Isavuconazole and Nine Comparator Antifungal Susceptibility Profiles for Common and Uncommon Opportunistic Fungi Collected in 2013: Application of New Clinical Breakpoints and Epidemiological Cutoff Values

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ABSTRACT

Background: The in vitro activity of isavuconazole and 9 comparator agents was assessed using CLSI reference broth microdilution methods against 1,613 common and uncommon yeasts and moulds from a 2013 global survey.

Methods: Identifications were performed using CHROMagar (yeasts), MALDI-TOF MS or DNA sequencing (ITS and/or 28S regions [all] or IGS for yeasts and β-tubulin, and TEF for moulds). Isolates were classified as either susceptible or resistant (R) and as wild-type (WT) or non-WT using CLSI clinical breakpoints (CBPs) or epidemiological cutoff values (ECVs), respectively for the antifungal agents.

Results: Isolates included 1,320 organisms from 21 species of *Candida*, 155 from 12 species/species complex of *Aspergillus*, 69 of *C. neoformans*, 34 from 9 other yeast species, and 35 from 14 mould species. Among *Candida* spp., R to all 10 tested antifungal agents ranged from 0.0% to 20.0%. The vast majority of each species of *Candida*, with the exception of *C. glabrata* (CGLA; MIC_{90}, 2 μg/ml), *C. krusei* (MIC_{90}, 1 μg/ml) and *C guilliermondii* (CGU; MIC_{90}, 8 μg/ml), were inhibited by ≤0.25 μg/ml of isavuconazole. CGLA and *C. krusei* were largely inhibited by ≤1 μg/ml of isavuconazole. R to fluconazole was seen in 0.5% of *C. albicans* isolates, 11.1% of CGLA isolates, 2.5% of *C. parapsilosis*, 4.5% of *C. tropicalis* (CTRO) and 20.0% of CGU. Cross-R with other azoles was most prominent with CGLA and CGU. R to the echinocandins was restricted to CGLA (1.3%-2.1%) and CTRO (0.9%-1.8%). All agents except for the echinocandins were active against *C. neoformans*; and the triazoles, including isavuconazole, were active against the other yeasts. Mould active triazoles and the echinocandins were active against *Aspergillus* spp., but less active against the rarer moulds. Cross-R to the triazoles was detected in 3 isolates of *A. fumigatus*.

Conclusions: These data document continued activity of isavuconazole against both common and uncommon fungal isolates. In general, there was low R levels to the available antifungals in a large, contemporary (2013), global collection of molecularly characterized yeasts and moulds. R to azoles and echinocandins was most prominent among isolates of CGLA, CTRO and CGU.

INTRODUCTION

Surveillance studies of antifungal resistance have largely focused on azole-resistant *Candida glabrata*. Previously, we have used the comprehensive database of the SENTRY Antimicrobial Surveillance Program to document a steady increase in both the frequency of isolation as well as azole resistance in bloodstream infection (BSI) isolates of *C. glabrata*. More recently, the emergence of echinocandin resistance among BSI isolates of *C. glabrata* has been noted in both population- and sentinel-based surveillance efforts as well as in more geographically delimited surveys and single center reports. With respect to both azole and echinocandin resistance, it is now clear that prior exposure to these classes of antifungal agents is a key factor in the development of resistance, especially regarding *C. glabrata*.

Whereas it is important to continue to follow resistance trends in species with known antifungal resistance patterns, such as *C. glabrata*, large-scale and continuous surveillance programs are also useful in detecting emerging resistance among usually susceptible species of *Candida* as well as other less common yeasts and moulds associated with invasive fungal infections (IFI). For example, resistance to both azole and echinocandin agents has been uncommon among BSI isolates of *C. tropicalis*; however, reports of increasing resistance to both classes of agents have been published in recent years. Likewise, many of the less common yeasts and moulds are now known to be intrinsically resistant to many of the existing antifungal agents.

In the present study, we examine the in vitro activities of isavuconazole and micafungin along with comparator agents against 1,613 clinical fungal isolates (1,320 isolates of *Candida* spp., 155 of *Aspergillus* spp., 103 of non-*Candida* yeasts, and 35 of non-*Aspergillus* moulds) collected in 2013 from BSI, normally sterile sites, and respiratory tract specimens. All isolates were tested using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods and results were interpreted using species-specific clinical breakpoints and epidemiological cutoff values (ECVs).

MATERIALS AND METHODS

Organisms. A total of 1,613 non-duplicate clinical isolates from patients with IFI were collected during 2013 from 70 medical centers in North America (695 isolates, 29 sites), Europe (511 isolates, 19 sites), the Asia-Pacific Region (222 isolates, 12 sites) and Latin America (185 isolates, 10 sites) as part of the SENTRY Program. These isolates were received consecutively from patients with BSI (964 isolates), from normally sterile body fluids, tissues, or abscesses (110 isolates), from respiratory tract specimens (278 isolates), or from unspecified infection sites (261 isolates).

Species identification. Yeast isolates were subcultured and screened using CHROMagar *Candida* (Becton Dickinson, Sparks, MD) to ensure purity and to differentiate *Candida albicans/Candida dubliniensis, Candida tropicalis* and *C. krusei.* Isolates suspected to be either *C. albicans* or *C. dubliniensis* (green colonies on CHROMagar) were incubated at 45°C. All other yeast isolates were submitted to Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS) using the MALDI Biotyper according to the manufacturer's instructions (Bruker Daltonics, Billerica, MA). Yeasts that were not identified by either phenotypic or proteomic methods were identified using sequencing-based methods for internal transcribed spacer (ITS) region, 28S ribosomal subunit (D1/D2), and intergenic spacer 1 (IGS1) (*Trichosporon* spp.) according to protocols previously described. All mould isolates were subcultured and identified by MALDI-TOF MS or sequencing analysis of 28S ribosomal subunit (all isolates) and one of the following: β-tubulin for *Aspergillus* spp., translation elongation factor (TEF) for *Fusarium* spp. or ITS for all other species of filamentous fungi when acceptable identification was not achieved by MALDI-TOF MS.

Nucleotide sequences were examined using Lasergene software (DNAStar, Madison, WI, USA) and then compared to database sequences using BLAST (http://www.ncbi.nlm.nih.gov/blast). *Fusarium* spp. isolates were analyzed for TEF sequences using *Fusarium*-ID database (http://www.isolate.fusariumdb.org) and the *Fusarium* multilocus sequence typing (MLST) database (http://chs.knaw.nl/fusarium). Results were considered acceptable if homology was >99.5% with other entries in the databases used for comparison. Available sequences that were considerably different from the majority of entries for one species were considered outliers and were discarded in the analysis. Additionally, if no match was found in the database, the identification was based on species complex (SC), genus, family, or order, according to the most current classification systems.

Antifungal susceptibility testing. All isolates were tested by broth microdilution according to CLSI methods outlined in documents M27-A3 and M38-A2. Frozen-form panels used RPMI 1640 broth supplemented with MOPS (morpholinepropane sulfonic acid) buffer and 0.2% glucose and inoculated with 0.5 to 2.5 X 10^3 cells/ml suspensions. MIC/MEC values were determined visually, after 24, 48 or 72 hours of incubation at 35ºC, as the lowest concentration of drug that resulted in ≥50% inhibition of growth relative to the growth control or complete (100%) inhibition. Isavuconazole was read 50% inhibition at 24 h for yeasts (48 h for *Cryptococcus* spp.) and 100% at 48 h for moulds, as recommended by CLSI documents for other triazoles. Recently published CLSI clinical breakpoints were used for the five most common species of *Candida* (*C. albicans, C. glabrata, C. parapsilosis, C. tropicalis,* and *C. krusei*) for echinocandins, fluconazole and voriconazole. Epidemiological cutoff values (ECV) were applied when available.

Quality control was performed as recommended in CLSI documents M27-A3 (CLSI, 2008b) and M38-A2 (CLSI, 2008a) using strains *C. krusei* ATCC 6258, *C. parapsilosis* ATCC 22019, *A. flavus* ATCC 204304 and *A. fumigatus* MYA-3626.

RESULTS

- Among the 1,613 fungal clinical isolates, 1,320 (81.8%) were *Candida* spp., 103 (6.4%) were non-candidal yeasts, including 69 *Cryptococcus neoformans* (3.0%), 155 (9.6%) were *Aspergillus* spp., and 35 (2.2%) were other moulds, including 10 isolates of *Sarocladium kiliense* (**Table 1**).
- Among 621 *C. albicans* isolates, only two (0.3%) were not inhibited by isavuconazole at ≤0.12 μg/ml (**Table 2**). Among three fluconazole-resistant *C. albicans* isolates, two (USA and Hungary) had MIC values >128 μg/ml and were also resistant to voriconazole (MIC, >8 μg/ml) and isavuconazole (MIC, >8 μg/ml). One isolate from Israel had fluconazole MIC values at 8 μg/ml (Israel) and was voriconazole- and isavuconazole-susceptible (0.12 and 0.06 μg/ml, respectively).
- *C. glabrata* MIC values for isavuconazole ranged from 0.03 to 8 μg/ml and this newer azole ($MIC_{50/90}$, 0.5/2 μg/ml) displayed activity similar to posaconazole ($MIC_{50/90}$,1/2 μg/ml) and was two-fold less active than voriconazole ($MIC_{50/90}$, 0.12/1 μg/ml; **Tables 2** and **3**). A total of 11.1 and 20.9% of the *C. glabrata* isolates were categorized as resistant and non-wildtype to fluconazole, respectively.
- Isavuconazole ($MIC_{50/90}$, 0.06/0.12 μg/ml; **Table 3**) was very active against *C. parapsilosis* isolates and this azole inhibited all isolates at ≤1 μg/ml and 99.0% of the isolates at ≤0.5 μg/ml (**Table 2**). Five isolates displayed resistance to fluconazole (Turkey [n=2], USA, Israel and Colombia) and three had intermediate MIC values for voriconazole (Turkey [n=2] and USA).
- A total of 98.2% of the *C. tropicalis* isolates were inhibited by isavuconazole at ≤0.5 μg/ml (**Table 2**). The two isolates displaying isavuconazole MIC values at 1 and 4 μg/ml were from Los Angeles and New York, USA and displayed elevated fluconazole MIC values (32 and 64 μg/ml) and voriconazole MIC results at 2 μg/ml.
- *C. krusei* isolates displayed isavuconazole MIC values ranging from 0.12 to 4 μg/ml, and 100.0% of *C. lusitaneae* and *C. dubliniensis* were inhibited at ≤0.12 and ≤0.015 μg/ml of isavuconazole, respectively (**Table 2**).
- The activity of isavuconazole against *C. neoformans* isolates was very good ($MIC_{50/90}$, 0.06/0.12 μg/ml; **Table 2**). All isolates were inhibited at 0.5 μg/ml of isavuconazole and the activity of this newer azole was similar to that of other newer azoles ($MIC_{50/90}$, 0.12/0.25, 0.12/0.25 and 0.03/0.06 μg/ml for itraconazole, posaconazole and voriconazole, respectively).
- Isavuconazole and itraconazole ($MIC_{50/90}$, 1/2 and 1/1 μg/ml, respectively; **Table 3**) had similar activities against 120 *A. fumigatus* isolates that was slightly lower than those of voriconazole and posaconazole ($MIC_{50/90}$, 0.25/0.5 μg/ml for both compounds). Isavuconazole MIC values ranged from 0.12 to 8 μg/ml and the two isolates with MIC values at 8 μg/ml, also displayed elevated itraconazole MIC values (4 μg/ml). These isolates are being further investigated for mutations on *cyp51A* and *cyp51B*.
- Isavuconazole MIC_{90} values were 2 μg/ml for *A. flavus* (**Table 3**) and the activity of this newer azole was slightly lower when compared to other azoles for these species (MIC_{90} for itraconazole, posaconazole and voriconazole was 0.5, 0.5 and 1 μg/ml, respectively).

Table 1. Geographic distribution of organisms collected during 2013 in hospitals worldwide.

Organism/organism group	No. of isolates in each indicated geographic region: North America	Europe	Latin America	Asia-Pacific	Total
Total yeasts and moulds	695	511	185	222	1,613
Yeasts					
All *Candida* spp.	522	427	142	209	1,320
C. albicans	231	228	62	100	621
C. glabrata	133	46	9	47	235
C. parapsilosis	64	81	36	16	197
C. tropicalis	38	33	16	23	110
C. krusei	21	9	3	4	37
C. lusitaniae	19	3	4	7	33
C. dubliniensis	17	8	1	5	31
C. guilliermondii	4	7	1	3	15
C. orthopsilosis	3	1	5	1	10
Other *Candida* spp.[a]	12	11	5	3	31
Cryptococcus neoformans	21	29	16	3	69
Other yeasts[b]	14	9	4	7	34
Moulds					
All *Aspergillus* spp.	100	42	10	3	155
A. fumigatus	73	40	5	2	120
A. flavus species complex	8	1	4		13
Other *Aspergillus* spp.[c]	19	1	1	1	22
Sarocladium kiliense			10		10
Other moulds[d]	18	4	3		25

a. Other *Candida* spp. include *C. auris* (1 strain), *C. bracarensis* (1 strain), *C. fabianii* (4 strains), *C. fermentat* (3 strains), *C. haemulonii* (1 strain), *C. kefyr* (7 strains), *C. lipolytica* (1 strain), *C. metapsilosis* (7 strains), *C. norvegensis* (1 strain), *C. pararugosa* (2 strains), *C. pelliculosa* (2 strains), *C. thermophila* (1 strain).

b. Other yeasts include *Cryptococcus gattii* (3 strains), *Geotrichum clavatum* (4 strains), *Pichia manshurica* (1 strain), *Rhodotorula glutinis* (1 strain), *R. mucilaginosa* (5 strains), *Saccharomyces cerevisiae* (9 strains), *Trichosporon asahii* (9 strains), unspecified *Geotrichum* (1 strain), unspecified *Trichosporon* (1 strain).

c. Other *Aspergillus* spp. include *A. clavatus* (1 strain), *A. nidulans* (3 strains), *A. niger* species complex (8 strains), *A. sydowii* (1 strain), *A. terreus* species complex (4 strains), *A. tubingensis* (1 strain), *A. ustus* (1 strain), *A. versicolor* species complex (3 strains)

d. Other moulds include *Fonsecaea pedrosoi* (1 strain), *Fusarium solani* species complex (5 strains), *Gibberella fujikuroi* species complex (2 strains), *Geosmithia argillacea* (1 strain), *Microascus cirrosus* (1 strain), *Purpureocillium* (*Paecilomyces*) *lilacinum* (3 strains), *Rhizomucor miehei* (1 strain), *Scedosporium apiospermum* (4 strains), *Scedosporium prolificans* (1 strain), *Rhizopus microsporus* group (2 strains), unspecified *Alternaria* (1 strain), unspecified *Curvularia* (1 strain), unspecified *Paecilomyces* (1 strain), unspecified *Ramichloridium* (1 strain).

Table 2. Antifungal activity of isavuconazole against organism species/groups tested as part of the 2013 international surveillance program.

Organism species/groups (no. tested)	Number (cumulative %) of isolates inhibited at isavuconazole MIC (μg/ml)[a]: ≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
Candida spp. (1320)	42 (3.2)	142 (13.9)	388 (43.3)	192 (57.9)	167 (70.5)	94 (77.7)	93 (84.7)	119 (93.7)	44 (97.0)	18 (98.4)	12 (99.3)	6 (99.8)	3 (100.0)
Candida albicans (621)	36 (5.8)	126 (26.1)	334 (79.9)	95 (95.2)	23 (98.9)	5 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	0 (99.7)	2 (100.0)
Candida glabrata (235)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)	4 (2.6)	23 (12.3)	61 (38.3)	87 (75.3)	28 (87.2)	17 (94.5)	9 (98.3)	4 (100.0)	
Candida parapsilosis (197)	1 (0.5)	5 (3.0)	21 (13.7)	56 (42.1)	76 (80.7)	25 (93.4)	9 (98.0)	2 (99.0)	2 (100.0)				
Candida tropicalis (110)	0 (0.0)	0 (0.0)	6 (5.5)	18 (21.8)	43 (60.9)	31 (89.1)	8 (96.4)	2 (98.2)	1 (99.1)	0 (99.1)	1 (100.0)		
Candida krusei (37)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.4)	5 (18.9)	20 (73.0)	8 (94.6)	0 (94.6)	2 (100.0)		
Candida lusitaniae (33)	1 (3.0)	2 (9.1)	5 (24.2)	14 (66.7)	9 (93.9)	2 (100.0)							
Candida dubliniensis (31)	3 (9.7)	9 (38.7)	19 (100.0)										
Candida guilliermondii (15)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)	4 (40.0)	4 (66.7)	2 (80.0)	0 (80.0)	0 (80.0)	2 (93.3)	1 (100.0)
Candida orthopsilosis (10)	0 (0.0)	0 (0.0)	1 (10.0)	4 (50.0)	3 (80.0)	0 (80.0)	1 (90.0)	1 (100.0)					
Other *Candida* spp. (31)	1 (3.2)	0 (3.2)	2 (9.7)	3 (19.4)	9 (48.4)	4 (61.3)	5 (77.4)	3 (87.1)	3 (96.8)	1 (100.0)			
Cryptococcus neoformans SC (69)	3 (4.3)	1 (5.8)	6 (14.5)	21 (44.9)	23 (78.3)	11 (94.2)	3 (98.6)	1 (100.0)					
Other yeasts	1 (2.9)	1 (5.9)	0 (5.9)	0 (5.9)	2 (11.8)	8 (35.3)	6 (52.9)	10 (82.4)	0 (82.4)	3 (91.2)	2 (97.1)	1 (100.0)	
Aspergillus spp. (155)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.6)	1 (1.3)	5 (4.5)	15 (14.2)	105 (81.9)	24 (97.4)	2 (98.7)	2 (100.0)	
Aspergillus fumigatus (120)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	2 (2.5)	10 (10.8)	94 (89.2)	11 (98.3)	0 (98.3)	2 (100.0)	
Aspergillus flavus SC (13)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (46.2)	7 (100.0)			
Other *Aspergillus* spp. (22)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)	0 (4.5)	0 (4.5)	3 (18.2)	5 (40.9)	5 (63.6)	6 (90.9)	2 (100.0)		
Sarocladium kiliense (10)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (10.0)	0 (10.0)	9 (100.0)
Other moulds (190)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)	1 (8.0)	1 (12.0)	2 (20.0)	2 (28.0)	4 (44.0)	2 (52.0)	2 (60.0)	10 (100.0)

Table 3. Antifungal activity of isavuconazole and comparator antifungal agents against key organism species/groups tested as part of the 2013 international surveillance program[a].

Species (no. tested)/ Antifungal agent	MIC/MEC (μg/ml) Range	50%	90%	% by category[b] CLSI %S	CLSI %R	ECV %WT	ECV %NWT
C. albicans (621)							
Isavuconazole	≤0.008->8	0.015	0.03				
Posaconazole	≤0.008->8	0.06	0.06			94.4	5.6
Voriconazole	≤0.008->8	≤0.008	0.015	99.7	0.3	99.4	0.6
Fluconazole	0.06->128	0.12	0.25	99.5	0.5	98.4	1.6
Micafungin	≤0.008-0.06	0.015	0.03	100.0	0.0	99.8	0.2
Caspofungin	<0.008-0.25	0.03	0.03	100.0	0.0	99.8	0.2
C. glabrata (235)							
Isavuconazole	0.03-8	0.5	2				
Posaconazole	0.06->8	1	2			97.4	2.6
Voriconazole	≤0.008-8	0.12	1			88.9	11.1
Fluconazole	0.12->128	8	64	(88.9)[c]	11.1	79.1	20.9
Micafungin	≤0.008-1	0.015	0.03	98.3	1.3	97.4	2.6
Caspofungin	0.015-1	0.03	0.06	97.9	2.1	97.9	2.1
C. parapsilosis (197)							
Isavuconazole	≤0.008-1	0.06	0.12				
Posaconazole	0.03-0.5	0.12	0.25			98.5	1.5
Voriconazole	≤0.008-0.5	0.015	0.06	98.5	0.0	98.5	1.5
Fluconazole	0.25-2	1	2	94.4	2.5	81.7	18.3
Micafungin	0.12-2	1	2	100.0	0.0	100.0	0.0
Caspofungin	0.06-1	0.25	0.5	100.0	0.0	100.0	0.0
C. tropicalis (110)							
Isavuconazole	0.015-4	0.06	0.25				
Posaconazole	0.015-0.5	0.06	0.12			90.0	10.0
Voriconazole	≤0.008-2	0.03	0.06	95.5	2.7	94.5	5.5
Fluconazole	0.12-64	0.5	1	95.5	4.5	93.6	6.4
Micafungin	≤0.008-1	0.03	0.06	98.2	0.9	97.3	2.7
Caspofungin	0.015-2	0.03	0.06	98.2	0.9	98.2	1.8
C. krusei (37)							
Isavuconazole	0.12-4	0.5	1				
Posaconazole	0.25-1	0.5	0.5			97.3	2.7
Voriconazole	0.06-2	0.25	0.5	94.6	2.7	94.6	5.4
Fluconazole	8->128	32	64			70.3	29.7
Micafungin	0.06-0.12	0.12	0.12	100.0	0.0	100.0	0.0
Caspofungin	0.06-0.25	0.12	0.25	100.0	0.0	100.0	0.0
C. lusitaniae (33)							
Isavuconazole	≤0.008-0.12	0.03	0.06				
Posaconazole	0.015-0.12	0.06	0.12			100.0	0.0
Voriconazole	≤0.008-0.03	≤0.008	0.015			100.0	0.0
Fluconazole	≤0.06-2	0.5	1			100.0	0.0
Micafungin	0.03-0.5	0.25	0.25			100.0	0.0
Caspofungin	0.03-0.5	0.25	0.5			100.0	0.0
C. dubliniensis (31)							
Isavuconazole	≤0.008-0.015	0.015	0.015				
Posaconazole	0.015-0.12	0.06	0.12			100.0	0.0
Voriconazole	≤0.008-0.015	≤0.008	≤0.008			100.0	0.0
Fluconazole	≤0.06-0.5	0.12	0.25			100.0	0.0
Micafungin	≤0.008-0.12	0.03	0.06			100.0	0.0
Caspofungin	0.015-0.12	0.06	0.12			100.0	0.0
Cryptococcus neoformans(69)							
Isavuconazole	≤0.008-0.5	0.06	0.12				
Itraconazole	0.03-0.5	0.12	0.25			100.0	0.0
Posaconazole	0.06-0.25	0.12	0.25			100.0	0.0
Voriconazole	≤0.008-0.12	0.03	0.06			100.0	0.0
Fluconazole	0.25-8	2	4			100.0	0.0
Aspergillus fumigatus (120)							
Isavuconazole	0.12-8	1	2				
Itraconazole	0.25-4	1	1			98.3	1.7
Posaconazole	0.06-1	0.25	0.5			97.5	2.5
Voriconazole	0.12-2	0.25	0.5			98.3	1.7
Micafungin	≤0.008-0.03	≤0.008	0.015				
Caspofungin	≤0.008-0.06	0.03	0.03			100.0	0.0
A. flavus species complex (13)							
Isavuconazole	1-2	2	2				
Itraconazole	0.25-1	0.5	0.5			100.0	0.0
Posaconazole	0.12-0.5	0.25	0.5			100.0	0.0
Voriconazole	0.5-1	1	1			100.0	0.0
Micafungin	≤0.008-0.015	≤0.008	0.015				
Caspofungin	0.015-0.03	0.015	0.015			100.0	0.0

a. Abbreviations: MEC, minimum effective concentration; 50% and 90%, MIC value encompassing 50% and 90% of isolates tested, respectively; CLSI, Clinical and Laboratory Standards Institute; ECV, epidemiological cutoff value; %S, % susceptible; %R, % Resistant; WT, %wild-type; %NWT, %non-WT.

b. Interpretive categories as recommended by CLSI (2012) and by the use of ECVs (Espinel-Ingroff et al, 2010; Espinel-Ingroff et al, 2012; Pfaller and Diekema, 2012).

c. Category designation is susceptible dose dependent (SDD).

CONCLUSIONS

- Isavuconazole showed good coverage for most common contemporary and geographically diverse isolates of *Candida* spp. and *Aspergillus* spp. tested as part of this study.
- Among common *Candida* species, fluconazole-resistant isolates have been observed mostly in the USA and Asia-Pacific countries.
- The spectrum of opportunistic fungal pathogens continues to grow with the increasing application of molecular and proteomic methods of identification. Isavuconazole exhibit excellent activity against most species of *Candida* and *Aspergillus* and is comparable to posaconazole and voriconazole against the less common yeasts and moulds.

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