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In Vitro Susceptibilities of *Candida* spp. to Caspofungin: Four Years of Global Surveillance

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Caspofungin is being used increasingly as therapy for invasive candidiasis. Prospective sentinel surveillance for emergence of in vitro resistance to caspofungin among invasive *Candida* spp. isolates is indicated. We determined the in vitro activity of caspofungin against 8,197 invasive (bloodstream or sterile-site) unique patient isolates of *Candida* collected from 91 medical centers worldwide from 1 January 2001 to 31 December 2004. We performed antifungal susceptibility testing according to the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) M27-A2 method and used a 24-h prominent inhibition endpoint for determination of the MIC. Of 8,197 invasive *Candida* spp. isolates, species distribution was as follows: 54% *Candida albicans*, 14% *C. glabrata*, 14% *C. parapsilosis*, 11% *C. tropicalis*, 3% *C. krusei*, and 4% other *Candida* spp. Overall, caspofungin was very active against *Candida* (MIC_{50}/MIC_{90}, 0.03/0.25 μg/ml; 98.2% were inhibited at a MIC of ≤0.5 μg/ml and 99.7% were inhibited at a MIC of ≤1 μg/ml). Results by species (expressed as MIC_{50}/MIC_{90} and the percentage inhibited at ≤1 μg/ml) were as follows: *C. albicans*, 0.03/0.06, 99.9; *C. glabrata*, 0.03/0.06, 99.9; *C. parapsilosis*, 0.5/0.5, 99.0; *C. tropicalis*, 0.03/0.06, 99.7; *C. krusei*, 0.12/0.5, 99.0; and *C. guilliermondii*, 0.5/1, 94.4. Of the 25 isolates with caspofungin MICs of >1 μg/ml, 12 isolates were *C. parapsilosis*, 6 isolates were *C. guilliermondii*, 2 isolates were *C. rugosa*, and 1 isolate each was *C. albicans*, *C. glabrata*, *C. krusei*, *C. lusitaniae*, and *C. tropicalis*. There was no significant change in caspofungin activity over the 4-year study period. Likewise, there was no difference in activity by geographic region. Caspofungin has excellent in vitro activity against invasive clinical isolates of *Candida* from centers worldwide. Our prospective sentinel surveillance reveals no evidence of emerging caspofungin resistance among invasive clinical isolates of *Candida*.

Caspofungin is the first of three new echinocandin antifungal agents to become available for the treatment of invasive mycoses (3, 7, 11, 17, 19, 21, 22, 26, 28). Like other echinocandins, caspofungin acts via inhibition of 1,3-β-D-glucan synthase, an enzyme necessary for the formation of the essential cell wall component of *Candida* and other important fungal pathogens (3). First introduced in 2001, caspofungin is now approved for the treatment of candidemia and other forms of invasive candidiasis, treatment of invasive aspergillosis in patients refractory to or intolerant of other licensed antifungal agents, and empirical antifungal therapy of febrile neutropenia (1, 13, 14, 27). The potent, broad-spectrum fungicidal activity of caspofungin against *Candida* spp. has led to extensive use of this agent for the treatment of all forms of serious candidal infections over the past 4 years (9, 12, 17, 25). Thus far, clinical experience with caspofungin and invasive candidiasis has been good (9, 14, 17). However, recent reports describing the emergence of caspofungin resistance during treatment of esophagitis (6) and endocarditis (15) raise concerns about the potential emergence of caspofungin-resistant *Candida* species. Specific mutations in the *FKS1* genes (which encode essential components of the glucan synthase complex) have been found to confer resistance to echinocandins among *Candida* spp. (10, 20). Ongoing surveillance of the activity of caspofungin and other echinocandins will be important as these agents are used more broadly worldwide.

The optimization of in vitro susceptibility testing of caspofungin against *Candida* spp. has been a difficult process (2). A recent multicenter (17-laboratory) study by Odds and colleagues (18) indicated that the optimal method for testing caspofungin against *Candida* spp. included the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) broth microdilution method with RPMI 1640 broth, incubation for no longer than 24 h, and an MIC endpoint criterion of prominent reduction in growth (MIC-2, defined as ≥50% inhibition relative to control growth) (16, 18). These testing conditions not only provided excellent reproducibility of results within and between laboratories but were also sufficient to differentiate isolates with "normal" or "wild-type" susceptibilities from glucan synthesis mutant strains with decreased susceptibilities to caspofungin. These results were further validated by a subsequent study using a large (3,322-isolate) international collection of *Candida* spp. (23). The latter isolate collection represented bloodstream infection isolates of *Candida* spp. collected from >100 medical centers prior to the introduction of caspofungin (1992 to 2000); thus, the MIC distribution profile may be considered to represent the "wild-type" distribution for caspofungin and *Candida* (8).

In the present study, we have employed the optimal testing conditions, as described by Odds et al. (18) and Pfaller et al. (23), to examine the temporal and geographic trends in the

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TABLE 1. Caspofungin MIC distribution for 8,197 isolates of *Candida* spp. collected from 91 institutions between 2001 and 2004[a,b]

Species	No. of isolates tested	Cumulative % at MIC (μg/ml)											
		0.007	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
C. albicans	4,454	22	45	80	98	99	99	99	99	99	100		
C. glabrata	1,120	1	6	64	96	99	99	99	99	99	100		
C. tropicalis	911	12	37	79	96	99	99	99	99	99	99	99	100
C. kefyr	38	18	87	97	100								
C. pelliculosa	25	4	56	92	100								
C. parapsilosis	1,158	1	1	1	4	13	49	90	99	99	100		
C. krusei	238			1	39	65	88	98	99	100			
C. guilliermondii	107			1	5	19	39	82	94	96	96	96	100
C. lusitaniae	105		2	4	8	48	84	98	99	99	100		
Candida spp.[c]	41		2	17	37	51	78	88	95	98	100		
All species	8,197	13	30	62	80	84	91	98	99	99	99	99	100

[a] All isolates tested in RPMI 1640 broth with 24-h incubation and a prominent reduction endpoint criteria (MIC-2).
[b] All isolates were from blood or normally sterile site infections.
[c] Includes *C. famata* (12 isolates), *C. rugosa* (8 isolates), *C. dubliniensis* (10 isolates), *C. lipolytica* (7 isolates), and *C. zeylanoides* (4 isolates).

susceptibility of *Candida* spp. to caspofungin since the clinical availability of the drug. An international collection of 8,197 isolates of *Candida* spp. obtained from 91 medical centers between 2001 and 2004 was tested in a central laboratory, and the MIC results were compared to the previously defined "wild-type" MIC distribution.

MATERIALS AND METHODS

Organisms. A total of 8,197 clinical isolates obtained internationally from 91 medical centers from 2001 through 2004 were tested. The collection included 4,454 strains of *C. albicans*, 1,120 strains of *C. glabrata*, 1,158 strains of *C. parapsilosis*, 911 strains of *C. tropicalis*, 238 strains of *C. krusei*, 107 strains of *C. guilliermondii*, 105 strains of *C. lusitaniae*, 38 strains of *C. kefyr*, 25 strains of *C. pelliculosa*, 12 strains of *C. famata*, 8 strains of *C. rugosa*, 10 strains of *C. dubliniensis*, 7 strains of *C. lipolytica*, and 4 strains of *C. zeylanoides*. All isolates were obtained from blood or other normally sterile sites, and each represented an individual infectious episode. The isolates were collected at the individual study sites and were sent to the University of Iowa (Iowa City) for identification and susceptibility testing as described previously (24). The isolates were identified by standard methods (5) and stored as water suspensions until used in the study. Prior to testing, each isolate was passaged at least twice onto potato dextrose agar (Remel) and CHROMagar Candida (Hardy Diagnostics, Santa Maria, Calif.) to ensure purity and viability.

Antifungal agents. Reference powder of caspofungin was obtained from Merck. Stock solutions were prepared in water, and serial twofold dilutions were prepared exactly as outlined in CLSI document M27-A2 (16). Final dilutions were made in RPMI 1640 medium (Sigma, St. Louis, Mo.) buffered to pH 7.0 with 0.165 M morpholenepropanesulfonic acid (MOPS) buffer (Sigma).

Antifungal susceptibility testing. Broth microdilution testing was performed in accordance with the guidelines in CLSI document M27-A2 (16) using RPMI 1640 medium, an inoculum of 0.5×10^3 to 2.5×10^3 cells per ml, and incubation at 35°C. MICs were determined visually after 24-h incubation as the lowest concentration of drug that caused a significant diminution (MIC-2 or ≥50%) of growth below growth control levels (18, 23).

Quality control. Quality control was performed by testing the CLSI-recommended strains *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 (16).

RESULTS AND DISCUSSION

Table 1 summarizes the in vitro susceptibilities of 8,197 isolates of *Candida* spp. to caspofungin when tested in RPMI 1640 medium with a 24-h incubation and the prominent reduction endpoint criteria. The isolates represent blood and normally sterile site infections occurring at 91 different institutions between 2001 and 2004. In contrast to the data published previously (23), these isolates were obtained during a time period when caspofungin was being actively used for investigational and clinically approved indications.

The MIC distributions generated for 8,197 clinical isolates of *Candida* spp. (Table 1) provide a robust data set for both common and uncommon species of *Candida* and reveal two important findings. First, isolates for which caspofungin MICs exceeded 1 μg/ml rarely occurred in clinical situations. Only 25 (12 *C. parapsilosis*, 6 *C. guilliermondii*, 2 *C. rugosa*, and 1 each of *C. albicans*, *C. glabrata*, *C. krusei*, *C. lusitaniae*, and *C. tropicalis*) out of 8,197 (0.3%) clinical isolates exhibited decreased susceptibilities to caspofungin with MICs of ≥2 μg/ml. Second, as was seen previously (23), the MIC distributions identified two broad groups among the nine different species tested. The most susceptible species (MIC_{90}, 0.03 to 0.06 μg/ml) were *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. kefyr*, and *C. pelliculosa*, whereas *C. parapsilosis* (MIC_{90}, 0.5 μg/ml), *C. guilliermondii* (MIC_{90}, 1 μg/ml), *C. krusei* (MIC_{90}, 0.5 μg/ml), and *C. lusitaniae* (MIC_{90}, 0.5 μg/ml) were all significantly less susceptible to caspofungin. These data are essentially identical to those reported previously for a smaller collection of isolates (23) and suggest that there may be a biological difference in the susceptibility of these two groups of *Candida* to caspofungin. This difference is likely due to differences in the sensitivity of the glucan synthesis enzyme complex of each species to inhibition by caspofungin (4, 10). Limited data suggest that the species within these two groups both respond to caspofungin treatment (9, 14), and MICs for >99% of isolates in both groups were ≤1 μg/ml. In contrast, MICs for strains of *Candida* with documented *FKS*1 gene mutations (18, 23) and for those published resistant strains (6, 15) were all >2 μg/ml and were usually >8 μg/ml.

The caspofungin susceptibility of isolates stratified by geographic region and by species is shown in Table 2. Among the 91 medical centers contributing isolates, 16 were located in the Asia-Pacific region, 32 were in Europe, 15 were in Latin America, and 28 were in North America. In each of the geographic regions, *C. albicans* accounted for approximately 50% of the isolates submitted for testing; however, the percentage of isolates of non-*C. albicans* species varied considerably from region to region. Whereas *C. glabrata* was the most common non-*C. albicans* species in North America, it was surpassed by

TABLE 2. Caspofungin susceptibility by geographic region, 2001–2004[a]

Species	Region[b]	No. of isolates tested	Cumulative % at MIC (μg/ml)											
			0.007	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
C. albicans	Asia-Pac.	750	24	43	74	98	99	100						
	Europe	1,510	20	44	80	99	99	99	99	100				
	L. Am.	787	19	49	83	98	99	100						
	N. Am.	1,407	25	46	83	98	99	99	99	99	99	100		
C. glabrata	Asia-Pac.	140		3	69	96	99	100						
	Europe	256	1	9	72	98	99	99	100					
	L. Am.	102		6	66	97	100							
	N. Am.	622		5	60	94	98	99	99	99	99	100		
C. tropicalis	Asia-Pac.	183	9	30	74	96	99	100						
	Europe	224	11	41	79	95	97	99	100					
	L. Am.	306	14	42	82	98	99	100						
	N. Am.	198	10	33	80	96	98	99	99	99	99	99	99	100
C. parapsilosis	Asia-Pac.	209			1	4	12	43	87	99	99	100		
	Europe	304		1	1	5	14	46	94	99	100			
	L. Am.	249			1	4	15	55	94	99	99	100		
	N. Am.	396	1	1	1	3	11	50	87	98	99	100		
C. krusei	Asia-Pac.	29				38	69	90	97	100				
	Europe	116			2	45	66	91	98	100				
	L. Am.	26				35	77	92	100					
	N. Am.	67			2	31	58	82	99	99	100			
C. guilliermondii	Asia-Pac.	9			11	11	22	44	78	89	89	89	89	100
	Europe	31				3	12	36	68	90	97	97	97	100
	L. Am.	56				4	14	39	88	96	96	96	96	100
	N. Am.	11				9	27	46	100					
All species	Asia-Pac.	1,344	14	29	59	80	84	90	98	99	99	99	99	100
	Europe	2,515	13	32	64	82	86	92	99	99	99	99	99	100
	L. Am.	1,565	12	34	63	77	81	90	98	99	99	99	99	100
	N. Am.	2,773	14	27	62	80	84	91	98	99	99	99	99	100

[a] All isolates tested in RPMI 1640 broth with 24-h incubation and a prominent reduction endpoint criteria (MIC-2).
[b] Geographic region: Asia-Pac., Asia-Pacific region (16 study sites); Europe (32 study sites); L. Am., Latin America (15 study sites); N. Am., North America (28 study sites).

C. parapsilosis and/or *C. tropicalis* in the other three regions. Interestingly, *C. guilliermondii*, a distinctly uncommon species of *Candida* throughout most of the world (0.4 to 1.5% of *Candida* isolates), was almost as common as *C. glabrata* (4.0% versus 6.5%, respectively) in Latin America. Despite these differences in species distribution, isolates of *Candida* from throughout the world were all comparably susceptible to caspofungin.

The caspofungin susceptibility profile of all 8,197 isolates of *Candida* spp. submitted for testing between 2001 and 2004 was unchanged over the 4-year study period, with >99% of isolates tested in each year inhibited by ≤1 μg/ml (Table 3). This MIC distribution was virtually identical to the "wild-type" MIC distribution reported previously (23) for isolates collected in years prior to the introduction of caspofungin (1992 to 2000) (Table 3). Thus, despite the recent case reports of caspofungin resistance developing during treatment of complicated candidal infections (6, 15), there was no evidence for a shift in the caspofungin MIC distribution profile towards higher MICs over the most recent 4-year period.

In summary, we have documented a stable MIC distribution profile for caspofungin over time and across four broad geographic regions. We provide further evidence for significant differences in the susceptibility of various species of *Candida* to

TABLE 3. Comparison of the in vitro susceptibility of *Candida* isolates collected before (1992–2000) and after (2001–2004) the clinical introduction of caspofungin[a,b]

Yr	No. of isolates tested	Cumulative % at MIC (μg/ml)											
		0.007	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
1992–2000[c]	3,322[d]	23	38	68	84	88	93	98	99	99	99	99	100
2001	1,783	16	35	68	83	88	95	99	99	99	100		
2002	2,239	28	42	68	81	85	91	98	99	99	99	99	100
2003	2,287	7	28	60	78	81	89	98	99	99	99	99	100
2004	1,888	1	14	54	78	82	89	98	99	99	99	99	100
2001–2004	8,197	13	30	62	80	84	91	98	99	99	99		100

[a] All isolates tested in RPMI 1640 broth with 24-h incubation and a prominent reduction endpoint criteria (MIC-2).
[b] All isolates were from blood or from normally sterile site infections.
[c] Data were compiled from reference 23.
[d] Eight of 11 isolates for which MICs were ≥2 μg/ml are glucan synthesis mutants.

caspofungin but have shown that well over 99% of significant clinical isolates remain susceptible to concentrations of 1 μg/ml or less. Importantly, the caspofungin MIC distribution remains unchanged when comparing that obtained for isolates collected before and after the introduction of caspofungin into clinical use. The accumulated database of 11,519 isolates and their respective caspofungin MIC results, all determined by a single optimized test method, can serve as a robust benchmark for other studies of this agent.

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