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

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SENTRY ANTIMICROBIAL SURVEILLANCE

Introduction

- Invasive fungal infections (IFIs) are associated with high morbidity and mortality rates and elevated hospitalisation costs
  - *Candida* species are among the most frequent causes of IFI
- Resistance to clinically available antifungal agents among *Candida* spp. is still uncommon, but these isolates are increasingly reported worldwide
  - Monitoring antifungal susceptibility patterns and resistance mechanisms to clinically available antifungal agents is of continuing importance
- The SENTRY Antifungal Surveillance Program is a global program that has been ongoing for 20 years (1997-2016) and collects consecutive invasive isolates of *Candida* from hospitals located in North America, Europe, Latin America, and Asia-Pacific regions during each calendar year
- In this study, we reviewed the geographic and temporal variations in the frequency of the *Candida* species causing invasive candidiasis (IC) and the associated antifungal resistance profiles

Materials and Methods

- A total of 20,788 invasive isolates of *Candida* spp. (37 species) were collected as part of a global surveillance initiative in 151 hospitals located in 41 countries (Table 1)
- Isolate identification was confirmed at the central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) using molecular and proteomic methods
- Susceptibility testing was performed for anidulafungin, caspofungin, micafungin, fluconazole, and voriconazole using the CLSI reference broth microdilution method
- Fluconazole has been tested since 1997, and the echinocandins have been tested since 2006
- CLSI clinical breakpoints were used for the most common species of *Candida*, and recently published epidemiologic cutoff values (ECOFFs) in CLSI M59 were applied for less common *Candida* species
- Quality control was performed as recommended in CLSI M27, and all results were within established ranges
- *Candida* spp. isolates with MIC values higher than the ECOFF for the echinocandins were screened for *FKS* hot spot (HS) mutations as previously described

Results

- Among the 20,788 isolates of *Candida* submitted for testing from 1997 to 2016, 49.3% were *C. albicans*, 17.9% were *C. glabrata*, 15.1% were *C. parapsilosis*, 9.4% were *C. tropicalis,* 2.6% were *C. krusei*, and 5.7% were miscellaneous *Candida* spp.
  - Species distribution by time period is displayed in Table 1
  - The relative 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 (17.9%) and showed a steady increase from 16.0% in 1997–2001 to 19.6% in 2015–2016
- 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 Figure 1
- Only 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 from New York)
  - These isolates were all from nosocomial bloodstream infections; 4 were from the intensive care unit, and 3 from the same institution in New York
  - Fluconazole MIC values for *C. auris* isolates were all ≥64 mg/L

Table 1. Species distribution of *Candida* isolates: SENTRY, 1997–2016

Year	No. tested	% by species				
		CA	CG	CP	CT	CK
1997–2001	5,067	57.4	16.0	12.3	9.1	2.5
2006–2008	2,648	51.2	15.8	16.8	10.6	2.0
2009–2011	4,197	45.4	18.6	17.8	10.1	2.5
2012–2014	5,223	45.8	19.1	15.3	9.2	3.1
2015–2016	3,653	46.4	19.6	14.4	8.3	2.8

CA, *Candida albicans*; CG, *Candida glabrata*; CP, *Candida parapsilosis*; CT, *Candida tropicalis*; CK, *Candida krusei*

Table 2. Trends in fluconazole resistance: SENTRY 1997–2016

Species	Year	No. tested	% Resistant (n)[a]
C. albicans	1997–2001	2,907	1.2 (36)
	2006–2008	1,356	0.2 (3)
	2009–2011	1,904	0.3 (5)
	2012–2014	2,393	0.4 (10)
	2015–2016	1,694	0.1 (2)
	1997–2016	10,254	0.5 (56)
C. glabrata	1997–2001	813	6.3 (51)
	2006–2008	418	8.6 (36)
	2009–2011	781	7.8 (61)
	2012–2014	999	10.1 (101)
	2015–2016	717	5.6 (40)
	1997–2016	3,728	7.8 (289)
C. parapsilosis	1997–2001	625	2.6 (16)
	2006–2008	444	5.4 (24)
	2009–2011	749	3.1 (23)
	2012–2014	798	3.1 (25)
	2015–2016	526	5.5 (29)
	1997–2016	3,142	3.7 (117)
C. tropicalis	1997–2001	460	2.4 (11)
	2006–2008	281	2.5 (5)
	2009–2011	424	1.9 (8)
	2012–2014	478	6.3 (30)
	2015–2016	304	3.3 (10)
	1997–2016	1,947	3.3 (64)

[a] % resistant (n = no. resistant isolates) by CLSI (2012) criteria

- Resistance to fluconazole was observed among 0.5% of *C. albicans*, 3.7% of *C. parapsilosis*, 3.3% of *C. tropicalis*, and 7.8% of *C. glabrata* (Table 2)
  - Fluconazole resistance rates against the 4 most common species of *Candida* stratified by geographic region are displayed in Figure 2
  - An increase in fluconazole resistance among *C. glabrata* and *C. tropicalis* was reflected in high rates of resistance in isolates from the Asia-Pacific region (7.9% and 10.2%, respectively) and North America (10.6% *C. glabrata* only)
- Cross-resistance between fluconazole and voriconazole was common in fluconazole-resistant strains of *C. albicans* (35.0% susceptible to voriconazole) and *C. parapsilosis* (32.7% susceptible to voriconazole)
- Voriconazole resistance was virtually complete for fluconazole-resistant *C. glabrata* (0.0% susceptible [MIC, ≥0.5 mg/L] to voriconazole) and *C. tropicalis* (3.6% susceptible to voriconazole)
- Temporal variation in the resistance to echinocandins for the 5 most common *Candida* species is shown in Table 3
  - Resistance to 1 or more of the echinocandins was uncommon (range, 0.1% to 2.0%) among isolates of *C. albicans* (0.0% to 0.1%), *C. parapsilosis* (0.0% to 0.1%), and *C. tropicalis* (0.5% to 0.7%)
  - Resistance to anidulafungin (2.2%), caspofungin (3.4%), and micafungin (1.6%) was most common among *C. glabrata* isolates
- The majority of echinocandin-resistant or non-wild-type isolates (54/71; 76.1%) were collected from North America and 51/71 (71.8%) isolates were *C. glabrata*
- Among 51 *C. glabrata* isolates displaying nonsusceptible (NS) echinocandin MIC values, 40 (78.4%) were NS to all 3 and all were NS to at least 2 of the tested echinocandins

Table 3. Trends in echinocandin resistance: SENTRY, 2006–2016

Group	2006–2008	2009–2011	2012–2014	2015–2016	2006–2016
Candida albicans	0.1% (1/1,356)	0.2% (4/1,904)	<0.1% (1/2,393)	0.2% (3/1,694)	0.1% (9/7,347)
Candida glabrata	6.7% (28/418)	4.9% (38/781)	3.3% (33/999)	1.5% (11/717)	3.8% (110/2,915)
Candida parapsilosis	0.0% (0/444)	0.4% (3/749)	0.0% (0/798)	0.0% (0/526)	0.1% (3/2,517)
Candida tropicalis	1.1% (3/281)	0.2% (1/424)	0.4% (2/478)	2.0% (6/304)	0.8% (12/1,487)
Candida krusei	7.4% (4/54)	1.9% (2/107)	0.6% (1/161)	0.0% (0/101)	1.7% (7/423)

Figure 1 Species distribution of *Candida* BSI isolates by geographic region: SENTRY, 2006–2016

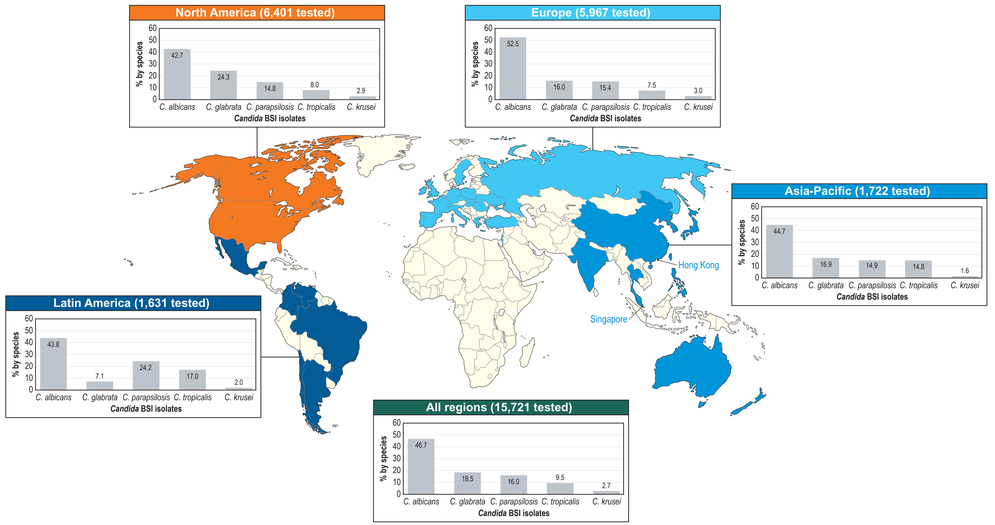
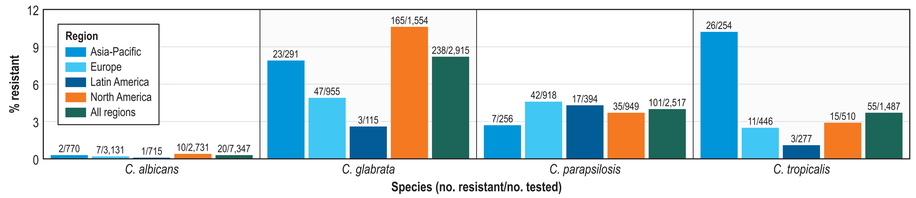


Figure 2 Fluconazole resistance by geographic region: SENTRY, 2006–2016



- All of these isolates harbored *FKS* HS alterations and *FKS2* HS1 S663P/F (16/3 isolates), *FKS2* HS1 F659S/V/Y (8 isolates), and *FKS1* HS1 S629P (6 isolates) were the most common mutations detected
  - 5 isolates carried double mutations
- 9 *C. albicans* isolates were NS to caspofungin and 8 were NS to micafungin: all exhibited mutations encoding an *FKS1* HS1 alteration (S645P [5 isolates] and 4 others)
- Among 9 isolates of *C. tropicalis* NS to echinocandins and 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 3 others
  - 5 (55.6%) isolates were resistant to all 3 agents
- Notable observations included elevated echinocandin MICs (MIC ≥0.5 mg/L) among *C. auris, C. fermentati, C. guilliermondii, C. haemulonii, C. lipolytica, C. lusitaniae, C. orthopsilosis*, and *C. metapsilosis*
- Elevated fluconazole MIC values (MIC >4 mg/L) were observed for isolates of *C. auris, C. fermentati, C. guilliermondii, C. haemulonii, C. inconspicua, C. lipolytica, C. lusitaniae, C. metapsilosis, C. norvegensis*, and *C. orthopsilosis*

Conclusions

- 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: North America, Latin America, Europe, and Asia-Pacific
- The results document the sustained activities of fluconazole and echinocandin antifungal agents against all IC isolates except for multidrug-resistant species, such as *C. glabrata*, *C. krusei,* and *C. auris*
- Differences in species distribution observed among the 4 regions may be due to several factors, but they most likely reflect differences in antifungal usage and local 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 new pathogenic species

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