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Potency of Anidulafungin Compared to Nine Other Antifungal Agents Tested against *Candida* spp., *Cryptococcus* spp., and *Aspergillus* spp.: Results from the Global SENTRY Antimicrobial Surveillance Program (2008)▽

Shawn A. Messer,[1]* Ronald N. Jones,[1,2] Gary J. Moet,[1] Jeffrey T. Kirby,[1] and Mariana Castanheira[1]

JMI Laboratories, North Liberty, Iowa 52317,[1] and Tufts University School of Medicine, Boston, Massachusetts 02111[2]

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The SENTRY Antimicrobial Surveillance Program regularly monitors global susceptibility rates for a spectrum of both novel and established antifungal agents. Anidulafungin and the other echinocandins displayed sustained, excellent activity against *Candida* spp. and *Aspergillus fumigatus*, with ≥98% of MIC results at ≤2 μg/ml. Six yeast isolates (all *Candida glabrata*) showing caspofungin MIC values of ≥0.5 μg/ml were further analyzed for potential *fks* hot spot (HS) mutations; three isolates had confirmed mutations in the *fks1* HS1 region (S645P), and three exhibited mutations in the *fks2* HS1 region (S645F and S645P).

Opportunistic fungal infections are increasing in incidence (18) and are associated with high rates of morbidity and mortality (1, 11, 13). The rise in prevalence of individuals with short-term neutropenia (cancer patients undergoing chemotherapy regimens), long-term immunosuppression (organ transplant patients), immune system disorders (patients with HIV/AIDS), or central venous catheters has coincided with the increased occurrence of problematic opportunistic fungal infections (11). At this time, only a limited number of azole and echinocandin antifungal agents are available for therapeutic intervention against these infections.

Anidulafungin (9, 14–17) is a novel semisynthetic agent that targets cell wall structural integrity via noncompetitive inhibition of β-1,3-D-glucan synthesis, resulting in cell rupture and death. Excellent broad-spectrum *in vitro* and *in vivo* activities against a variety of fungal pathogens have been demonstrated (16). We present here contemporary data (2008) from the global SENTRY Antimicrobial Surveillance Program comparing the activity of anidulafungin to those of nine additional antifungal agents by use of reference methods (5–7).

A collection of 1,201 clinical yeasts from bloodstream infections (BSI) and 79 molds from pneumonias (lower respiratory tract infections [LRTI]) in the United States, Europe, Latin America, and the Asia-Pacific region (APAC) was processed by Clinical and Laboratory Standards Institute (CLSI) methods and included (in rank order) *Candida albicans* (587 isolates), *C. glabrata* (218), *C. parapsilosis* (196), *C. tropicalis* (126), *C. krusei* (24), *C. lusitaniae* (19), *C. dubliniensis* (12), *C. guilliermondii* (4), *C. kefyr* (4), *C. famata* (3), *C. rugosa* (2), *C. haemulonii* (1), *C. inconspicua* (1), *C. lambica* (1), *C. norvegensis* (1), *C. pelliculosa* (1), and *C. sake* (1). The collection also included *Cryptococcus neoformans* (43 isolates), *Aspergillus fumigatus* (60), and 19 other molds (data not shown: *Aspergillus flavus* [3], *Aspergillus niger* [3], *Fusarium* spp. [4], *Penicillium* spp. [3], *Rhizopus* spp. [2], *Bipolaris* sp. [1], and *Mucor* sp. [1], as well as 2 molds not identified to the species level). Laboratories were instructed to submit unique BSI and LRTI isolates obtained in consecutive order, allowing prevalence of the fungal isolates in participating centers to be determined.

All fungal isolates were identified at the participant's medical center by established laboratory methods in use at each institution and confirmed at the central reference laboratory (JMI Laboratories, North Liberty, IA) using Vitek (bioMerieux, Hazelwood, MO) and conventional reference procedures (12, 19). All yeasts were tested by broth microdilution using the CLSI M27-A3 (5) standardized reference method. Preparation of inocula for molds followed procedures described in the CLSI M38-A2 reference method for filamentous fungi (7). Quality control (QC) isolates *C. krusei* ATCC 6258 and *C. parapsilosis* ATCC 22019 were used, and all QC results were within published ranges (6).

Anidulafungin and voriconazole (Pfizer, Inc., New York, NY), amphotericin B, fluconazole, itraconazole, ketoconazole, and flucytosine (Sigma Chemical Co., St. Louis, MO), caspofungin (Merck Research Laboratories, Rahway, NJ), micafungin (Astellas Toyama Co., Ltd., Toyama, Japan), and posaconazole (Schering-Plough Research Institute, Kenilworth, NJ) were obtained as standard powders and prepared according to CLSI guidelines (5–7). The final concentration ranges (in μg/ml) were as follows: for anidulafungin, 0.001 to 32; for caspofungin and micafungin, 0.008 to 16; for amphotericin B, 0.12 to 8; for flucytosine and fluconazole, 0.5 to 64; for itraconazole, 0.015 to 2; and for posaconazole, voriconazole, and ketoconazole, 0.06 to 8. Antifungal dilution testing ranges were selected for maximal capture of MIC_{50} and MIC_{90} wild-type and mutant populations, including expanded ranges for newer and investigational agents to detect organism populations exhibiting potential resistance to these compounds. MIC values (yeasts and molds) and 90% minimal effective concentrations (MEC_{90}) (echinocandins, molds only) were determined as described in the CLSI reference methods (5, 7).

* Corresponding author. Mailing address: JMI Laboratories, 345 Beaver Kreek Centre, Suite A, North Liberty, IA 52317. Phone: (319) 665-3370. Fax: (319) 665-3371. E-mail: sam-messer@jmilabs.com.

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TABLE 1. *In vitro* activities of anidulafungin and nine other selected antifungal agents tested against yeast BSI isolates and mold LRTI isolates from the 2008 SENTRY Antimicrobial Surveillance Program (North America, Latin America, Europe, and Asia-Pacific region)

Organism (no. of isolates tested) and antimicrobial agent	MIC (μg/ml)			% susceptible/ resistant[a]
	50%	90%	Range	
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	0.12	≤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	—/—
A. fumigatus (60)				
Anidulafungin[d]	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[e]	≤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[e]	0.015	0.03	≤0.008–0.03	—/—
Posaconazole	0.25	0.5	0.12–1	—/—

[a] Criteria as published by the CLSI (5). —, 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] Minimal effective concentrations (MECs).

Table 1 displays the *in vitro* activities of 10 antifungal agents tested against yeast BSI isolates collected from the 2008 SENTRY Program. Anidulafungin was the most active agent against (MIC_{90} in μg/ml) *C. albicans* (0.06), *C. glabrata* (0.12), *C. tropicalis* (0.06), and *C. krusei* (0.12) and was less potent against *C. parapsilosis* (MIC_{90}, 2 μg/ml) and *C. guilliermondii* (data not shown). The echinocandin potency against *A. fumigatus* was greatest for anidulafungin (MEC_{90}, 0.002 μg/ml) and caspofungin (MEC_{90}, 0.008 μg/ml) (Table 1). The results demonstrate the expanded utility of these agents against the most common mold species identified in lower respiratory tract infections.

The most active agents against *Cryptococcus neoformans* were the azoles voriconazole and ketoconazole (MIC_{90}, ≤0.06 μg/ml), itraconazole and posaconazole (MIC_{90}, 0.12 μg/ml), and fluconazole (MIC_{90}, 4 μg/ml). Susceptibility rates (MIC, ≤2 μg/ml) for the three echinocandins (Table 2) ranged from 98.4 to 99.9%, and these agents inhibited nearly all yeasts

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

Echinocandin	No. of occurrences (cumulative %) at MIC (μg/ml) of:										
	≤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)[a]	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)[a]	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)[a]	0 (99.9)	1 (100.0)

[a] Breakpoint concentration for susceptibility (5, 6).

except *C. neoformans.* Yeast MIC values when tested against the echinocandins did not vary significantly for the four most common *Candida* spp. among the monitored geographic regions of this surveillance (Table 3). However, some *C. glabrata* isolates displayed non-wild-type elevated MIC values for one or more echinocandins (MIC, ≥0.5 μg/ml), specifically, caspofungin (1 to >16 μg/ml), micafungin (0.25 to 8 μg/ml), and anidulafungin (1 to 4 μg/ml).

Elevated MIC values of echinocandin compounds have been associated with mutations within two highly conserved regions of *fks1* and *fks2* that encode the subunits of β-1,3-D-glucan synthase (GS), the target in the fungal cell wall (3). Six *C. glabrata* isolates were selected for *fks1* hot spot 1 (HS1) and *fks2* HS1 sequencing, since mutations in these regions have commonly been associated with elevated echinocandin MIC values and/or reduced susceptibility of GS to these compounds (8, 10). These strains were isolated in the United States (five strains, from Indiana, Ohio, and Washington) and Germany (one strain). DNA extraction was performed using a QIAamp DNA mini kit (Qiagen, Hilden, Germany). Singleplex PCRs were set up with generic or specific (*C. glabrata*) *fks1* HS1 or *fks2* HS1 primers (4). PCR amplicons were sequenced on both strands. The nucleotide sequence-deduced amino acid sequences were analyzed using the Lasergene software package (DNA STAR, Madison, WI). Sequences were then compared to other available sequences through Internet sources (http://www.ncbi.nlm.nih.gov/blast/).

TABLE 3. Comparisons of echinocandin activities tested against *Candida* spp.[a] from bloodstream infections in four geographic regions (from the SENTRY Antimicrobial Surveillance Program, 2008)

Organism and antifungal agent	MIC_{50}/MIC_{90} for isolates from:			
	North America	Europe	Latin America	Asia-Pacific region
C. albicans				
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				
Anidulafungin	0.06/0.12	0.06/0.12	—[b]	—
Caspofungin	0.25/0.25	0.25/0.25	—	—
Micafungin	0.03/0.06	0.03/0.06	—	—
C. parapsilosis				
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				
Anidulafungin	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] Species with >25 strains only. The numbers of strains tested were as follows: for *C. albicans*, 216 strains from North America, 242 strains from Europe, 100 strains from Latin America, and 29 strains from the Asia-Pacific region; for *C. glabrata*, 129 strains from North America, 74 strains from Europe, 8 strains from Latin America, and 7 strains from the Asia-Pacific region; for *C. parapsilosis*, 79 strains from North America, 61 strains from Europe, 49 strains from Latin America, and 7 strains from the Asia-Pacific region; and for *C. tropicalis*, 53 strains from North America, 29 strains from Europe, 38 strains from Latin America, and 6 strains from the Asia-Pacific region.

[b] —, less than a significant sample size (≤10 isolates).

Amino acid substitutions in the serine residue of position 645 in the *fks1* and *fks2* regions have been detected in several *Candida* species clinical isolates obtained from therapeutic failures or patients showing poor response to treatment with echinocandin compounds (8). Our results showed that three of the six *C. glabrata* strains harbored mutations encoding the S645P *fks1* HS1 alteration, corroborating prior observations (8, 10), and that the three remaining isolates exhibited *fks2* HS1 alterations (S645F, 1 strain; S645P, 2 strains).

The SENTRY Program surveillance of echinocandins and established antifungal agents demonstrates that the echinocandins continue to provide the most potent activity against yeasts isolated from BSI and *A. fumigatus* implicated in LRTI. *Candida* spp. (*C. parapsilosis*, *C. guilliermondii*, and some *C. glabrata* isolates) with less susceptible echinocandin profiles were detected with MIC values at or near the CLSI breakpoint of 2 μg/ml. However, recent findings by Arendrup et al. (2) have illustrated the challenges in using susceptibility testing methods for differentiating wild-type populations from *fks* HS mutants. In the SENTRY Program, follow-up sequencing of *fks1* HS1 and *fks2* HS1 regions confirmed strains with amino acid substitutions and reduced susceptibility to these agents. The SENTRY Program findings demonstrate the need for continued international surveillance to detect emerging resistance patterns among the classes of antifungal agents currently in clinical use. Correlation of higher or non-wild-type MIC values and genetic studies is critical in the recognition and elucidation of resistance mechanisms as well as the selection of appropriate antifungal interventions.

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REFERENCES

1. **Abi-Said, D., E. Anaissie, O. Uzun, I. Raad, H. Pinzcowski, and S. Vartivarian.** 1997. The epidemiology of hematogenous candidiasis caused by different *Candida* species. Clin. Infect. Dis. **24:**1122–1128.
2. **Arendrup, M. C., G. Garcia-Effron, C. Lass-Florl, A. G. Lopez, J. L. Rodriguez-Tudela, M. Cuenca-Estrella, and D. S. Perlin.** 2010. Echinocandin

susceptibility testing of *Candida* species: comparison of EUCAST EDef7.1, CLSI M27-A3, Etest, disk diffusion, and agar dilution methods with RPMI and IsoSensitest media. Antimicrob. Agents Chemother. **54:**426–439.
3. **Baixench, M. T., N. Aoun, M. Desnos-Ollivier, D. Garcia-Hermoso, S. Bretagne, S. Ramires, C. Piketty, and E. Dannaoui.** 2007. Acquired resistance to echinocandins in *Candida albicans*: case report and review. J. Antimicrob. Chemother. **59:**1076–1083.
4. **Castanheira, M., L. N. Woosley, D. J. Diekema, S. A. Messer, R. N. Jones, and M. A. Pfaller.** 2010. Low prevalence of *fks1* hot spot 1 mutations in a worldwide collection of *Candida* strains. Antimicrob. Agents Chemother. **54:**2655–2659.
5. **CLSI.** 2008. M27-A3. Reference method for broth dilution antifungal susceptibility testing of yeasts, 3rd ed. Clinical and Laboratory Standards Institute, Wayne, PA.
6. **CLSI.** 2008. M27-S3. Reference method for broth dilution antifungal susceptibility testing of yeasts, 3rd informational supplement. Clinical and Laboratory Standards Institute, Wayne, PA.
7. **CLSI.** 2008. M38-A2. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi, 2nd ed. Clinical and Laboratory Standards Institute, Wayne, PA.
8. **Desnos-Ollivier, M., S. Bretagne, D. Raoux, D. Hoinard, F. Dromer, and E. Dannaoui.** 2008. Mutations in the *fks1* gene in *Candida albicans*, *C. tropicalis*, and *C. krusei* correlate with elevated caspofungin MICs uncovered in AM3 medium using the method of the European Committee on Antibiotic Susceptibility Testing. Antimicrob. Agents Chemother. **52:**3092–3098.
9. **Espinel-Ingroff, A., A. Fothergill, M. Ghannoum, E. Manavathu, L. Ostrosky-Zeichner, M. A. Pfaller, M. G. Rinaldi, W. Schell, and T. J. Walsh.** 2007. Quality control and reference guidelines for CLSI broth microdilution method (M38-A document) for susceptibility testing of anidulafungin against molds. J. Clin. Microbiol. **45:**2180–2182.
10. **Garcia-Effron, G., S. Lee, S. Park, J. D. Cleary, and D. S. Perlin.** 2009. Effect of *Candida glabrata FKS1* and *FKS2* mutations on echinocandin sensitivity and kinetics of 1,3-beta-D-glucan synthase: implication for the existing susceptibility breakpoint. Antimicrob. Agents Chemother. **53:**3690–3699.
11. **Hajjeh, R. A., M. E. Brandt, and R. W. Pinner.** 1995. Emergence of cryptococcal disease: epidemiologic perspectives 100 years after its discovery. Epidemiol. Rev. **17:**303–320.
12. **Hazen, K. C., and S. A. Howell.** 2007. *Candida*, *Cryptococcus*, and other yeasts of medical importance, p. 1762–1788. *In* P. R. Murray, E. J. Baron, J. H. Jorgensen, M. L. Landry, and M. A. Pfaller (ed.), Manual of clinical microbiology, 9th ed., vol. 2. ASM Press, Washington, DC.
13. **Hsueh, P. R., J. R. Graybill, E. G. Playford, S. P. Watcharananan, M. D. Oh, K. Ja'alam, S. Huang, V. Nangia, A. Kurup, and A. A. Padiglione.** 2009. Consensus statement on the management of invasive candidiasis in intensive care units in the Asia-Pacific region. Int. J. Antimicrob. Agents **34:**205–209.
14. **Messer, S. A., J. T. Kirby, H. S. Sader, T. R. Fritsche, and R. N. Jones.** 2004. Initial results from a longitudinal international surveillance programme for anidulafungin (2003). J. Antimicrob. Chemother. **54:**1051–1056.
15. **Messer, S. A., G. J. Moet, J. T. Kirby, and R. N. Jones.** 2009. Activity of contemporary antifungal agents, including the novel echinocandin anidulafungin, tested against *Candida* spp., *Cryptococcus* spp., and *Aspergillus* spp.: report from the SENTRY Antimicrobial Surveillance Program (2006 to 2007). J. Clin. Microbiol. **47:**1942–1946.
16. **Odabasi, Z., V. L. Paetznick, J. R. Rodriguez, E. Chen, and L. Ostrosky-Zeichner.** 2004. In vitro activity of anidulafungin against selected clinically important mold isolates. Antimicrob. Agents Chemother. **48:**1912–1915.
17. **Pfaller, M. A., D. J. Diekema, L. Ostrosky-Zeichner, J. H. Rex, B. D. Alexander, D. Andes, S. D. Brown, V. Chaturvedi, M. A. Ghannoum, C. C. Knapp, D. J. Sheehan, and T. J. Walsh.** 2008. Correlation of MIC with outcome for *Candida* species tested against caspofungin, anidulafungin, and micafungin: analysis and proposal for interpretive MIC breakpoints. J. Clin. Microbiol. **46:**2620–2629.
18. **Spanakis, E. K., G. Aperis, and E. Mylonakis.** 2006. New agents for the treatment of fungal infections: clinical efficacy and gaps in coverage. Clin. Infect. Dis. **43:**1060–1068.
19. **Verweij, P. E., and M. E. Brandt.** 2007. *Asperigillus*, *Fusarium*, and other opportunistic moniliaceous fungi, p. 1802–1838. *In* P. R. Murray, E. J. Baron, J. H. Jorgensen, M. L. Landry, and M. A. Pfaller (ed.), Manual of clinical microbiology, 9th ed., vol. 2. ASM Press, Washington, DC.