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Anidulafungin Potency Compared to other Antifungal Agents: SENTRY Antimicrobial Surveillance Program Results for 2008 (Worldwide)

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Abstract

Background: Yeast and mold continue to cause serious invasive infections (bloodstream [BSI], pneumonia [LRTI]) and widespread use of various antifungals (azoles [AZ], echinocandins [EC]) require structured surveillance programs to record changes in pathogen prevalence or emerging resistance (R). SENTRY Program annually monitors AZ and EC susceptibility (S) rates.

Methods: 1,339 fungal organisms were collected from BSI (yeasts) and LRTI (*Aspergillus* spp., 66) during 2008 in hospitals located in North America (NA; 573), Europe (471), Latin America (243) and Asia-Pacific (52). The most commonly tested *Candida* were: *C. albicans* (Ca; 587) > *C. glabrata* (Cg; 218) > *C. parapsilosis* (Cp; 196) > *C. tropicalis* (126) > *C. krusei* (24); plus *A. fumigatus* (60) and *C. neoformans* (Cn; 43). S testing used reference CLSI methods and interpretations. Ca, Cg and *C. guilliermondii* showing caspofungin (CASP) MIC at ≥0.5 µg/ml were tested for *fks1* HS1 mutations. DNA preparations were used for amplification and amplicons were sequenced. Species were confirmed by ITS sequencing.

Results: Anidulafungin (ANID) and all ECs were very active against yeasts and *A. fumigatus* (Table) with ≥98% of MICs at ≤2 µg/ml (CLSI). EC potencies didn't significantly vary by region. Cp was less EC-S with *fks1* HS1 amino acid substitutions related to EC-R, also detected in Cg (S645P) with a CASP MIC at 16 µg/ml, and only 2 µg/ml (S) for micafungin (MICA) and ANID. This strain was a BSI in a 49 y/o female patient from NA. AZ agents were generally less active against yeast except versus Cp (%R=0.5). Cn MICs for the EC agents were generally ≥16 µg/ml.

	Echinocandin MIC$_{50}$ (µg/ml)			
Species (no. tested)	ANID	CASP	MICA	% ANID-S
C. albicans (587)	0.015	0.12	0.03	100.0
C. glabrata (218)	0.06	0.25	0.03	99.5
C. krusei (24)	0.06	0.5	0.12	100.0
C. parapsilosis (196)	2	0.5	1	90.8
C. tropicalis (126)	0.03	0.12	0.06	100.0
A. fumigatus (60)	0.002	≤0.008	0.015	100.0[a]

a. All isolates inhibited at ≤0.015 µg/ml.

Conclusions: ANID and other ECs showed near-complete activity against *Candida* spp. and *Aspergillus* spp. worldwide. *fks1* HS1 mutations were detected in 3 of 12 strains showing increased non-wildtype EC MIC values.

Introduction

Opportunistic fungal infections represent a significant risk to immunocompromised individuals and are associated with high rates of morbidity and mortality. The rise in numbers of individuals with neutropenia (cancer patients, transplant recipients) and immune system disorders (patients with HIV/AIDS) or those having central venous catheters has paralleled the rise in numbers of fungal infections. Currently, a limited number of echinocandin and azole antifungal agents are available for therapeutic use for these infections.

Candida species currently rank as the fourth most frequent source of nosocomial bloodstream infections (BSI) in the United States (USA). The emergence of mold pathogens and yeast species with decreased susceptibility to contemporary antifungal regimens demonstrates the need for new agent development to manage these infections. The echinocandins (anidulafungin, caspofungin, and micafungin) offer an alternative to the time-honored regimens of antifungal agents and provide additional advantages of reduced toxicity.

Anidulafungin is a novel semi-synthetic echinocandin agent that compromises cell wall structural integrity through non-competitive inhibition of β-1, 3-glucan synthase complex, causing cell death. It has demonstrated excellent broad-spectrum *in vitro* and *in vivo* activity against a wide variety of fungal pathogens. We present here, contemporary data (2008) from a longitudinal study (SENTRY Antimicrobial Surveillance Program platform) comparing the activity of anidulafungin, as well as activities of two other echinocandins compared to seven additional antifungal agents.

Methods

The SENTRY Program collection of BSI yeasts included *Candida albicans* (587 isolates), *C. glabrata* (218 isolates), *C. parapsilosis* (196 isolates), *C. tropicalis* (126 isolates), *C. krusei* (24 isolates), *C. lusitaniae* (19 isolates), *C. dubliniensis* (12 isolates), *C. guilliermondii* (4 isolates), *C. kefyr* (4 isolates), *C. famata* (3 isolates), *C. rugosa* (2 isolates) and other *Candida* spp. (6 isolates). The collection also contained *C. neoformans* (43 isolates), and among 79 molds, only *Aspergillus fumigatus* (60 isolates from respiratory tract infections) are presented here. These yeast and mold isolates were identified at the participating medical centers by the established methods in use at each institution. Laboratories were instructed to submit unique bloodstream isolates obtained in consecutive order. The frequency of each *Candida* spp. in participating laboratories could then be detected by this prevalence design. Confirmation of species identification was performed at the central reference laboratory (JMI Laboratories, North Liberty, Iowa, USA) by using Vitek (bioMerieux, Hazelwood, Missouri, USA) and by conventional reference methods.

Broth microdilution testing for yeasts followed standardized procedures described in CLSI M27-A3 reference method. All of the filamentous fungi were tested under conditions described for the CLSI M38-A2 reference method. Quality control (QC) isolates *C. krusei* ATCC 6258, *C. parapsilosis* ATCC 22019, and *C. tropicalis* ATCC 750 were used as recommended (CLSI), and all QC results were observed within published ranges. All panels (yeast and mold) were incubated in enclosed, humid containers at 35ºC and visualized with a reading mirror at 24 h (echinocandins) and 48 h (all other agents).

MIC values of amphotericin B were determined for yeast and mold as the concentration at which no discernible growth was detected. MIC endpoints of flucytosine and azoles were determined as the lowest concentration at which predominant decrease in growth (≥50%) was visualized compared to the growth control well. Itraconazole, posaconazole and voriconazole against mold were the exception, which were read at 100% inhibition of growth. MICs (yeast) and MECs (mold) for echinocandins were determined as the lowest concentration at which pronounced decrease in turbidity or approximately 50% reduction in growth, or pronounced morphological change from filamentous to non-filamentous growth was observed, respectively (CLSI).

The dilution scheme was selected to maximize capture of the MIC$_{50}$ and MIC$_{90}$ for wildtype (WT) and resistant mutant populations. Further, the ranges of newer or investigational agents were expanded in order to identify populations potentially resistant to these newer agents.

*fks*1 hot spot (HS) 1 was amplified from DNA preparations as described elsewhere. PCR amplicons were sequenced on both strands and results were analyzed.

Results

- A total of 1,339 fungal isolates were processed by reference CLSI methods, with organisms derived from patient BSI (yeasts) or lower respiratory tract infections (molds) in the USA, Europe, Latin America and the Asia-Pacific (APAC) region.
- Compared to the prior annual report (Messer et al., 2008), the frequency of occurrence of *C. albicans* decreased slightly in the USA, but increased in APAC. Also *C. glabrata* became the second most cultured *Candida* spp. replacing *C. parapsilosis* that continued to be most prevalent in Latin America.
- Anidulafungin was most active (Table 1) against *C. albicans* (MIC$_{90}$, 0.06 µg/ml), *C. glabrata* (0.12 µg/ml), *C. tropicalis* (0.06 µg/ml), *C. krusei* (0.12 µg/ml) and *C. dubliniensis* (0.12 µg/ml); and was less effective in vitro when testing *C. parapsilosis* (MIC$_{90}$, 2 µg/ml) or *C. guilliermondii* (data not shown).
- Table 2 shows that the susceptibility rates for the echinocandins (MIC, ≤2 µg/ml) were very similar at 98.4-99.9%. Anidulafungin inhibited all yeasts except *Cryptococcus* at ≤4 µg/ml.

Table 1. In vitro activity of anidulafungin and nine other selected antifungal agents tested against yeast bloodstream isolates from the SENTRY Antimicrobial Surveillance Program for 2008 (North America, Latin America, Europe, Asia Pacific).

Organism (no. tested) Antifungal agent	MIC (µg/ml): 50%	90%	Range	% by category: Susceptible/Resistant[a]
Candida spp. (1,201)[b]				
Anidulafungin	0.03	2	0.004-4	98.4/-
Fluconazole	≤0.5	4	≤0.5->64	94.3/2.5
Voriconazole	≤0.06	0.5	≤0.06->8	97.1/1.2
Amphotericin B	0.5	1	≤0.12-2	-/-
Caspofungin	0.25	0.5	0.06->16	99.8/-
Flucytosine	≤0.5	1	≤0.5->64	95.5/3.1
Itraconazole	0.06	1	≤0.015->2	68.4/11.2
Ketoconazole	≤0.06	0.5	≤0.06->8	-/-
Micafungin	0.06	1	≤0.008-8	99.9/-
Posaconazole	≤0.06	0.5	≤0.06->8	-/-
C. albicans (587)				
Anidulafungin	0.015	0.06	0.004-0.06	100.0/-
Fluconazole	≤0.5	≤0.5	≤0.5-64	99.8/0.2
Voriconazole	≤0.06	≤0.06	≤0.06-0.12	100.0/0.0
Amphotericin B	0.5	1	≤0.12-1	-/-
Caspofungin	0.12	0.25	0.06-0.5	100.0/-
Flucytosine	≤0.5	2	≤0.5->64	97.6/2.4
Itraconazole	0.03	0.06	≤0.015-0.12	100.0/0.0
Ketoconazole	≤0.06	≤0.06	≤0.06	-/-
Micafungin	0.03	0.06	≤0.008-0.06	100.0/-
Posaconazole	≤0.06	≤0.06	≤0.06-0.12	-/-
C. glabrata (218)				
Anidulafungin	0.06	0.12	0.008-4	99.5/-
Fluconazole	4	32	≤0.5->64	84.4/7.8
Voriconazole	0.25	2	≤0.06-8	87.2/4.1
Amphotericin B	1	1	0.25-1	-/-
Caspofungin	0.25	0.25	0.12->16	98.6/-
Flucytosine	≤0.5	≤0.5	≤0.5-4	100.0/0.0
Itraconazole	1	>2	0.03->2	2.3/57.3
Ketoconazole	0.5	2	≤0.06-8	-/-
Micafungin	0.03	0.06	≤0.008-8	99.5/-
Posaconazole	0.5	2	≤0.06->8	-/-
C. parapsilosis (196)				
Anidulafungin	2	2	0.25-4	90.8/-
Fluconazole	≤0.5	1	≤0.5-64	98.5/0.5
Voriconazole	≤0.06	0.12	≤0.06-0.5	100.0/0.0
Amphotericin B	1	1	0.25-1	-/-
Caspofungin	0.5	1	0.25-1	100.0/-
Flucytosine	≤0.5	≤0.5	≤0.5->64	99.0/0.5
Itraconazole	0.12	0.25	0.03-1	54.6/0.5
Ketoconazole	≤0.06	0.25	≤0.06-0.5	-/-
Micafungin	1	2	0.06-2	100.0/-
Posaconazole	0.12	0.25	≤0.06-0.5	-/-
C. tropicalis (126)				
Anidulafungin	0.03	0.06	0.008-0.25	100.0/-
Fluconazole	≤0.5	1	≤0.5->64	96.8/3.2
Voriconazole	≤0.06	0.12	≤0.06->8	96.8/3.2
Amphotericin B	1	1	0.25-1	-/-
Caspofungin	0.12	0.25	0.06-0.5	100.0/-
Flucytosine	≤0.5	>64	≤0.5->64	89.7/10.3
Itraconazole	0.12	0.25	≤0.015->2	72.2/2.4
Ketoconazole	≤0.06	0.12	≤0.06->8	-/-
Micafungin	0.06	0.06	0.015-0.12	100.0/-
Posaconazole	≤0.06	0.25	≤0.06->8	-/-
C. krusei (24)				
Anidulafungin	0.06	0.12	0.03-0.12	100.0/-
Fluconazole	32	>64	8->64	4.2/29.2
Voriconazole	0.5	2	0.25-4	87.5/4.2
Amphotericin B	1	1	0.25-1	-/-
Caspofungin	0.5	0.5	0.25-0.5	100.0/-
Flucytosine	16	32	4-32	8.3/29.2
Itraconazole	0.5	1	0.12-2	4.2/20.8
Ketoconazole	1	2	0.25-4	-/-
Micafungin	0.12	0.25	0.03-0.25	100.0/-
Posaconazole	0.25	0.5	0.12-1	-/-
C. lusitaniae (19)				
Anidulafungin	0.5	0.5	0.25-0.5	100.0/-
Fluconazole	≤0.5	1	≤0.5-2	100.0/0.0
Voriconazole	≤0.06	≤0.06	≤0.06	100.0/0.0
Amphotericin B	0.25	0.5	0.25-0.5	-/-
Caspofungin	0.5	0.5	0.25-0.5	100.0/-
Flucytosine	≤0.5	≤0.5	≤0.5-32	94.7/5.3
Itraconazole	0.12	0.25	0.03-0.25	68.4/0.0
Ketoconazole	≤0.06	≤0.06	≤0.06-0.12	-/-
Micafungin	0.12	0.25	0.12-0.25	100.0/-
Posaconazole	≤0.06	0.12	≤0.06-0.12	-/-
C. dubliniensis (12)				
Anidulafungin	0.06	0.12	0.015-0.12	100.0/-
Fluconazole	≤0.5	≤0.5	≤0.5-4	100.0/0.0
Voriconazole	≤0.06	≤0.06	≤0.06	100.0/0.0
Amphotericin B	0.5	0.5	0.25-0.5	-/-
Caspofungin	0.25	0.25	0.12-0.25	100.0/-
Flucytosine	≤0.5	≤0.5	≤0.5	100.0/0.0
Itraconazole	0.06	0.25	≤0.015-0.25	83.3/0.0
Ketoconazole	≤0.06	≤0.06	≤0.06	-/-
Micafungin	0.06	0.12	0.015-0.12	100.0/-
Posaconazole	≤0.06	0.012	≤0.06-0.12	-/-
Other *Candida* spp. (19)[c]				
Anidulafungin	0.5	2	0.015-2	100.0/-
Fluconazole	1	32	≤0.5/32	84.2/0.0
Voriconazole	0.12	0.25	≤0.06-1	100.0/0.0
Amphotericin B	0.5	1	0.25-2	-/-
Caspofungin	0.5	1	0.12-1	100.0/-
Flucytosine	≤0.5	16	≤0.5->64	89.5/5.3
Itraconazole	0.25	0.5	0.03-1	42.1/5.3
Ketoconazole	0.12	0.25	≤0.06-0.5	-/-
Micafungin	0.25	1	0.03-1	100.0/-
Posaconazole	0.12	0.5	≤0.06-0.5	-/-
Cryptococcus neoformans (43)				
Anidulafungin	>32	>32	8->32	-/-
Fluconazole	4	4	1-8	-/-
Voriconazole	≤0.06	≤0.06	≤0.06-0.25	-/-
Amphotericin B	0.5	0.5	0.25-1	-/-
Caspofungin	16	>16	4->16	-/-
Flucytosine	8	8	2-16	-/-
Itraconazole	0.06	0.12	≤0.015-0.5	-/-
Ketoconazole	≤0.06	≤0.06	≤0.06-0.25	-/-
Micafungin	>16	>16	>16	-/-
Posaconazole	≤0.06	0.12	≤0.06-0.5	-/-
Other yeast spp. (16)[d]				
Anidulafungin	2	>32	0.12->32	-/-
Fluconazole	4	>64	1->64	-/-
Voriconazole	0.25	2	≤0.06-4	-/-
Amphotericin B	1	1	0.5-1	-/-
Caspofungin	4	>16	0.25->16	-/-
Flucytosine	≤0.5	32	≤0.5->64	-/-
Itraconazole	0.5	1	0.03-2	-/-
Ketoconazole	0.25	1	≤0.06-1	-/-
Micafungin	2	>16	0.12->16	-/-
Posaconazole	0.5	1	≤0.06-2	-/-

a. Criteria as published by the CLSI (2009). - = no criteria for this interpretive category.
b. Includes: *Candida albicans* (587 strains), *C. dubliniensis* (12 strains), *C. famata* (3 strains), *C. glabrata* (218 strains), *C. guilliermondii* (4 strains), *C. haemulonii* (1 strain), *C. inconspicua* (1 strain), *C. kefyr* (4 strains), *C. krusei* (24 strains), *C. lambica* (1 strain), *C. lusitaniae* (19 strains), *C. norvegensis* (1 strain), *C. parapsilosis* (196 strains), *C. pelliculosa* (1 strain), *C. rugosa* (2 strains), *C. sake* (1 strain), and *C. tropicalis* (126 strains).
c. Includes: *Candida famata* (3 strains), *C. guilliermondii* (4 strains), *C. haemulonii* (1 strain), *C. inconspicua* (1 strain), *C. kefyr* (4 strains), *C. lambica* (1 strain), *C. norvegensis* (1 strain), *C. pelliculosa* (1 strain), *C. rugosa* (2 strains), and *C. sake* (1 strain).
d. Includes: *Geotricum candidum* (1 strain), *G. capitatum* (2 strains), *Rhodotorula glutinous* (1 strain), *R. minuta* (1 strain), *Saccharomyces cerevisiae* (4 strains), *Trichosporon asahii* (1 strain), *T. beigelii* (2 strain), unspeciated *Rhodotorula* (2 strains), unspeciated *Trichosporon* (1 strain), and unspeciated yeast (1 strain).

Table 2. MIC distributions for three echinocandin agents tested against over 1,200 candidemia isolates from the 2008 SENTRY Antimicrobial Surveillance Program.

	Occurrences (cum. %) at MIC (µg/ml):										
Echinocandin	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	≥8
Anidulafungin	61(5.1)	301(30.1)	244(50.5)	257(71.9)	99(80.1)	15(81.4)	22(83.2)	78(89.7)	105(98.4)	19(100.0)	-
Caspofungin	0(0.0)	0(0.0)	0(0.0)	12(1.0)	565(48.0)	378(79.5)	193(95.6)	50(99.8)	0(99.8)	1(99.8)	2(100.0)
Micafungin	24(2.0)	237(21.7)	339(50.0)	331(77.5)	44(81.2)	21(82.9)	33(85.7)	123(95.9)	48(99.9)	0(99.9)	1(100.0)

- Echinocandins were not active against *C. neoformans in vitro* (Table 1) and the most active agents tested against this species were the azoles, e.g. voriconazole (MIC$_{90}$, ≤0.06 µg/ml) and ketoconazole (MIC$_{90}$, ≤0.06 µg/ml).
- Yeast MIC values did not significantly vary among geographic regions (Table 3).
- Some *Candida* spp. (*C. albicans, C. glabrata* and *C. guilliermondii*) had non-WT elevated MIC values for echinocandins (MIC values at ≥0.5 µg/ml). *C. parapsilosis* strains were least susceptible to all tested echinocandins and *fks*1 HS1 amino acid substitutions were noted, but also detected in *C. glabrata* (S645P; a strain with a caspofungin MIC at 16 µg/ml, but having susceptible anidulafungin MIC results). Only 25% of strains tested with non-WT echinocandin MIC values had *fks*1 HS1 mutations.

Table 3. Comparisons of echinocandin activity tested against *Candida* spp. from bloodstream infections in four geographic regions (species with >25 strains only), SENTRY Antimicrobial Surveillance Program (2008).

Organism/ antifungal agent	MIC$_{50/90}$ (µg/ml) by geographic region: North America	Europe	Latin America	Asia-Pacific
C. albicans (no.)	(216)	(242)	(100)	(29)
Anidulafungin	0.015/0.06	0.015/0.06	0.015/0.06	0.015/0.06
Caspofungin	0.12/0.25	0.12/0.25	0.12/0.25	0.12/0.25
Micafungin	0.03/0.06	0.03/0.06	0.03/0.06	0.06/0.06
C. glabrata (no.)	(129)	(74)	(8)	(7)
Anidulafungin	0.06/0.12	0.06/0.12	-[a]	-
Caspofungin	0.25/0.25	0.25/0.25	-	-
Micafungin	0.03/0.06	0.03/0.06	-	-
C. parapsilosis (no.)	(79)	(61)	(49)	(7)
Anidulafungin	2/2	2/2	2/4	-
Caspofungin	0.5/1	0.5/1	0.5/1	-
Micafungin	1/2	1/2	1/2	-
C. tropicalis (no.)	(53)	(29)	(38)	(6)
Andiulafungin	0.03/0.06	0.03/0.06	0.03/0.03	-
Caspofungin	0.12/0.25	0.12/0.25	0.12/0.25	-
Micafungin	0.06/0.06	0.06/0.12	0.06/0.06	-

a. - = less than a significant sample size.

Table 4. Activity of anidulafungin and nine other antifungal agents tested against *A. fumigatus* (60 strains) and 13 additional mold isolates from the SENTRY Antimicrobial Surveillance Program (2008).

Organism (no. tested)/ antifungal agent	MIC or MEC (µg/ml) 50%	90%	Range
A. fumigatus (60)			
Anidulafungin	0.002	0.008	≤0.001-0.015
Fluconazole	>64	>64	>64
Voriconazole	0.5	0.5	0.25-1
Amphotericin B	0.5	1	0.25-1
Caspofungin	≤0.008	≤0.008	≤0.008-0.06
Flucytosine	>64	>64	>64
Itraconazole	0.5	1	0.25-1
Ketoconazole	8	8	2->8
Micafungin	0.015	0.03	≤0.008-0.03
Posaconazole	0.25	0.5	0.12-1
Other molds (13)[a]			
Anidulafungin	8	>32	≤0.001->32
Fluconazole	>64	>64	8->64
Voriconazole	8	>8	1->8
Amphotericin B	1	2	0.25-2
Caspofungin	>16	>16	≤0.008->16
Flucytosine	>64	>64	16->64
Itraconazole	>2	>2	0.25->2
Ketoconazole	>8	>8	0.5->8
Micafungin	>16	>16	≤0.008->16
Posaconazole	2	>8	0.25->8

a. Includes: unspeciated *Bipolaris* (1 strain), unspeciated *Exserohilum* (1 strain), unspeciated *Fusarium* (4 strains), unspeciated *Mucor* (1 strain), unspeciated *Penicillium* (3 strains), unspeciated *Rhizopus* (2 strains), and unspeciated mold (1 strain).

- Echinocandin potency versus *A. fumigatus* was outstanding, greatest for anidulafungin (MIC$_{50}$, 0.002 µg/ml) and caspofungin (MIC$_{50}$, ≤0.008 µg/ml), see Table 4.

Conclusions

- SENTRY Program surveillance of anidulafungin, other echinocandins and older antifungal agents shows that the echinocandins provide the most potent activity against BSI yeast (1,201; Table 1) and *A. fumigatus* pneumonia isolates.
- Some species of *Candida* were less susceptible to echinocandins (*C. parapsilosis, C. guilliermondii*, and a few *C. glabrata*) with MIC values at or near the CLSI breakpoint (≤2 µg/ml). These isolates may have mutations in other *fks* complex regions that were not evaluated.
- Continued monitoring for emerging resistances to all antifungal agent classes should be sustained at the international level, with correlations of high MIC values and genetic studies to recognize mechanisms.

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