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Activity of Anidulafungin and Other Antifungal Agents: Results from an International Surveillance Program (2006-2007)

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AMENDED ABSTRACT

Background: Anidulafungin, a novel echinocandin targeting fungal cell wall synthesis, was recently approved by the US-FDA for treatment of candidal infections. Results from an international surveillance program for 2006-7 are presented here.

Methods: A total of 1,448 *Candida* spp., 61 *Aspergillus* spp. (80.3% *A. fumigatus*), and 33 *Cryptococcus neoformans* were collected from infected sterile-site sources in patients from North America, Europe, Latin America and Asia-Pacific, and susceptibility tested. MICs for anidulafungin, caspofungin, 5-fluorocytosine, fluconazole, itraconazole, posaconazole, voriconazole, and amphotericin B were determined using CLSI reference methods (M38-A2, M27-A3).

Results: Rank order of *Candida* spp. occurrence was: *C. albicans* (53.2%), *C. parapsilosis* (16.4%), *C. glabrata* (13.9%), *C. tropicalis* (10.8%), *C. krusei* (2.0%) and other *Candida* spp. (3.7%). *C. albicans* accounted for 51.9, 60.6, 46.0, and 42.1% of candidal infections in North America, Europe, Latin America and Asia-Pacific, respectively. *C. albicans*, *C. glabrata* and *C. tropicalis* were all susceptible to anidulafungin and caspofungin (100.0%); *C. parapsilosis* displayed resistance to anidulafungin (4.6%) and *C. krusei* to caspofungin (3.4%). Anidulafungin (MIC_{50}, 0.03 µg/ml) was four-fold more active than caspofungin against *Candida* spp. overall (highest MIC values, 4 and >16 µg/ml, respectively). Voriconazole was among the most active azoles (MIC_{90}, 0.5 vs 1, 0.5 and 8 µg/ml for posaconazole, itraconazole and fluconazole, respectively) against *Candida* spp., and inhibited most *C. krusei* (93.1% susceptible). Agents most active (MIC_{90}, µg/ml) against *Aspergillus* spp. included anidulafungin (0.008), caspofungin (0.12), posaconazole (0.5) and itraconazole = voriconazole = amphotericin B (1).

Conclusions: Anidulafungin displayed broad activity against *Candida* spp. and *Aspergillus* spp. from four geographic regions with results largely unchanged from earlier (2003) surveillance.

INTRODUCTION

Anidulafungin, a fungicidal echinocandin-class antifungal agent, was approved by the United States Food and Drug Administration (USA-FDA) in 2006 for the treatment of invasive candidiasis and joins another approved echinocandin, caspofungin, for the same indication. Micafungin was approved in 2005 for the treatment of esophageal candidiasis. All echinocandins act through inhibition of synthesis of 1,3-ß-D-glucan in the fungal cell wall and appear to provide good clinical efficacy along with minimal toxicity in the treatment of serious candidal infections. The addition of new antifungal agents comes at a critical time, when fungal infections are increasing due to advanced therapies for malignancies and immunosuppressive disorders, and resistance among yeast pathogens is being increasingly documented.

The development of standardized antifungal testing methodologies are allowing investigators and surveillance networks to generate meaningful data to detect and track resistance to antifungal agents, and monitor the emergence of yeast species with innate resistance profiles, as well as those of mould pathogens. Here we summarize the results of the International Anidulafungin Antimicrobial Surveillance Program for the regions including North America, Europe, Latin America and Asia-Pacific (APAC) comparing the activity of anidulafungin with currently marketed antifungal agents against contemporary, clinical isolates (2006-2007). A total of 1,542 fungal (yeast and mould) strains were tested by reference CLSI [2008] methods with susceptibilities to comparator agents interpreted by CLSI published breakpoint criteria.

MATERIALS AND METHODS

Organism collection studied: A total of 1,448 *Candida* spp. (predominantly from bloodstream infections), 61 *Aspergillus* spp. (respiratory tract infections), and 33 *C. neoformans* were submitted from participating medical centers in North America (761 strains), Europe (460 strains), Latin America (302 strains) and APAC (19 strains) to the central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) for testing. Confirmation of identification was performed using standard biochemical methods and use of the Vitek identification system (Hazelwood, Missouri, USA).

Susceptibility test methods: All strains were tested by the reference broth microdilution methods for yeasts and filamentous fungi as recommended by the CLSI M27-A3 and M38-A2 approved standards [2008] using MOPS-buffered RPMI 1640 medium. Agents routinely tested included: anidulafungin, caspofungin, 5-fluorocytosine, fluconazole, itraconazole, ketoconazole, voriconazole, posaconazole and amphotericin B. Interpretive criteria used for yeasts when testing fluconazole, itraconazole, voriconazole, flucytosine, caspofungin and anidulafungin were those of CLSI [M27-S3, 2008]; interpretive breakpoints for moulds have not been established. A susceptible breakpoint of ≤1 µg/ml was used with amphotericin B for comparative purposes (Diagn. Microbiol. Infect. Dis. 2004; 48:101). Quality control strains utilized included *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 [CLSI, 2008].

RESULTS

- Rank order of *Candida* spp. occurrence was: *C. albicans* (53.2%), *C. parapsilosis* (16.4%) *C. glabrata* (13.9%), *C. tropicalis* (10.8%), *C. krusei* (2.0%) and other *Candida* spp. (3.7%).
- *C. albicans* accounted for 51.9, 60.6, 46.0, and 42.1% of candidal infections in North America, Europe, Latin America and APAC, respectively.
- *C. albicans*, *C. glabrata*, *C. lusitaniae* and *C. tropicalis* were all susceptible to anidulafungin and caspofungin (100.0%); *C. parapsilosis* and *C. guilliermondii* displayed resistance to anidulafungin and caspofungin while *C. krusei* only had resistance to caspofungin (3.4%), see Table 1.
- Anidulafungin (MIC_{50}, 0.03 µg/ml) was four-fold more active than caspofungin against *Candida* spp. overall (highest MIC values, 4 and >16 µg/ml, respectively). Anidulafungin inhibited 99.0% of all yeast at ≤2 µg/ml ($MIC_{50/90}$, 0.03/1 µg/ml).
- Voriconazole was among the most active newer azole (MIC_{90}, 0.5 compared to 1, and 8 µg/ml for posaconazole, and fluconazole, respectively) against *Candida* spp.; and voriconazole inhibited many *C. krusei* (93.1% susceptible).
- Agents most active against *Aspergillus* spp. (MIC_{90}) included anidulafungin (0.008 µg/ml), caspofungin (0.12 µg/ml), posaconazole (0.5 µg/ml) and itraconazole = voriconazole = amphotericin B (1 µg/ml).

Table 1. In vitro susceptibilities of *Candida* spp. and *Crytococcus neoformans* isolates to nine antifungal agents (SENTRY Program, 2006-2007).

	MIC (µg/ml)		% by category[a]		
Species (no. tested)	50/90%	Range	Susceptible	Susceptible-dose dependent	Resistant
All *Candida* spp. (1448)					
Anidulafungin	0.03/1	0.002-4	99.0	-	1.0
Caspofungin	0.12/0.5	0.03->16	99.8	-	0.2
Amphotericin B	0.5/1	≤0.12-2	99.6	-	0.4
5-FC[b]	≤0.5/1	≤0.5->64	95.9	(2.2)	1.9
Fluconazole	≤0.5/8	≤0.5->64	93.4	4.7	1.9
Ketoconazole	≤0.06/1	≤0.06->8	-	-	-
Itraconazole	0.06/0.5	≤0.015->2	67.9	20.6	11.5
Posaconazole	≤0.06/1	≤0.06->8	-	-	-
Voriconazole	≤0.06/0.5	≤0.06-8	98.3	0.8	0.9
C. albicans (771)					
Anidulafungin	0.015/0.06	0.002-1	100.0	-	0.0
Caspofungin	0.12/0.25	0.03-1	100.0	-	0.0
Amphotericin B	0.5/1	≤0.12-1	100.0	-	0.0
5-FC[b]	≤0.5/1	≤0.5->64	97.9	(0.1)	2.0
Fluconazole	≤0.5/≤0.5	≤0.5-16	99.7	0.3	0.0
Ketoconazole	≤0.06/≤0.06	≤0.06-1	-	-	-
Itraconazole	0.03/0.06	≤0.015-1	97.7	2.0	0.3
Posaconazole	≤0.06/0.12	≤0.06-1	-	-	-
Voriconazole	≤0.06/≤0.06	≤0.06-0.25	100.0	0.0	0.0
C. parapsilosis (238)					
Anidulafungin	2/2	0.03-4	95.4	-	4.6
Caspofungin	0.5/1	0.06-4	99.6	-	0.4
Amphotericin B	1/1	0.25-1	99.6	-	0.4
5-FC[b]	≤0.5/≤0.5	≤0.5->64	98.7	(0.0)	1.3
Fluconazole	1/4	≤0.5-32	96.6	3.4	0.0
Ketoconazole	0.12/0.5	≤0.06-4	-	-	-
Itraconazole	0.25/0.5	≤0.015-2	40.8	57.1	2.1
Posaconazole	0.12/0.25	≤0.06-1	-	-	-
Voriconazole	≤0.06/0.12	≤0.06-2	99.6	0.4	0.0
C. glabrata (202)					
Anidulafungin	0.015/0.12	0.015-1	100.0	-	0.0
Caspofungin	0.25/0.25	0.06-2	100.0	-	0.0
Amphotericin B	1/1	≤0.12-1	100.0	-	0.0
5-FC[b]	≤0.5/≤0.5	≤0.5	100.0	(0.0)	0.0
Fluconazole	8/64	≤0.5->64	74.3	15.3	10.4
Ketoconazole	1/4	≤0.06->8	-	-	-
Itraconazole	1/>2	≤0.015->2	3.5	26.7	69.8
Posaconazole	1/4	≤0.06->8	-	-	-
Voriconazole	0.25/1	≤0.06-8	90.1	3.5	6.4
C. tropicalis (157)					
Anidulafungin	0.03/0.06	0.008-0.5	100.0	-	0.0
Caspofungin	0.12/0.5	0.06-2	100.0	-	0.0
Amphotericin B	1/1	≤0.12-2	98.1	-	1.9
5-FC[b]	≤0.5/≤0.5	≤0.5->64	94.9	(0.6)	4.5
Fluconazole	≤0.5/1	≤0.5-32	99.4	0.6	0.0
Ketoconazole	≤0.06/0.12	≤0.06-8	-	-	-
Itraconazole	0.12/0.5	0.03->2	65.6	30.6	3.8
Posaconazole	0.12/0.25	≤0.06->8	-	-	-
Voriconazole	≤0.06/≤0.06	≤0.06-0.5	98.1	0.6	1.3
C. krusei (29)					
Anidulafungin	0.06/0.5	0.03-2	100.0	-	0.0
Caspofungin	0.5/1	0.25-4	96.6	-	3.4
Amphotericin B	1/1	0.25-2	93.1	-	6.9
5-FC[b]	16/16	4-32	3.4	(93.2)	3.4
Fluconazole	32/64	8->64	3.5	79.3	17.2
Ketoconazole	1/4	0.25-4	-	-	-
Itraconazole	0.5/1	0.25->2	0.0	79.3	20.7
Posaconazole	0.5/1	≤0.06-1	-	-	-
Voriconazole	0.25/1	0.12-2	93.1	6.9	0.0
C. lusitaniae (14)					
Anidulafungin	0.25/0.5	0.12-0.5	100.0	-	0.0
Caspofungin	0.5/0.5	0.25-1	100.0	-	0.0
Amphotericin B	0.5/0.5	≤0.12-0.5	100.0	-	0.0
5-FC[b]	≤0.5/≤0.5	≤0.5	100.0	(0.0)	0.0
Fluconazole	≤0.5/1	≤0.5-32	92.9	7.1	0.0
Ketoconazole	≤0.06/0.12	≤0.06-0.25	-	-	-
Itraconazole	0.12/0.5	0.03-1	64.3	28.6	7.1
Posaconazole	≤0.06/0.12	≤0.06-0.25	-	-	-
Voriconazole	≤0.06/≤0.06	≤0.06-0.25	100.0	0.0	0.0
Candida spp. other (37)[c]					
Anidulafungin	0.06/2	0.015-4	91.9	-	8.1[d]
Caspofungin	0.5/1	0.06->16	97.3	-	2.7
Amphotericin B	0.5/1	≤0.12-2	97.3	-	2.7
5-FC[b]	≤0.5/16	≤0.5-64	89.2	8.1	2.7
Fluconazole	2/16	≤0.5->64	89.2	5.4	5.4
Ketoconazole	0.12/1	≤0.06-2	-	-	-
Itraconazole	0.25/2	≤0.015-2	37.8	46.0	16.2
Posaconazole	0.25/1	≤0.06-1	-	-	-
Voriconazole	≤0.06/0.5	≤0.06-2	97.3	2.7	0.0
C. neoformans (33)					
Anidulafungin	>32/>32	8->32	-	-	-
Caspofungin	16/16	4-16	-	-	-
Amphotericin B	0.25/0.25	≤0.12-0.5	-	-	-
5-FC[b]	4/8	2-16	-	-	-
Fluconazole	4/8	1-32	-	-	-
Ketoconazole	≤0.06/0.25	≤0.06-0.5	-	-	-
Itraconazole	0.06/0.25	≤0.015-0.25	-	-	-
Posaconazole	≤0.06/0.12	≤0.06-0.5	-	-	-
Voriconazole	≤0.06/0.12	≤0.06-0.5	-	-	-

a. Breakpoint criteria are those of the CLSI [2008]; when testing amphotericin B, a susceptible breakpoint of ≤1 µg/ml was used (*Diagn. Microbiol. Infect. Dis.* 2004; 48:101); number in parenthesis = % intermediate [CLSI, 2008]; - = no established breakpoint.
b. 5-FC = 5-Flucytosine.
c. Includes: *C. dubliniensis* (7), *C. famata* (6), *C. guilliermondii* (9), *C. kefyr* (5), *C. pelliculosa* (4) and one strain each of *C. inconspicua*, *C. intermedia*, *C. lipolytica* and *C. sake*; plus two unspecified isolates.
d. Three resistant (MIC, 4 µg/ml) strains of *C. guilliermondii*.

Table 2. Activities of nine antifungal agents to *fumigatus* (49 strains) and other *Aspergillus* spp. (SENTRY Program, 2006-2007).

	MIC or MEC (µg/ml)		
Species (no. tested)	50/90%	Range	% at ≤1 µg/ml[a]
Aspergillus spp. (61 strains)			
Anidulafungin	0.002/0.008	≤0.001-0.008	100.0
Caspofungin	0.12/0.12	≤0.008-0.12	100.0
Amphotericin B	0.5/1	≤0.12-2	93.3
5-FC[b]	64/>64	1->64	10.0
Fluconazole	>64/>64	64->64	0.0
Ketoconazole	4/8	0.5->8	4.9
Itraconazole	0.5/1	0.12->2	96.7
Posaconazole	0.25/0.5	≤0.06-0.5	100.0
Voriconazole	0.25/1	0.12-2	96.7

a. Breakpoint criteria have not been established by CLSI [2008]; for comparative purposes, the percent inhibited by ≤1 µg/ml was used (Antimicrob. Agents Chemother. 2002; 46:1032).
b. 5-FC = 5-Flucytosine.

Table 3. In vitro susceptibilities of *Candida* spp. isolates from North America, Europe, Latin America, and Asia Pacific (APAC) to nine antifungal agents (SENTRY Program, 2006-2007).

	$MIC_{50/90}$ in µg/ml (% susceptible)[a]			
Species (no. tested)	North America	Europe	Latin America	APAC
All *Candida* spp.	(726)	(429)	(274)	(19)
Anidulafungin	0.03/2 (98.9)	0.03/1 (99.3)	0.03/1 (98.5)	0.015/0.5 (100.0)
Caspofungin	0.12/0.5 (99.7)	0.12/0.5 (100.0)	0.12/0.5 (99.6)	0.25/0.5 (100.0)
Amphotericin B	0.5/1 (99.9)	0.5/1 (99.5)	1/1 (98.9)	0.5/1 (100.0)
5-FC[b]	≤0.5/≤0.5 (95.7)	≤0.5/≤0.5 (95.3)	≤0.5/≤0.5 (97.1)	≤0.5/2 (100.0)
Fluconazole	≤0.5/ 8 (91.3)	≤0.5/8 (94.4)	≤0.5/2 (97.1)	≤0.5/8 (94.7)
Ketoconazole	≤0.06/1	≤0.06/1	≤0.06/0.25	≤0.06/1
Itraconazole	0.06/1 (64.9)	0.06/1 (72.3)	0.06/0.5 (68.6)	0.06/0.5 (73.7)
Posaconazole	≤0.06/1	≤0.06/1	≤0.06/0.25	0.12/0.5
Voriconazole[a]	≤0.06/0.25 (97.9)	≤0.06/0.25 (98.4)	≤0.06/≤0.06 (99.3)	≤0.06/0.25 (100.0)
C. albicans	(377)	(260)	(126)	(8)
Anidulafungin	0.015/0.06 (100.0)	0.015/0.06 (100.0)	0.015/0.06 (100.0)	NC[c]
Caspofungin	0.12/0.25 (100.0)	0.12/0.25 (100.0)	0.12/0.25 (100.0)	NC
Amphotericin B	0.5/1 (100.0)	0.5/1 (100.0)	0.5/1 (100.0)	NC
5-FC[b]	≤0.5/≤0.5 (96.8)	≤0.5/≤0.5 (98.8)	≤0.5/≤0.5 (99.2)	NC
Fluconazole	≤0.5/≤0.5 (99.5)	≤0.5/≤0.5 (100.0)	≤0.5/≤0.5(100.0)	NC
Ketoconazole	≤0.06/≤0.06	≤0.06/≤0.06	≤0.06/≤0.06	NC
Itraconazole	0.03/0.12 (97.3)	0.03/0.06 (98.1)	0.03/0.12 (97.6)	NC
Posaconazole	≤0.06/0.12	≤0.06/≤0.06	≤0.06/0.12	NC
Voriconazole[a]	≤0.06/≤0.06 (100.0)	≤0.06/≤0.06 (100.0)	≤0.06/≤0.06 (100.0)	NC
C. parapsilosis	(122)	(53)	(60)	(3)
Anidulafungin	2/2 (93.4)	2/2 (94.3)	1/2 (98.3)	NC
Caspofungin	0.5/1 (99.2)	0.5/1 (100.0)	0.5/1 (100.0)	NC
Amphotericin B	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	NC
5-FC[b]	≤0.5/≤0.5 (99.2)	≤0.5/≤0.5 (100.0)	≤0.5/≤0.5 (96.7)	NC
Fluconazole	1/4 (95.9)	1/2 (100.0)	1/4 (95.0)	NC
Ketoconazole	0.12/0.5	0.12/0.25	0.12/0.5	NC
Itraconazole	0.25/0.5 (43.4)	0.25/0.25 (43.4)	0.25/0.5 (30.0)	NC
Posaconazole	0.12/0.25	0.12/0.25	0.12/0.25	NC
Voriconazole[a]	≤0.06/0.12 (100.0)	≤0.06/≤0.06(100.0)	≤0.06/0.12 (98.3)	NC
C. glabrata	(133)	(57)	(11)	(1)
Anidulafungin	0.06/0.12 (100.0)	0.06/0.12 (100.0)	0.06/0.12 (100.0)	NC
Caspofungin	0.12/0.25 (100.0)	0.25/0.25 (100.0)	0.25/0.5 (100.0)	NC
Amphotericin B	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)	NC
5-FC[b]	≤0.5/≤0.5 (100.0)	≤0.5/≤0.5 (100.0)	≤0.5/≤0.5 (100.0)	NC
Fluconazole	8/>64 (71.4)	8/16 (78.9)	4/16 (81.8)	NC
Ketoconazole	1/4	1/2	0.5/2	NC
Itraconazole	1/>2 (2.3)	1/>2 (5.3)	1/2 (9.1)	NC
Posaconazole	1/4	1/4	0.5/1	NC
Voriconazole[a]	0.25/2 (88.7)	0.25/1 (93.0)	0.12/0.5 (90.9)	NC
C. tropicalis	(53)	(36)	(62)	(6)
Anidulafungin	0.03/0.06 (100.0)	0.03/0.6 (100.0)	0.03/0.06 (100.0)	NC
Caspofungin	0.12/0.5 (100.0)	0.12/0.25 (100.0)	0.12/0.5 (100.0)	NC
Amphotericin B	1/1 (100.0)	1/1 (100.0)	1/1 (95.2)	NC
5-FC[b]	≤0.5/≤0.5 (96.2)	≤0.5/≤0.5 (91.7)	≤0.5/≤0.5 (95.2)	NC
Fluconazole	≤0.5/1 (100.0)	≤0.5/1 (97.2)	≤0.5/≤0.5 (100.0)	NC
Ketoconazole	≤0.06/0.25	≤0.06/0.12	≤0.06/0.12	NC
Itraconazole	0.12/0.5 (62.3)	0.12/0.5 (72.2)	0.12/0.5 (66.1)	NC
Posaconazole	0.12/0.25	≤0.06/0.25	0.12/0.25	NC
Voriconazole[a]	≤0.06/≤0.06 (100.0)	≤0.06/≤0.06 (100.0)	≤0.06/≤0.06 (100.0)	NC

a. Breakpoint criteria are those of the CLSI [2008]; when testing amphotericin B, a susceptible breakpoint of ≤1 µg/ml was used (Diagn. Microbiol. Infect. Dis. 2004; 48:101).
b. 5-FC = 5-Flucytosine.
c. NC= not calculated, no results given for categories with <10 isolates.

CONCLUSIONS

- Anidulafungin displayed broad activity against *Candida* spp. and *Aspergillus* spp. from North America, Europe, Latin America and APAC with results largely unchanged from our earlier results (2003) and recent surveillance studies describing thousands of isolates.
- There was no difference in anidulafungin activity by geographic region.
- Anidulafungin was more active when compared with fluconazole, itraconazole, and posaconazole against *C. albicans* (MIC_{90}, 0.06 µg/ml), *C. glabrata* (MIC_{90}, 0.12 µg/ml), *C. tropicalis* (MIC_{90}, 0.06 µg/ml), and *C. krusei* (MIC_{90}, 0.5 µg/ml).
- Anidulafungin was less active against *C. parapsilosis* (MIC_{90}, 2 µg/ml).
- There was no evidence of emerging anidulafungin resistance among recent clinical isolates processed by reference CLSI methods.

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