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International Surveillance of Bloodstream Infections Due to *Candida* Species: Frequency of Occurrence and Antifungal Susceptibilities of Isolates Collected in 1997 in the United States, Canada, and South America for the SENTRY Program

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An international program of surveillance of bloodstream infections (BSIs) in the United States, Canada, and South America between January and December 1997 detected 306 episodes of candidemia in 34 medical centers (22 in the United States, 6 in Canada, and 6 in South America). Eighty percent of the BSIs were nosocomial and 50% occurred in patients hospitalized in an intensive care unit. Overall, 53.3% of the BSIs were due to *Candida albicans*, 15.7% were due to *C. parapsilosis*, 15.0% were due to *C. glabrata*, 7.8% were due to *C. tropicalis*, 2.0% were due to *C. krusei*, 0.7% were due to *C. guilliermondii*, and 5.8% were due to *Candida* spp. However, the distribution of species varied markedly by country. In the United States, 43.8% of BSIs were due to non-*C. albicans* species. *C. glabrata* was the most common non-*C. albicans* species in the United States. The proportion of non-*C. albicans* BSIs was slightly higher in Canada (47.5%), where *C. parapsilosis*, not *C. glabrata*, was the most common non-*C. albicans* species. *C. albicans* accounted for 40.5% of all BSIs in South America, followed by *C. parapsilosis* (38.1%) and *C. tropicalis* (11.9%). Only one BSI due to *C. glabrata* was observed in South American hospitals. Among the different species of *Candida*, resistance to fluconazole (MIC, ≥64 μg/ml) and itraconazole (MIC, ≥1.0 μg/ml) was observed with *C. glabrata* and *C. krusei* and was observed more rarely among other species. Isolates of *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. guilliermondii* were all highly susceptible to both fluconazole (99.4 to 100% susceptibility) and itraconazole (95.8 to 100% susceptibility). In contrast, 8.7% of *C. glabrata* isolates (MIC at which 90% of isolates are inhibited [MIC_{90}], 32 μg/ml) and 100% of *C. krusei* isolates were resistant to fluconazole, and 36.9% of *C. glabrata* isolates (MIC_{90}, 2.0 μg/ml) and 66.6% of *C. krusei* isolates were resistant to itraconazole. Within each species there were no geographic differences in susceptibility to fluconazole or itraconazole.

National and international surveillance of bloodstream infections (BSIs) due to *Candida* spp. has been limited to date (6, 8–11). Recent studies by Nguyen et al. (6) and Pfaller et al. (9, 11) have documented a slight increase in the proportion of *Candida* BSIs due to non-*C. albicans* species and the emergence of *Candida glabrata* as an important cause of BSIs in the United States. These studies have also reported important changes in antifungal susceptibility profiles among *Candida* isolates causing BSIs, such as decreased susceptibility to fluconazole and itraconazole (6, 9–11). Pfaller et al. (11) observed substantial differences in susceptibility to fluconazole and itraconazole among *C. albicans* isolates from different regions of the United States. Likewise, Nguyen et al. (6) reported elevated fluconazole MICs for isolates of non-*C. albicans* species and episodes of breakthrough fungemia due to isolates for which fluconazole MICs were >8 μg/ml.

Although we now have a basic understanding of trends in species distribution and antifungal susceptibility among *Candida* isolates causing BSIs in the United States (7), there is a lack of information from other countries (2, 15). As part of the comprehensive SENTRY Antimicrobial Resistance Surveillance Program, we collected isolates of *Candida* spp. causing BSIs from medical centers in the United States (30 centers), Canada (8 centers), and South America (10 centers) from January through December 1997. The present report describes the species distribution and antifungal susceptibility profiles of isolates from each of these three geographic areas.

MATERIALS AND METHODS

Study design. The SENTRY Program was established to monitor the predominant pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections via a broad network of sentinel hospitals distributed by geographic location and size (12). The monitored infections include bacteremia and fungemia (objective A), outpatient and inpatient respiratory infections (objectives B and C, respectively), and wound (objective D) and urinary tract (objective E) infections in hospitalized patients. The participating institutions include 72 medical centers in the United States, Canada, South America, and Europe. The present report will focus on BSIs due to *Candida* spp. from North America (30 U.S. and 8 Canadian sites) and South America (10 sites). The U.S. sites were located in 23 different states and represented institutions ranging in size from 250 to 4,000 beds (mean, 760 beds). The Canadian sites were located in five provinces (Alberta, Manitoba, Nova Scotia, Ontario, and Quebec) and represented institutions ranging in size from 400 to 1,200 beds (mean, 726 beds). The South American sites were located in five different nations (Argentina, Brazil, Chile, Colombia, and Uruguay) and represented institutions ranging in size from 130 to 600 beds (mean, 393 beds).

Each participant hospital contributed results (organism identification, date of isolation, hospital location) on consecutive blood culture isolates of *Candida* spp. judged to be clinically significant by local criteria (one isolate per patient) detected in each calendar month during the 12-month period January through December 1997. All isolates were saved on agar slants and were sent on a weekly basis to the University of Iowa College of Medicine (Iowa City) for storage and further characterization by reference identification and susceptibility testing methods (5, 16).

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TABLE 1. Species distribution of *Candida* blood stream isolates, SENTRY Program, January through December 1997

Species	% of isolates by geographic area (no. of isolates tested)			
	United States (203)	Canada (61)	South America (42)	All (306)
C. albicans	56.2	52.5	40.5	53.3
C. glabrata	18.7	11.5	2.4	15.0
C. parapsilosis	8.9	22.9	38.1	15.7
C. tropicalis	6.9	8.2	11.9	7.8
C. krusei	2.5	1.6		2.0
C. guilliermondii	0.5		2.4	0.7
Candida spp.	6.4	3.3	4.7	5.8

Organism identification. All fungal blood culture isolates were identified at the participating institution 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 (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 (16). Isolates were stored as suspensions in water or on agar slants at 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 National Committee for Clinical Laboratory Standards (NCCLS) (5). Reference powders of fluconazole and itraconazole were obtained from their respective manufacturers. Quality control was performed by testing *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258.

Interpretive susceptibility criteria for fluconazole and itraconazole were those published by Rex et al. (14) and the NCCLS (5). As stated in the NCCLS M27-A document (5), isolates for which MICs are ≤8.0 μg/ml are susceptible to fluconazole, whereas those for which MICs are ≥64 μg/ml are resistant. Isolates for which the MIC of fluconazole is 16 to 32 μg/ml are considered susceptible dependent upon dose (S-DD), on the basis of data indicating a clinical response when >100 mg of fluconazole per day is given. For the purposes of this study, isolates were classified as susceptible to fluconazole if the MIC was ≤32 μg/ml and resistant if the MIC was ≥64 μg/ml. This designation encompasses both the susceptible and S-DD categories defined by NCCLS (5). As discussed by Rex et al. (14), the distinction between susceptible and S-DD is moot for patients with invasive candidiasis (candidemia) because these patients are treated with high doses of fluconazole (≥400 mg/day) that provide comparable responses in patients infected with isolates classified as either susceptible or S-DD. These breakpoints apply to all *Candida* species (including *C. glabrata*) with the exception of *C. krusei*, which is considered inherently resistant to fluconazole.

The interpretive breakpoints defined by NCCLS (5) for itraconazole are as follows: susceptible, ≤0.12 μg/ml; S-DD, 0.25 to 0.5 μg/ml; and resistant, ≥1.0 μg/ml. Although clinical correlates for itraconazole MICs and invasive candidal infections are not yet available, we have combined the susceptible and S-DD categories for itraconazole in the present study as described above for fluconazole. Thus, isolates in this study were classified as susceptible to itraconazole if the MIC was ≤0.5 μg/ml and resistant if the MIC was ≥1.0 μg/ml.

RESULTS AND DISCUSSION

During the 12-month study period a total of 306 *Candida* BSIs were reported by 34 SENTRY Program participants (22 in the United States, 6 in Canada, and 6 in South America). The original identification assigned by the participating center was confirmed for 97% of the isolates. Among the 306 BSIs, 80.2% were nosocomial (75% in the United States, 93% in Canada, and 82% in South America) and 50% occurred in patients hospitalized in an intensive care unit.

The frequencies of BSIs due to the various species of *Candida* in each country are presented in Table 1. Overall, 163 (53.3%) were due to *C. albicans*, 48 (15.7%) were due to *C. parapsilosis*, 46 (15.0%) were due to *C. glabrata*, 24 (7.8%) were due to *C. tropicalis*, 6 (2.0%) were due to *C. krusei*, 2 (0.7%) were due to *C. guilliermondii*, and 17 (5.6%) were due to *Candida* spp., not otherwise specified. However, the distribution of species varied markedly by country. In the United States, the distribution was very similar to that reported earlier (7, 9, 11), with 43.8% of BSIs due to non-*C. albicans* species. As observed by both Pfaller et al. (9, 11) and Nguyen et al. (6), *C. glabrata* was the most common non-*C. albicans* species in the United States. The proportion of non-*C. albicans* BSIs was slightly higher in Canada (47.5%). *C. parapsilosis*, not *C. glabrata*, was the most common non-*C. albicans* species in Canadian centers. Remarkably, *C. parapsilosis* accounted for 38.1% of all BSIs in South America. Virtually all of these infections were nosocomial and 87% occurred in patients hospitalized in intensive care units. *C. albicans* (40.5%) was the most common species seen in South America, and *C. tropicalis* accounted for 11.9% of BSIs. Only one BSI due to *C. glabrata* was observed in South American hospitals.

The difference in species distribution observed among the three countries is striking. As noted by Wingard (17), the frequency of candidemia due to non-*C. albicans* species may be quite variable among different institutions and is likely influenced by many factors including underlying disease, cytotoxic chemotherapy, and antimicrobial usage patterns including usage of antifungal agents. The influence of antifungal therapy on infection with various species of *Candida* has been documented by both Wingard et al. (18, 19) and Abi-Said et al. (1). These two groups of investigators reported independently that BSIs due to *C. albicans* and *C. tropicalis* were more likely to occur among hospitalized individuals who had not received fluconazole, whereas those patients who had received fluconazole were more likely to become infected with *C. glabrata* or *C. krusei*. In contrast, Abi-Said et al. (1) observed that infections due to *C. parapsilosis* were not influenced by exposure to fluconazole or other antifungal agents and were associated with the presence of intravascular catheters. Notably, a recent report by Levin et al. (4) described a cluster of *C. parapsilosis* BSIs occurring in a Brazilian hospital. They found the presence of intravascular catheters to be a significant risk factor and documented carriage of the infecting strain on the hands of health care workers. Given these observations, it is likely that differences in antifungal usage and in infection control practices are responsible for the differences in species distribution observed in the present study.

In vitro susceptibility testing of the 306 isolates of *Candida* species against fluconazole and itraconazole revealed that 97.7% were susceptible to fluconazole and 91.5% were susceptible to itraconazole at the recently published NCCLS MIC interpretive breakpoint concentrations (Table 2) (5, 14). Differences in the susceptibilities of isolates from the three areas to these triazole antifungal agents were noted. The proportion of isolates resistant to itraconazole was higher in the United States (11.3%; MIC at which 90% of isolates are inhibited [MIC_{90}], 1.0 μg/ml) than in Canada (3.3%; MIC_{90}, 0.25 μg/ml) or South America (2.4%; MIC_{90}, 0.25 μg/ml). Only small differences in the proportion of isolates resistant to fluconazole were noted: 2.5% of U.S. isolates were resistant to fluconazole (MIC_{90}, 16 μg/ml), whereas 1.6% (MIC_{90}, 8.0 μg/ml) and 2.4% (MIC_{90}, 4.0 μg/ml) of isolates in Canada and South America, respectively, were resistant to fluconazole.

The differences in antifungal susceptibilities among isolates from the three countries is almost entirely explained by differences in species distribution. Among the different species of *Candida*, high-level resistance to fluconazole (MIC, ≥64 μg/ml) and itraconazole (MIC, ≥1.0 μg/ml) was observed with *C. glabrata* and *C. krusei* and more rarely among the other *Candida* species (Table 3). Isolates of *C. albicans*, *C. parapsilosis*, *C. tropicalis*, and *C. guilliermondii* were all highly susceptible to both fluconazole (99.4 to 100% susceptible) and itraconazole (95.8 to 100% susceptible). In contrast, 8.7% of *C. glabrata* isolates (MIC_{90}, 32 μg/ml) and 100% of *C. krusei* isolates were

TABLE 2. Antifungal activities of fluconazole and itraconazole against BSIs of *Candida* spp. from three geographic regions

Country	No. of isolates	Antifungal agent	MIC (μg/ml)			% R[a]
			Range	50%	90%	
United States	203	Fluconazole	0.12–>128	0.5	16	2.5
		Itraconazole	0.015–>8.0	0.12	1.0	11.3
Canada	61	Fluconazole	0.12–128	0.5	8.0	1.6
		Itraconazole	0.015–0.5	0.12	0.25	3.3
South America	42	Fluconazole	0.12–>128	0.5	4.0	2.4
		Itraconazole	0.015–8.0	0.12	0.25	2.4
All	306	Fluconazole	0.12–>128	0.5	8.0	2.3
		Itraconazole	0.015–>8.0	0.12	0.5	8.5

[a] % R, percent resistant by using the interpretive breakpoint criteria of NCCLS (5): fluconazole resistance, ≥64 μg/ml; itraconazole resistance, ≥1.0 μg/ml.

resistant to fluconazole and 36.9% of *C. glabrata* (MIC_{90}, 2.0 μg/ml) and 66.6% of *C. krusei* isolates (MIC_{50}, 1.0 μg/ml) were resistant to itraconazole. Within each species there were no geographic differences in the susceptibilities of the isolates to either fluconazole or itraconazole (data not shown). Thus, the overall differences in antifungal susceptibility among stated areas (Table 2) were influenced by the higher proportion of *C. glabrata* and *C. krusei* in the United States compared to that in Canada or South America.

Although these data support a consistent pattern among U.S. medical centers toward higher rates of BSI due to species of *Candida*, such as *C. glabrata* and *C. krusei*, that are less susceptible to the triazoles, the situation is somewhat different in Canada and South America. The predominance of *C. parapsilosis* over *C. glabrata* and the almost total absence of triazole-resistant strains of *Candida* spp. in Canada are similar to those in early reports of *Candida* BSIs in the United States (8, 13). This suggests that less selection pressure for triazole resistance exists in Canada. The prominence of *C. parapsilosis* and the almost complete lack of *C. glabrata* and *C. krusei* in South America also suggests reduced triazole selective pressure but raises the specter of significant infection control issues given the recognized role of *C. parapsilosis* as an exogenous pathogen (4, 7, 9).

Aside from *C. glabrata* and *C. krusei*, the activities of fluconazole and itraconazole remained excellent against *Candida* species causing BSIs in the Americas. This is consistent with earlier reports from the United States (8, 13); however, it differs from recent data reported by Pfaller et al. (11) from the SCOPE Nosocomial BSI Surveillance Program. Data from the SCOPE Program in 1995 and 1996 indicated that although approximately 90% of U.S. *C. albicans* isolates causing BSIs were susceptible to fluconazole and itraconazole, there were significant regional differences in susceptibility to these agents. Decreased susceptibility to fluconazole and itraconazole was observed among *C. albicans* isolates in the Southeast and Northwest regions of the United States, with fluconazole and itraconazole MIC_{90}s of >128 and >8.0 μg/ml, respectively. In contrast, the present study (SENTRY Program) showed no regional variation (data not shown) and the virtually complete susceptibility of *C. albicans* isolates causing BSIs to both tested triazoles (Table 3). The reasons for these differences are not immediately apparent, although the study populations in these two surveillance programs were dissimilar. In particular, the

TABLE 3. In vitro susceptibilities of BSIs of *Candida* spp. tested to fluconazole and itraconazole

Species	No. of isolates	Antifungal agent	MIC (μg/ml)			% R[a]
			Range	50%	90%	
C. albicans	163	Fluconazole	0.12–>128	0.25	1.0	0.6
		Itraconazole	0.015–>8.0	0.06	0.12	0.6
C. glabrata	46	Fluconazole	1.0–>128	8.0	32	8.7
		Itraconazole	0.12–>8.0	0.5	2.0	36.9
C. parapsilosis	48	Fluconazole	0.12–4.0	1.0	2.0	0
		Itraconazole	0.015–0.5	0.12	0.25	0
C. tropicalis	24	Fluconazole	0.25–4.0	0.5	2.0	0
		Itraconazole	0.03–1.0	0.12	0.5	4.2
C. krusei	6	Fluconazole	32–64	32		100[b]
		Itraconazole	0.12–2.0	1.0		66.6
Candida spp.[c]	19	Fluconazole	0.25–16	2.0	16	0
		Itraconazole	0.03–2.0	0.25	1.0	15.8

[a] % R, percent resistant by using interpretive breakpoint criteria of the NCCLS (5): fluconazole resistance, ≥64 μg/ml; itraconazole resistance, ≥1.0 μg/ml.
[b] Isolates of *C. krusei* are considered resistant to fluconazole, irrespective of the MIC.
[c] Includes *C. guilliermondii* (2 isolates) and *Candida* spp. (17 isolates).

SENTRY Program does not include hospitals in Georgia or Florida, whereas 60% of triazole-resistant *C. albicans* isolates in the SCOPE Program came from hospitals in those two states (11).

In comparing these data it is important to realize that the results of most surveillance studies have potential biases that reflect the population surveyed, the method for data collection, and the underlying purposes for data collection (3). Significant differences may exist regarding patterns of antimicrobial resistance and usage, and these differences are likely to affect the ability to compare data among different studies (3). Thus, longitudinal surveillance (SENTRY Program) by the same methods and study sites is important in providing accurate estimates of trends in antibacterial and antifungal resistance (9–12).

In summary, we have provided an initial comparison of differences in species distribution and overall antifungal susceptibility profiles among BSI-causing *Candida* isolates from regions of the Americas (the United States, Canada, and South America). The results document the sustained activities of the triazole antifungal agents, fluconazole and itraconazole, against all BSI isolates except *C. glabrata* and *C. krusei*. The differences in species distribution observed among the three areas may be due to several factors, but they most likely reflect differences in antifungal usage and infection control practices. These issues must now be prospectively addressed in future surveillance activities.

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