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Geographic and Temporal Trends in Isolation and Antifungal Susceptibility of *Candida parapsilosis*: a Global Assessment from the ARTEMIS DISK Antifungal Surveillance Program, 2001 to 2005▽

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We examined data from the ARTEMIS DISK Antifungal Surveillance Program to describe geographic and temporal trends in the isolation of *Candida parapsilosis* from clinical specimens and the in vitro susceptibilities of 9,371 isolates to fluconazole and voriconazole. We also report the in vitro susceptibility of bloodstream infection (BSI) isolates of *C. parapsilosis* to the echinocandins, anidulafungin, caspofungin, and micafungin. *C. parapsilosis* represented 6.6% of the 141,383 isolates of *Candida* collected from 2001 to 2005 and was most common among isolates from North America (14.3%) and Latin America (9.9%). High levels of susceptibility to both fluconazole (90.8 to 95.8%) and voriconazole (95.3 to 98.1%) were observed in all geographic regions with the exception of the Africa and Middle East region (79.3 and 85.8% susceptible to fluconazole and voriconazole, respectively). *C. parapsilosis* was most often isolated from blood and skin and/or soft tissue specimens and from patients hospitalized in the medical, surgical, intensive care unit (ICU) and dermatology services. Notably, isolates from the surgical ICU were the least susceptible to fluconazole (86.3%). There was no evidence of increasing azole resistance over time among *C. parapsilosis* isolates tested from 2001 to 2005. Of BSI isolates tested against the three echinocandins, 92, 99, and 100% were inhibited by concentrations of ≤2 μg/ml of anidulafungin (621 isolates tested), caspofungin (1,447 isolates tested), and micafungin (539 isolates tested), respectively. *C. parapsilosis* is a ubiquitous pathogen that remains susceptible to the azoles and echinocandins; however, both the frequency of isolation and the resistance of *C. parapsilosis* to fluconazole and voriconazole may vary by geographic region and clinical service.

Candida parapsilosis is the most common non-*albicans* species of *Candida* isolated from blood cultures in most regions of the world outside of the United States (2, 3, 8, 12, 24, 37, 44, 45, 50). *C. parapsilosis* is an exogenous pathogen that may be found on skin rather than mucosal surfaces (3, 5, 10, 18, 36, 56, 58). *C. parapsilosis* is known for the ability to form biofilms on catheters and other implanted devices (6, 10, 13, 17, 18, 20, 53), for nosocomial spread by hand carriage, and for persistence in the hospital environment (3, 8, 10, 14, 18, 20, 35, 48, 50, 51, 58). It is also well known for causing infections in infants and neonates (10, 15, 18, 21, 22, 45, 49, 51, 52, 59).

The frequency of invasive candidiasis due to *C. parapsilosis* has increased in recent years (44, 45), most notably in Spain (3) and in Latin America (8, 11, 20, 24, 37, 50). Fortunately, bloodstream infection (BSI) due to this species is associated with a significantly lower mortality rate than are infections due to other common species of *Candida* (1, 2, 16, 29, 31, 48).

Although *C. parapsilosis* is not considered prone to developing antifungal resistance (2, 8, 12, 14, 16, 29, 37, 44, 45, 48, 54, 55), several recent reports suggest that decreased susceptibility of *C. parapsilosis* to azoles and echinocandins may be cause for concern (3, 5, 8–10, 25, 26, 29, 46, 51, 54, 55, 57). As early as 1994, Nguyen et al. (29) noted that *C. parapsilosis* was the most common non-*albicans* species of *Candida* recovered in fluconazole-breakthrough fungemia in a prospective multicenter observational study of candidemia. Two recent outbreaks of *C. parapsilosis* BSI, one in an adult intensive care unit (ICU) (10) and one in a neonatal ICU (NICU) (51), serve to emphasize the importance of the confluence of patient, organism, and environmental or behavioral factors in perpetuating the spread of this exogenous pathogen. In both instances, extensive use of fluconazole, suboptimal hand hygiene and catheter care, and a seriously ill patient population conspired to generate an epidemic strain of *C. parapsilosis* with decreased susceptibility to fluconazole that was transmitted throughout the respective ICU environments. It was postulated that the decreased susceptibility of the epidemic strains to fluconazole provided a selective advantage, allowing *C. parapsilosis* colonization of skin and catheter surfaces with subsequent transmission facilitated by poor handwashing practices (10, 51).

The fact that *C. parapsilosis* is intrinsically less susceptible to the echinocandin class of antifungal agents relative to that of *C. albicans* or *C. glabrata* is well known (30, 38–41, 45, 47) and

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is supported by the documentation of *Fks*1 polymorphisms that are characteristic of the species and confer reduced susceptibility to all three echinocandins (anidulafungin, caspofungin, and micafungin) (33, 34). Furthermore, caspofungin has been shown to exhibit markedly delayed killing kinetics against *C. parapsilosis* compared to *C. albicans* (4). Although in their phase III clinical trials both caspofungin (25) and micafungin (19) were found to be as effective against *C. parapsilosis* as amphotericin B deoxychocolate and liposomal amphotericin B, respectively, it is notable that in the subgroup of patients with *C. parapsilosis* infection, 5 of 20 patients had persistently positive cultures at the end of caspofungin therapy compared to none in the amphotericin B group. Likewise, Reboli et al. reported that anidulafungin had a lower rate than fluconazole (69% versus 88%, respectively) at mediating microbiological eradication of *C. parapsilosis* invasive infection (46).

Perhaps the most alarming evidence regarding the emergence of echinocandin resistance in *C. parapsilosis* is that reported by Moudgal et al. (26) and Vazquez et al. (57) from Detroit, MI. In a case report of *C. parapsilosis* prosthetic valve endocarditis, Moudgal et al. (26) described the emergence of resistance to fluconazole, voriconazole, caspofungin, and micafungin (but not anidulafungin) after initial therapy with fluconazole and caspofungin. Subsequently, Vazquez et al. (57) documented an increase in the recovery of multi-echinocandin, multi-azole-resistant *C. parapsilosis* from patients in the burn unit of their hospital. The development, and subsequent nosocomial expansion, of echinocandin- and azole-resistant *C. parapsilosis* has important clinical implications. Continued monitoring for the emergence of this multidrug-resistant phenotype of *C. parapsilosis* is clearly warranted.

Despite the importance of *C. parapsilosis* as a nosocomial fungal pathogen, few studies have addressed the global epidemiology and antifungal susceptibility profile of *C. parapsilosis* (3, 58). Most of the available information regarding *C. parapsilosis* comes from single institutions (5, 10, 24, 26, 48, 50, 51) or represents a limited geographical region (3, 8, 29) and does not address frequency of isolation or resistance over time and among various clinical services or specimen types. Given the potential for decreased susceptibility of *C. parapsilosis* to azoles and echinocandins, it seems prudent to gather additional information regarding this opportunistic fungal pathogen. In the present study, we use the extensive database provided by the ARTEMIS DISK Antifungal Surveillance Program (44) to describe geographical and temporal trends in the isolation of *C. parapsilosis* from clinical specimens collected in 124 medical centers worldwide between 2001 and 2005, the types of specimens and clinical services in which *C. parapsilosis* infections are recognized, and the in vitro susceptibilities of 9,371 clinical isolates, including 2,834 BSI isolates of this species, to fluconazole and voriconazole, as determined by standardized disk diffusion testing. The in vitro susceptibility of BSI isolates to caspofungin, anidulafungin, and micafungin was also determined by using Clinical and Laboratory Standards Institute (CLSI) broth microdilution (BMD) methods.

MATERIALS AND METHODS

Organisms and test sites. A total of 141,383 isolates of *Candida* spp., including 9,371 isolates of *C. parapsilosis*, from 124 different medical centers in various regions—Asia-Pacific (23 sites), Latin America (16 sites), Europe (64 sites), Africa and the Middle East (11 sites), and North America (10 sites)—were collected and tested against fluconazole and voriconazole between January 2001 and December 2005. All *Candida* spp. considered pathogens from all body sites (e.g., blood, normally sterile body fluids [NSBF], deep tissue biopsy, genital tract, urine, respiratory tract, skin, and soft tissue) and isolates from all in-hospital and outpatient locations during the study period from 2001 thru 2005 were tested. Of the 2,834 BSI isolates of *C. parapsilosis* collected, 1,447 were sent to the University of Iowa (Iowa City) for testing against caspofungin; 621 of these isolates were also tested against anidulafungin, and 539 were tested against micafungin based on the availability of the antifungal agents from their respective manufacturers.

Data for *C. parapsilosis* were stratified by year of isolation, geographic region, clinical service (hospital location), and specimen type. *Candida* spp. considered by the local site investigator to be colonizers, i.e., not associated with pathology, were excluded, as were duplicate isolates (the same species and the same susceptible-resistant biotype profile within any 7-day period). Identification of isolates was performed in accordance with each site's routine methods (44).

Susceptibility test methods. Disk diffusion testing of fluconazole and voriconazole was performed as described previously (44) and in accordance with CLSI document M44-A (28). Agar plates (90, 100, or 150 mm in diameter) containing Mueller-Hinton agar (obtained locally at all sites) supplemented with 2% glucose and 0.5 μg of methylene blue per ml at a depth of 4.0 mm were used. The agar surface was inoculated by using a swab dipped in a cell suspension adjusted to the turbidity of a 0.5 McFarland standard. Fluconazole (25 μg) and voriconazole (1 μg) disks (Becton Dickinson, Sparks, MD) were placed onto the surfaces of the inoculated plates, and the plates were incubated in air at 35 to 37°C and read at 18 to 24 h. Zone diameter endpoints were read at 80% growth inhibition by using a BIOMIC image analysis plate reader system (Giles Scientific, Santa Barbara, CA) (44).

The MICs of anidulafungin, caspofungin, and micafungin were determined by BMD as described previously (39–41). All isolates were tested in RPMI broth with 24 h of incubation and a prominent reduction in growth (≥50%) relative to control (MIC-2) endpoint criteria.

The interpretive criteria for fluconazole and voriconazole disk diffusion tests were those of the CLSI (28, 42, 43) and are as follows: susceptible (S), zone diameters of ≥19 mm (fluconazole) and ≥17 mm (voriconazole); susceptible dose dependent (SDD), zone diameters of 15 to 18 mm (fluconazole) and 14 to 16 mm (voriconazole); and resistant (R), zone diameters of ≤14 mm (fluconazole) and ≤13 mm (voriconazole). The corresponding MIC breakpoints (27, 42, 43) are as follows: S, MICs of ≤8 μg/ml (fluconazole) and ≤1 μg/ml (voriconazole); SDD, MICs of 16 to 32 μg/ml (fluconazole) and 2 μg/ml (voriconazole); and R, MICs of ≥64 μg/ml (fluconazole) and ≥4 μg/ml (voriconazole).

The interpretive criteria for all three echinocandins were those recently assigned by the CLSI (June 2007): S, ≤2 μg/ml; a category of R has not been established for the echinocandins due to the paucity of "resistant" isolates treated with an echinocandin. Isolates for which the echinocandin MIC is >2 μg/ml are designated "nonsusceptible" (NS).

QC. Quality control (QC) was performed in accordance with CLSI documents M44-A (fluconazole and voriconazole) and M27-A2 (all other agents) by using *C. albicans* ATCC 90029, *C. parapsilosis* ATCC 22019, and *C. krusei* ATCC 6258 (27, 28). More than 99% of the QC results were within the acceptable limits (44).

Analysis of results. All disk zone diameters were read by electronic image analysis and interpreted and recorded with the BIOMIC plate reader system (Giles). Test results were sent by e-mail to Giles Scientific for analysis. The zone diameter, susceptibility category (S, SDD, or R), and QC results were all recorded electronically. Patient and doctor names, duplicate test results (same patient, same species, and same biotype results), and uncontrolled results were automatically eliminated by the BIOMIC system prior to analysis. In the present study, the fluconazole and voriconazole S, SDD, and R results for *C. parapsilosis* were stratified by year of collection, geographic region, clinical specimen type, and hospital location.

RESULTS

Isolation rates of *C. parapsilosis* over time and by geographic region. A total of 141,383 isolates of *Candida* spp. were isolated and identified at 124 study sites between January 2001 and December 2005 (44). *C. parapsilosis* ranked fourth among 22 different species of *Candida*, accounting for 6.6% of all isolates (Table 1). Although the overall frequency of *C. parapsilosis* increased from 4.8% in the years 1997 to 2000 to 6.6.%

TABLE 1. Variation in frequency of *C. parapsilosis* by geographic region[a]

Region	Total no. of *Candida* species isolates	Total no. (%) of *C. parapsilosis* isolates
Asia-Pacific	27,845	2,263 (8.1)
Africa and Middle East	6,523	348 (5.3)
Europe	77,268	3,388 (4.4)
Latin America	19,895	1,960 (9.9)
North America	9,852	1,412 (14.3)
Total	141,383	9,371 (6.6)

[a] Data were obtained from the ARTEMIS DISK Global Antifungal Surveillance Program (2001 to 2005). Isolates represent all incident isolates from all sites of infection.

in the years 2001 to 2005 (44), the annual isolation rates were relatively stable during the latter time period ranging from 6.9% in 2001 to 7.3% in 2003 and 5.6% in 2005.

C. parapsilosis was most frequently isolated in North America (14.3% of all *Candida* isolates) and Latin America (9.9%), although the frequency of isolation varied considerably within each of the five geographic locations, ranging from 0% (Indonesia) to 16.9% (Australia) in the Asia-Pacific region, from 1.3% (Slovakia) to 7.8% (Spain and Turkey) in Europe, and from 1.2% (Ecuador) to 12.8% (Brazil) in Latin America (Tables 1 and 2).

Geographic variation in susceptibility of *C. parapsilosis* to fluconazole and voriconazole. Table 2 represents the in vitro susceptibilities of *C. parapsilosis* to fluconazole and voriconazole stratified by country and geographic region of origin, as

TABLE 2. Geographic variation in susceptibility of *C. parapsilosis* to fluconazole and voriconazole

Region or country	% by category[a]							
	Fluconazole				Voriconazole			
	N	S	SDD	R	N	S	SDD	R
Asia-Pacific	2,263	90.8	4.6	4.6	2,092	95.3	2.6	2.1
Australia	124	99.2		0.8	124	99.2		0.8
China	121	87.6	4.1	8.3	121	92.6	3.3	4.1
India	32	90.6	6.3	3.1	31	100.0		
Malaysia	1,521	89.2	5.5	5.3	1,353	94.6	3.4	2.0
South Korea	186	99.5	0.5		185	99.5		0.5
Taiwan	262	92.0	3.4	4.6	261	94.6	1.6	3.8
Thailand	17	88.2	11.8		17	100.0		
Europe	3,388	95.8	1.8	2.4	3,298	98.1	0.8	1.1
Belgium	104	98.1		1.9	103	98.1		1.9
Czech Republic	300	99.0	1.0		283	100.0		
France	94	84.0	8.6	7.4	77	96.1	2.6	1.3
Germany	135	99.3		0.7	135	99.3		0.7
Greece	36	83.3	5.6	11.1	36	94.4	2.8	2.8
Hungary	259	90.3	3.5	6.2	237	95.4	1.2	3.4
Italy	374	97.9	1.0	1.1	374	99.2	0.5	0.3
The Netherlands	151	95.4	2.6	2.0	151	96.7	1.3	2.0
Norway	7	100.0			7	100.0		
Poland	68	91.2	1.4	7.4	68	95.6	1.5	2.9
Portugal	215	96.7	0.5	2.8	215	97.7	0.4	1.9
Russia	213	87.8	3.7	8.5	213	96.7	1.9	1.4
Slovakia	47	91.5	4.2	4.3	47	93.6		6.4
Spain	496	99.0	0.6	0.4	496	99.6	0.2	0.2
Switzerland	88	98.9	1.1		89	100.0		
Turkey	109	96.3	1.9	1.8	93	98.9		1.1
United Kingdom	692	96.8	1.9	1.3	674	97.9	1.2	0.9
Latin America	1,960	93.7	4.0	2.3	1,910	97.8	1.2	1.0
Argentina	715	93.7	4.8	1.5	702	98.4	1.0	0.6
Brazil	500	97.2	1.2	1.6	496	97.8	1.0	1.2
Colombia	465	89.9	5.4	4.7	440	96.4	1.8	1.8
Ecuador	32	87.5	12.5		32	96.9	3.1	
Mexico	98	95.9	3.1	1.0	88	98.9		1.1
Venezuela	150	93.3	4.0	2.7	152	98.7	0.6	0.7
Africa and Middle East	348	79.3	5.2	15.5	345	85.8	2.9	11.3
South Africa	256	74.2	5.5	20.3	253	81.0	4.0	15.0
Israel	54	94.4	3.7	1.9	54	100.0		
Saudi Arabia	38	92.1	5.3	2.6	38	97.4		2.6
North America	1,412	94.3	1.8	3.9	1,396	97.1	0.9	2.0
Canada	69	97.1	1.5	1.4	69	100.0		
United States	1,343	94.2	1.8	4.0	1,327	96.9	0.9	2.2
Total	9,371	93.3	3.0	3.6	9,041	96.8	1.4	1.9

[a] All isolates were tested by the disk diffusion method performed in accordance with CLSI standard M44-A. S, susceptible, with zone diameters of ≥19 mm for fluconazole and ≥17 mm for voriconazole; SDD, susceptible dose dependent, with zone diameters of 15 to 18 mm for fluconazole and 14 to 16 mm for voriconazole; R, resistant, with zone diameters of ≤14 mm for fluconazole and ≤13 mm for voriconazole.

TABLE 3. Susceptibility of *C. parapsilosis* to fluconazole and voriconazole by clinical service

Clinical service (total no. of isolates)[a]	Antifungal agent	No. of isolates tested	% of isolates from service[b]	% of isolates[c]		
				S	SDD	R
Hematology-oncology (8,432)	Fluconazole	305	3.6	94.8	2.6	2.6
	Voriconazole	301		98.7	0.7	0.7
Medical (33,681)	Fluconazole	2,144	6.4	93.7	2.6	3.7
	Voriconazole	2,100		96.7	1.4	2.0
Surgical (8,869)	Fluconazole	561	6.3	93.9	3.0	3.0
	Voriconazole	547		96.9	1.3	1.8
ICU (18,691)	Fluconazole	1,119	6.0	91.3	3.6	5.1
	Voriconazole	1,083		95.3	1.4	3.3
Dermatology (2,519)	Fluconazole	527	20.9	93.0	4.0	3.0
	Voriconazole	502		97.2	1.2	1.6
Urology (1,293)	Fluconazole	61	4.7	91.8	4.9	3.3
	Voriconazole	60		96.7	3.3	
Outpatient (11,621)	Fluconazole	811	7.0	95.2	2.8	2.0
	Voriconazole	797		98.4	0.8	0.9
Other, NOS[d] (38,649)	Fluconazole	3,843	9.9	93.2	3.1	3.7
	Voriconazole	3,653		96.5	1.6	1.9

[a] That is, the total number of *Candida* isolates from each service.
[b] *C. parapsilosis* as a percentage of all isolates from that clinical service.
[c] S, SDD, and R are as defined in Table 2, footnote *a*.
[d] Other, NOS, other, not otherwise specified.

determined by CLSI disk diffusion testing. Overall, *C. parapsilosis* exhibited slightly decreased susceptibility to fluconazole (93.3% S, 3.6% R) compared to that of *C. albicans* (97.9% S, 1.5% R) (data not shown).

A surprising degree of variation in the susceptibility of *C. parapsilosis* to fluconazole was observed across the first five broad regions: isolates from Europe were the most susceptible (95.8% S, 2.4% R), and the lowest overall susceptibility was seen among isolates from the Africa and Middle East region (79.3% S, 15.5% R), the latter being largely accounted for by isolates from South Africa (74.2% S, 20.3% R). No other country reported susceptibility rates of less than 80%; however, the susceptibility rates were less than 90% in eight countries: China (87.6%), Malaysia (89.2%), Thailand (88.2%), France (84.0%), Greece (83.3%), Russia (87.8%), Colombia (89.9%), and Ecuador (87.5%). More than 95% of isolates were susceptible to fluconazole in 16 countries: Australia (99.2%), South Korea (99.5%), Belgium (98.1%), the Czech Republic (99.0%), Germany (99.3%), Italy (97.9%), The Netherlands (95.4%), Norway (100%), Portugal (96.7%), Spain (99.0%), Switzerland (98.9%), Turkey (96.3%), the United Kingdom (96.8%), Brazil (97.2%), Mexico (95.9%), and Canada (97.1%).

Voriconazole was always more active against *C. parapsilosis* than fluconazole, irrespective of geographic region. In contrast to fluconazole, only a slight variation in voriconazole activity was observed across the different countries and regions, ranging from a low of 81% susceptible in South Africa to a high of 100% in India, Thailand, Czech Republic, Norway, Switzerland, Israel, and Canada. More than 98% of isolates in 17 of the 35 countries were susceptible to voriconazole.

Trends in resistance to fluconazole and voriconazole among *C. parapsilosis* isolates over time. There was no evidence of increasing resistance to the azoles among *C. parapsilosis* isolates tested between 2001 and 2005. Resistance to fluconazole ranged from 4.2% in 2001 to 3.1% in 2003 and was 4.2% in 2005. Resistance to voriconazole was 1.9% in 2001, peaked at 2.3% in 2002, and was 1.9% in 2005.

Variation in the frequency of isolation and antifungal susceptibility profile of *C. parapsilosis* by clinical service. The clinical services reporting the isolation of *C. parapsilosis* from patient specimens included the hematology-oncology service, medical and surgical services, intensive care units (medical, surgical, and neonatal), the dermatology service, the urology service, and the outpatient service (Table 3). Those strains from services with only a few isolates and those for which a clinical service was not specified were included in the category "other, not otherwise specified (NOS)".

Candida parapsilosis was isolated most frequently from patients on the Dermatology service (20.9%) and least frequently from patients on the Hematology-Oncology service (3.6%). Only 6% of the *Candida* spp. isolated from ICU patients in the present study were *C. parapsilosis*. However, *C. parapsilosis* was isolated much more frequently from patients in the NICU (15.4% of all *Candida* spp. from NICU).

There was little variation in susceptibility to either triazole across the different services. More than 90% of isolates were susceptible to both fluconazole and voriconazole irrespective of the different clinical services.

Variation in the frequency of isolation and antifungal susceptibility profile of C. parapsilosis by clinical specimen type. The major specimen types yielding *C. parapsilosis* as a putative

TABLE 4. Susceptibility of *C. parapsilosis* to fluconazole and voriconazole by specimen type

Specimen type/site (total no. of isolates)[a]	Antifungal agent	No. of isolates tested	% of isolates from site[b]	% of isolates[c]		
				S	SDD	R
Blood (14,887)	Fluconazole	2,834	19.0	93.1	2.7	4.2
	Voriconazole	2,755		96.8	1.0	2.2
NSBF (6,055)	Fluconazole	373	6.2	94.1	2.7	3.2
	Voriconazole	368		97.3	0.5	2.2
Urine (18,168)	Fluconazole	806	4.4	91.1	4.5	4.5
	Voriconazole	771		96.1	1.8	2.1
Respiratory (39,523)	Fluconazole	1,008	2.6	94.2	3.4	2.4
	Voriconazole	979		97.3	1.2	1.5
Skin or soft tissue (8,290)	Fluconazole	1,220	14.7	95.1	3.0	1.9
	Voriconazole	1,196		97.9	1.2	0.9
Genital (31,157)	Fluconazole	1,009	3.2	95.7	2.3	2.0
	Voriconazole	926		97.3	1.3	1.4
Misc. NOS (23,303)	Fluconazole	2,121	9.1	91.7	3.3	5.0
	Voriconazole	2,046		95.7	2.0	2.3

[a] That is, the total number of *Candida* isolates from each specimen type. Misc. NOS, miscellaneous, not otherwise specified.
[b] *C. parapsilosis* as a percentage of all isolates from that specimen type.
[c] S, SDD, and R are as defined in Table 2, footnote *a*.

pathogen included blood, NSBF, urine, respiratory, skin and soft tissue, and genital specimens (Table 4). The isolates from uncommon specimen types and those for which a specimen type was not recorded were grouped under the category "Misc., NOS" (miscellaneous, not otherwise specified).

C. parapsilosis was isolated most frequently from blood and skin and soft tissue specimens and was isolated infrequently from urine, respiratory, and genital tract specimens. Both fluconazole and voriconazole were quite active (>90% S) against isolates of *C. parapsilosis* irrespective of specimen type.

Activity of echinocandin antifungal agents against bloodstream isolates of *C. parapsilosis*. Previously, we and others have shown that echinocandin MICs are consistently higher for *C. parapsilosis* than for *C. albicans* when tested by BMD methods (30, 39–41). When tested against anidulafungin, caspofungin, and micafungin using the CLSI BMD method, 93.2, 99.6, and 100% of the BSI isolates of *C. parapsilosis* were susceptible to the three echinocandins, respectively, at the recently assigned (June 2007) CLSI breakpoint concentration of ≤2 μg/ml (Table 5). The differences in potency among the three agents are best reflected by the modal MICs: caspofungin (0.25 to 0.5 μg/ml), micafungin (1.0 μg/ml), and anidulafungin (2.0 μg/ml). This pattern was unchanged across the different geographic regions (data not shown). Importantly, we did not observe a multi-echinocandin, multi-azole-resistant phenotype such as that reported by Moudgal et al. (26) and Vazquez et al. (57). Among nine isolates that were found to be resistant to fluconazole (MIC, ≥64 μg/ml), all were susceptible (MIC, ≤2 μg/ml) to anidulafungin (range, 1 to 2 μg/ml), caspofungin (range, 0.25 to 2 μg/ml), and micafungin (range, 1 to 2 μg/ml). Likewise, the Detroit phenotype for echinocandin resistance (i.e., caspofungin- and micafungin-resistant, anidulafungin-susceptible) was not detected among 539 isolates tested against all three echinocandins.

DISCUSSION

The results of this extensive survey of *C. parapsilosis* both confirm and extend previous observations regarding this species (1, 3, 8, 15, 29, 48, 50, 58). We have demonstrated that the frequency of isolation of *C. parapsilosis* varies considerably among countries, clinical services, and specimen types and confirm the increased frequency in Latin America, neonatal ICUs, and blood and dermatologic specimens. Likewise, we confirm the general susceptibility of *C. parapsilosis* to both fluconazole and voriconazole and yet document an unusual pocket of azole resistance in South Africa.

Although fluconazole is well known to have good activity

TABLE 5. In vitro activity of anidulafungin, caspofungin, and micafungin against bloodstream isolates of *C. parapsilosis*[a]

Antifungal agent	No. tested	Cumulative % of isolates at an MIC (μg/ml) of:								
		0.015	0.03	0.06	0.12	0.25	0.5	1	2	4
Anidulafungin	621	0.3	0.8	0.8	0.8	1.9	4.7	29.3	93.2	100
Caspofungin	1,447	0.3	0.9	3.7	12.4	49.9	89.4	98.8	99.6	100
Micafungin	539	0.2	0.2	0.2	0.6	5.2	22.5	75.3	100	

[a] Isolates were tested in RPMI 1640 broth with 24 h of incubation and a prominent reduction endpoint criterion (MIC-2).

against *C. parapsilosis*, it is clear from this survey that decreased susceptibility may occur in certain geographic regions and in select institutions (10, 26, 51, 57), suggesting that monitoring of local susceptibility profiles may be useful. Decreased susceptibility to fluconazole among *C. parapsilosis* may be enhanced by the proclivity of this species to form extensive biofilms on catheters and other devices (13, 17, 18, 20). Because the source of *C. parapsilosis* fungemia is a vascular catheter in more than 50% of cases and such infections occur commonly in patients who had received prior antifungal treatment (3), an adequate response to fluconazole alone may not be achieved, and administration of this agent should be coupled with prompt removal of the catheter to ensure an optimal response (32). Furthermore, despite excellent overall activity of voriconazole against *C. parapsilosis*, it must be recognized that only 36.7% of fluconazole-resistant isolates of *C. parapsilosis* retain susceptibility to voriconazole (44).

Given that *C. parapsilosis* is well known as a superficial colonizer of cutaneous surfaces and as a cause of onychomycosis (5, 7, 23, 56), it is not surprising that we found it to be isolated commonly from skin and soft tissue infections in patients on the Dermatology service. Bonassoli et al. (5) found a high frequency of *C. parapsilosis* colonization of the hands of healthy volunteers and health care workers and noted that these colonizing strains exhibited the same potential virulence characteristics as those isolated from sites of infection. Thus, hand colonization with virulent strains of *C. parapsilosis* coupled with poor hand washing and catheter care may serve as a nosocomial threat to seriously ill patients (10, 18).

Although *C. parapsilosis* is often reported to cause infections among patients hospitalized in the ICU (1, 3, 10, 51), only 6% of the *Candida* spp. isolated from ICU patients in the present study were *C. parapsilosis*. However, *C. parapsilosis* was isolated much more frequently from patients in the NICU (15.4% of all *Candida* spp.) than from those in the medical (5.8%) or surgical (3.4%) ICU. This finding supports previous observations regarding candidiasis in the NICU (15, 21, 22, 49, 51, 52, 58, 59).

Although the role of *C. parapsilosis* as a pathogen when isolated from nonsterile sites such as the respiratory, urinary, and genital tracts is debated, isolation from blood and NSBF must be considered significant. Thus, it is worth noting that the single most common specimen to yield *C. parapsilosis* in culture was blood (Table 4). Prior colonization of mucosal sites is rare among patients with *C. parapsilosis* fungemia, further confirming the exogenous nature of this pathogen (3).

Perhaps the most encouraging information from this survey is the lack of any multi-azole, multi-echinocandin-resistant strains of *C. parapsilosis*. Although this species is innately less susceptible to the echinocandins than many other species of *Candida*, the vast majority of isolates remain susceptible to all three echinocandins (Table 5). Specifically, the epidemic phenotype reported from Detroit, MI (57), was not detected. Potency differences among the three echinocandins were detected; however, previous studies have found that such differences in vitro were normalized by the addition of serum to the test medium and did not prove to be important in vivo (34). Nevertheless, the experience in Detroit (26, 57) and the less-than-stellar results against *C. parapsilosis* in clinical trials (25, 46, 54) suggest that this species should be carefully monitored with respect to emerging echinocandin resistance.

In summary, we have used the extensive and validated database of the ARTEMIS DISK Antifungal Surveillance Program (44) to increase our understanding of *C. parapsilosis* as an opportunistic pathogen. Our findings confirm that this species is an emerging pathogen in Latin America and is also important in North America. This species may exhibit decreased susceptibility to fluconazole in some geographic locations and is generally susceptible to voriconazole and the echinocandins. It is most likely to be isolated from blood and is often associated with intravascular catheters and parenteral nutrition. The detection of BSIs with *C. parapsilosis* should raise a "red flag" regarding breaks in catheter care and infection control procedures, since it usually signifies the exogenous introduction of the offending pathogen into an already compromised host (3, 10, 44, 58).

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