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Triazole and Echinocandin MIC Distributions with Epidemiological Cutoff Values for Differentiation of Wild-Type Strains from Non-Wild-Type Strains of Six Uncommon Species of *Candida*▽

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When clinical susceptibility breakpoints (CBPs) are absent, establishing wild-type (WT) MIC distributions and epidemiological cutoff values (ECVs) provides a sensitive means for detecting emerging resistance. We determined species-specific ECVs for anidulafungin (ANF), caspofungin (CSF), micafungin (MCF), fluconazole (FLC), posaconazole (PSC), and voriconazole (VRC) for six rarer *Candida* species (819 strains) using isolates obtained from the ARTEMIS Program and the SENTRY Antimicrobial Surveillance Program, all tested by a reference broth microdilution method. The calculated ECVs, expressed in μg/ml (and the percentages of isolates that had MICs less than or equal to the ECVs), for ANF, CSF, MCF, FLC, PSC, and VRC, respectively, were 0.12 (95.2), 0.12 (97.8), 0.12 (100.0), 0.5 (95.7), 0.12 (98.6), and 0.03 (100.0) for *Candida dubliniensis*; 4 (100.0), 2 (96.0), 2 (99.1), 8 (95.0), 0.5 (97.5), and 0.25 (98.0) for *C. guilliermondii*; 0.25 (98.9), 0.03 (98.0), 0.12 (97.5), 1 (99.1), 0.25 (99.1), and 0.015 (100.0) for *C. kefyr*; 2 (100.0), 1 (99.6), 0.5 (96.6), 2 (96.1), 0.25 (98.6), and 0.03 (96.6) for *C. lusitaniae*; and 2 (100.0), 0.5 (100.0), 1 (100.0), 2 (98.0), 0.25 (97.1), and 0.06 (98.0) for *C. orthopsilosis*, but for *C. pelliculosa*, ECVs could be determined only for CSF (0.12 [94.4]), FLC (4 [98.2]), PSC (2 [98.2]), and VRC (0.25 [98.2]). In the absence of species-specific CBP values, these WT MIC distributions and ECVs will be useful for monitoring the emergence of reduced susceptibility to the triazole and echinocandin antifungals.

Presently, there are more than 200 species of *Candida*, 30 to 40 of which are known to cause human infections (6). The Clinical and Laboratory Standards Institute (CLSI) has recently established species-specific clinical breakpoints (CBPs) for broth microdilution (BMD) susceptibility testing of the five most common species (*Candida albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei*) and the currently available systemically active triazole (fluconazole and voriconazole) and echinocandin (anidulafungin, caspofungin, and micafungin) antifungal agents (12, 18, 19). These CBPs were established by considering the MIC distributions for each agent and species, as well as the most recent and comprehensive molecular, biochemical, pharmacodynamic, and clinical data as they relate to MIC values. In lieu of CBPs for posaconazole and these five species of *Candida*, the CLSI Subcommittee on Antifungal Testing has elected to establish epidemiological cutoff values (ECVs) to differentiate wild-type (WT) strains (those without mutational or acquired resistance mechanisms) from non-WT strains (those having mutational or acquired resistance mechanisms) as a means of tracking the emergence of reduced susceptibility to posaconazole among *Candida* spp. (13). ECVs may be used to identify isolates that are less likely to respond to contemporary therapy due to acquired resistance mechanisms when limited clinical data preclude the development of CBPs (7, 12–15).

Aside from the five most common *Candida* species noted above, which account for 95 to 97% of all episodes of invasive candidiasis (IC), the remaining species include (in rank order) *C. guilliermondii*, *C. lusitaniae*, *C. kefyr*, and *C. pelliculosa*, as well as the cryptic species *C. orthopsilosis* and *C. dubliniensis* (4, 6, 16, 17). Whereas the CBPs for triazole and echinocandin antifungal agents may be used to identify those isolates of *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei* that are likely to respond to treatment with a given antifungal agent administered under the approved dosing regimen (21), the low frequency of occurrence and the lack of clinical data preclude the establishment of a CBP for the less commonly cultured species. However, several of these rare 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, 16, 17). Thus, it is prudent to develop criteria, such as an ECV, to provide the means for tracking the emergence of reduced susceptibility to clinically available antifungal agents. For these reasons, we considered that the determination of 24-h WT MIC distributions (13, 14) and ECVs for the triazole (fluconazole, posaconazole, and voriconazole) and echinocandin (anidulafungin, caspofungin, and micafungin) antifungal agents would be useful in surveillance for emergence of reduced susceptibility to these agents among the less common species of *Candida*. This process would be considered a first step toward the development of species-specific CBPs (12, 18, 19). In the present study, we analyzed the extensive global databases from two independent antifungal surveys, the ARTEMIS Program (13, 14) and the SENTRY Antimicrobial Surveillance Program (11, 15), to establish ECVs for each species and antifungal agent.

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TABLE 1. WT MIC distributions of azole and echinocandin antifungal agents for six uncommon species of *Candida* obtained using CLSI BMD methods[a]

Species	Antifungal agent (no. tested)	No. of isolates with MIC (μg/ml) of:														ECV (%)[c]
		≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	
C. dubliniensis	Anidulafungin (63)		5	26	24	5[b]	3									0.12 (95.2)
	Caspofungin (45)		4	16	22	2[b]	1									0.12 (97.8)
	Micafungin (53)		11	17	19	6[b]										0.12 (100.0)
	Fluconazole (70)					20	24	23[b]		1	1			1		0.5 (95.7)
	Posaconazole (70)	1	7	28	25	8[b]		1								0.12 (98.6)
	Voriconazole (46)	43	2	1[b]												0.03 (100.0)
C. guilliermondii	Anidulafungin (126)				1	5	7	5	41	53	14[b]					4 (100.0)
	Caspofungin (176)			1	13	21	34	66	28	6[b]		3	4			2 (96.0)
	Micafungin (107)		1		5	9	18	36	34	3[b]			1			2 (99.1)
	Fluconazole (196)							8	32	88	52	6[b]	5	3	2	8 (95.0)
	Posaconazole (197)		3	16	24	78	53	18[b]	3	2						0.5 (97.5)
	Voriconazole (198)	2	23	71	74	15	9[b]	3		1						0.25 (98.0)
C. kefyr	Anidulafungin (89)		2	20	39	26	1[b]	1								0.25 (98.9)
	Caspofungin (101)	18	72	9[b]	1	1										0.03 (98.0)
	Micafungin (80)		5	34	36	3[b]	1	1								0.12 (97.5)
	Fluconazole (113)					16	61	27	8[b]	1						1 (99.1)
	Posaconazole (112)	1	5	26	40	30	9[b]	1								0.25 (99.1)
	Voriconazole (101)	84	17[b]													0.015 (100.0)
C. lusitaniae	Anidulafungin (206)		1		7	21	74	86	17	–[b]						2 (100.0)
	Caspofungin (276)		1	5	9	81	98	67	14[b]		1					1 (99.6)
	Micafungin (176)	2	1	4	9	76	67	10[b]	5	2						0.5 (96.6)
	Fluconazole (272)					47	81	99	34	9[b]				1	1	2 (99.3)
	Posaconazole (279)	3	39	76	112	29	16[b]	1	3							0.25 (98.6)
	Voriconazole (233)	185	33	7[b]	1		5	2								0.03 (96.6)
C. orthopsilosis	Anidulafungin (52)						3	12	28	9[b]						2 (100.0)
	Caspofungin (91)	1		3	17	37	25	8[b]								0.5 (100.0)
	Micafungin (51)					2	25	21	3[b]							1 (100.0)
	Fluconazole (102)					3	30	46	9	12[b]		1		1		2 (98.0)
	Posaconazole (102)		14	28	26	20	11[b]	3								0.25 (97.1)
	Voriconazole (102)	30	43	16	11[b]	1	1									0.06 (98.0)
C. pelliculosa	Anidulafungin (31)	5	18	5	1	2										
	Caspofungin (54)	1	23	19	5	3[b]	2	1								0.12 (94.4)
	Micafungin (27)		10	12	5											
	Fluconazole (57)							3	4	31	18[b]	1				4 (98.2)
	Posaconazole (57)				2	7	9	13	20	5[b]	1					2 (98.2)
	Voriconazole (57)	1	3	2	18	27	5[b]	1								0.25 (98.2)

[a] All MICs were determined after 24-h incubation (2,3).
[b] Proposed ECV.
[c] Percentage of isolates at less than or equal to the ECV (μg/ml).

MATERIALS AND METHODS

Organisms. A total of 819 clinical isolates obtained from more than 60 medical centers worldwide from 2001 through 2010 were tested (653 isolates from ARTEMIS and 166 from SENTRY). The collection included 70 isolates of *C. dubliniensis*, 198 isolates of *C. guilliermondii*, 112 isolates of *C. kefyr*, 280 isolates of *C. lusitaniae*, 102 isolates of *C. orthopsilosis*, and 57 isolates of *C. pelliculosa* (Table 1). All isolates were obtained from blood or other normally sterile sites and represented the incident isolates from individual infectious episodes. The isolates were collected at individual study sites and were sent to the University of Iowa (Iowa City, IA) (ARTEMIS isolates) and JMI Laboratories (North Liberty, IA) (SENTRY isolates) for identification and susceptibility testing as described previously (11, 13–15). The isolates were identified by standard methods (5) supplemented by molecular identification (8–10) as needed and stored as water suspensions until used in the study. Prior to being tested, each isolate was passaged at least twice onto potato dextrose agar (Remel, Lenexa, Kansas) and Chromagar *Candida* medium (Becton Dickinson and Company, Sparks, MD) to ensure purity and viability.

Antifungal agents. Reference powders of fluconazole, posaconazole, voriconazole, anidulafungin, caspofungin, and micafungin were obtained from their respective manufacturers. Stock solutions were prepared in water (caspofungin and micafungin) or dimethyl sulfoxide (fluconazole, posaconazole, voriconazole, and anidulafungin), and serial 2-fold dilutions were made in RPMI 1640 medium (Sigma, St. Louis, MO) buffered to pH 7.0 with 0.165 M MOPS (morpholinepropanesulfonic acid) buffer (Sigma).

Antifungal susceptibility testing. BMD testing was performed in accordance with the guidelines in CLSI document M27-A3 (2), using RPMI 1640 medium, an inoculum of 0.5×10^3 to 2.5×10^3 cells/ml, and incubation at 35°C. MIC values were determined visually, after 24 h of incubation, as the lowest concentration of drug that caused a significant diminution (≥50% inhibition) of growth relative to that of the growth control (2, 13, 14).

Quality control. Quality control (QC) was performed on each day of testing by using CLSI-recommended strains of *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 (2, 3). All QC values were within the ranges established by CLSI (3).

Definitions. The definitions of WT organisms and ECVs were those outlined previously (7, 12–14, 20). A WT organism is defined as a strain that does not harbor any acquired resistance to the particular antimicrobial agent being examined. The typical MIC distribution for WT organisms covers three to five

TABLE 2. Current breakpoints and proposed ECVs for 11 *Candida* spp.[a]

Organism	Breakpoint (μg/ml)[b]				ECV (μg/ml)[c]	
	Susceptible	S-DD	Intermediate	Resistant	WT	Non-WT
C. albicans						
Caspofungin	≤0.25		0.5	≥1	≤0.12	>0.12
Anidulafungin	≤0.25		0.5	≥1	≤0.12	>0.12
Micafungin	≤0.25		0.5	≥1	≤0.03	>0.03
Fluconazole	≤2.0	4.0		≥8	≤0.5	>0.5
Voriconazole	≤0.12		0.25–0.5	≥1	≤0.03	>0.03
Posaconazole					≤0.06	>0.06
C. parapsilosis						
Caspofungin	≤2		4	≥8	≤1	>1
Anidulafungin	≤2		4	≥8	≤4	>4
Micafungin	≤2		4	≥8	≤4	>4
Fluconazole	≤2	4.0		≥8	≤2	>2
Voriconazole	≤0.12		0.25–0.5	≥1	≤0.12	>0.12
Posaconazole					≤0.25	>0.25
C. tropicalis						
Caspofungin	≤0.25		0.5	≥1	≤0.12	>0.12
Anidulafungin	≤0.25		0.5	≥1	≤0.12	>0.12
Micafungin	≤0.25		0.5	≥1	≤0.12	>0.12
Fluconazole	≤2.0	4.0		≥8	≤2	>2
Voriconazole	≤0.12		0.25–0.5	≥1	≤0.06	>0.06
Posaconazole					≤0.12	>0.12
C. glabrata						
Caspofungin	≤0.12		0.25	≥0.5	≤0.12	>0.12
Anidulafungin	≤0.12		0.25	≥0.5	≤0.25	>0.25
Micafungin	≤0.06		0.12	≥0.25	≤0.03	>0.03
Fluconazole		≤32		≥64	≤32	>32
Voriconazole					≤0.5	>0.5
Posaconazole					≤2	>2
C. krusei						
Caspofungin	≤0.25		0.5	≥1	≤0.25	>0.25
Anidulafungin	≤0.25		0.5	≥1	≤0.12	>0.12
Micafungin	≤0.25		0.5	≥1	≤0.12	>0.12
Fluconazole					≤64	>64
Voriconazole	≤0.5		1	≥2	≤0.5	>0.5
Posaconazole					≤0.5	>0.5
C. dubliniensis						
Caspofungin					≤0.12	>0.12
Anidulafungin					≤0.12	>0.12
Micafungin					≤0.12	>0.12
Fluconazole					≤0.5	>0.5
Voriconazole					≤0.03	>0.03
Posaconazole					≤0.12	>0.12
C. guilliermondii						
Caspofungin	≤2		4	≥8	≤2	>2
Anidulafungin	≤2		4	≥8	≤4	>4
Micafungin	≤2		4	≥8	≤2	>2
Fluconazole					≤8	>8
Voriconazole					≤0.25	>0.25
Posaconazole					≤0.5	>0.5
C. kefyr						
Caspofungin					≤0.03	>0.03
Anidulafungin					≤0.25	>0.25
Micafungin					≤0.12	>0.12
Fluconazole					≤1	>1
Voriconazole					≤0.015	>0.015
Posaconazole					≤0.25	>0.25
C. lusitaniae						
Caspofungin					≤1	>1
Anidulafungin					≤2	>2
Micafungin					≤0.5	>0.5
Fluconazole					≤2	>2
Voriconazole					≤0.03	>0.03
Posaconazole					≤0.25	>0.25

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TABLE 2—*Continued*

Organism	Breakpoint (μg/ml)[b]				ECV (μg/ml)[c]	
	Susceptible	S-DD	Intermediate	Resistant	WT	Non-WT
C. orthopsilosis						
Caspofungin					≤0.05	>0.5
Anidulafungin					≤2	>2
Micafungin					≤1	>1
Fluconazole					≤2	>2
Voriconazole					≤0.06	>0.06
Posaconazole					≤0.25	>0.25
C. pelliculosa						
Caspofungin					≤0.12	>0.12
Fluconazole					≤4	>4
Voriconazole					≤0.25	>0.25
Posaconazole					≤2	>2

[a] Reportable reading conditions, 50% diminution at 24 h.
[b] The breakpoints used were according to references 12, 18, and 19. S-DD, susceptible-dose dependent.
[c] The ECVs are those documented in references 12-14 and the present study.

doubling dilutions surrounding the modal MIC (1, 7, 20). Inclusion of WT strains in the present study was ensured by testing only the incident isolate for each infectious episode.

The ECVs for fluconazole, posaconazole, voriconazole, anidulafungin, caspofungin, and micafungin and the six species of *Candida* were obtained, as described previously (12–14), by considering the WT MIC distribution, the modal MIC for each distribution, and the inherent variability of the test (usually within one doubling dilution). In general, the ECV should encompass at least 95% of the isolates in the WT distribution (12–14, 20). Organisms with acquired or mutational resistance mechanisms may be included among those for which the MIC results are higher than the ECV (1, 7, 18).

RESULTS AND DISCUSSION

The WT MIC distributions for anidulafungin, caspofungin, micafungin, fluconazole, posaconazole, and voriconazole and each of the six rarer species of *Candida* are shown in Table 1. These distributions show the overall favorable susceptibilities of these less common species to both triazole and echinocandin classes of antifungal agents. As noted previously, *C. guilliermondii*, *C. lusitaniae*, and *C. orthopsilosis* were less susceptible to fluconazole and the echinocandins than the other three species (9, 10, 12, 16–18).

The modal MIC values at 24 h of incubation for anidulafungin, caspofungin, micafungin, fluconazole, posaconazole, and voriconazole, respectively, were as follows (Table 1): for *C. dubliniensis*, 0.03, 0.06, 0.06, 0.25, 0.03, and 0.008 μg/ml; for *C. guilliermondii*, 2, 0.5, 0.5, 2, 0.12, and 0.06 μg/ml; for *C. kefyr*, 0.06, 0.015, 0.06, 0.25, 0.06, and 0.008 μg/ml; for *C. lusitaniae*, 0.5, 0.25, 0.12, 0.5, 0.06, and 0.008 μg/ml; for *C. orthopsilosis*, 1, 0.12, 0.25, 0.5, 0.03, and 0.015 μg/ml; and for *C. pelliculosa*, 0.015, 0.015, 0.03, 2, 1, and 0.12 μg/ml. The MIC distributions in this study were determined in two different laboratories by standardized BMD methods (2, 3) and thus may be less broad, with lower modal MIC values, than distributions generated by multiple (3 or more) laboratories. This is recognized as a potential limitation of the study. These concerns are mitigated by the fact that the data were generated over a 10-year period and employed multiple lots of BMD trays and antifungal agents, as well as numerous readers of the MIC endpoints.

The 24-h endpoint ECVs and percentages of isolates for which the MIC was below the ECV were determined for each organism and drug combination with 40 or more results (12–14) and were as follows for anidulafungin, caspofungin, micafungin, fluconazole, posaconazole, and voriconazole, respectively (Table 1): 0.12 μg/ml (95.2% of results less than or equal to the ECV), 0.12 μg/ml (97.8%), 0.12 μg/ml (100.0%), 0.5 μg/ml (95.7%), 0.12 μg/ml (98.6%), and 0.03 μg/ml (100.0%) for *C. dubliniensis*; 4 μg/ml (100.0%), 2 μg/ml (96.0%), 2 μg/ml (99.1%), 8 μg/ml (95.0%), 0.5 μg/ml (97.5%), and 0.25 μg/ml (98.0%) for *C. guilliermondii*; 0.25 μg/ml (98.9%), 0.03 μg/ml (98.0%), 0.12 μg/ml (97.5%), 1 μg/ml (99.1%), 0.25 μg/ml (99.1%), and 0.015 μg/ml (100.0%) for *C. kefyr*; 2 μg/ml (100.0%), 1 μg/ml (99.6%), 0.5 μg/ml (96.6%), 2 μg/ml (96.1%), 0.25 μg/ml (98.6%), and 0.03 μg/ml (96.6%) for *C. lusitaniae*; and 2 μg/ml (100.0%), 0.5 μg/ml (100.0%), 1 μg/ml (100.0%), 2 μg/ml (98.0%), 0.25 μg/ml (97.1%), and 0.06 μg/ml (98.0%) for *C. orthopsilosis*. For *C. pelliculosa*, ECVs could be determined only for caspofungin (0.12 μg/ml [94.4%]), fluconazole (4 μg/ml [98.2%]), posaconazole (2 μg/ml [98.2%]), and voriconazole (0.25 μg/ml [98.2%]). The ECVs proposed demonstrated that ≥94.4% of the strains were within the susceptible WT population of MIC results (Table 1; lowest for caspofungin and C. *pelliculosa*).

CBPs are used to indicate those isolates that are likely to respond to treatment with a given antifungal agent, whereas the ECV can be used as the most sensitive measure for screening strains for the emergence of decreased susceptibility (non-WT) to a given agent. The proposed ECVs for the six *Candida* species in this study compare favorably to those of other common species for which CBP values have been assigned (Table 2). Previous publications have demonstrated that the ECV applied to triazoles and echinocandins and the five common species accurately separate WT strains from those non-WT strains with acquired or mutational resistance mechanisms, as well as encompass the vast majority of clinically treatable isolates (12, 18, 19).

Given the similar ECV results for each antifungal agent calculated for both common and uncommon species of *Candida*, it is tempting to assign the same CBPs to the rarer species (e.g., *C. guilliermondii* in Table 2). This possibility must be considered by international standard organizations but will require considerably more clinical outcome data. Furthermore, investigations of resistance mechanisms prevalent among the

less common yeast species will be needed. Until such critical data become available, the ECVs determined for *C. dubliniensis*, *C. guilliermondii*, *C. kefyr*, *C. lusitaniae*, *C. orthopsilosis*, and *C. pelliculosa* will be important to detect the emergence of strains having decreased susceptibility to triazoles and echinocandins as these agents are more widely employed in the prevention and treatment of IC.

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