditions (6, 30). *C. lusitaniae* is often mentioned in the literature as being capable of developing resistance to amphotericin B during the course of therapy, and infection may present as breakthrough fungemia in immunocompromised patients (10, 34, 50, 53, 55, 56, 60, 65, 66, 112). Although this species clearly can develop secondary resistance to amphotericin B (6, 28, 71), the frequency with which this resistance may be seen clinically is not known. Among the 171 BSI isolates of *C. lusitaniae* tested for amphotericin B resistance by Etest (Table 2), 98% were susceptible at concentrations of ≤1 μg/ml whereas two isolates appeared to be highly resistant (MICs, 8 and 16 μg/ml). Etest has been shown to be both sensitive and specific for detecting amphotericin B resistance among isolates of *C. lusitaniae* and other species of *Candida* (71, 72, 108). Thus, it appears that primary amphotericin B resistance is rare among incident BSI isolates of *C. lusitaniae*: however, caution is urged if amphotericin B is used to treat infections due to this species, as secondary resistance may emerge during treatment (66). Indeed, Atkinson et al. (6) found that compared to patients with *C. albicans* BSI, those with candidemia due to *C. lusitaniae* had an increased rate of treatment failure (38% versus 10%; $P = 0.0282$) when treated with an amphotericin B-based regimen and increased frequency of subsequent intensive care unit admission (54% versus 22%; $P = 0.04$). Furthermore, Atkinson et al. (6) showed that amphotericin B-resistant strains may be readily selected out from originally amphotericin B-susceptible strains in vitro and that amphotericin B is considerably less fungicidal toward *C. lusitaniae* than toward *C. albicans*. These findings indicate that *C. lusitaniae*, even strains originally susceptible to amphotericin B, may be less amenable to therapy with this agent. Fortunately, *C. lusitaniae* remains quite susceptible to both the triazoles and the echinocandins (Table 2).

C. guilliermondii and *C. rugosa* both appear to be increasing in frequency as causes of invasive candidiasis, especially in Latin America (19, 20, 68, 79, 80). Both species have been responsible for clusters of infections in hospital settings, and both demonstrate decreased susceptibilities to amphotericin B, fluconazole, and the echinocandins (Table 2) (19, 20, 24, 26, 27, 36, 48, 49, 70, 79, 80).

C. guilliermondii (teleomorph, *Pichia guilliermondii*) is known to be a normal component of the human skin and mucosal flora (51, 57) and is rarely associated with invasive infections such as endocarditis (104), pericarditis (105), osteomyelitis (103), and peritonitis and fungemia (27, 36, 48, 49, 68, 70, 79). Infection with this species is often catheter-related and has been found to be more common among patients with cancer than among the general hospital population (27, 48). Others have noted

TABLE 2. Antifungal susceptibilities of rare *Candida* bloodstream isolates

Species	No. of isolates	Antifungal agent	No. inhibited at MIC (μg/ml) of:														
			0.007	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16[b]	32	64[c]	≥128
C. lusitaniae	171	Amphotericin[a]				3	18	74	66	7	1	0	1	1			
	171	Fluconazole					20	52	64	20	5	3	1	1	3	2	
	171	Posaconazole	2	25	63	58	15	4	1	3							
	171	Voriconazole	123	33	3	4	2	3	2	1							
	96	Anidulafungin				5	13	36	40	2							
	166	Caspofungin		1	4	6	68	66	17	3	0	1					
	80	Micafungin	1	0	4	8	44	21	1	1							
C. guilliermondii	174	Amphotericin	1	0	1	8	63	62	24	6	2	1	1	0	0	5	
	175	Fluconazole						1	4	4	69	68	13	7	2	3	4
	175	Posaconazole		1	9	10	44	73	25	3	4	0	0	6			
	175	Voriconazole	2	11	19	83	43	8	1	0	2	0	0	6			
	107	Anidulafungin		1		2	6	5	7	37	41	8					
	156	Caspofungin			2	9	21	33	58	21	4	2	2	4			
	96	Micafungin		3	1	4	10	13	33	27	4	0	0	1			
C. orthopsilosis	102	Amphotericin						7	29	35	23	8					
	102	Fluconazole						6	28	45	9	8	4	1	0	1	
	102	Posaconazole		1	12	40	30	8	11								
	102	Voriconazole	1	24	40	24	1	10	1	1							
	52	Anidulafungin						3	12	28	9						
	91	Caspofungin	1	0	3	17	37	25	8								
	51	Micafungin					2	25	21	3							
C. kefyr	74	Amphotericin							20	43	10	0	0	0	0	1	
	74	Fluconazole					11	44	12	6	1						
	74	Posaconazole	1	3	17	21	23	8	1								
	74	Voriconazole	50	18	4	2											
	58	Anidulafungin		1	5	31	21										
	74	Caspofungin	11	56	6	1											
	53	Micafungin		4	22	26	1										
C. pelliculosa	40	Amphotericin					3	14	21	2							
	40	Fluconazole								2	7	24	7				
	40	Posaconazole				1	1	6	4	14	12	2					
	40	Voriconazole		1	1	1	21	13	3								
	14	Anidulafungin	2	9	2	1											
	37	Caspofungin	1	16	17	3											
	14	Micafungin		5	7	2											
C. famata	16	Amphotericin					1	6	8	0	0	1					
	16	Fluconazole								1	5	6	1	3			
	16	Posaconazole		2	0	0	1	5	7	1	2						
	16	Voriconazole			2	5	4	3	0	1	1						
	16	Anidulafungin				2	0	0	0	5	9						
	16	Caspofungin			1	2	2	5	3	2	1						
	16	Micafungin			1	1	0	2	5	5	2						
C. metapsilosis	30	Amphotericin					1	5	12	9	2	1					
	30	Fluconazole						1	0	19	9	1					
	30	Posaconazole		1	7	15	5	1	0	1							
	30	Voriconazole	1	4	22	2	1										
	11	Anidulafungin						5	3	2	1						
	24	Caspofungin			1	5	14	3	0	1							
	11	Micafungin						7	3	1							
C. dubliniensis	18	Amphotericin				1	8	7	1	1							
	18	Fluconazole					8	9	0	0	0	0	1				
	18	Posaconazole		4	6	7	1										
	18	Voriconazole	11	5	2												
	11	Anidulafungin			7	2	0	2									
	17	Caspofungin		2	6	9											
	9	Micafungin		4	3	2											
C. lipolytica	16	Amphotericin							1	5	5	4	1				
	16	Fluconazole							1	1	6	6	1	0	0	1	

Continued on following page

TABLE 2—*Continued*

Species	No. of isolates	Antifungal agent	No. inhibited at MIC (μg/ml) of:													
			0.007	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16[b]	32	64[c]	≥128
	16	Posaconazole					2	1	8	4	0	1					
	16	Voriconazole		1	5	7	2	0	0	1							
	10	Anidulafungin						3	4	2	1						
	15	Caspofungin					6	9									
	10	Micafungin						6	3	1							
C. rugosa	16	Amphotericin							4	3	7	1	0	0	0	1	
	16	Fluconazole							1	0	4	3	2	4	1	1	
	16	Posaconazole				6	2	5	3								
	16	Voriconazole	2	1	4	3	1	3	2								
	16	Anidulafungin				3	1	4	3	3	0	0	2				
	16	Caspofungin			1	1	0	1	2	8	0	1	0	2			
	16	Micafungin			1	3	3	5	2	0	0	0	0	2			

[a] Amphotericin B MICs were determined by Etest.
[b] For posaconazole, voriconazole, anidulafungin, caspofungin, and micafungin, isolates for which MICs are reported to be 16 μg/ml encompass all isolates for which MICs were >8 μg/ml.
[c] For amphotericin B, isolates for which the MIC is reported to be 64 μg/ml encompass all isolates for which MICs were >32 μg/ml.

catheter-related fungemia with *C. guilliermondii* among patients with prior cardiovascular or abdominal surgery (38, 49).

One of the initial descriptions of invasive candidiasis due to *C. guilliermondii* was that of a fatal case of disseminated infection in which the patient died despite amphotericin B therapy (24). The isolate was shown by in vitro testing to be resistant to amphotericin B. Subsequently, others have documented the failure of amphotericin B therapy in invasive or ocular infections with potential in vitro resistance (MICs, 1 to 4 μg/ml) or neutropenia (3, 14, 39). Among the 174 isolates tested against amphotericin B by Etest, 9 isolates (5.2%) appeared to be resistant to amphotericin B, with MICs for these isolates ranging from 2 μg/ml (2 isolates) to 64 μg/ml (5 isolates) (Table 2).

Although the majority of *C. guilliermondii* isolates are susceptible to fluconazole and the other azoles, the MIC_{50} and MIC_{90} of fluconazole for *C. guilliermondii* are considerably higher than those observed for *C. albicans* (4 and 8 μg/ml versus 0.25 and 0.5 μg/ml, respectively) (Table 2) (78). Both in vitro resistance and clinical resistance to fluconazole have been documented (39, 103).

The MICs of anidulafungin, caspofungin, and micafungin for *C. guilliermondii* have been observed to be 2- to 16-fold higher than those for other species of *Candida*, with the exception of *C. parapsilosis* (Table 2) (64, 79, 85). Although clinical experience in treating *C. guilliermondii* infections with echinocandins is limited, Kabbara et al. (36) recently reported a breakthrough *C. guilliermondii* BSI in a hematopoietic stem cell transplant recipient receiving caspofungin prophylaxis. The clinical importance of the reduced susceptibility of *C. guilliermondii* to the echinocandins may become evident when infections with this organism involve anatomical sites where adequate free-drug levels cannot be readily obtained (85, 86).

C. rugosa has been implicated in clusters of nosocomial fungemias in the United States and in Latin America (20, 26). Like *C. guilliermondii*, *C. rugosa* is reported to exhibit decreased susceptibilities to polyenes, azoles, and echinocandins and may cause catheter-related fungemia in seriously ill patients. The decreased susceptibilities to both amphotericin B and fluconazole are readily apparent from the data shown in Table 2. Although both voriconazole and posaconazole appear to be active against *C. rugosa*, previous work has shown that fewer than 30% of fluconazole-resistant strains of this species remain susceptible to these newer triazoles (84). All three of the echinocandins appear to be active against *C. rugosa*, although elevated MICs of anidulafungin, caspofungin, and micafungin of 4 to >8 μg/ml were seen (Table 2).

C. orthopsilosis (formerly *C. parapsilosis* group II) and *C. metapsilosis* (formerly *C. parapsilosis* group III) are newly recognized members of the *C. parapsilosis* complex (101). Lockhart et al. (44) recently demonstrated that among 1,929 BSI isolates presumed to be *C. parapsilosis*, 91.3% were *C. parapsilosis*, 6.1% were *C. orthopsilosis*, and 1.8% *C. metapsilosis*. Notably, the percentage of *C. parapsilosis* isolates that were confirmed to be *C. orthopsilosis* increased from 4.5% in the years 2001 to 2004 to 8.3% in the years 2005 and 2006 (44). *C. orthopsilosis* accounted for only 5% of *C. parapsilosis* complex isolates from North America, 59% of which were isolated from patients in the ≥60-year-old age group (versus only 38% of *C. parapsilosis* isolates). *C. orthopsilosis* isolates constituted much higher proportions of *C. parapsilosis* complex isolates in Latin America (12.7%) and the Asia-Pacific region (11%) than in either Europe (3.9%) or the United States (5.1%) (44). None of the *C. orthopsilosis* or *C. metapsilosis* isolates were resistant to fluconazole or the echinocandins; however, elevated MICs of amphotericin B of 2 to 4 μg/ml were observed for isolates of both of these species (31 of 102 *C. orthopsilosis* isolates and 3 of 30 *C. metapsilosis* isolates) (Table 2).

C. kefyr (formerly *C. pseudotropicalis*; teleomorph, *Kluyveromyces marxianus*) is a well-known component of dairy products (42, 90) and recently has been described as an emerging pathogen causing nosocomial BSI in patients with hematologic malignancies (88, 92). Sendid et al. (92) found that *C. kefyr* was isolated twice as often from patients in oncology-hematology wards as from those hospitalized in other wards. Likewise, 9 of 10 fungemias due to *C. kefyr* occurred in patients hospitalized in oncology-hematology wards (92). Although MICs of amphotericin B for *C. kefyr* may be high (MICs for 11 of 74 isolates tested were 2 to 64 μg/ml), *C. kefyr* appears to be quite sus-

ceptible to both the azoles and echinocandins (Table 2). Despite the fact that *C. kefyr* is found in certain foods (mainly dairy products), it is not known why it is isolated more frequently from patients with hematologic malignancies (92).

C. pelliculosa (formerly *Hansenula anomala*; teleomorph, *Pichia anomala*) is a yeast found in plants, fruits, soil, and other organic matter. Human infections are generally sporadic, but outbreaks have been reported (4, 7, 13, 37, 67, 69). *C. pelliculosa* has been recognized as an emerging opportunistic pathogen, mainly in immunocompromised patients and patients in neonatal intensive care units, resulting in serious nosocomial infections (4, 7, 13, 37, 67, 69). The most extensive outbreak of *C. pelliculosa* fungemia occurred over a period of 23 months and involved a total of 379 neonates and children in a pediatric service unit in India (13). Colonization was detected in 28% of neonates, and 20% of these neonates subsequently developed fungemia. Molecular epidemiologic studies suggested a common source. An additional seven outbreaks of *C. pelliculosa* (*P. anomala*) fungemia in either neonatal or pediatric intensive care units, affecting patients ranging in number from 2 to 24 (4, 7, 59, 67, 69, 102, 111), and two outbreaks involving adult patients (4 and 8 patients, respectively) (37, 54) have been reported in the literature. In several of these outbreaks, analyses of the epidemic curve and molecular epidemiologic markers suggested a common exogenous source for *C. pelliculosa* (*P. anomala*) fungemia. Crude mortality rates as high as 41% have been reported (13, 54, 67), underscoring the severely compromised nature of the infected patients.

Data on the antifungal susceptibility of *C. pelliculosa* (*P. anomala*) are scarce (2, 7, 22, 33, 67). Amphotericin B remains the drug of choice for *C. pelliculosa* infections due to its in vitro and in vivo activity (Table 2) (29, 47). Fluconazole exhibits modest activity (MIC_{90}, 8 μg/ml) (Table 2) and has been used successfully in treating *C. pelliculosa* fungemia (33); however, fluconazole-resistant *C. pelliculosa* has emerged in immunocompromised patients receiving fluconazole prophylaxis or therapy (2). Voriconazole, posaconazole, and the echinocandins exhibit good levels of activity (Table 2), although there is no clinical experience with these agents in treating *C. pelliculosa* infections.

C. famata (formerly *Torulopsis candida*; teleomorph, *Debaromyces hansenii*) has been implicated in fungemia, osteomyelitis, peritonitis, and ocular disease (11, 12, 87, 97, 106, 110). Infections have been treated successfully by the removal of infected catheters coupled with the administration of either amphotericin B or fluconazole (12, 97); however, Quindos et al. (87) describe a case of fatal peritonitis in a patient treated with fluconazole, and Wagner et al. (106) reported breakthrough fungemia in a patient receiving liposomal amphotericin B and caspofungin for suspected aspergillosis. In the latter instance, Wagner et al. (106) found elevated MICs of both amphotericin B (3 μg/ml) and fluconazole (32 μg/ml) but did not test caspofungin. Our data indicate modest activity of fluconazole (MIC_{90}, 16 μg/ml) against *C. famata* compared to that against other species of *Candida* and show an amphotericin MIC of 4 μg/ml for 1 of 16 isolates (Table 2). Similar to *C. parapsilosis* and *C. guilliermondii*, *C. famata* appears to be less susceptible to the echinocandins than other species of *Candida* (Table 2) (5, 85).

C. dubliniensis is phenotypically similar to *C. albicans*, and although originally associated strictly with oropharyngeal candidiasis, it is now recognized as an (uncommon) cause of BSI (17, 18, 52, 58). Although fluconazole resistance was previously reported to be common among isolates from oropharyngeal candidiasis (17, 18), subsequent studies have found most isolates to be susceptible to fluconazole and the newer azoles (52, 74). Among the 18 BSI isolates of *C. dubliniensis* described herein, all were susceptible to the azoles and echinocandins, as well as amphotericin B (Table 2).

C. lipolytica (teleomorph, *Yarrowia lipolytica*) is ubiquitous in the environment (41) and has also been shown to colonize mucosal surfaces in humans (107). Although rare, infections with this species in two patients with candidemia, three patients with traumatic ocular infections, one patient with chronic sinusitis, and children and adults with catheter-related fungemia have been documented (1, 9, 23, 61, 62, 107, 109). Patients described in the literature have been successfully treated with catheter removal and amphotericin B therapy (1, 23), although Belet et al. (9) described fungemia due to *C. lipolytica* that persisted in two infants despite catheter removal and amphotericin B treatment. Both infections resolved following the addition of caspofungin to amphotericin B. Shin et al. (93) reported an outbreak of fungemia due to *C. lipolytica* ($n = 5$ cases) in a pediatric ward.

The little antifungal susceptibility data that are available for *C. lipolytica* indicate that most strains are susceptible to amphotericin B and fluconazole (23, 93, 107). However, among the 16 BSI isolates of *C. lipolytica* included in the present study, 10 (62%) exhibited decreased susceptibility to amphotericin B, with MICs for these isolates ranging from 2 to 8 μg/ml (Table 2). Likewise, the MIC_{90}s of fluconazole and posaconazole were elevated, at 8 and 1 μg/ml, respectively. Voriconazole and the echinocandins were all active against this species (Table 2).

Among the 10 species of *Candida* discussed herein, most remain reliably susceptible to the azole and echinocandin antifungal agents. Elevated fluconazole MICs for *C. guilliermondii*, *C. famata*, *C. lipolytica*, and *C. rugosa* were confirmed. Likewise, elevated echinocandin MICs for both *C. guilliermondii* and *C. rugosa* were detected; however, 80 to 100% of all BSI isolates of these species were susceptible to the echinocandins at the CLSI breakpoint of ≤2 μg/ml (85, 86).

Although interpretive breakpoints for amphotericin B have not been established, isolates of *Candida* spp. for which MICs are >1 μg/ml are unusual and possibly resistant or, at the very least, may require high doses of amphotericin B (≥1 mg/kg of body weight/day) for optimal treatment (66, 89, 96). Given these considerations, it is now evident that *C. orthopsilosis*, *C. kefyr*, *C. famata*, *C. metapsilosis*, *C. lipolytica*, and *C. rugosa* must be considered to exhibit decreased susceptibilities to amphotericin B compared with *C. albicans*. Whereas *C. guilliermondii* and *C. lusitaniae* have been described to be amphotericin B-resistant *Candida* species (6, 24, 79), both of these species appear to be susceptible to amphotericin B upon initial isolation from blood (Table 2). Thus, resistance to amphotericin B may develop secondarily during treatment, and repeat amphotericin B susceptibility testing is recommended for patients with persistent infection with these (and other) species while on amphotericin B therapy (6, 50, 79).

Although rare, each of the *Candida* species discussed herein may pose difficult problems for individual patients, and thus,

reporting of the in vitro susceptibility profiles of the rare *Candida* species may be useful in guiding treatment decisions. By testing these rare isolates with a standardized method and reporting the MIC distribution profiles for each species (Table 2), we hope to make the data more useful and available for ready comparison with those generated by other studies using the CLSI method (35). The results of this study indicate that, compared to the more common species of *Candida* causing BSI, these rare *Candida* species may often exhibit decreased susceptibilities to several classes of antifungal agents They thus pose a potential threat for immunocompromised patients in the future.

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