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International Surveillance of Bloodstream Infections Due to *Candida* Species: Frequency of Occurrence and In Vitro Susceptibilities to Fluconazole, Ravuconazole, and Voriconazole of Isolates Collected from 1997 through 1999 in the SENTRY Antimicrobial Surveillance Program

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A surveillance program (SENTRY) of bloodstream infections (BSI) in the United States, Canada, Latin America, and Europe from 1997 through 1999 detected 1,184 episodes of candidemia in 71 medical centers (32 in the United States, 23 in Europe, 9 in Latin America, and 7 in Canada). Overall, 55% of the yeast BSIs were due to *Candida albicans*, followed by *Candida glabrata* and *Candida parapsilosis* (15%), *Candida tropicalis* (9%), and miscellaneous *Candida* spp. (6%). In the United States, 45% of candidemias were due to non-*C. albicans* species. *C. glabrata* (21%) was the most common non-*C. albicans* species in the United States, and the proportion of non-*C. albicans* BSIs was highest in Latin America (55%). *C. albicans* accounted for 60% of BSI in Canada and 58% in Europe. *C. parapsilosis* was the most common non-*C. albicans* species in Latin America (25%), Canada (16%), and Europe (17%). Isolates of *C. albicans, C. parapsilosis*, and *C. tropicalis* were all highly susceptible to fluconazole (97 to 100% at ≤8 μg/ml). Likewise, 97 to 100% of these species were inhibited by ≤1 μg/ml of ravuconazole (concentration at which 50% were inhibited [MIC_{50}], 0.007 to 0.03 μg/ml) or voriconazole (MIC_{50}, 0.007 to 0.06 μg/ml). Both ravuconazole and voriconazole were significantly more active than fluconazole against *C. glabrata* (MIC_{90}s of 0.5 to 1.0 μg/ml versus 16 to 32 μg/ml, respectively). A trend of increased susceptibility of *C. glabrata* to fluconazole was noted over the three-year period. The percentage of *C. glabrata* isolates susceptible to fluconazole increased from 48% in 1997 to 84% in 1999, and MIC_{50}s decreased from 16 to 4 μg/ml. A similar trend was documented in both the Americas (57 to 84% susceptible) and Europe (22 to 80% susceptible). Some geographic differences in susceptibility to triazole were observed with Canadian isolates generally more susceptible than isolates from the United States and Europe. These observations suggest susceptibility patterns and trends among yeast isolates from BSI and raise additional questions that can be answered only by continued surveillance and clinical investigations of the type reported here (SENTRY Program).

It is now well accepted that antimicrobial resistance is an important concern with respect to virtually all major groups of pathogenic microorganisms, including viruses, bacteria, parasites, and fungi. Numerous approaches to control this ever-increasing problem have been suggested (2, 10, 27, 30). One critical component in every suggested mode of intervention is the need for continued monitoring or surveillance of resistance on a global scale. Surveillance of antibacterial resistance is now being conducted by several different groups with the common goal of providing accurate data for use in the development of empiric treatment recommendations, for the development of guidelines and policies for appropriate antimicrobial utilization, for assessing the progress and effectiveness of various intervention efforts, and for tailoring or improving antimicrobial susceptibility testing (AST) methods and resistance screening (2, 10, 13).

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Although innate or acquired resistance to available antifungal agents is now recognized among pathogenic fungi, particularly the *Candida* species, the true extent of the resistance problem among fungi causing hematogenously disseminated or bloodstream infections (BSI) is largely unknown. Among the several active antimicrobial resistance surveillance programs now in existence, the SENTRY Antimicrobial Surveillance Program is the only system that monitors BSI due to *Candida* spp. as well as bacterial species (5, 6, 13, 22). The SENTRY Program is comprehensive, longitudinal, and global in scope and utilizes a central laboratory concept to monitor trends in microbial spectra and resistance in 74 sentinel sites in 22 nations.

Since 1997, one of the important objectives of the SENTRY Program has been the study of the frequency of occurrence and antifungal resistance among species of *Candida* causing BSI in the United States, Canada, Latin America, and Europe (5, 16, 21, 22). The rank order of occurrence and resistance profiles of the various species of *Candida* causing BSI is important in establishing empiric treatment protocols and in judging the potential impact of newer antifungal agents. Using this approach, a number of important and unusual resistance phenotypes have been detected over the three-year period from 1997

to 1999 (5, 16, 21, 22). Examples that will be discussed herein include *Candida glabrata* isolates resistant to amphotericin B, *Candida krusei* isolates resistant to amphotericin B, fluconazole, and 5-fluorocytosine (5FC), cross-resistance to established and investigational triazoles, and decreased resistance to fluconazole among *C. glabrata* isolates and to itraconazole among *Candida tropicalis* isolates. Species differences occurring among different geographic regions have also been noted.

MATERIALS AND METHODS

Study design. The SENTRY Program was established in 1997 to monitor the predominant pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections via a broad network of sentinel hospitals categorized by geographic location and size (5, 16, 21, 22). The present report focuses on BSI due to *Candida* spp. from U.S., Canadian, Latin American, and European sites. BSI due to *Candida* spp. were reported from 32 monitored medical centers in the United States, 23 in Europe, 9 in Latin America, and 7 in Canada over the three-year period from January 1997 through December 1999.

Each participant hospital contributed results (organism identification, date of isolation, and hospital location) for consecutive blood culture isolates (one isolate per patient) of *Candida* spp. judged to be clinically significant by local criteria, detected in each calendar month during the study period. All isolates were stored on agar slants and sent on a regular basis to the University of Iowa College of Medicine (Iowa City) for storage and further characterization by reference identification and susceptibility testing (14, 29).

Organism identification. All fungal blood culture isolates were identified at the participating institutions by the routine method in use at each laboratory. Upon receipt at the University of Iowa, the isolates were subcultured onto potato dextrose agar (Remel, Lenexa, Kans.) and CHROMagar Candida medium (Hardy Laboratories, Santa Maria, Calif.) to ensure viability and purity. Confirmation of species identification was performed with Vitek and API products (bioMerieux, St. Louis, Mo.) as recommended by the manufacturer or by conventional methods as required (29). Isolates were stored as suspensions in water or on agar slants at an ambient temperature until needed.

Susceptibility testing. Antifungal susceptibility testing of isolates of *Candida* spp. was performed by the reference broth microdilution method described by the NCCLS (14). Susceptibility of isolates to amphotericin B was determined using Etest (AB BIODISK, Sonia, Sweden) and RPMI 1640 agar with 2% glucose (Remel, Lenexa, Kans.) as described previously (17). Standard powders of fluconazole (Pfizer, Inc., New York, N.Y.), voriconazole (Pfizer), ravuconazole (Bristol-Myers Squibb, Wallingford, Conn.), itraconazole (Janssen, Beerse, Belgium), and 5-fluorocytosine (5FC; Sigma, St. Louis, Mo.) were obtained from their respective manufacturers. Following incubation at 35°C for 48 h, the MICs of fluconazole, voriconazole, ravuconazole, itraconazole, and 5FC were read as the lowest concentration at which a prominent decrease in turbidity relative to the growth control well was observed (14). Amphotericin B MICs determined by Etest were read after 48 h of incubation at 35°C and were determined to be at 100% inhibition of growth where the border of the elliptical inhibition zone intercepted the scale on the strip edge (17). Quality control (QC) was ensured by testing the NCCLS (14)-recommended strains, *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019.

Interpretive criteria for susceptibility to fluconazole (susceptibility breakpoint, MIC of $\leq$8 μg/ml), itraconazole (susceptible, MIC of $\leq$0.12 μg/ml), and 5FC (susceptible, MIC of $\leq$4 μg/ml) were those published by Rex et al. (23) and the NCCLS (14). These breakpoints apply to all *Candida* spp. (including *C. glabrata*) with the exception of *C. krusei*, which is considered inherently resistant to fluconazole regardless of the MIC obtained (14). Interpretive criteria have not yet been defined for amphotericin B; however, because the study of Nguyen et al. (15) suggested that amphotericin B MICs of $>$1 μg/ml may indicate clinically resistant isolates of *Candida* spp., we determined the percentage of isolates inhibited by $\leq$1 μg/ml to be susceptible in this surveillance study. Likewise, the investigational triazoles, voriconazole and ravuconazole, have not been assigned interpretive breakpoints. For purposes of comparison and because preliminary pharmacokinetic data indicate that achievable serum levels for these agents may range from 2 to 6 μg/ml depending on the dosing regimen (26), we have employed a susceptibility breakpoint of $\leq$1 μg/ml for both voriconazole and ravuconazole.

Statistical analysis. Comparison of species distribution and/or MIC distribution by other factors (e.g., year, geographic region) were made using the chi-square test with Yates' correction for categorical variables and the Wilcoxon rank sum test for ordinal variables (MICs). All reported *P* values are two-tailed.

TABLE 1. Species distribution of *Candida* bloodstream isolates: SENTRY Program, 1997 to 1999

Species	% Isolates by geographic area[a]			
	U.S. (n = 589)	Canada (n = 161)	Latin America (n = 132)	Europe (n = 302)
C. albicans	55	60	45	58
C. glabrata	21[b]	12	6	10
C. parapsilosis	11	16	25[c]	19[c]
C. tropicalis	9	6	16[d]	7
C. krusei	2	2	1	1
Candida spp.	2	4	7	5

[a] n, no. tested. U.S., United States.
[b] $P \leq 0.01$ compared to prevalence in other geographic areas.
[c] $P \leq 0.001$ compared to prevalence in the United States.
[d] $P \leq 0.03$ compared to prevalence in other geographic areas.

RESULTS AND DISCUSSION

During the 36-month study period, a total of 1,184 BSI isolates (episodes) of *Candida* spp. were submitted by 71 study centers in the United States (32 centers, 589 isolates), Canada (7 centers, 161 isolates), Latin America (9 centers, 132 isolates), and Europe (23 centers, 302 isolates). These isolates accounted for 3% of all BSI isolates (bacterial and fungal) from nosocomial and community-acquired infections and 9% of nosocomial BSI (bacterial and fungal) isolates submitted by SENTRY participants from 1997 to 1999. *Candida* spp. was the fourth-most-common nosocomial BSI isolate category, preceded only by *Staphylococcus aureus*, coagulase-negative staphylococci, and enterococci (data not shown). The original identification assigned by the participating center was confirmed for 97% of the isolates submitted. Among the 1,184 BSI, 75% were nosocomial (detected more than 48 h after admission to a hospital), and 50% occurred in patients hospitalized in an intensive care unit (ICU).

The frequencies of BSI due to the various species of *Candida* in each country over the three-year period are presented in Table 1. Of the 1,184 yeast BSI whose organisms were identified, 55% were due to *C. albicans*, 15% were due to *C. glabrata*, 15% were due to *C. parapsilosis*, 9% were due to *C. tropicalis*, and 6% were due to miscellaneous *Candida* spp. The rank order of the various species differed according to geographic location. *C. albicans* was the predominant species in all four geographic areas, accounting for 45 to 60% of all BSI. *C. glabrata* was the second-most-common species in the United States (21% of BSI; $P \leq 0.01$ compared to prevalence in other geographic areas) but ranked either third or fourth in the other areas. In contrast to the case in the United States, *C. glabrata* was very uncommon in Latin America (6% of all isolates; $P \leq 0.001$ compared to U.S. results). *C. parapsilosis* was the second-most-common *Candida* species, causing BSI in Latin America (25%; $P \leq 0.001$ compared to U.S. results), Canada (16%), and Europe (19%; $P \leq 0.001$ compared to U.S. results). *C. krusei* was encountered infrequently (1 to 2%) in all geographic areas.

The rank order of species in all four geographic areas was relatively stable over the three-year period. However, the overall rank order may not represent the situation in individual

TABLE 2. Geographic location and percent of *Candida* bloodstream infections attributable to *C. albicans* (SENTRY Program, 1997 to 1999)

Location[a]	No. of isolates	% *C. albicans*
Europe		
Turkey-1	11	73
Turkey-2	23	74
France-1	11	55
France-3	11	73
Germany-1	19	21
Italy-1	35	66
Italy-2	17	88
Portugal	39	46
Spain-1	21	67
Spain-2	14	29
Switzerland	15	80
United States		
Indiana	31	48
Arizona	13	62
New Mexico	22	82
Chicago	58	52
Iowa	24	58
Massachusetts	29	38
New York-1	29	41
New York-2	38	37
New York-3	44	70
California-1	17	53
California-2	25	56
Washington	17	47
Missouri	64	52
Texas-1	16	50
Texas-2	12	83
Texas-3	12	58
Kentucky	17	59
North Carolina	17	35
Virginia	44	68
Utah	12	58
Canada		
Alberta	26	54
Manitoba	37	62
Nova Scotia	34	71
Ontario	13	85
Quebec	35	51
Latin America		
Argentina	14	43
Brazil-1	29	24
Brazil-2	24	50
Brazil-3	35	54
Chile	14	64

[a] Only those sites with ≥10 BSI isolates are shown. Where results were available for more than one site within a state or country, the numerical suffix indicates the individual site.

medical centers. The percentages of candidemias due to *C. albicans* varied considerably among the individual participating study sites (Table 2). *C. albicans* was clearly the predominating species in certain medical centers, accounting for ≥70% of candidemias in Turkey-3 (73%), France-3 (73%), Italy-2 (88%), Switzerland (80%), Turkey-2 (74%), New Mexico (82%), New York-3 (70%), Texas-2 (83%), Nova Scotia (71%), and Ontario (85%) (a numerical suffix indicates a particular site within a state or country). In contrast, *C. albicans* accounted for ≤40% of BSI in Germany-1 (21%), Spain-2 (29%), Massachusetts (38%), New York-2 (37%), North Carolina (35%), and Brazil-1 (24%).

These data demonstrate that although *C. albicans* may continue to play a dominant role as a cause of fungemia in many centers, it has been supplanted by *C. glabrata* in certain U.S. centers and by *C. parapsilosis* or *C. tropicalis* in some European and Latin American centers. The reasons for such dramatic differences in *Candida* species causing BSI remains speculative, although the emergence of *C. glabrata* in certain centers has been linked to utilization of fluconazole prophylaxis (1, 3), and infections attributable to *C. parapsilosis* are often associated with hyperalimentation and breaches of catheter care and of infection control practice (12, 18, 19, 22).

In vitro susceptibility results for the 1,184 isolates tested with fluconazole, ravuconazole, and voriconazole are shown in Table 3. Fluconazole was active in all regions, with 90 to 98% of isolates susceptible (S) to a drug concentration of ≤8 μg/ml. Isolates from Canada (concentration at which 90% of the isolates are inhibited [MIC_{90}], 4 μg/ml; 96% S) and Latin America (MIC_{90}, 4 μg/ml; 98% S) were more susceptible than those from the United States (MIC_{90}, 16; 90% S) and Europe (MIC_{90}, 8 μg/m; 90% S) due to the presence of resistance (MIC, ≥64 μg/ml) among *C. glabrata* isolates in the latter two regions. Both ravuconazole (MIC_{90}, 0.12 to 0.5 μg/m; 98 to 99% S) and voriconazole (MIC_{90}, 0.12 to 0.25 μg/ml; 98 to 99% S) were considerably more potent than fluconazole against isolates from all four geographic areas.

Table 4 summarizes the in vitro susceptibilities to fluconazole, ravuconazole, and voriconazole for the individual species of *Candida* from all areas stratified by year. Isolates of *C. albicans, C. parapsilosis*, and *C. tropicalis* were all highly susceptible (97 to 100%) to fluconazole and the investigational triazoles. Interestingly, *C. glabrata* demonstrated a trend towards increased susceptibility to fluconazole from 1997 (MIC_{50}, 16 μg/ml; 48% S) to 1999 (MIC_{50}, 4 μg/ml; 83% S; $P = 0.004$ for the trend). This trend was apparent in both the Americas and Europe (data not shown). Reasons for this trend are unclear but may be related to more appropriate uses and improved dosing of fluconazole (3). Both ravuconazole and voriconazole were quite active (MIC_{50}, 0.12 to 0.5 μg/ml; 97 to 100% S) against both *C. glabrata* and *C. krusei*. Notably, no trend towards increased resistance to any of the agents tested was observed over the three-year period.

TABLE 3. Activities of fluconazole and investigational antifungal agents against 1,184 BSI isolates of *Candida* spp. from four geographic regions (SENTRY Program, 1997 to 1999)

Antifungal agent	MIC (μg/ml) and % susceptible by country[a]							
	U.S. (n = 589)		Canada (n = 161)		Latin America (n = 132)		Europe (n = 302)	
	50/90%	% S	50/90%	% S	50/90%	% S	50/90%	% S
Fluconazole	0.25/16	90	0.25/4	96	0.25/4	98	0.25/8	90
Ravuconazole	0.015/0.25	98	0.015/0.12	99	0.015/0.25	99	0.007/0.5	98
Voriconazole	0.015/0.25	98	0.015/0.12	99	0.015/0.12	99	0.007/0.25	99

[a] n, no. tested. U.S., United States. % S, percent susceptible at a MIC of ≤8 μg/ml (fluconazole) or ≤1 μg/ml (all other agents).

TABLE 4. In vitro susceptibilities of blood stream infection isolates of *Candida* spp. to fluconazole and investigational antifungal agents (SENTRY Program, 1997 to 1999)

Species (no. tested)	Antifungal agent	MIC (μg/ml) and % susceptible by year					
		1997		1998		1999	
		50/90%	% S[a]	50/90%	% S[a]	50/90%	% S[a]
C. albicans (658)	Fluconazole	0.25/0.5	99	0.25/0.5	98	0.25/0.25	100
	Ravuconazole	0.007/0.03	99	0.007/0.03	99	0.007/0.015	100
	Voriconazole	0.015/0.06	98	0.007/0.03	99	0.007/0.015	100
C. glabrata (180)	Fluconazole[b]	16/32	48	8/16	63	4/16	83
	Ravuconazole	0.25/1	92	0.25/1	95	0.12/1	94
	Voriconazole	0.25/1	91	0.25/1	95	0.12/0.5	96
C. parapsilosis (179)	Fluconazole	0.5/2	100	0.5/1	98	0.5/1	100
	Ravuconazole	0.015/0.06	100	0.015/0.06	100	0.015/0.06	100
	Voriconazole	0.03/0.12	100	0.015/0.06	100	0.015/0.03	100
C. tropicalis (104)	Fluconazole	1/2	100	0.5/1	100	0.5/2	97
	Ravuconazole	0.03/0.12	100	0.03/0.12	100	0.015/0.12	97
	Voriconazole	0.06/0.12	100	0.03/0.12	100	0.03/0.12	97
C. krusei (20)	Fluconazole	32/—[c]	0	32/—	0	16/—	0
	Ravuconazole	0.25/—	100	0.25/—	100	0.25/—	100
	Voriconazole	0.5/—	100	0.25/—	100	0.25/—	100

[a] % S, percent susceptible at a MIC of ≤8 μg/ml (fluconazole) or ≤1 μg/ml (all other agents).
[b] $P = 0.0004$ for trend in susceptibility by year.
[c] —, MIC_{90} not calculated because <10 isolates were identified during the year.

Although it is not shown in Table 4, *C. tropicalis* demonstrated a trend towards increased susceptibility to itraconazole (susceptible MIC, ≤0.12 μg/ml) from 1997 (MIC_{50}, 0.25 μg/ml; 48% S) to 1999 (MIC_{50}, 0.06 μg/ml; 82% S; $P = 0.005$). A similar shift was not observed with itraconazole and any other species. More than 97% of *C. tropicalis* isolates were inhibited by ≤1 μg/ml of itraconazole. This trend is similar to the shift observed with *C. glabrata* and fluconazole and bears watching.

Despite excellent activity against the vast majority of *Candida* BSI isolates, cross-resistance was observed with both ravuconazole and voriconazole when they were tested against 12 isolates of *C. albicans* that were resistant to both fluconazole (MIC, ≥64 μg/ml) and itraconazole (MIC, ≥1 μg/ml) (data not shown) (20). Such isolates are quite rare among those organisms causing BSI but are indicative of the potential for development of complete class resistance against the azoles if fluconazole or itraconazole are misused.

Fluconazole was equally active against *Candida* BSI isolates from patients hospitalized in the ICU (93% S) and the non-ICU (92% S) setting (Table 5). This finding was in contrast to that observed with bacterial BSI isolates, where ICU-related infection isolates were generally less susceptible to antimicrobial agents than non-ICU strains (5, 7, 9). Similarly, no difference in susceptibility to six different antifungal agents was noted between nosocomial and community-acquired BSI isolates of *Candida* spp. Again, this observation was distinctly different from the experience with bacterial BSI isolates, where nosocomial strains were almost always more resistant to antimicrobial agents than community-acquired strains (5). Notably, only 70 to 72% of *Candida* spp. were found to be susceptible to amphotericin B at concentrations of ≤1 μg/ml when tested on RPMI agar using Etest (17). The Etest method has been shown to be the most sensitive and reliable method for identifying strains of *Candida* with clinically significant resistance to amphotericin B (4, 17, 28).

Further examination of selected species susceptibility to amphotericin B revealed striking differences when the isolates were tested on RPMI agar using Etest (Table 6). As has been noted previously, approximately 95% of *C. albicans* isolates were inhibited by ≤1 μg/ml of amphotericin B compared to only 41% of *C. glabrata* isolates and 0% of *C. krusei* isolates ($P \leq 0.01$ for comparison of susceptibility by species) (8, 11, 15, 17, 24, 25). This in vitro data is consistent with the clinical experience of breakthrough fungemias with *C. glabrata* and *C. krusei* despite treatment with amphotericin B at standard doses of 0.5 to 0.6 mg/kg of body weight/day (25). Current Infectious Diseases Society of America (IDSA) treatment guidelines recommend higher doses of amphotericin B (1 mg/kg/day) when treating *C. glabrata* and *C. krusei* fungemia (25). Thus, both *C. glabrata* and *C. krusei* may be relatively resistant to both azoles and polyenes and could pose significant therapeutic problems in the future if such strains proliferate. *C. krusei* is also often resistant (70%) to 5FC as well (20).

Summary and conclusions. This most recent analysis of data from the SENTRY Antimicrobial Surveillance Program confirms the fact that *Candida* spp. remain the fourth-most-com-

TABLE 5. Activity of fluconazole against *Candida* blood stream isolates from ICU and non-ICU settings (SENTRY Program, 1997 to 1999)

Setting (no. tested)	Cumulative % occurrence at MIC (μg/ml) of:									
	0.12	0.25	0.5	1	2	4	8	16	32	≥64
ICU (393)	18.8	59.0	70.7	77.1	83.7	88.8	92.9	97.7	99.0	100.0
Non-ICU (402)	12.7	49.3	68.4	76.4	82.1	87.6	91.5	95.5	97.0	100.0

TABLE 6. Activity of amphotericin B (Etest) versus selected *Candida* species (SENTRY Program, 1997 to 1999)

Species (no. tested)	Cumulative % occurrence at MIC (μg/ml) of:							
	0.06	0.12	0.25	0.5	1	2	4	8
C. albicans (501)	0.4	0.8	5.0	53.1	94.6[a]	99.6	100.0	100.0
C. glabrata (131)	0.8	0.8	2.3	8.4	41.2[a]	90.1	98.5	100.0
C. krusei (15)	0.0	0.0	0.0	0.0	0.0[a]	20.0	80.0	100.0

[a] Susceptible breakpoint, $P \leq 0.01$ for comparison of susceptibility by species.

mon cause of nosocomial BSI (7, 18). Although *C. albicans* continues to account for approximately one-half of candidemias world-wide, its frequency may vary widely from institution to institution, emphasizing the need for yeast species identification of BSI isolates in individual institutions. Different, and as yet unknown, factors may influence the species distribution of *Candida* spp. causing BSI. The prominence of *C. glabrata* in the United States as opposed to the other regions in the SENTRY Program may be influenced by extensive utilization of fluconazole at relatively low doses (<400 mg/day), enhancing selection of this species (3). In contrast, the frequent isolation of *C. parapsilosis* in other regions may reflect issues of suboptimal catheter care and infection control (1, 12).

Importantly, no increase in resistance to azoles was observed in any of the geographic regions over the three-year study period. The trend towards decreased resistance to fluconazole among *C. glabrata* isolates and to itraconazole among *C. tropicalis* isolates is interesting and will require further investigation to determine the factors behind these observations. Although there is some evidence in the literature that both *C. glabrata* and *C. krusei* may be relatively resistant to amphotericin B (15, 17, 24, 25), the application of the Etest to a large international collection of *Candida* spp., such as the SENTRY Program collection, provides information suggesting that elevated MICs of drugs for these species may be more common than anticipated.

Additional data, not previously available, indicate that in contrast to the experience with antibacterial agents, no difference in susceptibility to the existing antifungal agents was observed among ICU versus non-ICU isolates and nosocomial versus community-acquired strains of *Candida* spp. This may reflect the fact that to the best of our knowledge *Candida* spp. lack mobile resistance genes and thus require considerably different circumstances and exposures in order to develop high levels of resistance compared to bacterial pathogens.

Finally, although the new triazoles (ravuconazole and voriconazole) display improved potency compared to fluconazole, it is apparent that cross-resistance to these agents may be observed among the rare BSI isolates of *Candida* that are resistant to both fluconazole and itraconazole. These observations suggest certain susceptibility patterns and trends among yeast isolates from BSI and raise additional questions that can be answered only by continued surveillance and clinical investigations of the type reported here (SENTRY Program).

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