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SUPPLEMENT ARTICLE

Twenty Years of the SENTRY Antifungal Surveillance Program: Results for *Candida* Species From 1997–2016

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Background. The emergence of antifungal resistance threatens effective treatment of invasive fungal infection (IFI). Invasive candidiasis is the most common health care–associated IFI. We evaluated the activity of fluconazole (FLU) against 20 788 invasive isolates of *Candida* (37 species) collected from 135 medical centers in 39 countries (1997–2016). The activity of anidulafungin, caspofungin, and micafungin (MCF) was evaluated against 15 308 isolates worldwide (2006–2016).

Methods. Species identification was accomplished using phenotypic (1997–2001), genotypic, and proteomic methods (2006–2016). All isolates were tested using reference methods and clinical breakpoints published in the Clinical and Laboratory Standards Institute documents.

Results. A decrease in the isolation of *Candida albicans* and an increase in the isolation of *Candida glabrata* and *Candida parapsilosis* were observed over time. *Candida glabrata* was the most common non–*C. albicans* species detected in all geographic regions except for Latin America, where *C. parapsilosis* and *Candida tropicalis* were more common. Six *Candida auris* isolates were detected: 1 each in 2009, 2013, 2014, and 2015 and 2 in 2016; all were from nosocomial bloodstream infections and were FLU-resistant (R). The highest rates of FLU-R isolates were seen in *C. glabrata* from North America (NA; 10.6%) and in *C. tropicalis* from the Asia-Pacific region (9.2%). A steady increase in isolation of *C. glabrata* and resistance to FLU was detected over 20 years in the United States. Echinocandin-R (EC-R) ranged from 3.5% for *C. glabrata* to 0.1% for *C. albicans* and *C. parapsilosis*. Resistance to MCF was highest among *C. glabrata* (2.8%) and *C. tropicalis* (1.3%) from NA. Mutations on FKS hot spot (HS) regions were detected among 70 EC-R isolates (51/70 were *C. glabrata*). Most isolates harboring FKS HS mutations were resistant to 2 or more ECs.

Conclusions. EC-R and FLU-R remain uncommon among contemporary *Candida* isolates; however, a slow and steady emergence of resistance to both antifungal classes was observed in *C. glabrata* and *C. tropicalis* isolates.

Keywords. *Candida*; SENTRY; surveillance.

Antimicrobial resistance (AMR) is a serious problem with multidrug-resistant (MDR) (resistant to at least 2 classes of agents) strains of fungi and bacteria that affect medical progress in many regions of the world [1–4]. Collecting AMR surveillance data is essential to define the scope of the resistance problem and to develop interventions that improve the appropriate use of antimicrobial agents and decrease resistance selection pressure [5–7]. Another important effort is to understand the mechanisms of resistance whereby microorganisms avoid the effects of antimicrobial agents and to use this information to develop new agents, or modify older agents, that retain potent activity against the key target pathogens [1, 8, 9]. AMR reduces the potential efficacy of agents, including antifungal agents such as the azole and echinocandin classes, that are commonly used to treat or prevent serious fungal infections in target patient populations [6, 10, 11].

The burden of invasive fungal infections (IFIs) for patients and health care systems is difficult to measure [2, 12]; however, it is well recognized that IFIs are associated with high morbidity and mortality rates and elevated health care costs. A higher prevalence of IFI has been observed in recent decades due to the increasing immunocompromised patient population, including individuals living with HIV, organ transplant recipients, and cancer patients [13, 14]. Increasing populations of the elderly, neonates, and patients requiring invasive therapies also contribute to higher IFI rates [5, 6, 15].

Candidemia and other forms of invasive candidiasis (IC; including infections of normally sterile body fluids, deep tissues, and organs) are the most important of the invasive mycoses [1, 16–18]. Although *Candida* isolates displaying resistance to clinically available antifungal agents are still uncommon, these organisms are increasingly reported worldwide [19, 20]. Thus, continuously monitoring antifungal susceptibility patterns and resistance mechanisms to clinically used antifungal agents is increasingly important.

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The epidemiology of candidemia and IC (collectively referred to as IC for the purposes of this discussion) has been described in numerous single-center, sentinel, and population-based surveys conducted worldwide [5–7, 21, 22]. However, the dynamic nature of IC trends in the United States and elsewhere suggests that this issue still merits considerable monitoring [6, 12, 23–26]. The SENTRY Antifungal Surveillance Program is a global program that has been ongoing for 20 years (1997–2016) and collects consecutive invasive *Candida* isolates from medical centers located in North America (NA), Europe (EUR), Latin America (LATAM), and the Asia-Pacific (APAC) region during each calendar year. *Candida* spp. isolates are evaluated for susceptibility against various antifungal agents used clinically to treat and prevent IC [27]. Applying modern methods for species identification, testing antifungal susceptibility, and characterizing antifungal resistance mechanisms provides a level of standardization and clarity that makes these observations useful in the ongoing fight against antifungal resistance [1, 5, 6, 9, 28–33].

We have reported broad geographic trends in the isolation of various *Candida* species from clinical specimens and the accompanying rates of antifungal resistance in the United States and internationally in numerous SENTRY Program publications in the peer-reviewed literature spanning 1997 through 2016 [9, 29, 34]. We now summarize the geographic and temporal variations in the frequency of *Candida* species that cause IC and associated antifungal resistance profiles using the extensive SENTRY Antifungal Surveillance Program database, which includes results for 20 788 invasive isolates of *Candida* species from 135 medical centers in 39 nations. In this analysis, we emphasize regional epidemiological data and their impact on empiric antifungal therapy.

METHODS

Study Design

The SENTRY Program was established to monitor the predominant pathogens and antimicrobial resistance patterns of nosocomial and community-onset infections via a broad network of sentinel medical centers distributed by geographic location and size. Participating medical centers submit organisms each calendar year through a prevalence-based approach across several infection types. The current study design collects clinical isolates under the following objectives: bloodstream, skin and skin structure, respiratory, urinary tract, intra-abdominal, and invasive fungal infections, as well as pathogens from patients hospitalized with pneumonia (described at https://www.jmilabs.com/sentry-surveillance-program/). Participating institutions contributing *Candida* spp. isolates have included 135 medical centers in 39 countries: 41 in the United States, 4 in Canada, 14 in LATAM, 25 in APAC, and 51 in EUR.

Each participating medical center contributed findings (organism identification, isolation date, and site) on consecutive IC episodes in each calendar month. Additional demographic and epidemiological data were recorded on a data form forwarded with each isolate. All isolates were saved and sent weekly to either the University of Iowa (Iowa City, IA; 1997–2005) or JMI Laboratories (North Liberty, IA; 2006–2016) for storage and for further characterization by reference identification and susceptibility testing methods.

Organism Identification

Isolates (1 per patient infection episode) were identified at participating institutions using methods routinely employed at the submitting laboratory, including the use of the Vitek, MicroScan, API, and AuxaColor systems supplemented by classical methods for yeast identification [35]. Isolates were submitted to the 2 monitoring laboratories, where identification was confirmed by morphological, biochemical, and molecular methods [9, 23, 30, 35]. All isolates were subcultured to CHROMagar (Becton, Dickinson and Company, Sparks, MD) to differentiate *Candida albicans*/*Candida dubliniensis, Candida tropicalis*, and *Candida krusei*. Isolates collected and tested from 2006 to 2009 showing morphology discrepant with the identification submitted by the participating laboratory had identification confirmed using the Vitek yeast identification system (bioMerieux, Hazelwood, MO). Any further discrepancies were resolved by molecular or proteomic methods, as described below. Biochemical and physiological tests such as growth at 45°C (*C. albicans*, *C. dubliniensis*) and assimilation of trehalose (*Candida glabrata*) were applied centrally to isolates submitted from 2010 through 2016. *C. albicans, C. glabrata, C. parapsilosis, C. tropicalis*, and *C. krusei* isolates that were not identified by these methods during 2010 and 2011, and all uncommon species were identified using sequence-based methods for internal transcribed spacer region and/or 28S ribosomal subunits, according to protocols previously described [9, 30]. From 2012 to 2016, isolate identification was confirmed by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker, Billerica, MA). Isolates that were not identified by either phenotypic or proteomic methods were identified using sequence-based methods, as previously described [30, 36, 37].

Susceptibility Testing

All isolates were tested by broth microdilution according to Clinical and Laboratory Standards Institute (CLSI) methods, as outlined in documents M27-A3 and M27-S4 [38, 39]. The systemically active antifungal agents tested were anidulafungin, caspofungin, micafungin, fluconazole, and voriconazole. This report focuses primarily on resistance to fluconazole and the echinocandins. The results for voriconazole will only be used when discussing cross-resistance between azoles and echinocandins. The range of antifungal agent concentrations tested was 0.008–16 mg/L for the echinocandins and voriconazole and 0.12–128 mg/L for fluconazole. Minimum inhibitory

concentration (MIC) results for all tested agents were determined visually after 24 hours of incubation at 35°C as the lowest concentration of agent that resulted in ≥50% inhibition of growth relative to the growth control. CLSI clinical breakpoints (CBPs) were applied for the 5 most "common" species of *Candida* (*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis,* and *C. krusei*), for which echinocandins, fluconazole, and voriconazole are used in treatment. Epidemiological cutoff values (ECVs) were applied when available for the other species tested [37, 38, 40]. Recognizing that CBPs for fluconazole and the echinocandins have changed over the last 20 years, we have applied only the most contemporary CBPs and ECVs to the entire *Candida* spp. collection [38–40]. Quality control was performed as recommended in CLSI M27-A3 using *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019. All results were within established ranges.

Screening for FKS HS Mutations

Candida spp. isolates with MIC values higher than the CBP for the echinocandin compounds were submitted to polymerase chain reaction (PCR) and sequencing for hot spots (HS) of the *FKS* genes encoding the 1,3 β-D-glucan synthase (GS) subunits. PCR amplification was completed using previously described oligonucleotides for the *FKS1* and *FKS2* HS 1 and 2 [41, 42].

RESULTS

Organism Collection

A total of 20 788 invasive isolates of *Candida* spp. (37 species) were submitted to the SENTRY Program central monitoring sites for identification and antifungal susceptibility testing of fluconazole between 1997 and 2016, and of echinocandins between 2006 and 2016. The number of isolates submitted each year ranged from 320 to 2770. Since 2006, isolates submitted have undergone the most rigorous identification (confirmation of species identification using either sequence-based or proteomic methods) and included *C. albicans* (7179), *Candida auris* (6), *Candida blankii* (1), *Candida bracarensis* (5), *Candida cacao* (1), *Candida catenulata* (3), *C. dubliniensis* (264), *Candida duobushaemulonii* (3), *Candida fabianii* (14), *Candida famata* (2), *Candida fermentati* (29), *Candida fluviatilis* (1), *C. glabrata* (2860), *Candida guilliermondii* (91), *Candida haemulonii* (10), *Candida inconspicua* (12), *Candida intermedia* (4), *C. intermedia/pseduointermedia* (2), *Candida kefyr* (94), *C. krusei* (421), *Candida lambica* (1), *Candida lipolytica* (10), *Candida lusitaniae* (277), *Candida metapsilosis* (33), *Candida nivariensis* (4), *Candida norvegensis* (4), *Candida orthopsilosis* (82), *C. parapsilosis* (2433), *Candida pararugosa* (7), *Candida pelliculosa* (22), *Candida quercitrusa* (2), *Candida rugosa* (4), *Candida sojae* (1), *Candida thasaenensis* (1), *Candida thermophila* (2), *C. tropicalis* (1418), *Candida utilis* (3), and unspeciated *Candida* (6).

Global Trends in Species Distribution and Antifungal Susceptibility Among *Candida* Isolates From IC

Temporal Distribution

Among the 20 788 *Candida* isolates submitted for testing from 1997 to 2016, 46.9% were *C. albicans*, 18.7% were *C. glabrata*, 15.9% were *C. parapsilosis*, 9.3% were *C. tropicalis,* 2.8% were *C. krusei*, and 6.5% were miscellaneous *Candida* spp. (Table 1). The rank order of the 5 most common species varied slightly over time, although *C. albicans* was the predominant species each year. Notably, the frequency of *C. albicans* decreased steadily from 57.4% in 1997–2001 to 46.4% in 2015–2016. *C. glabrata* was the most common non-*albicans* species overall and showed a steady increase from 16.0% in 1997–2001 to 19.6% in 2015–2016. *C. parapsilosis* was third in rank order and increased in frequency from 12.3% in the 1997–2001 time period to 17.8% in 2009–2011; however, the frequency of this species as a cause of IC decreased after 2011 and was 14.4% in 2015–2016. Given the well-recognized association of *C. parapsilosis* bloodstream infection (BSI) with central venous catheters [43], it is notable that a marked decrease in central line–associated BSIs has been identified in US hospitals over this time period [44, 45]. The frequency of *C. tropicalis* and *C. krusei* as IC isolates was more stable over time, with IC ranges of 8.3%–10.7% and 2.1%–3.2%, respectively. Notably, the overall frequency of *C. krusei* as a cause of IC remained low at 2.8% (range, 2.1%–3.2%) for the 20-year period despite continued utilization of fluconazole in most medical centers [46–49]. In aggregate, the frequency of miscellaneous species of *Candida* (non-top-5 species) showed a steady increase from 2.7% of infections in 1997–2001 to 8.5% in 2015–2016.

Table 1. Species Distribution of *Candida* Isolates: SENTRY Program, 1997–2016

		% by Species				
Year	No. Tested	CA	CG	CP	CT	CK
1997–2001	5067	57.4	16.0	12.3	9.1	2.5
2006–2008	2647	51.2	15.9	16.8	10.7	2.1
2009–2011	4080	45.3	18.9	17.6	10.0	2.6
2012–2014	4928	46.3	19.3	15.1	8.6	3.2
2015–2016	3653	46.4	19.6	14.4	8.3	2.8

Abbreviations: CA, *C. albicans*; CG, *C. glabrata*; CK, *C. krusei*; CP, *C. parapsilosis*; CT, *C. tropicalis*.

Geographic Distribution

The frequencies of IC due to the 5 most common species of *Candida* in the 4 geographic areas participating in the SENTRY Program are shown in Table 2. *C. albicans* was most common in EUR (52.5%) and least common in NA (United States and Canada; 42.7%), whereas *C. glabrata* was most common in NA (24.3%) and least common in LATAM (7.1%). *C. parapsilosis* and *C. tropicalis* were more common than *C. glabrata* in LATAM (24.3% and 17.0% vs 7.1%, respectively). *C. tropicalis* was also a frequent cause of IC in the APAC region (14.1%). *C. krusei* was more common in NA (2.9%) and EUR (3.0%), and other miscellaneous species of *Candida* were common in APAC (7.3%) and NA (7.3%) (data not shown).

Trends in Fluconazole Resistance in Relation to Time, Geographic Area, and Species of *Candida* in IC

Fluconazole Resistance Variation by Species and by Year

The fluconazole resistance profile of the 4 most common species of *Candida* ranged from 0.3% (*C. albicans*) to 8.1% resistant (*C. glabrata*) using the most recent CBPs (Table 3): *C. krusei* is not listed as it is considered intrinsically (100.0%) resistant to fluconazole [38, 39, 50]. The low fluconazole resistance rate among *C. albicans* isolates is consistent with previous reports [51] and showed very little change from 0.2% in 1997–2001 to 0.1% in 2015–2016. Resistance to fluconazole showed an increase from 1997 through 2014 for *C. glabrata* (8.6% to 10.1%) and *C. tropicalis* (2.5% to 4.9%), with a slight decline for both species in 2015–2016, possibly due to increased use of echinocandins over fluconazole in those years [26, 44, 46, 48]. Given past recommendations to use fluconazole as firstline therapy for *C. parapsilosis* infections [52], it is notable that fluconazole resistance increased over time for this species (Table 3).

Fluconazole Resistance by Geographic Area and Species

Table 4 presents the resistance rates for fluconazole tested against the 4 most common species of *Candida* stratified by geographic region from 2006 through 2016. Just as geographic variation was observed in the frequency of isolation of these species (Table 2), variation in the frequency of fluconazole resistance was noted as well. Although fluconazole was highly active against *C. albicans* in all geographic regions, slightly higher rates of resistance were seen in isolates from NA (0.4%) compared with those from the other 3 regions (range, 0.1%–0.2%).

The overall increase in fluconazole resistance for *C. glabrata* in this survey was reflected in high rates of resistance in isolates from APAC (6.8%) and NA (10.6%). Not only was *C. glabrata* an uncommon cause of IC in LATAM, it was also less resistant to this agent (2.6%) compared with the other monitored regions.

C. parapsilosis isolates from EUR (4.6% resistance) and LATAM (4.3% resistance) showed the highest rates of resistance to fluconazole, whereas only 0.6% of C. *parapsilosis* isolates from the APAC region were resistant.

Resistance to fluconazole was detected in 9.2% of *C. tropicalis* isolates from the APAC region and was considerably less frequent in the other 3 regions (range, 1.1%–2.9%) (Table 4). These findings build upon our previous global surveillance data that indicate that the highest rates of fluconazole resistance among *C. tropicalis* BSI isolates were observed among isolates from the APAC region [53].

Previously, we examined the fluconazole susceptibilities of BSI isolates of *C. glabrata* from US centers participating in the SENTRY Program and grouped the isolates by geographic location within the United States from 1992 to 2007 [54]. In the present study, we build upon this experience and report the fluconazole susceptibilities of an additional 5366 *C. glabrata* isolates collected from sentinel surveillance sites throughout the United States from 2008 through 2016 and stratify the results by US region (Table 5). Overall, *C. glabrata* accounted for 25% of all US IC isolates, ranging from 22% in the Northeast to 27% in the West (Table 5). Compared with 1992–2001 [29] and 2001–2007 surveys [54], the proportion of IC isolates that were *C. glabrata* increased in all 4 regions.

Fluconazole susceptibilities of *C. glabrata* isolates also varied by US region (Table 5). The rates of fluconazole resistance among the *C. glabrata* isolates from 2001–2007 increased compared with those from 1992–2001 in all regions except for the South, where the rate was unchanged. Fluconazole resistance rates decreased slightly in all regions except the West in the most recent (2008–2016) survey period. Overall, 11% of the 2008–2016 US *C. glabrata* isolates were resistant to fluconazole, compared with 9% in 1992–2001 (Table 5).

Table 2. Species Distribution of *Candida* Isolates by Geographic Region: SENTRY Program, 2006–2016

		% by Species				
Region	No. Tested	CA	CG	CP	CT	CK
APAC	1314	46.0	17.9	12.9	14.1	1.8
EUR	5964	52.5	16.0	15.4	7.5	3.0
LATAM	1629	43.9	7.1	24.3	17.0	2.0
NA	6401	42.7	24.3	14.8	8.0	2.9
Total	15 308	46.7	18.7	15.9	9.3	2.8

Abbreviations: APAC, Asia-Pacific; CA, *C. albicans*; CG, *C. glabrata*; CK, *C. krusei*; CP, *C. parapsilosis*; CT, *C. tropicalis*; EUR, Europe; LATAM, Latin America; NA, North America.

Table 3. Trends in Fluconazole Resistance: SENTRY Program, 2006–2016

Species	Year	No. Tested	% Resistant (No.)[a]
C. albicans	2006–2008	1356	0.2 (3)
	2009–2011	1849	0.2 (4)
	2012–2014	2283	0.4 (10)
	2015–2016	1691	0.1 (2)
	2006–2016	7179	0.3 (19)
C. glabrata	2006–2008	420	8.6 (36)
	2009–2011	773	7.6 (59)
	2012–2014	951	10.1 (96)
	2015–2016	716	5.6 (40)
	2006–2016	2860	8.1 (231)
C. parapsilosis	2006–2008	446	5.4 (24)
	2009–2011	717	2.5 (18)
	2012–2014	744	3.2 (24)
	2015–2016	526	5.5 (29)
	2006–2016	2433	3.9 (95)
C. tropicalis	2006–2008	282	2.5 (7)
	2009–2011	407	2.0 (8)
	2012–2014	426	4.9 (21)
	2015–2016	303	3.3 (10)
	2006–2016	1418	3.2 (46)

[a]Percent resistant (no. of resistant isolates) by CLSI [38] criteria.

Studies have shown that the prevalence of *C. glabrata* as a cause of BSI is potentially related to many disparate factors in addition to fluconazole exposure, including geography, patient age, and other characteristics of the patient population studied [6, 16, 24, 26, 55, 56]. Few surveys have examined the frequency of isolation and resistance to fluconazole among *C. glabrata* isolates according to patient age group [5, 17, 23–25, 33, 54, 56, 57]. Table 6 shows the frequency of isolation and fluconazole resistance among *C. glabrata* isolates stratified according to patient age group for all geographic regions from 2006 through 2016. Previously, we demonstrated that although the proportion of BSI isolates of *Candida* that were *C. glabrata* increased with patient age in the United States, the rate of fluconazole resistance declined [54]. An identical trend was observed in the present geographically diverse study. The frequency of *C. glabrata* causing IC increased steadily from 6.4% in the ≤1–19-year age group to 22.3% in the ≥70-year age group, but only 4.0% of isolates in the older age group were resistant to fluconazole. The highest resistance rates were in the 20–49-year (11.8% resistant) and 50–69-year (9.8% resistant) age groups.

Table 4. Fluconazole Resistance by Geographic Region: SENTRY Program, 2006–2016

Species	Region	No. Tested	% Resistant (No.)[a]
C. albicans	APAC	605	0.2 (1)
	EUR	3129	0.2 (7)
	LATAM	715	0.1 (1)
	NA	2731	0.4 (10)
C. glabrata	APAC	235	6.8 (16)
	EUR	955	4.9 (47)
	LATAM	114	2.6 (3)
	NA	1556	10.6 (165)
C. parapsilosis	APAC	169	0.6 (1)
	EUR	918	4.6 (42)
	LATAM	396	4.3 (17)
	NA	950	3.7 (35)
C. tropicalis	APAC	185	9.2 (17)
	EUR	446	2.5 (11)
	LATAM	277	1.1 (3)
	NA	510	2.9 (15)

Abbreviations: APAC, Asia-Pacific; EUR, Europe; LATAM, Latin America; NA, North America.

[a]Fluconazole-resistant breakpoint values are ≥8 mg/L for *C. albicans, C. parapsilosis*, and *C. tropicalis* and ≥64 mg/L for *C. glabrata*.

Consistent with previous observations [54–56, 58, 59], very few infections due to *C. glabrata* were seen in the pediatric and adolescent age groups (≤19 years) (Table 6). Only 134 *C. glabrata* IC isolates from patients who were ≤19 years of age were submitted to the SENTRY Program. In contrast to the percentage of resistant isolates observed in 2008–2009 for isolates from this age group (0.0%) [56], 8.2% of the current isolates were resistant to fluconazole. This increased resistance may reflect the increased use of fluconazole prophylaxis and treatment in these groups of younger patients [16, 47, 60].

Cross-Resistance Between Fluconazole and Voriconazole

Voriconazole has been demonstrated to have useful clinical activity in treating mucosal and invasive forms of candidiasis [61, 62]. The clinical indication for using voriconazole in IC has been primarily for oral step-down therapy in patients with infections due to *C. krusei* and fluconazole-resistant, voriconazole-susceptible *C. glabrata* [50]. We have shown variable cross-resistance between fluconazole and voriconazole when tested against the common species of *Candida* causing IC [53, 63, 64]. These findings were confirmed in the present survey, where cross-resistance between fluconazole and voriconazole was common in fluconazole-resistant *C. albicans* (35.0% susceptible to voriconazole) and *C. parapsilosis* (32.7% susceptible to voriconazole) strains and virtually complete for fluconazole-resistant strains of *C. glabrata* (0.0% susceptible [MIC, ≤0.5 mg/L] to voriconazole) and *C. tropicalis* (3.6% susceptible to voriconazole) (data not shown). Conversely, voriconazole was reliably active against *C. krusei* (95.0% susceptible) isolates, all of which were resistant to fluconazole (data not shown). Aside from *C. krusei,* the other species of *Candida* usually encountered in IC are not optimal targets for voriconazole when fluconazole resistance is observed [50].

Trends in Echinocandin Resistance in Relation to Time, Geographic Area, and Species of *Candida* in IC

Variation in Echinocandin Resistance by Species and Surveillance Year

The echinocandin class of antifungal agents acts by inhibition of the synthesis of 1,3-β-D-glucan in the fungal cell wall [65]. All 3 available echinocandins—anidulafungin (Pfizer), caspofungin

Table 5. Temporal and Geographic Trends in the Frequency of Isolation and Resistance to Fluconazole Among *C. glabrata* Isolates in the United States

Region	Study Period	Total No. of *Candida* BSI Isolates	% of *C. glabrata* Isolates[a]	
			Among all Isolates	Resistant to Fluconazole
West	1992–2001	700	17	7
	2001–2007	61	34	10
	2008–2016	1216	27	16
Midwest	1992–2001	678	23	7
	2001–2007	1420	28	12
	2008–2016	1393	26	9
Northeast	1992–2001	819	21	11
	2001–2007	897	19	17
	2008–2016	1519	22	9
South	1992–2001	1486	15	11
	2001–2007	619	21	11
	2008–2016	1238	25	9
Total	1992–2001	3683	18	9
	2001–2007	2536	25	14
	2008–2016	5366	25	11

[a]Data compiled from references 9, 23, 54, 55.

(Merck), and micafungin (Astellas)—possess fungicidal activity against most species of *Candida*, including those resistant to polyenes [66] and to azoles [8]. Caspofungin, micafungin, and anidulafungin were approved for clinical use by the US Food and Drug Administration (FDA) in 2001, 2005, and 2006, respectively, and are now recommended as firstline agents for treating IC [50, 67].

Temporal variations in resistance to echinocandins for the 5 most common *Candida* species are shown in Table 7. Resistance to 1 or more of the echinocandins was distinctly uncommon among isolates of *C. albicans* (0.0%–0.1%), *C. parapsilosis* (0.0%–0.1%), *C. tropicalis* (0.5%–0.7%), and *C. krusei* (0.0%–1.7%). Resistance to anidulafungin (2.2%), caspofungin (3.5%), and micafungin (1.7%) was most prominent among *C. glabrata* isolates. No trend toward increasing resistance was seen over time for any of these species, although *C. tropicalis* exhibited an increase in resistance in 2015–2016 compared with previous years.

Previously, our investigators and others found echinocandin resistance in 8.0%–9.0% of fluconazole-resistant BSI isolates of *C. glabrata* [68–72]. In the SENTRY Program from 2006–2016, we noted co-resistance in fluconazole-resistant isolates of *C. glabrata* (5.5%–7.6%) and in fluconazole-resistant isolates of *C. tropicalis* (1.9%–3.6%) and *C. krusei* (0.0%–1.7%) as well (data not shown).

Emerging MDR strains of *Candida* spp. isolates are sure to complicate clinical decision-making at a time when few options exist for alternative antifungal therapy [4, 11, 73, 74]. Although the MDR phenotype is most often detected after prolonged exposure to both classes of agents [1, 6, 26, 65, 68, 70], recent studies have demonstrated that under stress conditions, *MSH2* DNA mismatch repair gene mutations may produce a hypermutable state and facilitate rapid acquisition of fluconazole, echinocandin, and amphotericin B resistance [71]. These findings may help to explain why echinocandin resistance in some studies has been associated with fluconazole exposure, although the drug targets and resistance mechanisms are distinctly different [1, 6, 26, 68–72].

Micafungin Resistance by Geographic Area and by Species

Geographic trends in the resistance to micafungin for the 5 most common species of *Candida* are shown in Table 8. Resistance was not detected among *C. parapsilosis or C. krusei* isolates from the 4 global geographic regions when using the current CLSI CBP values [38]. Resistance to micafungin (2.8%) was most prominent among *C. glabrata* isolates from NA, whereas none of the *C. glabrata* isolates from LATAM were resistant to micafungin (Table 8). Micafungin resistance rates were 0.1% for *C. albicans* isolates collected in NA and

Table 6. Frequency of Isolation and Fluconazole Resistance of *C. glabrata* Isolates by Patient Age Group From All Geographic Regions, 2006–2016

Patient Age Group, y	Total No. of *Candida* Isolates (%)	No. of *C. glabrata* Isolates Tested (% of Total)	% (No.) of *C. glabrata* Isolates Resistant to Fluconazole
≤1–19	2104 (14.7)	134 (6.4)	8.2 (11)
20–49	2980 (21.0)	541 (18.2)	11.8 (64)
50–69	5067 (35.3)	1097 (21.6)	9.8 (107)
≥70	4111 (29.0)	916 (22.3)	4.0 (37)

Table 7. Trends in Echinocandin Resistance: SENTRY Program, 2006–2016

Species	Year	No. Tested	Antifungal Agent	% Resistant (No.)
C. albicans	2006–2008	1356	Anidulafungin	0.0 (0)
			Caspofungin	0.1 (1)
			Micafungin	0.0 (0)
	2009–2011	1849	Anidulafungin	0.0 (0)
			Caspofungin	0.2 (3)
			Micafungin	0.1 (2)
	2012–2014	2283	Anidulafungin	0.0 (0)
			Caspofungin	<0.1 (1)
			Micafungin	<0.1 (1)
	2015–2016	1691	Anidulafungin	0.0 (0)
			Caspofungin	0.2 (3)
			Micafungin	0.2 (3)
	2006–2016	7179	Anidulafungin	0.0 (0)
			Caspofungin	0.1 (8)
			Micafungin	0.1 (6)
C. glabrata	2006–2008	420	Anidulafungin	2.6 (11)
			Caspofungin	6.9 (29)
			Micafungin	2.8 (6)
	2009–2011	773	Anidulafungin	1.8 (14)
			Caspofungin	4.5 (35)
			Micafungin	1.0 (8)
	2012–2014	951	Anidulafungin	2.8 (27)
			Caspofungin	2.9 (28)
			Micafungin	2.4 (23)
	2015–2016	716	Anidulafungin	1.5 (11)
			Caspofungin	1.3 (9)
			Micafungin	1.3 (9)
	2006–2016	2860	Anidulafungin	2.2 (63)
			Caspofungin	3.5 (101)
			Micafungin	1.7 (46)
C. parapsilosis	2006–2008	446	Anidulafungin	0.0 (0)
			Caspofungin	0.0 (0)
			Micafungin	0.0 (0)
	2009–2011	717	Anidulafungin	0.4 (3)
			Caspofungin	0.0 (0)
			Micafungin	0.0 (0)
	2012–2014	744	Anidulafungin	0.0 (0)
			Caspofungin	0.0 (0)
			Micafungin	0.0 (0)
	2015–2016	526	Anidulafungin	0.0 (0)
			Caspofungin	0.0 (0)
			Micafungin	0.0 (0)
	2006–2016	2433	Anidulafungin	0.1 (3)
			Caspofungin	0.0 (0)
			Micafungin	0.0 (0)
C. tropicalis	2006–2008	282	Anidulafungin	0.0 (0)
			Caspofungin	1.1 (3)
			Micafungin	0.0 (0)
	2009–2011	407	Anidulafungin	0.2 (1)
			Caspofungin	0.0 (0)
			Micafungin	0.0 (0)
	2012–2014	426	Anidulafungin	0.5 (2)
			Caspofungin	0.2 (1)
			Micafungin	0.2 (1)
	2015–2016	303	Anidulafungin	1.3 (4)
			Caspofungin	2.0 (6)
			Micafungin	2.0 (6)

Table 7. Continued

Species	Year	No. Tested	Antifungal Agent	% Resistant (No.)
	2006–2016	1418	Anidulafungin	0.5 (7)
			Caspofungin	0.7 (10)
			Micafungin	0.6 (7)
C. krusei	2006–2008	55	Anidulafungin	3.6 (2)
			Caspofungin	7.3 (4)
			Micafungin	0.0 (0)
	2009–2011	107	Anidulafungin	0.0 (0)
			Caspofungin	1.9 (2)
			Micafungin	0.0 (0)
	2012–2014	158	Anidulafungin	0.6 (1)
			Caspofungin	0.6 (1)
			Micafungin	0.0 (0)
	2015–2016	101	Anidulafungin	0.0 (0)
			Caspofungin	0.0 (0)
			Micafungin	0.0 (0)
	2006–2016	421	Anidulafungin	0.7 (3)
			Caspofungin	1.7 (7)
			Micafungin	0.0 (0)

Echinocandin-resistant breakpoints are ≥1 mg/L for all 3 agents and *C. albicans, C. tropicalis*, and *C. krusei*; ≥8 mg/L for all 3 agents and *C. parapsilosis*; ≥0.5 mg/L for anidulafungin and caspofungin; and ≥0.25 mg/L for micafungin and *C. glabrata*.

EUR, but all isolates of *C. albicans* from other regions were susceptible to this agent. Similarly, micafungin-resistant *C. tropicalis* isolates were only detected in NA (1.3% resistant) and LATAM (0.5% resistant).

Previously, we examined the micafungin susceptibilities of BSI isolates of *C. glabrata* from US centers participating in the SENTRY Program and grouped the isolates by geographic area within the United States from 2001–2007 [54] and 2006–2011 [23]. In the present study, we build upon this experience and report the micafungin resistance for an additional 474 *C. glabrata* isolates collected from sentinel surveillance sites throughout the United States from 2014 through 2016 and stratify the results by US region (Table 9). Micafungin resistance rates among the *C. glabrata* isolates from 2014–2016 increased compared with rates from 2001–2007 and 2006–2011 in all regions except for the South, where the rate varied from 3.4% in 2001–2007 to 0.6% in 2006–2011 and was 2.0% in 2014–2016. The highest rates of resistance were noted in isolates from the West (5.1%) and the Northeast (6.3%). Notably, isolates of micafungin-resistant *C. glabrata* were detected in all 4 US regions in 2014–2016, compared with only 1 region (South) in 2001–2007, when caspofungin was the only echinocandin available for clinical use in the United States [48]. As seen with fluconazole (Table 6), the frequency of micafungin resistance varied with patient age; the highest rate of resistance was observed in the 20–49-year age group (5.1%), and the lowest rate in the ≥70-year age group (0.5%) (data not shown). These findings of increasing echinocandin resistance among invasive isolates of *C. glabrata* throughout the United States are comparable to findings reported from a population-based candidemia survey conducted from 2008 to 2014 [26].

Investigation of *FKS* Mutations in Echinocandin-Resistant *Candida* spp.

All 70 *Candida* spp. isolates displaying echinocandin MIC values higher than CBPs (either intermediate [I] or resistant [R]) or ECVs (*C. dubliniensis* and *C. kefyr* only) established by CLSI were screened for mutations in HS regions of the 1,3 β-D-GS-encoding genes. The majority of echinocandin-resistant or non-wild-type (non-WT) isolates (54/70, 77.1%) were from NA, and 51/70 (72.9%) were *C. glabrata* (Table 10). Eight *C. albicans* isolates were tested; all were nonsusceptible (NS; either intermediate [MIC, 0.5 mg/L] or resistant [MIC, ≥1 mg/L]) to caspofungin, and 7 were NS to micafungin. All exhibited mutations encoding an *FKS*1 HS1 alteration (S645P [4 isolates] and 1 each of F641S, F641I, S629P, and S654P) (Table 10). Only 4 (50.0%) of these isolates were NS (all were I) to anidulafungin; the remaining 4 isolates displayed susceptible (MIC, ≤0.25 mg/L) MIC values for anidulafungin despite harboring *FKS* mutations.

Fifty-one *C. glabrata* isolates displayed NS-type results for 1 or more of the echinocandins: 40 (78.4%) were NS to all 3, and all were NS to at least 2 echinocandins [40]. All 51 isolates harbored *FKS* HS alterations, including *FKS2* HS1 S663P (16 isolates), *FKS2* HS1 S663F (3 isolates), *FKS2* HS1 L662W (2 isolates), *FKS1* HS1 S629P (6 isolates), *FKS1* HS1 F625S (4 isolates), *FKS2* HS1 F659S/V/Y (8 isolates), and *FKS2* HS1 F659_del (3 isolates). Five isolates carried double mutations that were either *FKS1* HS1 S629P/*FKS2* HS1 S663P (2 isolates) or 1 isolate each of *FKS1* HS1 F625S/*FKS2* HS1 F659Y, *FKS1* HS1 R631S/S629P, or *FKS2* HS1 D666E/K753Q. The MIC for the double-mutant isolates *FKS1* HS1 S629P/*FKS2* HS1 S663P (recovered from Canada) were highly elevated for caspofungin (>8 mg/L) and

Table 8. Micafungin Resistance by Geographic Region: SENTRY Program, 2006–2016

Species	Region	No. Tested	% Resistant (No.)
C. albicans	APAC	597	0.0 (0)
	EUR	2869	0.1 (3)
	LATAM	590	0.0 (0)
	NA	2355	0.1 (3)
C. glabrata	APAC	234	0.4 (1)
	EUR	898	0.6 (5)
	LATAM	102	0.0 (0)
	NA	1420	2.8 (40)
C. parapsilosis	APAC	166	0.0 (0)
	EUR	863	0.0 (0)
	LATAM	334	0.0 (0)
	NA	827	0.0 (0)
C. tropicalis	APAC	179	0.0 (0)
	EUR	409	0.0 (0)
	LATAM	216	0.5 (1)
	NA	457	1.3 (6)
C. krusei	APAC	23	0.0 (0)
	EUR	169	0.0 (0)
	LATAM	30	0.0 (0)
	NA	168	0.0 (0)

Micafungin-resistant breakpoints are ≥1 mg/L for *C. albicans, C. tropicalis*, and *C. krusei*; ≥8 mg/L for *C. parapsilosis*; and ≥0.25 mg/L for *C. glabrata*.

Abbreviations: APAC, Asia-Pacific; EUR, Europe, LATAM, Latin America; NA, North America.

were at 4 mg/L for anidulafungin and micafungin; however, an isolate from Indiana carrying *FKS1* HS1 F625S/*FKS2* HS1 F659Y exhibited modestly elevated MIC values at 2 mg/L (resistant) for anidulafungin and caspofungin, and 0.5 mg/L (resistant) for micafungin, suggesting that these alterations might not have a cumulative effect. One isolate from Indiana carrying a double mutation on *FKS1* HS1 R631S/S629P was resistant to all 3 echinocandins, whereas another isolate from Germany with a double mutation on *FKS2* HS1 D666E/K753Q was resistant to anidulafungin and caspofungin but susceptible to micafungin. Finally, a mutation on *FKS2* HS1 P667T was observed in an isolate of *C. glabrata* from New York, and the MIC values for this isolate were low for anidulafungin (0.25 mg/L; intermediate) and micafungin (0.03 mg/L; susceptible) but resistant to caspofungin (MIC, 0.5 mg/L).

Among 9 isolates of *C. tropicalis* harboring *FKS* mutations, 8 were from the United States and 1 was from Brazil: *FKS1* HS1 mutations included S654P (3 isolates), S645P (3 isolates), and 1 each of F650S, F641S, and F641L. All isolates were NS, and 5 (55.6%) were resistant to all 3 agents. The single isolates of *C. dubliniensis* and *C. kefyr* that were non-WT (MIC>ECV) for 1 or more echinocandins were found to have mutations in either HS1 or HS2 of *FKS1*.

Whereas all HS mutations have been shown to influence the sensitivity of the GS enzyme complex to inhibition by the individual echinocandins, not all mutations will result in resistant or non-WT MIC values for all 3 echinocandins [75, 76]. For *C. albicans*, mutations at S641 and S645 are the most frequent and produce the most pronounced resistant phenotype [65, 76]. Previous reports indicated that *C. glabrata* isolates with the S663F mutation responded in vivo to high doses of either micafungin or caspofungin, but not to anidulafungin. In contrast, isolates with the S629P mutation failed to respond to even the highest dose of any of the 3 echinocandins [75]. Mutations at positions S663 and F659 in *C. glabrata* have been associated with breakthrough infections in patients receiving echinocandin therapy [68, 77, 78], whereas patients infected with *C. glabrata* strains containing the I1379V and I634V mutations (susceptible to both anidulafungin and caspofungin) tend to respond to echinocandin therapy [68].

Activity of Antifungal Agents Tested Against Uncommon Species of *Candida* (≥5 Isolates): SENTRY Program, 2006–2016

MIC distributions for the echinocandins and fluconazole for uncommon species of *Candida* (≥5 isolates) are shown in Table 11. We included the antifungal susceptibility profiles of less common species, all identified by sequence-based or proteomic

Table 9. Temporal and Geographic Trends in the Frequency of Isolation and Micafungin Resistance Among *C. glabrata* Isolates in the US SENTRY Program

			% of *C. glabrata* Isolates	
Region	Time Period	Total No. of *Candida* BSI Isolates	Among all Isolates	Resistant to Micafungin
West	2001–2007	61	34.0	0.0
	2006–2011	552	18.5	2.0
	2014–2016	462	29.9	5.1
Midwest	2001–2007	1420	28.0	0.0
	2006–2011	920	19.3	2.2
	2014–2016	385	28.6	2.7
Northeast	2001–2007	897	19.0	0.0
	2006–2011	727	15.1	1.8
	2014–2016	566	22.6	6.3
South	2001–2007	619	21.0	3.4
	2006–2011	845	19.5	0.6
	2014–2016	448	21.9	2.0

Table 10. Summary of *FKS* Alterations in Echinocandin-Resistant *Candida* spp. Strains: SENTRY Program, 2006–2016

						1,3-β-D-Glucan Synthase Alterations			
			MIC, mg/L			*FKS1*		*FKS2*	
Year	Species	State/Country	ANF	CSF	MCF	HS1	HS2	HS1	HS2
2006–2009	*C. albicans*	Germany	0.12	1	0.06	F641I	WT	NT	NT
	C. glabrata	Germany	1	1	0.25	WT	WT	S663P	WT
	C. glabrata	Indiana USA	1	1	0.5	R631S S629P	WT	WT	WT
	C. glabrata	Indiana USA	1	1	NT	WT	WT	F659S	WT
	C. glabrata	Massachusetts USA	0.5	1	0.12	L630I	WT	WT	WT
	C. glabrata	Ohio USA	2	16	2	S629P	WT	WT	WT
	C. glabrata	Virginia USA	1	2	NT	WT	WT	F659V	WT
	C. glabrata	Washington USA	1	1	0.25	WT	WT	S663F	WT
	C. glabrata	Washington USA	2	4	2	S629P	WT	WT	WT
	C. tropicalis	Texas USA	1	0.5	0.5	S645P	WT	NT	NT
2010–2011	*C. albicans*	Scotland	0.5	2	1	S629P	WT	NT	NT
	C. albicans	Sweden	0.5	1	1	S654P	WT	NT	NT
	C. albicans	United Kingdom	0.5	0.5	0.5	F641S	WT	NT	NT
	C. glabrata	Australia	1	1	0.5	WT	WT	S663P	WT
	C. glabrata	Australia	0.5	0.25	0.12	F625S	WT	WT	WT
	C. glabrata	Canada	1	1	0.25	WT	WT	S659Y	WT
	C. glabrata	Germany	1	0.5	0.5	WT	WT	L662W	WT
	C. glabrata	Germany	1	0.5	0.5	WT	WT	L644W	WT
	C. glabrata	Greece	2	1	1	WT	WT	S663P	WT
	C. glabrata	Indiana USA	1	4	0.06	WT	WT	F659V	WT
	C. glabrata	Indiana USA	1	4	0.06	WT	WT	F641V	WT
	C. glabrata	Indiana USA	1	0.5	0.5	WT	WT	S663Y	WT
	C. glabrata	Louisiana USA	4	16	2	S629P	WT	WT	WT
	C. glabrata	Michigan USA	0.25	0.5	0.03	WT	WT	D648E	WT
	C. glabrata	Texas USA	0.5	0.25	0.03	F625Y	WT	WT	WT
	C. glabrata	Texas USA	0.5	0.25	0.03	WT	WT	F641Y	WT
2012–2013	*C. dubliniensis*	Belgium	2	2	1	S645P	WT	NT	NT
	C. glabrata	Canada	2	1	1	WT	WT	F659_del	WT
	C. glabrata	Canada	1	0.5	0.5	WT	WT	F659_del	WT
	C. glabrata	France	2	1	0.5	WT	WT	S663P	WT
	C. glabrata	Germany	0.5	0.5	0.06	WT	WT	D666E K753Q	WT
	C. glabrata	Kentucky USA	2	2	0.5	D632V	WT	WT	WT
	C. glabrata	New York USA	2	4	2	WT	WT	S663P	WT
	C. glabrata	New York USA	4	16	4	WT	WT	S663F	WT
	C. glabrata	New York USA	2	0.5	1	WT	WT	S663P	WT
	C. glabrata	Washington USA	2	2	1	WT	WT	S663F	WT
	C. kefyr	New York USA	2	0.5	1	WT	R1344S	NT	NT
	C. tropicalis	California USA	2	2	1	F641S	WT	NT	NT
	C. tropicalis	Indiana USA	1	0.5	0.5	F641L	WT	NT	NT
2014–2016	*C. albicans*	Indiana USA	0.5	1	1	S645P	WT	NT	NT
	C. albicans	Ireland	0.12	1	1	S645P	WT	NT	NT
	C. albicans	New York USA	0.25	1	1	S645P	WT	NT	NT
	C. albicans	Wisconsin USA	0.25	1	1	S645P	WT	NT	NT
	C. glabrata	California USA	2	8	2	S629P	WT	WT	WT
	C. glabrata	California USA	0.25	0.5	0.25	WT	WT	F659S	WT
	C. glabrata	California USA	1	1	0.25	F625S	WT	WT	WT
	C. glabrata	Canada	4	>8	4	S629P	WT	S663P	WT
	C. glabrata	Canada	4	>8	4	S629P	WT	S663P	WT
	C. glabrata	Colorado USA	1	1	0.25	WT	WT	F659S	WT
	C. glabrata	Georgia USA	2	2	0.5	F625S	WT	WT	WT
	C. glabrata	Indiana USA	2	2	0.5	F625S	WT	F659Y	WT
	C. glabrata	Iowa USA	4	4	1	WT	WT	S663P	WT

Table 10. Continued

						1,3-β-D-Glucan Synthase Alterations			
			MIC, mg/L			*FKS1*		*FKS2*	
Year	Species	State/Country	ANF	CSF	MCF	HS1	HS2	HS1	HS2
	C. glabrata	Israel	2	2	2	WT	WT	F659S	WT
	C. glabrata	Michigan USA	0.25	0.5	0.06	WT	WT	L662W	WT
	C. glabrata	New Jersey USA	1	1	1	WT	WT	S663P	WT
	C. glabrata	New York USA	4	>8	4	WT	WT	F659_del	WT
	C. glabrata	New York USA	0.25	0.5	0.03	WT	WT	P667T	WT
	C. glabrata	New York USA	0.5	0.25	0.25	WT	WT	S663P	WT
	C. glabrata	New York USA	2	2	2	WT	WT	S663P	WT
	C. glabrata	New York USA	2	1	1	WT	WT	S663P	WT
	C. glabrata	Utah USA	2	1	2	WT	WT	S663P	WT
	C. glabrata	Virginia USA	0.5	0.06	0.12	WT	WT	F658_del	WT
	C. glabrata	Washington USA	2	8	2	WT	WT	S663P	WT
	C. glabrata	Washington USA	2	4	1	WT	WT	S663P	WT
	C. tropicalis	Brazil	1	2	1	F650S	WT	NT	NT
	C. tropicalis	Colorado USA	1	>8	2	S654P	WT	NT	NT
	C. tropicalis	New Jersey USA	0.5	4	1	S645P	WT	NT	NT
	C. tropicalis	New York USA	0.5	4	1	S654P	WT	NT	NT
	C. tropicalis	New York USA	2	4	2	S654P	WT	NT	NT
	C. tropicalis	New York USA	2	4	2	S654P	WT	NT	NT

Abbreviations: ANF, andulafungin; CSF, caspofungin; HS, hot spot; MCF, micafungin; NT, not tested; WT, wild-type.

methods, to provide MIC information for these opportunistic pathogens that may still pose problems in selecting optimal therapy. Among the miscellaneous species of *Candida,* the emerging MDR *C. auris* strain has been called the "new kid on the block" in hospital-associated infections [79, 80]. In the SENTRY Program, 6 *C. auris* isolates were detected: 1 each in 2009 (Germany), 2013 (New York), 2014 (Colombia), and 2015 (New Jersey), and 2 in 2016 (both in New York). The *C. auris* isolates were all from nosocomial BSIs and were fluconazole-resistant, 4 were from patients in intensive care units, and 3 were from the same institution in the United States.

Among the 992 isolates of the less common *Candida* species encountered from 2006 to 2016, we identified 30 additional species (15 with ≥5 isolates) (Table 11). Notable observations include elevated echinocandin MIC results ($MIC_{50/90}$, ≥0.5 mg/L) among *C. auris, C. fermentati, C. guilliermondii, C. haemulonii, C. lipolytica, C. lusitaniae, C. metapsilosis*, and *C. orthopsilosis* (Table 11). Isolates of *C. dubliniensis, C. kefyr*, and *C. pelliculosa,* as well as the azole-resistant species *C. norvegensis* and *C. inconspicua,* were all very susceptible to echinocandins ($MIC_{50/90}$, ≤0.25 mg/L), although we detected single echinocandin-resistant strains of *C. dubliniensis* and *C. kefyr,* both of which harbored *FKS* mutations (Table 10).

Elevated fluconazole MIC values ($MIC_{50/90}$, >4 mg/L) were observed for isolates of *C. auris, C. fermentati, C. guilliermondii, C. inconspicua, C. lipolytica, C. metapsilosis,* and *C. norvegensis* (Table 11). Additional species in which fluconazole MIC results appeared to be elevated (MIC, ≥8 mg/L) for 1 or more isolates included *C. dubliniensis* (MIC, 32 mg/L), *C. haemulonii* (MIC, 32 mg/L), *C. orthopsilosis* (MIC, >128 mg/L), *C. pararugosa* (MIC, >128 mg/L), and *C. pelliculosa* (MIC, 8 mg/L).

CONCLUSIONS

The SENTRY Antimicrobial Surveillance Program was designed to track antimicrobial resistance trends and the spectrum of microbial pathogens on a global scale. The SENTRY Antifungal Surveillance Program has unique features that distinguish it from other excellent surveillance programs, such as the PATH Alliance [24, 81, 82], the ARTEMIS DISK study [53], the SCOPE Program [83], the NEMIS study [84], and population-based surveillance conducted in the United States [44], Australia [85], Belgium [86], Denmark [5], Finland [87], France [46, 88], Norway [33], Spain [89], LATAM [90], and Asia [91]. Whereas these programs are based in a single country, may track only nosocomial infections, and/or rely primarily on diverse susceptibility testing results from participating centers, the SENTRY Program monitors nosocomial and community-onset infections on a global scale and uses validated reference identification and susceptibility testing methods at a central monitoring laboratory and has done so for 20 years [7, 9, 29].

Despite the low antifungal resistance rates among *Candida* isolates, continuously monitoring antifungal susceptibility patterns and understanding resistance mechanisms against antifungal agents seems to be a prudent endeavor. Reports of breakthrough infections [92], increasing prevalence of uncommon species refractory to clinically available antifungal agents

Table 11. Activity of 4 Antifungal Agents Tested Against 15 Uncommonly Isolated Species of *Candida* (≥5 Isolates Each): SENTRY Program, 2006–2016

			MIC, mg/L		
Species	No. Tested	Antifungal Agent	Range	50%	90%
C. auris	6	Fluconazole	64–>64	>64	
		Anidulafungin	0.25–1	0.5	
		Caspofungin	0.12–0.5	0.25	
		Micafungin	0.12–0.5	0.25	
C. bracarensis	5	Fluconazole	1–4	2	
		Anidulafungin	0.03–0.12	0.06	
		Caspofungin	0.03–0.06	0.03	
		Micafungin	0.015–0.03	0.015	
C. dubliniensis	264	Fluconazole	≤0.5–32	≤0.5	≤0.5
		Anidulafungin	≤0.008–2	0.06	0.12
		Caspofungin	≤0.008–2	0.03	0.12
		Micafungin	≤0.008–1	0.03	0.06
C. fabianii	14	Fluconazole	≤0.5–4	1	4
		Anidulafungin	0.015–0.12	0.015	0.12
		Caspofungin	0.015–0.25	0.03	0.06
		Micafungin	0.015–0.06	0.03	0.06
C. fermentati	29	Fluconazole	0.25–>128	2	32
		Anidulafungin	0.5–2	1	2
		Caspofungin	0.06–1	0.25	0.5
		Micafungin	0.12–1	0.25	1
C. guilliermondii	91	Fluconazole	≤0.5–>64	4	64
		Anidulafungin	0.06–8	2	4
		Caspofungin	0.06–>16	0.5	1
		Micafungin	0.03–8	1	1
C. haemulonii	10	Fluconazole	0.5–32	2	4
		Anidulafungin	0.06–1	0.12	0.5
		Caspofungin	0.03–0.12	0.06	0.12
		Micafungin	0.03–0.25	0.12	0.25
C. inconspicua	12	Fluconazole	4–>128	16	>64
		Anidulafungin	≤0.008–0.03	0.015	0.03
		Caspofungin	0.015–0.25	0.03	0.25
		Micafungin	≤0.008–0.12	0.03	0.06
C. kefyr	94	Fluconazole	≤0.5–1	≤0.5	≤0.5
		Anidulafungin	0.03–2	0.06	0.12
		Caspofungin	≤0.008–0.5	0.015	0.12
		Micafungin	0.015–1	0.06	0.12
C. lipolytica	10	Fluconazole	0.25–32	2	32
		Anidulafungin	0.25–0.5	0.25	0.5
		Caspofungin	0.12–0.25	0.12	0.25
		Micafungin	0.06–1	0.5	1
C. lusitaniae	277	Fluconazole	≤0.5–64	≤0.5	1
		Anidulafungin	0.015–2	0.25	0.5
		Caspofungin	0.015–2	0.25	0.5
		Micafungin	0.015–2	0.12	0.25
C. metapsilosis	33	Fluconazole	0.12–16	1	8
		Anidulafungin	0.015–2	0.25	0.5
		Caspofungin	0.03–0.5	0.12	0.25
		Micafungin	0.015–1	0.25	0.5
C. orthopsilosis	82	Fluconazole	≤0.12–>128	1	2
		Anidulafungin	0.12–2	0.5	2
		Caspofungin	0.03–0.5	0.12	0.25
		Micafungin	0.06–1	0.5	1
C. pararugosa	7	Fluconazole	1–>128	4	
		Anidulafungin	0.06–0.25	0.12	
		Caspofungin	0.06–0.25	0.12	

Table 11. Continued

Species	No. Tested	Antifungal Agent	MIC, mg/L		
			Range	50%	90%
		Micafungin	0.015–0.25	0.12	
C. pelliculosa	22	Fluconazole	0.5–8	2	4
		Anidulafungin	≤0.008–0.12	0.015	0.03
		Caspofungin	≤0.008–0.5	0.03	0.25
		Micafungin	≤0.008–0.06	0.03	0.06

[93, 94], and emerging resistance mechanisms [20, 68] highlight the importance of local and global surveillance studies.

If the goals of surveillance programs are to identify emerging infectious threats, to monitor trends in antimicrobial resistance, and to contribute data that may be used by individual practitioners, institutions, and organizations developing drugs, then the combination of population-based and sentinel surveillance programs for IC has served its purpose to date [6, 7, 17]. The findings of the SENTRY Program (sentinel surveillance) support reports from population-based surveys conducted in the United States and other countries worldwide [6, 21, 22]. Specifically, the trend of increasing infections due to *C. glabrata* noted in the United States has also been observed in Australia and several European countries [6]. *C. glabrata* as a cause of IC accounted for 27.0% of all isolates in Australia and 35.0% in Denmark in 2015 [5, 85] as well as 27.3% in Belgium in 2014 [86]. The increase in *C. glabrata* infections in these countries has been linked to an increased use of azoles, to which *C. glabrata* is intrinsically less susceptible [5, 6, 57, 95, 96]. Similar to the SENTRY Program findings (Table 2), *C. parapsilosis* and *C. tropicalis* were more prominent than *C. glabrata* in population-based surveys reported from India, LATAM, South Africa, and Asia [91, 97–100].

Likewise, trends in resistance to fluconazole documented in the SENTRY Program support observations reported from other sentinel and population-based surveys in the United States and other countries. Aside from intrinsically fluconazole-resistant species, such as *C. krusei* and *C. auris,* increasing rates of acquired resistance to fluconazole have been noted in other non-*albicans* species including *C. glabrata*, *C. parapsilosis,* and *C. tropicalis.* High rates of fluconazole-resistant *C. glabrata* have been reported from both the SENTRY Program and population-based surveillance conducted in the United States, Australia, Denmark, and Belgium [5, 6, 51, 85, 86]. Although fluconazole resistance is generally considered to be uncommon among *C. parapsilosis* isolates, SENTRY Program data from EUR and LATAM (Table 4) and reports from Brazil [101], Finland [102], and South Africa [99] suggest that fluconazole resistance in *C. parapsilosis* may emerge following drug pressure in the form of fluconazole treatment and prophylaxis, with subsequent patient-to-patient transmission within the hospital environment. *C. tropicalis* is generally susceptible to fluconazole [103], and prophylaxis with this agent has been associated with a decrease in the incidence of *C. tropicalis* BSIs in US cancer treatment centers [104]. The SENTRY Program data highlight elevated resistance to fluconazole among isolates of *C. tropicalis* from the APAC region (Table 4), supporting reports from Australia, Brazil, Taiwan, and Belgium documenting the emergence of fluconazole resistance in *C. tropicalis* clinical isolates [6, 85, 86].

It is important to realize that there is not a single best way to conduct surveillance and provide useful information [31]. Whereas population-based surveillance efforts are unsurpassed in providing incidence data and risk factor profiles [5, 7, 44], they are limited in time and space due to expense and labor-intensive designs. Sentinel surveillance programs designed to capture organisms and patient demographic data from representative sites spanning a larger geographical area and over a longer period of time serve to fill the gaps in time and space that are necessarily left by the more intensive and focused, yet intermittent, population-based programs [7, 111, 112]. Establishing the infrastructure necessary for conducting sentinel surveillance may facilitate more intensive surveillance in certain geographic areas, such as a single US state, and provide information that may approximate that obtained from a population-based program (eg, Emerging Infections and the Epidemiology of Iowa Organisms) [95, 113–115].

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 [31, 32, 108–110, 112]. 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 [31, 32, 109–111]. 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 [7, 9, 29, 34].

In summary, we have provided a 20-year comparison of differences in species distribution and overall antifungal susceptibility profiles among IC-causing *Candida* isolates from 4 broad geographic regions (NA, LATAM, EUR, and APAC). The results document the sustained activities of fluconazole (azoles) and echinocandin antifungal agents against all IC isolates, except for MDR species such as *C. glabrata*, *C. krusei*, and *C. auris.* The differences in species distribution observed among the geographic areas may be due to several factors, but they most

likely reflect variation in antifungal usage and infection control practices. The emergence of less common yet potentially MDR strains, such as *C. auris,* is a grave concern and argues in favor of continued global surveillance efforts to detect, characterize, and report emerging pathogenic species [73, 112, 113].

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