AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

In Vitro Activity of Isavuconazole against Opportunistic Fungal Pathogens from Two Mycology Reference Laboratories

Michael A. Pfaller,[a,b] Paul R. Rhomberg,[a] Nathan P. Wiederhold,[c] Connie Gibas,[c] Carmita Sanders,[c] Hongxin Fan,[c] James Mele,[c] Laura L. Kovanda,[d] Mariana Castanheira[a]

[a]JMI Laboratories, North Liberty, Iowa, USA
[b]University of Iowa College of Medicine, Iowa City, Iowa, USA
[c]Fungus Testing Laboratory, University of Texas Health Science Center, San Antonio, Texas, USA
[d]Astellas Pharma Global Development, Inc., Northbrook, Illinois, USA

ABSTRACT Monitoring antifungal susceptibility patterns for new and established antifungal agents seems prudent given the increasing prevalence of uncommon species associated with higher antifungal resistance. We evaluated the activity of isavuconazole against 4,856 invasive yeasts and molds collected worldwide. The 4,856 clinical fungal isolates, including 2,351 *Candida* species isolates, 97 non-*Candida* yeasts, 1,972 *Aspergillus* species isolates, and 361 non-*Aspergillus* molds, including 292 *Mucorales* isolates collected in 2015 to 2016, were tested using CLSI methods. The MIC values for isavuconazole versus *Aspergillus* ranged from 0.06 to ≥16 μg/ml. The modal MIC for isavuconazole was 0.5 μg/ml (range, 0.25 [*A. nidulans* and *A. terreus* species complex] to 4 μg/ml [*A. calidoustus* and *A. tubingensis*]). Eight *A. fumigatus* isolates had elevated isavuconazole MIC values at ≥8 μg/ml (non-wild type). Isavuconazole showed comparable activity to itraconazole against the *Mucorales*. The lowest modal isavuconazole MIC values were seen for *Rhizopus* spp., *R. arrhizus* var. *arrhizus*, and *R. microsporus* (all 1 μg/ml). *Candida* species isolates were inhibited by ≤0.25 μg/ml of isavuconazole (range, 96.1% [*C. lusitaniae*] to 100.0% [*C. albicans*, *C. dubliniensis*, *C. kefyr*, and *C. orthopsilosis*]). MIC values were ≤1 μg/ml for 95.5% of *C. glabrata* isolates and 100.0% of *C. krusei* isolates. Isavuconazole was active against the non-*Candida* yeasts, including *Cryptococcus neoformans* (100.0% at ≤0.5 μg/ml). Isavuconazole exhibited excellent activity against most species of *Candida* and *Aspergillus*. Isavuconazole was comparable to posaconazole and voriconazole against the less common yeasts and molds. Isavuconazole was generally less active than posaconazole and more active than voriconazole against the 292 *Mucorales* isolates. We confirm the potentially useful activity of isavuconazole against species of *Rhizopus* as determined by CLSI methods.

KEYWORDS azoles, isavuconazole, molds, yeasts

The burden of invasive fungal infections (IFIs) for patients and health care systems is difficult to measure (1, 2); however, it is well recognized that IFIs are associated with high morbidity and mortality rates and elevated health care costs. A higher prevalence of IFIs has been observed over the last 3 decades due to the increasing immunocompromised population, which includes individuals living with human immunodeficiency virus, transplant recipients, and cancer patients (1, 3–6). Additionally, increases in the elderly population, neonates, and patients requiring invasive therapies also contribute to the higher IFI rates (4, 7, 8).

The most common fungal pathogens associated with IFIs in humans include *Candida* spp., *Aspergillus* spp., and members of the order *Mucorales* (1). Notably, though the incidences of candidemia and invasive candidiasis (including infections of normally

Received 12 June 2018 **Returned for modification** 1 July 2018 **Accepted** 19 July 2018

Accepted manuscript posted online 30 July 2018

Citation Pfaller MA, Rhomberg PR, Wiederhold NP, Gibas C, Sanders C, Fan H, Mele J, Kovanda LL, Castanheira M. 2018. *In vitro* activity of isavuconazole against opportunistic fungal pathogens from two mycology reference laboratories. Antimicrob Agents Chemother 62:e01230-18. https://doi.org/10.1128/AAC.01230-18.

Address correspondence to Michael A. Pfaller, mike-pfaller@jmilabs.com.

sterile body fluids, deep tissues, and organs) have declined in recent U.S. surveys (9, 10), they are increasing in many other regions of the world (4, 11–19). Although much less common than candidiasis, invasive infections due to *Aspergillus* and the mucormycetes are increasing in the U.S. and elsewhere (12, 20–22). Infections due to members of each of these organism groups carry high rates of mortality and cost (1, 10, 20, 23–26). Isolates displaying resistance to clinically available antifungal agents are increasingly reported worldwide, but they are still uncommon (12, 25, 27–31). Emerging multidrug-resistant (MDR [resistant to 2 or more classes of agents]) species of *Candida* (7, 25, 32, 33) and azole-resistant *Aspergillus fumigatus* (30, 34, 35) are now reported globally and are associated with excess health care costs in addition to considerable morbidity and mortality (23, 36, 37). The increase in invasive mucormycosis is especially notable as these organisms are intrinsically resistant to many antifungal agents. Thus, the increasing number of breakthrough infections reported in patients receiving mold-active agents (e.g., voriconazole and echinocandins) is of great concern (20–22, 26, 38). For this reason, continuous monitoring of the antifungal susceptibility patterns and resistance mechanisms to clinically used antifungal agents is of increased importance.

The systemically active antifungal armamentarium currently includes the polyenes, flucytosine, fluconazole, the extended-spectrum (mold-active) triazoles (isavuconazole, itraconazole, posaconazole, and voriconazole), and the echinocandins. Despite the fact that these agents cover the vast majority of opportunistic fungal pathogens and are increasingly employed in either a prophylactic or preemptive treatment strategy, breakthrough invasive fungal infections continue to be reported and increasingly involve yeasts and/or molds that are relatively uncommon and tend to exhibit decreased susceptibility to the available antifungal agents (27, 29, 31).

Isavuconazole, a mold-active triazole, may be administered orally or parenterally and offers advantages in terms of predictable pharmacokinetics and safety over the other mold-active triazoles, including itraconazole, posaconazole, and voriconazole (39–42). Specifically, isavuconazonium sulfate (the prodrug formulation of isavuconazole) may be administered intravenously to patients with decreased renal function without the need for dose adjustment, due to the lack of cyclodextrin and minimal renal excretion (42).

Previous studies have documented activity of isavuconazole against common species of both *Candida* and *Aspergillus* (41, 43). Isavuconazole is also active against many of the less common yeasts and molds, including members of the order *Mucorales* (44–47), and has been approved by the U.S. Food and Drug Administration for the treatment of invasive aspergillosis and invasive mucormycosis (38–40, 42, 48, 49). Studies to assess the clinical activity of isavuconazole against *Candida* and uncommon yeasts and molds have been completed (42).

In the present study, we examined the *in vitro* activities of isavuconazole and comparator antifungal agents against 4,856 clinical fungal isolates (2,351 of *Candida* spp., 1,972 of *Aspergillus* spp., 97 of non-*Candida* yeasts, and 361 of non-*Aspergillus* molds, including 292 *Mucorales* isolates) collected in 2015 to 2016 from clinically significant infections as part of two fungal surveillance efforts: the global SENTRY Antimicrobial Surveillance Program (JMI Laboratories, North Liberty, IA [*Candida* spp., non-*Candida* yeasts, and rare molds]) and the Fungus Testing Laboratory (San Antonio, TX [*Aspergillus* spp. and *Mucorales*]). All isolates were tested using Clinical and Laboratory Standards Institute (CLSI) broth microdilution (BMD) methods, species-specific clinical breakpoints (CBPs), and proposed epidemiological cutoff values (ECVs), where available, for each agent to detect emerging resistance among *Candida* spp., *Aspergillus* spp., and selected mucormycetes. Molecular and proteomic methods were used to confirm the identification of the less common species of *Candida*, non-*Candida* yeasts, and all filamentous fungi.

RESULTS

All fungal clinical isolates (species with 10 or more isolates) collected and tested in surveillance years 2015 and 2016 are presented in Table 1. Of the 4,856 fungal clinical

TABLE 1 Cumulative geographic distribution of fungal species in 2015 to 2016

Organism[a]	No. (%) of isolates/total		
	United States	Non-United States	Total
Overall	2,937/4,856 (60.48)	1,919/4,856 (39.52)	4,856
Aspergillus			
Aspergillus spp.	1,550/1,972 (78.60)	422/1,972 (21.40)	1,972/4,856 (40.61)
A. calidoustus	34/1,972 (1.72)	2/1,972 (0.10)	36/4,856 (0.74)
A. flavus	108/1,972 (5.48)	0/1,972	108/4,856 (2.22)
A. flavus species complex	20/1,972 (1.01)	42/1,972 (2.13)	62/4,856 (1.28)
A. fumigatus	884/1,972 (44.83)	310/1,972 (15.72)	1,194/4,856 (24.59)
A. lentulus	9/1,972 (0.46)	2/1,972 (0.10)	11/4,856 (0.23)
A. nidulans	22/1,972 (1.12)	7/1,972 (0.35)	29/4,856 (0.60)
A. niger	48/1,972 (2.43)	14/1,972 (0.71)	62/4,856 (1.28)
A. niger species complex	87/1,972 (4.41)	16/1,972 (0.81)	103/4,856 (2.12)
A. sydowii	22/1,972 (1.12)	0/1,972	22/4,856 (0.45)
A. terreus	85/1,972 (4.31)	13/1,972 (0.66)	98/4,856 (2.02)
A. terreus species complex	7/1,972 (0.35)	7/1,972 (0.35)	14/4,856 (0.29)
A. tubingensis	65/1,972 (3.30)	1/1,972 (0.05)	66/4,856 (1.36)
A. welwitschiae	25/1,972 (1.27)	0/1,972	25/4,856 (0.51)
Mucorales			
Mucorales spp.	276/292 (94.52)	16/292 (5.48)	292/4,856 (6.01)
Lichtheimia spp.	20/23 (86.96)	3/23 (13.04)	23/4,856 (0.47)
Mucor spp.	67/69 (97.10)	2/69 (2.90)	69/4,856 (1.42)
M. circinelloides f. *circinelloides*	33/69 (47.83)	1/69 (1.45)	34/4,856 (0.70)
M. circinelloides f. *janssenii*	17/69 (24.64)	0/69	17/4,856 (0.35)
Rhizomucor spp.	12/14 (85.71)	2/14 (14.29)	14/4,856 (0.29)
R. pusillus	12/14 (85.71)	2/14 (14.29)	14/4,856 (0.29)
Rhizopus spp.	153/162 (94.44)	9/162 (5.56)	162/4,856 (3.34)
R. arrhizus var. *arrhizus*	61/162 (37.65)	1/162 (0.62)	62/4,856 (1.28)
R. arrhizus var. *delemar*	41/162 (25.31)	0/162	41/4,856 (0.84)
R. microsporus	41/162 (25.31)	1/162 (0.62)	42/4,856 (0.86)
Syncephalastrum spp.	11/11 (100)	0/11	11/4,856 (0.23)
Candida and other fungal species			
Candida spp.	969/2,351 (41.22)	1382/2,351 (58.78)	2,351/4,856 (48.41)
C. albicans	382/2,351 (16.25)	674/2,351 (28.67)	1,056/4,856 (21.75)
C. dubliniensis	43/2,351 (1.83)	19/2,351 (0.81)	62/4,856 (1.28)
C. glabrata	244/2,351 (10.38)	245/2,351 (10.42)	489/4,856 (10.07)
C. guilliermondii	3/2,351 (0.13)	10/2,351 (0.43)	13/4,856 (0.27)
C. kefyr	6/2,351 (0.26)	9/2,351 (0.38)	15/4,856 (0.31)
C. krusei	28/2,351 (1.19)	40/2,351 (1.70)	68/4,856 (1.40)
C. lusitaniae	29/2,351 (1.23)	22/2,351 (0.94)	51/4,856 (1.05)
C. orthopsilosis	9/2,351 (0.38)	13/2,351 (0.55)	22/4,856 (0.45)
C. parapsilosis	132/2,351 (5.61)	217/2,351 (9.23)	349/4,856 (7.19)
C. tropicalis	76/2,351 (3.23)	111/2,351 (4.72)	187/4,856 (3.85)
Cryptococcus spp.	46/84 (54.76)	38/84 (45.24)	84/4,856 (1.73)
C. neoformans var. *grubii*	41/84 (48.81)	35/84 (41.67)	76/4,856 (1.57)
Fusarium spp.	15/24 (62.50)	9/24 (37.50)	24/4,856 (0.49)
F. solani species complex	11/24 (45.83)	7/24 (29.17)	18/4,856 (0.37)
Saccharomyces spp.	3/13 (23.08)	10/13 (76.92)	13/4,856 (0.27)
S. cerevisiae	3/13 (23.08)	10/13 (76.92)	13/4,856 (0.27)
Scedosporium spp.	30/45 (66.67)	15/45 (33.33)	45/4,856 (0.93)
S. apiospermum/*S. boydii*	22/45 (48.89)	4/45 (8.89)	26/4,856 (0.54)

[a]Species with 10 or more isolates overall are included.

isolates tested, 40.6% (1,972 isolates) consisted of *Aspergillus* spp., the majority of which (78.6%; 1,550 isolates) were from the U.S. Species of the *Mucorales* order comprised 6.0% (292 isolates) of the tested isolates, including *Lichtheimia*, *Mucor*, *Rhizomucor*, *Rhizopus*, and *Syncephalastrum* species (Table 1). Most (94.5% or 276 isolates) of the *Mucorales* isolates were from the United States. Among the other fungal species tested, the majority were *Candida* spp. (48.41% overall [2,351 isolates]), most of which (58.8% [1,382 isolates]) were non-U.S. isolates (Table 1).

TABLE 2 MIC distributions for isavuconazole against *Aspergillus* spp. and species of the *Mucorales* order using CLSI broth microdilution methods

Species (no. tested)	No. of isolates with MIC (μg/ml) of[a]:									
	0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥16
Aspergillus spp. (1,964)	0	8	37	165	**751**	676	190	113	18	6
A. calidoustus (36)	0	0	0	0	0	0	2	**20**	14	0
A. flavus (107)	0	0	0	1	23	**65**	17	1	0	0
A. flavus species complex (62)	0	0	0	2	20	**40**	0	0	0	0
A. fumigatus (1189)	0	0	1	81	**611**	451	24	13	2	6
A. lentulus (11)	0	0	0	0	1	2	**6**	1	1	0
A. nidulans (29)	0	1	13	**14**	1	0	0	0	0	0
A. niger (62)	0	0	0	2	2	13	**39**	5	1	0
A. niger species complex (103)	0	1	2	1	3	27	**41**	25	3	0
A. sydowii (22)	0	0	0	5	6	**11**	0	0	0	0
A. terreus (96)	0	0	1	15	**49**	28	2	0	1	0
A. terreus species complex (14)	0	0	1	**8**	5	0	0	0	0	0
A. tubingensis (66)	0	0	0	0	0	3	10	**44**	9	0
A. welwitschiae (25)	0	0	0	0	0	10	**14**	1	0	0
Lichtheimia spp. (22)	0	0	0	0	0	3	6	**7**	6	0
Mucor spp. (69)	0	0	0	0	1	0	7	17	**26**	18
M. circinelloides f. *circinelloides* (34)	0	0	0	0	0	0	2	4	**19**	9
M. circinelloides f. *janssenii* (17)	0	0	0	0	0	0	5	**10**	2	0
Rhizomucor pusillus (14)	0	0	0	0	1	2	**9**	0	2	0
Rhizopus spp. (161)	0	0	0	0	22	**57**	37	20	9	15
R. arrhizus var. *arrhizus* (62)	0	0	0	1	13	**29**	17	2	0	0
R. arrhizus var. *delemar* (41)	0	0	0	0	0	1	8	**13**	7	12
R. microsporus (41)	0	0	0	0	6	**25**	5	3	1	1
Syncephalastrum spp. (11)	0	0	0	0	1	2	0	0	1	**7**

[a]Numbers in boldface are modal MIC values.

Isavuconazole activity against *Aspergillus* and *Mucorales* isolates. The most common *Aspergillus* species (with 10 or more isolates overall) in the 2015 and 2016 cumulative isolate collection that were tested against isavuconazole included the following 13 *Aspergillus* species, in order of frequency: *A. fumigatus*, *A. flavus*, *A. niger* species complex (SC), *A. terreus*, *A. tubingensis*, *A. flavus* SC, *A. niger*, *A. calidoustus*, *A. nidulans*, *A. welwitschiae*, *A. sydowi*, *A. terreus* SC, and *A. lentulus* (Table 2). The cumulative frequencies of MIC distributions for isavuconazole are presented for *Aspergillus* species in Table 2.

Among the tested species of *Aspergillus*, the MIC values for isavuconazole ranged from 0.06 to ≥16 μg/ml. The modal MIC for isavuconazole among all *Aspergillus* spp. was 0.5 μg/ml, with a low modal MIC of 0.25 μg/ml for *A. nidulans* and *A. terreus* SC and a high modal MIC of 4 μg/ml for *A. calidoustus* and *A. tubingensis*. Isavuconazole ECVs have been defined for *A. flavus*, *A. fumigatus*, *A. niger*, and *A. terreus* (50). According to the species-specific ECVs, the vast majority of isolates represented wild-type (WT) strains of *Aspergillus* spp. (MIC ≤ ECV; range, 83.2 to 100.0%) (Tables 2 and 3). The isavuconazole MIC values were elevated at ≥8 μg/ml for 8 *A. fumigatus* isolates, which suggests resistance mediated by mutations in *cyp51A*.

The activity of isavuconazole against *Mucorales* isolates was generally lower than that seen with *Aspergillus* spp., with a MIC range of 0.25 to ≥16 μg/ml (Table 2). Modal MIC values of 4 to ≥16 μg/ml were seen with *Lichtheimia* spp., *Mucor* spp., *Rhizopus arrhizus* var. *delemar*, and *Syncephalastrum* spp. The lowest modal MIC values were seen for *Rhizopus* spp., *R. arrhizus* var. *arrhizus*, and *R. microsporus* (all 1 μg/ml [Table 2]). ECV values have not been established for isavuconazole and the *Mucorales*.

Activity of isavuconazole and comparators against *Aspergillus* and *Mucorales* isolates. Isavuconazole and itraconazole (MIC_{90}, 1 μg/ml for both compounds [Table 3]) had similar activities against 1,189 *A. fumigatus* isolates that were one 2-fold dilution

TABLE 3 Antifungal activity of isavuconazole and comparator antifungal agents against *Aspergillus* spp. and species of the *Mucorales* order tested as part of the 2015-2016 international surveillance program

Species (no. of isolates collected)	Antifungal agent (no. of isolates tested)	MIC (μg/ml)			% ECV by category[a]:	
		Range	50%	90%	WT	NWT
Aspergillus spp. (1,964)	Isavuconazole (1,964)	0.015–32	1	2		
	Itraconazole (1,413)	0.12–32	1	2		
	Posaconazole (1,246)	0.008–16	0.25	0.5		
	Voriconazole (1,834)	0.03–32	0.5	1		
A. calidoustus (36)	Isavuconazole (36)	1–4	2	4		
	Itraconazole (14)	1–4	2	4		
	Posaconazole (28)	2–8	4	4		
	Voriconazole (31)	2–8	4	8		
A. flavus (107)	Isavuconazole (107)	0.25–4	1	2	83.2	16.8
	Itraconazole (57)	0.25–1	1	1	100.0	0.0
	Posaconazole (44)	0.12–0.5	0.25	0.5	63.6	36.4
	Voriconazole (95)	0.25–16	0.5	1	95.8	4.2
A. flavus SC (62)	Isavuconazole (62)	0.25–1	1	1	100.0	0.0
	Itraconazole (62)	0.25–1	0.5	1	100.0	0.0
	Posaconazole (62)	0.12–0.5	0.25	0.5	59.7	40.3
	Voriconazole (62)	0.12–1	1	1	100.0	0.0
A. fumigatus (1,189)	Isavuconazole (1,189)	0.12–32	0.5	1	96.2	3.8
	Itraconazole (876)	0.12–32	1	1	95.8	4.2
	Posaconazole (817)	0.008–4	0.25	0.5	79.4	20.6
	Voriconazole (1,122)	0.12–32	0.5	0.5	98.1	1.9
A. lentulus (11)	Isavuconazole (11)	0.5–8	2	4		
	Itraconazole (8)	0.25–4				
	Posaconazole (7)	0.25–1				
	Voriconazole (11)	0.5–8	2	4		
A. nidulans (29)	Isavuconazole (29)	0.06–0.5	0.25	0.25	96.6	3.4
	Itraconazole (17)	0.25–1	0.5	1	100.0	0.0
	Posaconazole (19)	0.12–0.5	0.25	0.5	100.0	0.0
	Voriconazole (25)	0.06–0.5	0.12	0.25	100.0	0.0
A. niger (62)	Isavuconazole (62)	0.25–8	2	2	98.4	1.6
	Itraconazole (50)	0.25–4	2	2	96.0	4.0
	Posaconazole (44)	0.06–1	0.5	0.5	95.5	4.5
	Voriconazole (59)	0.12–16	1	2	98.3	1.7
A. niger species complex (103)	Isavuconazole (103)	0.06–8	2	4	97.1	2.9
	Itraconazole (85)	0.25–4	2	2	92.9	7.1
	Posaconazole (47)	0.06–1	0.5	0.5	91.5	8.5
	Voriconazole (99)	0.03–2	1	2	100.0	0.0
A. sydowii (22)	Isavuconazole (22)	0.25–1	0.5	1		
	Itraconazole (13)	0.5–2	1	2		
	Posaconazole (10)	0.12–0.5	0.5	0.5		
	Voriconazole (21)	0.12–2	0.5	1		
A. terreus (96)	Isavuconazole (96)	0.12–8	0.5	1	96.9	3.1
	Itraconazole (63)	0.12–1	0.5	1	100.0	0.0
	Posaconazole (61)	0.12–1	0.25	0.25	98.4	1.6
	Voriconazole (89)	0.12–8	0.5	1	97.8	2.2
A. terreus species complex (14)	Isavuconazole (14)	0.12–0.5	0.25	0.5	100.0	0.0
	Itraconazole (14)	0.25–0.5	0.5	0.5	100.0	0.0
	Posaconazole (12)	0.12–0.25	0.25	0.25	100.0	0.0
	Voriconazole (14)	0.25–0.5	0.25	0.5	100.0	0.0
A. tubingensis (66)	Isavuconazole (66)	1–8	4	8		
	Itraconazole (48)	1–4	2	4		
	Posaconazole (13)	0.25–1	0.5	1		
	Voriconazole (56)	0.5–2	2	2		
A. welwitschiae (25)	Isavuconazole (25)	1–4	2	2		
	Itraconazole (17)	2–2	2	2		
	Posaconazole (3)	0.12–0.5				
	Voriconazole (21)	0.25–1	0.5	0.5		
Lichtheimia spp. (22)	Isavuconazole (22)	1–16	4	8		
	Itraconazole (9)	1–16				
	Posaconazole (20)	0.25–2	0.5	1		
	Voriconazole (12)	16–32	16	32		

(Continued on next page)

TABLE 3 (Continued)

Species (no. of isolates collected)	Antifungal agent (no. of isolates tested)	MIC (μg/ml)			% ECV by category[a]:	
		Range	50%	90%	WT	NWT
Mucor spp. (69)	Isavuconazole (69)	0.5–32	8	32		
	Itraconazole (23)	1–32	4	32		
	Posaconazole (52)	0.5–4	1	2		
	Voriconazole (33)	16–32	32	32		
M. circinelloides f. *circinelloides* (34)	Isavuconazole (34)	2–32	8	16		
	Itraconazole (8)	2–32				
	Posaconazole (24)	0.5–4	2	4	100.0	0.0
	Voriconazole (16)	32–32	32	32		
M. circinelloides f. *janssenii* (17)	Isavuconazole (17)	2–8	4	8		
	Itraconazole (6)	1–4				
	Posaconazole (14)	0.5–2	1	1	100.0	0.0
	Voriconazole (8)	16–32				
Rhizomucor pusillus (14)	Isavuconazole (14)	0.5–8	2	8		
	Itraconazole (4)	0.5–1				
	Posaconazole (13)	0.25–1	0.25	0.5		
	Voriconazole (7)	4–16				
Rhizopus spp. (161)	Isavuconazole (161)	0.25–32	2	8		
	Itraconazole (52)	0.12–32	1	4		
	Posaconazole (115)	0.06–32	0.5	1		
	Voriconazole (72)	0.06–32	8	16		
R. arrhizus var. *arrhizus* (62)	Isavuconazole (62)	0.25–4	1	2		
	Itraconazole (17)	0.12–2	1	1	100.0	0.0
	Posaconazole (39)	0.12–1	0.5	0.5	100.0	0.0
	Voriconazole (18)	2–16	4	8		
R. arrhizus var. *delemar* (41)	Isavuconazole (41)	1–16	4	16		
	Itraconazole (10)	1–32	2	4	90.0	10.0
	Posaconazole (32)	0.25–32	1	1	90.6	9.4
	Voriconazole (19)	8–32	16	32		
R. microsporus (41)	Isavuconazole (41)	0.5–32	1	4		
	Itraconazole (10)	1–32	1	2		
	Posaconazole (30)	0.12–32	0.5	1	93.3	6.7
	Voriconazole (20)	0.06–32	4	8		
Syncephalastrum spp. (11)	Isavuconazole (11)	0.5–32	≥16	≥16		
	Itraconazole (3)	1–4				
	Posaconazole (8)	0.25–4				
	Voriconazole (6)	4–32				

[a]Interpretive categories per references 50 to 54. ECV, epidemiological cutoff value; WT, wild type; NWT, non-wild type.

higher than those of posaconazole and voriconazole (MIC_{90}, 0.5 μg/ml for both). More than 95% of the *A. fumigatus* isolates tested were WT to isavuconazole (96.2%), itraconazole (95.8%), and voriconazole (98.1%), whereas only 79.4% were WT to posaconazole. Regarding the posaconazole data, note that there has been discussion whether the ECV should be 0.25 or 0.5 μg/ml (51). If the ECV for posaconazole were to be set at 0.5 μg/ml, the percentage of WT would be 97.9% for this collection, comparable to that of the other triazoles (data not shown). The recently revised ECV for posaconazole and *A. fumigatus* of 0.25 μg/ml was determined as the optimal cutoff for the separation of WT strains from mutants harboring *cyp51A* mutations (51).

The isavuconazole MIC_{90} values were 2 μg/ml for *A. flavus* and 1 μg/ml for *A. flavus* SC, resulting in 83.2% and 100.0% wild type, respectively (Table 3). There were 17 *A. flavus* isolates for which the isavuconazole MIC value was 2 μg/ml, and if the ECV was increased from 1 μg/ml to 2 μg/ml, the percentage of WT would increase to 99.1%, comparable to that seen for the *A. flavus* SC, itraconazole (100.0% WT), and voriconazole (95.8% WT). Whereas the isavuconazole ECV for this species was determined using MIC values from 7 different laboratories (50), the reproducibility of the CLSI method for a single laboratory (±one 2-fold dilution) should be kept in mind when evaluating such data. Given the potential for dose escalation with isavuconazole, it may be possible to

TABLE 4 MIC distributions for isavuconazole against *Candida* spp. using CLSI broth microdilution methods

Species (no. of isolates tested)	No. of isolates with MIC (μg/ml) of[a]:									
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	≥4
Candida spp. (2,351)	**1,494**	202	165	222	77	71	50	42	19	9
C. albicans (1,056)	**1,034**	20	2	0	0	0	0	0	0	0
C. dubliniensis (62)	**61**	0	0	0	0	0	0	0	0	0
C. glabrata (489)	10	33	108	**179**	51	24	26	36	16	6
C. guilliermondii (13)	0	0	1	0	1	2	**5**	0	2	2
C. kefyr (15)	**13**	1	1	0	0	0	0	0	0	0
C. krusei (68)	0	0	0	4	12	**38**	13	1	0	0
C. lusitaniae (51)	**35**	8	4	1	0	1	2	0	0	0
C. orthopsilosis (22)	**9**	4	5	3	1	0	0	0	0	0
C. parapsilosis (349)	**224**	86	19	15	3	1	1	0	0	0
C. tropicalis (187)	**104**	47	20	11	3	1	0	0	1	0

[a]Numbers in boldface are modal MIC values.

treat *Aspergillus* infections for which the isavuconazole MIC is 2 μg/ml (52). Although dose escalation is less feasible with posaconazole, similar considerations may apply where an ECV of 0.5 μg/ml applied to *A. flavus* and *A. flavus* SC would increase the percentage of WT from 63.6% and 59.7%, respectively (determined at the CLSI ECV of 0.25 μg/ml), to 100.0% for both organism groups (data not shown).

The respective isavuconazole MIC_{90} values of 2 and 4 μg/ml for *A. niger* and *A. niger* SC (Table 3) were comparable to that of itraconazole (2 μg/ml) and voriconazole (2 μg/ml) and higher than that of posaconazole (0.5 μg/ml). The wild-type percentages against *A. niger* and *A. niger* SC were 97.1 to 98.4% for isavuconazole, 92.9 to 96.0% for itraconazole, 91.5 to 95.5% for posaconazole, and 98.3 to 100.0% for voriconazole.

Greater than 95% of *A. nidulans*, *A. terreus*, and *A. terreus* SC isolates were WT to all four triazoles, and these species were among the most susceptible to these agents, with MIC_{90} values of 0.25 to 1 μg/ml. The highest MIC_{90} values (4 to 8 μg/ml) for the tested triazoles were seen with *A. calidoustus*, *A. lentulus*, and *A. tubingensis* (MIC_{90}, 8 μg/ml [isavuconazole]) (Table 3).

All triazole antifungal agents showed variable activity across the *Mucorales* tested (0.06 to 32 μg/ml), with the lowest MIC_{90} values observed for *Rhizomucor pusillus* (MIC_{90}, 0.5 to 8 μg/ml), *Rhizopus arrhizus* var. *arrhizus* (MIC_{90}, 0.5 to 8 μg/ml), and *R. microsporus* (MIC_{90}, 1 to 8 μg/ml) and the highest MIC values observed for *Mucor* spp. (MIC_{90}, 2 to 32 μg/ml), *Mucor circinelloides* f. *circinelloides* (MIC_{90}, 4 to 32 μg/ml), and *Syncephalastrum* spp. (MIC_{90}, ≥16 μg/ml [isavuconazole]) (Table 3). Whereas voriconazole lacked any useful activity against the *Mucorales* (MIC_{90}, 8 to 32 μg/ml across all species), the lowest MIC_{90} values were observed with posaconazole (MIC_{90} range, 0.5 to 4 μg/ml). Among the species for which an ECV has been proposed for posaconazole (53), 100.0% of *M. circinelloides* f. *circinelloides*, *M. circinelloides* f. *janssenii*, and *Rhizopus arrhizus* var. *arrhizus* isolates, 90.6% of *Rhizopus arrhizus* var. *delemar* isolates, and 93.3% of *Rhizopus microsporus* isolates expressed a WT phenotype: 100.0% of *Rhizopus arrhizus* var. *arrhizus* isolates and 90.0% of *Rhizopus arrhizus* var. *delemar* isolates were WT to itraconazole. The activity of isavuconazole against the *Mucorales* most closely mirrored that of itraconazole (Table 3).

Isavuconazole activity against *Candida* species isolates. Among the 10 species of *Candida* shown in Tables 4 and 5, isavuconazole was most active against *Candida dubliniensis* (MIC_{90}, 0.008 μg/ml) and *Candida albicans* (MIC_{90}, 0.008 μg/ml) and least active against *Candida krusei* (MIC_{90}, 0.5 μg/ml), *Candida glabrata* (MIC_{90}, 1 μg/ml), and *Candida guilliermondii* (MIC_{90}, 4 μg/ml). The vast majority of each species, except for *C. glabrata*, *C. krusei*, and *C. guilliermondii*, were inhibited by ≤0.25 μg/ml of isavuconazole (range, 96.1% [*Candida lusitaniae*] to 100.0% [*C. albicans*, *C. dubliniensis*, *Candida kefyr*, and *Candida orthopsilosis*]). *C. glabrata* and *C. krusei* were susceptible to isavuconazole at MIC values of ≤1 μg/ml (95.5 and 100.0%, respectively).

TABLE 5 Antifungal activity of isavuconazole and comparator antifungal agents against *Candida* spp. tested as part of the 2015-2016 international surveillance program

Species (no. of isolates collected)	Antifungal agent (no. of isolates tested)	MIC (μg/ml)			% by category[a]			
					CLSI		ECV	
		Range	50%	90%	S	R	WT	NWT
C. albicans (1,056)	Isavuconazole (1,056)	0.008–0.03	0.008	0.008				
	Posaconazole (1,056)	0.008–0.12	0.03	0.03			99.3	0.7
	Voriconazole (1,056)	0.008–0.06	0.008	0.015	100.0	0.0	99.5	0.5
	Fluconazole (1,056)	0.12–1	0.12	0.25	100.0	0.0	99.4	0.6
C. glabrata (489)	Isavuconazole (489)	0.008–8	0.06	1				
	Posaconazole (489)	0.03–16	0.25	1			99.2	0.8
	Voriconazole (489)	0.008–8	0.06	0.5			88.8	11.2
	Fluconazole (489)	0.25–256	2	16	93.7[b]	6.3	87.3	12.7
C. parapsilosis (349)	Isavuconazole (349)	0.008–0.5	0.008	0.03				
	Posaconazole (349)	0.008–0.5	0.06	0.12			97.7	2.3
	Voriconazole (349)	0.008–1	0.015	0.03	96.3	0.3	91.1	8.9
	Fluconazole (349)	0.12–128	0.5	2	94.8	4.3	89.4	10.6
C. tropicalis (187)	Isavuconazole (187)	0.008–2	0.008	0.03				
	Posaconazole (187)	0.015–1	0.03	0.06			98.4	1.6
	Voriconazole (187)	0.008–16	0.015	0.06	97.9	0.5	97.9	2.1
	Fluconazole (187)	0.12–256	0.25	0.5	97.9	1.6	97.3	2.7
C. krusei (68)	Isavuconazole (68)	0.06–1	0.25	0.5				
	Posaconazole (68)	0.12–0.5	0.25	0.5			100.0	0.0
	Voriconazole (68)	0.12–4	0.25	0.5	94.1	1.5	94.1	5.9
	Fluconazole (68)	16–128	32	64			85.3	14.7
C. lusitaniae (51)	Isavuconazole (51)	0.008–0.5	0.008	0.03				
	Posaconazole (51)	0.03–0.5	0.06	0.12			76.5	23.5
	Voriconazole (51)	0.008–0.5	0.008	0.015			94.1	5.9
	Fluconazole (51)	0.12–64	0.5	1			90.2	9.8
C. dubliniensis (62)	Isavuconazole (62)	0.008–0.06	0.008	0.008				
	Posaconazole (62)	0.008–0.12	0.03	0.03			100.0	0.0
	Voriconazole (62)	0.008–0.06	0.008	0.015			98.4	1.6
	Fluconazole (62)	0.12–16	0.12	0.25			98.4	1.6
C. guilliermondii (13)	Isavuconazole (13)	0.03–4	0.5	4				
	Posaconazole (13)	0.25–1	0.5	1			76.9	23.1
	Voriconazole (13)	0.015–2	0.25	2			46.2	53.8
	Fluconazole (13)	1–128	8	128			61.5	38.5
C. orthopsilosis (22)	Isavuconazole (22)	0.008–0.12	0.015	0.06				
	Posaconazole (22)	0.03–0.12	0.06	0.12			100.0	0.0
	Voriconazole (22)	0.008–0.25	0.015	0.03			90.9	9.1
	Fluconazole (22)	0.25–4	0.5	1			90.9	9.1
C. kefyr (15)	Isavuconazole (15)	0.008–0.03	0.008	0.015				
	Posaconazole (15)	0.03–0.25	0.12	0.25			100.0	0.0
	Voriconazole (15)	0.008–0.03	0.008	0.015			100.0	0.0
	Fluconazole (15)	0.12–1	0.25	0.5			100.0	0.0

[a]Interpretive categories as recommended by CLSI (70) and the use of ECVs (71, 73, 76). ECV, epidemiological cutoff value; S, susceptible; R, resistant; WT, wild type; NWT, non-wild type.
[b]Category designation is susceptible dose dependent.

Activity of isavuconazole and comparators against *Candida* species isolates. The antifungal activities of isavuconazole, fluconazole, posaconazole, and voriconazole against 2,351 *Candida* isolates (10 species) as determined by CLSI BMD methods are shown in Table 5. Results are categorized using CLSI CBPs and/or ECVs, as appropriate. The majority of these isolates represented WT strains, as determined by the respective ECVs, and few (*C. glabrata* and *C. parapsilosis*) were resistant to triazoles, based on CBPs. Neither CBPs nor ECV values have been established for isavuconazole and *Candida* spp.

TABLE 6 MIC distributions for isavuconazole against non-*Candida* yeasts and rare molds using CLSI broth microdilution methods

Species (no. of isolates tested)	No. of isolates with MIC (μg/ml) of[a]:									
	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	≥4
Cryptococcus spp. (84)	12	27	**28**	9	3	1	4	0	0	0
C. neoformans var. *grubii* (76)	11	**26**	24	9	2	1	3	0	0	0
Saccharomyces cerevisiae (13)	2	**5**	3	2	0	1	0	0	0	0
Fusarium spp. (24)	0	0	0	0	0	0	0	0	0	**24**
F. solani species complex (18)	0	0	0	0	0	0	0	0	0	**18**
Scedosporium spp. (45)	0	0	1	0	0	0	1	5	6	**32**
S. apiospermum/*S. boydii* (26)	0	0	0	0	0	0	0	3	5	**18**

[a]Numbers in boldface are modal MIC values.

Using species-specific breakpoints, 100.0% of *C. albicans* isolates were susceptible to fluconazole and voriconazole. Fluconazole and voriconazole were also active against *C. parapsilosis* (94.8 and 96.3% susceptible, respectively, at the CLSI CBP) and *Candida tropicalis* (97.9 and 97.9% susceptible, respectively, at the CLSI CBP). Voriconazole was also active against *C. krusei* (94.1% susceptible). Among the 10 species of *Candida* tested against posaconazole, 98.7% showed a WT phenotype based on the established ECVs (54). Only *C. lusitaniae* (76.5% WT) and *C. guilliermondii* (76.9% WT) exhibited greater than 3% strains non-WT to posaconazole (Table 5).

The *in vitro* potency of isavuconazole against *Candida* spp. was most comparable to that of voriconazole. Based on MIC_{90} values, isavuconazole was 2- to 16-fold more active than posaconazole against all species, although *C. guilliermondii* displayed much higher MIC_{90} values for all agents (Table 5). *C. guilliermondii* is known to exhibit decreased susceptibility to fluconazole, posaconazole, and voriconazole (55–57), and this phenotype was apparent in isolates from the present study as well (23.1 to 53.8% non-WT [Table 5]).

Isavuconazole activity against non-*Candida* yeasts and rare molds. Isavuconazole MIC ranges were 0.008 to 0.5 μg/ml across *Cryptococcus* spp. (modal MIC, 0.03 μg/ml), *Cryptococcus neoformans* var. *grubii* (modal MIC, 0.015 μg/ml), and *Saccharomyces cerevisiae* (modal MIC, 0.015 μg/ml). In contrast, the modal MICs were all ≥4 μg/ml for *Fusarium* spp. and *Scedosporium* spp. (Table 6).

DISCUSSION

Several important observations can be made from this global survey. First, we have used molecular methods of species identification to further document the broad array of fungi implicated as causes of IFI in U.S. and non-U.S. medical centers. We have tested all fungi for susceptibility to isavuconazole and the other systemically active triazoles using reference CLSI BMD methods and have applied the most recent CBPs and ECVs to assess the relative activity of these important antifungal agents. In general, the more common species of *Candida* and *Aspergillus* remain susceptible to all the mold-active triazole antifungal agents. Resistance to multiple azoles is apparent in both *C. glabrata* and *C. guilliermondii*, and both species must be monitored closely for the emergence of multidrug resistance. Likewise, the azole-resistant non-*fumigatus* species of *Aspergillus*, such as *A. calidoustus*, *A. lentulus*, and *A. tubingensis*, along with emerging MDR strains of *A. fumigatus*, must be actively sought in clinical material and undergo accurate species identification as well as antifungal susceptibility testing to ensure optimal patient management (29, 30, 34, 35). Whereas isavuconazole has been approved for the treatment of invasive mucormycosis (49), the available clinical and *in vitro* data to support this application have been limited to date (44–49). In the present study, we have documented the variable activities of isavuconazole, itraconazole, and posaconazole across all of the *Mucorales* isolates tested and have confirmed the potentially useful activity of isavuconazole against select species of *Rhizopus* as determined by CLSI methods (44–47). Given the modal MIC value of 1 μg/ml for isavuconazole and species of *Rhizopus*, it is important to note that an analysis of real-world usage, along with an analysis of clinical trial samples, showed that drug concentrations of >1 μg/ml are achieved with standard doses of isavuconazole (58).

Isavuconazole MIC distributions examined for *Candida* spp., *Aspergillus* spp., and the *Mucorales* from the most recent 2-year surveillance period (2015 to 2016) demonstrated little to no change in the distributions compared to reports from previous years (43, 46, 59, 60), with activity comparable to those of itraconazole, posaconazole, and voriconazole. Isavuconazole and the other triazoles continue to be highly active against *Aspergillus* spp., but are less potent against the non-*Aspergillus* molds, including the *Mucorales*. The triazoles, including isavuconazole, appear to be more reliably active against the non-*Candida* yeasts than against rare molds, such as *Fusarium* spp.

In summary, the increasing application of molecular and proteomic methods of identification reveals a broad spectrum of opportunistic fungal pathogens. Isavuconazole exhibited excellent activity against most species of *Candida* and *Aspergillus* and is comparable to posaconazole and voriconazole against the less common yeasts and molds. Whereas most *Candida* and *Aspergillus* spp. remain susceptible to isavuconazole and the other triazoles, emergence of resistance during therapy, especially in patients with previous antifungal exposure, must be kept in mind. Given the extensive use of voriconazole in prevention and treatment of invasive aspergillosis, emergence of the *Mucorales* as breakthrough infections is a clear threat and underscores the importance of new agents, such as isavuconazole, in patients with invasive mucormycosis who are unable to tolerate amphotericin B therapy (42, 49).

MATERIALS AND METHODS

Organisms. A total of 4,856 nonduplicate clinical isolates from patients with IFI were collected during 2015 to 2016 from U.S. (2,937 isolates) and non-U.S. (1,919 isolates) medical centers (Table 1). There were 75 isolates (1.5% of total) from species with <10 representatives (data not shown). The isolates were received from patients with bloodstream infections, from normally sterile body fluids (e.g., cerebrospinal, pleural, and peritoneal fluids), tissues, or abscesses, from respiratory tract specimens, or from unspecified infection sites. Molds included 1,194 isolates of *A. fumigatus sensu stricto* and 108 *A. flavus*, 62 *A. flavus* SC, 608 other *Aspergillus* species (36 *A. calidoustus*, 11 *A. lentulus*, 29 *A. nidulans*, 62 *A. niger*, 103 *A. niger* SC, 22 *Aspergillus sydowii*, 98 *A. terreus*, 14 *A. terreus* SC, 66 *A. tubingensis*, and 25 *A. welwitschiae* isolates), 24 *Fusarium* species, and 45 *Scedosporium* species isolates (Table 1). There were 292 isolates of the *Mucorales* order, including 23 *Lichtheimia* species, 69 *Mucor* species, 14 *R. pusillus* species, 162 *Rhizopus* species, and 11 *Syncephalastrum* species isolates. Among the 2,351 isolates of *Candida* spp. were 1,056 *C. albicans*, 489 *C. glabrata*, 349 *C. parapsilosis*, 187 *C. tropicalis*, 68 *C. krusei*, 51 *C. lusitaniae*, 62 *C. dubliniensis*, 13 *C. guilliermondii*, 22 *C. orthopsilosis*, and 15 *C. kefyr* isolates. The collection also included 84 *Cryptococcus* species and 13 *S. cerevisiae* isolates.

Isolates were identified at participating institutions using methods routinely employed at the submitting laboratory, including the use of Vitek, MicroScan, API strips, and AuxaColor systems supplemented by conventional methods for yeast and mold identification (61–63). Isolates were submitted to JMI Laboratories (North Liberty, IA) or the Fungus Testing Laboratory (San Antonio, TX), where species identification was confirmed using morphological, biochemical, molecular, and proteomic methods (64–66). Yeast isolates were subcultured and screened using CHROMagar *Candida* (Becton, Dickinson, Sparks, MD) to ensure purity and to differentiate *C. albicans*/*C. dubliniensis*, *C. tropicalis*, and *C. krusei*. Additionally, biochemical tests, including Vitek 2 (bioMérieux, Hazelwood, MO), trehalose assimilation (for *C. glabrata*), or growth at 45°C (for *C. albicans*/*C. dubliniensis*), were used to identify common *Candida* species. Identity of isolates was confirmed by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS [Bruker, Billerica, MA]). Isolates that were not identified by either phenotypic or proteomic methods, including all rare and sibling species, were identified using sequence-based methods as previously described (64).

Identification of *Aspergillus* spp. and the *Mucorales* spp. was performed by combined morphology/phenotypic assessment and DNA sequence analysis. All rare and sibling species were identified by DNA sequencing. For morphological/phenotypic assessment, macroscopic and microscopic features were evaluated and temperature studies performed. For DNA sequence analysis, regions of the β-tubulin and calmodulin genes were amplified and sequenced. For *Mucorales* isolates, the internal transcribed spacer and D1/D2 regions were amplified and sequenced. *Scedosporium* spp. were also identified by amplifying and sequencing regions of the β-tubulin and calmodulin genes. Nucleotide sequences were examined using Lasergene software (DNAStar, Madison, WI) or Sequencher software (Gene Codes, Ann Arbor, MI) and then compared to database sequences using BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi). *Fusarium* species isolates were analyzed for TEF sequence using the *Fusarium*-ID database through 2016 and the *Fusarium* multilocus sequence typing database (http://www.westerdijkinstitute.nl/fusarium/) (64). Results were considered acceptable if homology was >99.5% with other entries in the databases used for comparison. Sequences that were considerably different from the majority of entries for a species were considered outliers and were excluded from the analysis. The DNA sequence results were combined with the morphological/phenotypic assessment to assign a species identity to each isolate (67).

Antifungal susceptibility testing. All yeast isolates were tested for *in vitro* susceptibility to fluconazole, isavuconazole, posaconazole, and voriconazole using CLSI (68) BMD methods. MIC results for all agents were read after 24 h of incubation, when the agents were tested against *Candida* spp., whereas MIC results were read after 48 h, when the agents were tested against non-*Candida* yeasts. MIC values were determined visually as the lowest concentration of drug that caused significant (≥50%) growth diminution levels relative to the growth control (69, 70).

In vitro susceptibility testing of *Aspergillus* spp., members of the *Mucorales* order, and other molds against the triazoles (isavuconazole, itraconazole, posaconazole, and voriconazole) was performed by BMD as described in CLSI document M38-A2 (69). For *Aspergillus* spp., the MICs for isavuconazole and comparators were read as 100% inhibition of growth after 48 h of incubation at 35°C. Against the *Mucorales* isolates, MICs for isavuconazole and comparators were also read at 100% inhibition of growth, but after 24 h of incubation.

We used the revised species-specific CLSI CBPs to identify strains of the 6 most common species of *Candida* (*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and *C. guilliermondii*) that were susceptible and resistant to fluconazole and voriconazole (70, 71). All *C. krusei* isolates were defined as resistant to fluconazole. CLSI has not assigned CBPs for voriconazole and *C. glabrata* and recommends the ECV of 0.5 μg/ml to be used to differentiate WT (MIC ≤ ECV) from non-WT (MIC > ECV) strains of this species (54, 71).

CBPs have not been established for isavuconazole or posaconazole and the common species of *Candida* or for any antifungal agent and the less common species of *Candida*, non-*Candida* yeasts, *Aspergillus* spp., or the non-*Aspergillus* molds; however, ECVs have been proposed for the triazoles (fluconazole, posaconazole, and voriconazole) and 6 *Candida* species that are encountered less frequently (*C. lusitaniae*, *C. guilliermondii*, *C. dubliniensis*, *C. kefyr*, *C. orthopsilosis*, and *Candida pelliculosa*) (54, 71, 72). ECVs have also been developed for *A. fumigatus*, *A. flavus*, *A. terreus*, *A. nidulans*, and *A. niger* and isavuconazole, itraconazole, posaconazole, and voriconazole (50, 54, 73): isavuconazole, itraconazole, and voriconazole MIC values of >1 μg/ml were considered non-WT for *A. fumigatus*, *A. flavus*, and *A. terreus*, and itraconazole and posaconazole MIC values of >1 μg/ml and voriconazole MIC values of >2 μg/ml were considered non-WT for *A. nidulans*. Posaconazole MIC values of >0.25 μg/ml were considered non-WT for *A. fumigatus* and *A. flavus*, and MIC results of > 0.5 μg/ml were non-WT for *A. niger* and *A. terreus*; isavuconazole MIC values of >1 μg/ml were non-WT for *A. nidulans*, and MIC values of >4 μg/ml were non-WT for *A. niger*. Isolates of these *Aspergillus* spp. for which triazole MIC results exceed the ECV are considered to be non-WT and may harbor acquired mutations in the *cyp51A* gene (74, 75).

Among the *Mucorales*, there are no CBPs, and ECVs have only been proposed for posaconazole and *L. corymbifera* (2 μg/ml), *M. circinelloides* (4 μg/ml), *R. arrhizus* (2 μg/ml), and *R. microsporus* (2 μg/ml) and for itraconazole and *R. arrhizus* (2 μg/ml) (53).

Quality control was performed as recommended in CLSI documents M27-A3 (68) and M38-A2 (69) using strains *C. krusei* ATCC 6258, *C. parapsilosis* ATCC 22019, *A. flavus* ATCC 204304, and *A. fumigatus* MYA-3626.

ACKNOWLEDGMENTS

The studies were performed by JMI Laboratories and the Fungus Testing Laboratory and supported by Astellas Pharma Global Development, Inc., which included funding for services related to preparing this article.

JMI Laboratories was contracted to perform services in 2017 for Achaogen, Allecra Therapeutics, Allergan, Amplyx Pharmaceuticals, Antabio, API, Astellas Pharma, AstraZeneca, Athelas, Basilea Pharmaceutica, Bayer AG, BD, Becton, Dickinson and Co., Boston, CEM-102 Pharma, Cempra, Cidara Therapeutics, Inc., CorMedix, CSA Biotech, Cutanea Life Sciences, Inc., Entasis Therapeutics, Inc., Geom Therapeutics, Inc., GSK, Iterum Pharma, Medpace, Melinta Therapeutics, Inc., Merck & Co., Inc., MicuRx Pharmaceuticals, Inc., N8 Medical, Inc., Nabriva Therapeutics, Inc., NAEJA-RGM, Novartis, Paratek Pharmaceuticals, Inc., Pfizer, Polyphor, Ra Pharma, Rempex, Riptide Bioscience, Inc., Roche, Scynexis, Shionogi, Sinsa Labs, Inc., Skyline Antiinfectives, Sonoran Biosciences, Spero Therapeutics, Symbiotica, Synlogic, Synthes Biomaterials, TenNor Therapeutics, Tetraphase, The Medicines Company, Theravance Biopharma, VenatoRx Pharmaceuticals, Inc., Wockhardt, Yukon Pharma, Zai Laboratory, Zavante Therapeutics, Inc. There are no speakers' bureaus or stock options to declare.

N.P.W. has received research support to the UT Health San Antonio from Astellas, bioMérieux, Cidara, F2G, Merck, Pfizer, and Viamet and has served on advisory boards for Merck, Astellas, Toyama, and Viamet and as a speaker for Gilead.

This analysis was funded by Astellas Pharma, Inc. Isavuconazonium sulfate was codeveloped by Astellas Pharma Global Development, Inc., and Basilea Pharmaceuticals International, Ltd. L.L.K. is an employee of Astellas Pharm Global Development, Inc.

REFERENCES

1. Bongomin F, Gago S, Oladele RO, Denning DW. 2017. Global and multinational prevalence of fungal diseases-estimate precision. J Fungi (Basel) 3:E57. https://doi.org/10.3390/jof3040057.
2. Vallabhaneni S, Mody RK, Walker T, Chiller T. 2016. The global burden of fungal diseases. Infect Dis Clin North Am 30:1–11. https://doi.org/10.1016/j.idc.2015.10.004.
3. Pfaller MA. 2012. Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment. Am J Med 125:S3–S13. https://doi.org/10.1016/j.amjmed.2011.11.001.
4. Astvad KMT, Johansen HK, Roder BL, Rosenvinge FS, Knudsen JD, Lemming L, Schonheyder HC, Hare RK, Kristensen L, Nielsen L, Gertsen JB, Dzajic E, Pedersen M, Ostergard C, Olesen B, Sondergaard TS, Arendrup MC. 2018. Update from a 12-year nationwide fungemia surveillance: increasing intrinsic and acquired resistance causes concern. J Clin Microbiol 56:e01564-17. https://doi.org/10.1128/JCM.01564-17.
5. Bassetti M, Righi E, Montravers P, Cornely OA. 2018. What has changed in the treatment of invasive candidiasis? A look at the past 10 years and ahead. J Antimicrob Chemother 73:i14–i25. https://doi.org/10.1093/jac/dkx445.
6. Farmakiotis D, Kontoyiannis DP. 2017. Epidemiology of antifungal resistance in human pathogenic yeasts: current viewpoint and practical recommendations for management. Int J Antimicrob Agents 50:318–324. https://doi.org/10.1016/j.ijantimicag.2017.05.019.
7. Lamoth F, Lockhart SR, Berkow EL, Calandra T. 2018. Changes in the epidemiological landscape of invasive candidiasis. J Antimicrob Chemother 73:i4–i13. https://doi.org/10.1093/jac/dkx444.
8. Ramos-Martinez A, Vicente-Lopez N, Sanchez-Romero I, Padilla B, Merino-Amador P, Garnacho-Montero J, Ruiz-Camps I, Montejo M, Salavert M, Mensa J, Cuenca-Estrella M, Members of the CANDIPOP Project from GEIH-GEMICOMED (SEIMC) and REIPI. 2017. Epidemiology and prognosis of candidaemia in elderly patients. Mycoses 60:808–817. https://doi.org/10.1111/myc.12677.
9. Cleveland AA, Harrison LH, Farley MM, Hollick R, Stein B, Chiller TM, Lockhart SR, Park BJ. 2015. Declining incidence of candidemia and the shifting epidemiology of *Candida* resistance in two US metropolitan areas, 2008–2013: results from population-based surveillance. PLoS One 10:e0120452. https://doi.org/10.1371/journal.pone.0120452.
10. Strollo S, Lionakis MS, Adjemian J, Steiner CA, Prevots DR. 2016. Epidemiology of hospitalizations associated with invasive candidiasis, United States, 2002–2012. Emerg Infect Dis 23:7–13. https://doi.org/10.3201/eid2301.161198.
11. Bailly S, Maubon D, Fournier P, Pelloux H, Schwebel C, Chapuis C, Foroni L, Cornet M, Timsit JF. 2016. Impact of antifungal prescription on relative distribution and susceptibility of *Candida* spp.—trends over 10 years. J Infect 72:103–111. https://doi.org/10.1016/j.jinf.2015.09.041.
12. Bitar D, Lortholary O, Le Strat Y, Nicolau J, Coignard B, Tattevin P, Che D, Dromer F. 2014. Population-based analysis of invasive fungal infections, France, 2001–2010. Emerg Infect Dis 20:1149–1155. https://doi.org/10.3201/eid2007.131869.
13. Chapman B, Slavin M, Marriott D, Halliday C, Kidd S, Arthur I, Bak N, Heath CH, Kennedy K, Morrissey CO, Sorrell TC, van Hal S, Keighley C, Goeman E, Underwood N, Hajkowicz K, Hofmeyr A, Leung M, Macesic N, Botes J, Blyth C, Cooley L, George CR, Kalukottege P, Kesson A, McMullan B, Baird R, Robson J, Korman TM, Pendle S, Weeks K, Liu E, Cheong E, Chen S, Australian and New Zealand Mycoses Interest Group. 2017. Changing epidemiology of candidaemia in Australia. J Antimicrob Chemother 72:1103–1108. https://doi.org/10.1093/jac/dkx047.
14. Colombo AL, Nucci M, Park BJ, Nouer SA, Arthington-Skaggs B, da Matta DA, Warnock D, Morgan J, Brazilian Network Candidemia Study. 2006. Epidemiology of candidemia in Brazil: a nationwide sentinel surveillance of candidemia in eleven medical centers. J Clin Microbiol 44:2816–2823. https://doi.org/10.1128/JCM.00773-06.
15. Hesstvedt L, Gaustad P, Andersen CT, Haarr E, Hannula R, Haukland HH, Hermansen NO, Larssen KW, Mylvaganam H, Ranheim TE, Sandven P, Nordoy I, Norwegian Yeast Study Group, Kanestrom A, Grub C, Onken A, Thielsen C, Skaare D, Tofteland S, Sonsteby LJ, Hjetland R, Hide R, Vik E, Kummel A, Asheim S. 2015. Twenty-two years of candidaemia surveillance: results from a Norwegian national study. Clin Microbiol Infect 21:938–945. https://doi.org/10.1016/j.cmi.2015.06.008.
16. Poikonen E, Lyytikainen O, Anttila VJ, Koivula I, Lumio J, Kotilainen P, Syrjala H, Ruutu P. 2010. Secular trend in candidemia and the use of fluconazole in Finland, 2004–2007. BMC Infect Dis 10:312. https://doi.org/10.1186/1471-2334-10-312.
17. Puig-Asensio M, Padilla B, Garnacho-Montero J, Zaragoza O, Aguado JM, Zaragoza R, Montejo M, Munoz P, Ruiz-Camps I, Cuenca-Estrella M, Almirante B, CANDIPOP Project, GEIH-GEMICOMED (SEIMC), REIPI. 2014. Epidemiology and predictive factors for early and late mortality in *Candida* bloodstream infections: a population-based surveillance in Spain. Clin Microbiol Infect 20:O245–O254. https://doi.org/10.1111/1469-0691.12380.
18. Tan BH, Chakrabarti A, Li RY, Patel AK, Watcharananan SP, Liu Z, Chindamporn A, Tan AL, Sun PL, Wu UI, Chen YC, Asia Fungal Working Group. 2015. Incidence and species distribution of candidaemia in Asia: a laboratory-based surveillance study. Clin Microbiol Infect 21:946–953. https://doi.org/10.1016/j.cmi.2015.06.010.
19. Trouve C, Blot S, Hayette MP, Jonckheere S, Patteet S, Rodriguez-Villalobos H, Symoens F, Van Wijngaerden E, Lagrou K. 2017. Epidemiology and reporting of candidaemia in Belgium: a multi-centre study. Eur J Clin Microbiol Infect Dis 36:649–655. https://doi.org/10.1007/s10096-016-2841-3.
20. Kontoyiannis DP, Yang H, Song J, Kelkar SS, Yang X, Azie N, Harrington R, Fan A, Lee E, Spalding JR. 2016. Prevalence, clinical and economic burden of mucormycosis-related hospitalizations in the United States: a retrospective study. BMC Infect Dis 16:730–736. https://doi.org/10.1186/s12879-016-2023-z.
21. Petrikkos G, Skiada A, Drogari-Apiranthitou M. 2014. Epidemiology of mucormycosis in Europe. Clin Microbiol Infect 20(Suppl 6):S67–S73. https://doi.org/10.1111/1469-0691.12563.
22. Vallabhaneni S, Benedict K, Derado G, Mody RK. 2017. Trends in hospitalizations related to invasive aspergillosis and mucormycosis in the United States, 2000–2013. Open Forum Infect Dis 4:ofw268. https://doi.org/10.1093/ofid/ofw268.
23. Dodds Ashley E, Drew R, Johnson M, Danna R, Dabrowski D, Walker V, Prasad M, Alexander B, Papadopoulos G, Perfect J. 2012. Cost of invasive fungal infections in the era of new diagnostics and expanded treatment options. Pharmacotherapy 32:890–901. https://doi.org/10.1002/j.1875-9114.2012.01124.
24. Gudlaugsson O, Gillespie S, Lee K, Vande Berg J, Hu J, Messer S, Herwaldt L, Pfaller M, Diekema D. 2003. Attributable mortality of nosocomial candidemia, revisited. Clin Infect Dis 37:1172–1177. https://doi.org/10.1086/378745.
25. Vallabhaneni S, Cleveland AA, Farley MM, Harrison LH, Schaffner W, Beldavs ZG, Derado G, Pham CD, Lockhart SR, Smith RM. 2015. Epidemiology and risk factors for echinocandin nonsusceptible *Candida glabrata* bloodstream infections: data from a large multisite population-based Candidemia Surveillance Program, 2008–2014. Open Forum Infect Dis 2:ofv163. https://doi.org/10.1093/ofid/ofv163.
26. Zilberberg MD, Shorr AF, Huang H, Chaudhari P, Paly VF, Menzin J. 2014. Hospital days, hospitalization costs, and inpatient mortality among patients with mucormycosis: a retrospective analysis of US hospital discharge data. BMC Infect Dis 14:310. https://doi.org/10.1186/1471-2334-14-310.
27. Arendrup MC, Patterson TF. 2017. Multidrug-resistant Candida: epidemiology, molecular mechanisms, and treatment. J Infect Dis 216:S445–S451. https://doi.org/10.1093/infdis/jix131.
28. Borman AM, Fraser M, Palmer MD, Szekely A, Houldsworth M, Patterson Z, Johnson EM. 2017. MIC distributions and evaluation of fungicidal activity for amphotericin B, itraconazole, voriconazole, posaconazole and caspofungin and 20 species of pathogenic filamentous fungi determined using the CLSI broth microdilution method. J Fungi (Basel) 3:E27. https://doi.org/10.3390/jof3020027.
29. Chowdhary A, Sharma C, Meis JF. 2017. Azole-resistant aspergillosis: epidemiology, molecular mechanisms, and treatment. J Infect Dis 216:S436–S444. https://doi.org/10.1093/infdis/jix210.
30. Heo ST, Tatara AM, Jimenez-Ortigosa C, Jiang Y, Lewis RE, Tarrand J, Tverdek F, Albert ND, Verweij PE, Meis JF, Mikos AG, Perlin DS, Kontoyiannis DP. 2017. Changes in in vitro susceptibility patterns of Aspergillus to triazoles and correlation with aspergillosis outcome in a tertiary care cancer center, 1999–2015. Clin Infect Dis 65:216–225. https://doi.org/10.1093/cid/cix297.
31. Kontoyiannis DP. 2017. Antifungal resistance: an emerging reality and a

global challenge. J Infect Dis 216:S431–S435. https://doi.org/10.1093/infdis/jix179.
32. Perlin DS. 2015. Echinocandin resistance in *Candida*. Clin Infect Dis 61(Suppl 6):S612–S617. https://doi.org/10.1093/cid/civ791.
33. Pfaller MA, Castanheira M, Lockhart SR, Ahlquist AM, Messer SA, Jones RN. 2012. Frequency of decreased susceptibility and resistance to echinocandins among fluconazole-resistant bloodstream isolates of *Candida glabrata*. J Clin Microbiol 50:1199–1203. https://doi.org/10.1128/JCM.06112-11.
34. Pham CD, Reiss E, Hagen F, Meis JF, Lockhart SR. 2014. Passive surveillance for azole-resistant *Aspergillus fumigatus*, United States, 2011–2013. Emerg Infect Dis 20:1498–1503. https://doi.org/10.3201/eid2009.140142.
35. van der Linden JW, Arendrup MC, Warris A, Lagrou K, Pelloux H, Hauser PM, Chryssanthou E, Mellado E, Kidd SE, Tortorano AM, Dannaoui E, Gaustad P, Baddley JW, Uekotter A, Lass-Florl C, Klimko N, Moore CB, Denning DW, Pasqualotto AC, Kibbler C, Arikan-Akdagli S, Andes D, Meletiadis J, Naumiuk L, Nucci M, Melchers WJ, Verweij PE. 2015. Prospective multicenter international surveillance of azole resistance in *Aspergillus fumigatus*. Emerg Infect Dis 21:1041–1044. https://doi.org/10.3201/eid2106.140717.
36. Meis JF, Chowdhary A, Rhodes JL, Fisher MC, Verweij PE. 2016. Clinical implications of globally emerging azole resistance in *Aspergillus fumigatus*. Philos Trans R Soc Lond B Biol Sci. 371:20150460. https://doi.org/10.1098/rstb.2015.0460.
37. Verweij PE, Chowdhary A, Melchers WJ, Meis JF. 2016. Azole resistance in *Aspergillus fumigatus*: can we retain the clinical use of mold-active antifungal azoles? Clin Infect Dis 62:362–368. https://doi.org/10.1093/cid/civ885.
38. Natesan SK, Chandrasekar PH. 2016. Isavuconazole for the treatment of invasive aspergillosis and mucormycosis: current evidence, safety, efficacy, and clinical recommendations. Infect Drug Resist 9:291–300. https://doi.org/10.2147/IDR.S102207.
39. Miceli MH, Kauffman CA. 2015. Isavuconazole: a new broad-spectrum triazole antifungal agent. Clin Infect Dis 61:1558–1565. https://doi.org/10.1093/cid/civ571.
40. Pettit NN, Carver PL. 2015. Isavuconazole: a new option for the management of invasive fungal infections. Ann Pharmacother 49:825–842. https://doi.org/10.1177/1060028015581679.
41. Thompson GR, III, Wiederhold NP. 2010. Isavuconazole: a comprehensive review of spectrum of activity of a new triazole. Mycopathologia 170:291–313. https://doi.org/10.1007/s11046-010-9324-3.
42. Wilson DT, Dimondi VP, Johnson SW, Jones TM, Drew RH. 2016. Role of isavuconazole in the treatment of invasive fungal infections. Ther Clin Risk Manag 12:1197–1206. https://doi.org/10.2147/TCRM.S90335.
43. Pfaller MA, Rhomberg PR, Messer SA, Jones RN, Castanheira M. 2015. Isavuconazole, micafungin, and 8 comparator antifungal agents' susceptibility profiles for common and uncommon opportunistic fungi collected in 2013: temporal analysis of antifungal drug resistance using CLSI species-specific clinical breakpoints and proposed epidemiological cutoff values. Diagn Microbiol Infect Dis 82:303–313. https://doi.org/10.1016/j.diagmicrobio.2015.04.008.
44. Arendrup MC, Jensen RH, Meletiadis J. 2015. In vitro activity of isavuconazole and comparators against clinical isolates of the mucorales order. Antimicrob Agents Chemother 59:7735–7742. https://doi.org/10.1128/AAC.01919-15.
45. Chowdhary A, Singh PK, Kathuria S, Hagen F, Meis JF. 2015. Comparison of the EUCAST and CLSI broth microdilution methods for testing isavuconazole, posaconazole, and amphotericin B against molecularly identified *Mucorales* species. Antimicrob Agents Chemother 59:7882–7887. https://doi.org/10.1128/AAC.02107-15.
46. Guinea J, Pelaez T, Recio S, Torres-Narbona M, Bouza E. 2008. In vitro antifungal activities of isavuconazole (BAL4815), voriconazole, and fluconazole against 1,007 isolates of zygomycete, *Candida*, *Aspergillus*, *Fusarium*, and *Scedosporium* species. Antimicrob Agents Chemother 52:1396–1400. https://doi.org/10.1128/AAC.01512-07.
47. Verweij PE, Gonzalez GM, Wiedrhold NP, Lass-Florl C, Warn P, Heep M, Ghannoum MA, Guinea J. 2009. In vitro antifungal activity of isavuconazole against 345 Mucorales isolates collected at study centers in eight countries. J Chemother 21:272–281. https://doi.org/10.1179/joc.2009.21.3.272.
48. Maertens JA, Raad II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, Bow EJ, Rahav G, Neofytos D, Aoun M, Baddley JW, Giladi M, Heinz WJ, Herbrecht R, Hope W, Karthaus M, Lee DG, Lortholary O, Morrison VA, Oren I, Selleslag D, Shoham S, Thompson GR, III, Lee M, Maher RM, Schmitt-Hoffmann AH, Zeiher B, Ullmann AJ. 2016. Isavuconazole versus voriconazole for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet 387:760–769. https://doi.org/10.1016/S0140-6736(15)01159-9.
49. Marty FM, Ostrosky-Zeichner L, Cornely OA, Mullane KM, Perfect JR, Thompson GR, III, Alangaden GJ, Brown JM, Fredricks DN, Heinz WJ, Herbrecht R, Klimko N, Klyasova G, Maertens JA, Melinkeri SR, Oren I, Pappas PG, Racil Z, Rahav G, Santos R, Schwartz S, Vehreschild JJ, Young JH, Chetchotisakd P, Jaruratanasirikul S, Kanj SS, Engelhardt M, Kaufhold A, Ito M, Lee M, Sasse C, Maher RM, Zeiher B, Vehreschild M, Vital and FungiScope Mucormycosis Investigators. 2016. Isavuconazole treatment for mucormycosis: a single-arm open-label trial and case-control analysis. Lancet Infect Dis 16:828–837. https://doi.org/10.1016/S1473-3099(16)00071-2.
50. Espinel-Ingroff A, Chowdhary A, Gonzalez GM, Lass-Florl C, Martin-Mazuelos E, Meis J, Pelaez T, Pfaller MA, Turnidge J. 2013. Multicenter study of isavuconazole MIC distributions and epidemiological cutoff values for *Aspergillus* spp. for the CLSI M38-A2 broth microdilution method. Antimicrob Agents Chemother 57:3823–3828. https://doi.org/10.1128/AAC.00636-13.
51. Espinel-Ingroff A, Turnidge J, Alastruey-Izquierdo A, Dannaoui E, Garcia-Effron G, Guinea J, Kidd S, Pelaez T, Sanguinetti M, Meletiadis J, Botterel F, Bustamante B, Chen YC, Chakrabarti A, Chowdhary A, Chryssanthou E, Cordoba S, Gonzalez GM, Guarro J, Johnson EM, Kus JV, Lass-Florl C, Linares-Sicilia MJ, Martin-Mazuelos E, Negri CE, Pfaller MA, Tortorano AM. 2018. Posaconazole MIC distributions for *Aspergillus fumigatus* species complex by four methods: impact of cyp51A mutations on estimation of epidemiological cutoff values. Antimicrob Agents Chemother 62:e01916-17. https://doi.org/10.1128/AAC.01916-17.
52. Buil JB, Bruggemann RJM, Wasmann RE, Zoll J, Meis JF, Melchers WJG, Mouton JW, Verweij PE. 2018. Isavuconazole susceptibility of clinical *Aspergillus fumigatus* isolates and feasibility of isavuconazole dose escalation to treat isolates with elevated MICs. J Antimicrob Chemother 73:134–142. https://doi.org/10.1093/jac/dkx354.
53. Espinel-Ingroff A, Chakrabarti A, Chowdhary A, Cordoba S, Dannaoui E, Dufresne P, Fothergill A, Ghannoum M, Gonzalez GM, Guarro J, Kidd S, Lass-Florl C, Meis JF, Pelaez T, Tortorano AM, Turnidge J. 2015. Multicenter evaluation of MIC distributions for epidemiologic cutoff value definition to detect amphotericin B, posaconazole, and itraconazole resistance among the most clinically relevant species of *Mucorales*. Antimicrob Agents Chemother 59:1745–1750. https://doi.org/10.1128/AAC.04435-14.
54. CLSI. 2018. M59. Epidemiological cutoff values for antifungal susceptibility testing, 2nd ed. Clinical and Laboratory Standards Institute, Wayne, PA.
55. Diekema DJ, Messer SA, Boyken LB, Hollis RJ, Kroeger J, Tendolkar S, Pfaller MA. 2009. In vitro activity of seven systemically active antifungal agents against a large global collection of rare *Candida* species as determined by CLSI broth microdilution methods. J Clin Microbiol 47:3170–3177. https://doi.org/10.1128/JCM.00942-09.
56. Pfaller MA, Diekema DJ, Mendez M, Kibbler C, Erzsebet P, Chang SC, Gibbs DL, Newell VA. 2006. *Candida guilliermondii*, an opportunistic fungal pathogen with decreased susceptibility to fluconazole: geographic and temporal trends from the ARTEMIS DISK Antifungal Surveillance Program. J Clin Microbiol 44:3551–3556. https://doi.org/10.1128/JCM.00865-06.
57. Savini V, Catavitello C, Onofrillo D, Masciarelli G, Astolfi D, Balbinot A, Febbo F, D'Amario C, D'Antonio D. 2011. What do we know about *Candida guilliermondii*? A voyage throughout past and current literature about this emerging yeast. Mycoses 54:434–441. https://doi.org/10.1111/j.1439-0507.2010.01960.x.
58. Kleiboeker SB, Altrich M. 2018. Comparison of therapeutic drug levels of adult and pediatric patients undergoing treatment for fungal diseases, poster 552. Am Soc Blood Bone Marrow Transplant Tandem Meet, Salt Lake City, UT, 21–25 February 2018.
59. Astvad KMT, Hare RK, Arendrup MC. 2017. Evaluation of the in vitro activity of isavuconazole and comparator voriconazole against 2635 contemporary clinical *Candida* and *Aspergillus* isolates. Clin Microbiol Infect 23:882–887. https://doi.org/10.1016/j.cmi.2017.03.023.
60. Castanheira M, Messer SA, Jones RN, Farrell DJ, Pfaller MA. 2014. Activity of echinocandins and triazoles against a contemporary (2012) worldwide collection of yeast and moulds collected from invasive infections. Int J Anti-

microb Agents 44:320–326. https://doi.org/10.1016/j.ijantimicag.2014.06.007.
61. Chen SCA, Sorrell TC, Meyer W. 2015. *Aspergillus* and *Penicillium*, p 2030–2056, In Jorgensen JH, Pfaller MA, Carroll KC, Funke G, Landry ML, Richter SS, Warnock DW (ed), Manual of clinical microbiology, 11th ed. ASM Press, Washington, DC.
62. Howell SA, Hazen KC, Brandt ME. 2015. *Candida*, *Cryptococcus*, and other yeasts of medical importants, p 1984–2014. *In* Jorgensen JH, Pfaller MA, Carroll KC, Funke G, Landry ML, Richter SS, Warnock DW (ed), Manual of clinical microbiology, 11th ed. ASM Press, Washington, DC.
63. Zhang SX, O'Donnell K, Sutton DA. 2015. *Fusarium* and other opportunistic hyaline fungi, p 2057–2086. *In* Jorgensen JH, Pfaller MA, Carroll KC, Funke G, Landry ML, Richter SS, Warnock DW (ed), Manual of clinical microbiology, 11th ed. ASM Press, Washington, DC.
64. Castanheira M, Messer SA, Rhomberg PR, Dietrich RR, Jones RN, Pfaller MA. 2014. Isavuconazole and nine comparator antifungal susceptibility profiles for common and uncommon Candida species collected in 2012: application of new CLSI clinical breakpoints and epidemiological cutoff values Mycopathologia 178:1–9. https://doi.org/10.1007/s11046-014-9772-2.
65. Pfaller MA, Woosley LN, Messer SA, Jones RN, Castanheira M. 2012. Significance of molecular identification and antifungal susceptibility of clinically significant yeasts and moulds in a global antifungal surveillance program. Mycopathologia 174:259–271. https://doi.org/10.1007/s11046-012-9551-x.
66. Rychert J, Slechta ES, Barker AP, Miranda E, Babady NE, Tang YW, Gibas C, Wiederhold N, Sutton D, Hanson KE. 2018. Multicenter evaluation of the Vitek MS v3.0 system for the identification of filamentous fungi. J Clin Microbiol 56:e01353-17. https://doi.org/10.1128/JCM.01353-17.
67. Siqueira JP, Sutton DA, Gene J, Garcia D, Wiederhold N, Peterson SW, Guarro J. 2017. Multilocus phylogeny and antifungal susceptibility of *Aspergillus* section *Circumdati* from clinical samples and description of *A. pseudosclerotiorum* sp. nov. J Clin Microbiol 55:947–958. https://doi.org/10.1128/JCM.02012-16.
68. CLSI. 2008. M27-A3. Reference method for broth dilution antifungal susceptibility testing of yeasts, 3rd ed. Clinical and Laboratory Standards Institute, Wayne, PA.
69. CLSI. 2008. M38-A2. Reference method for broth dilution antifungal susceptibility testing of filamentous fungi, 2nd ed. Clinical and Laboratory Standards Institute, Wayne, PA.
70. CLSI. 2012. M27-S4. Reference method for broth dilution antifungal susceptibility testing of yeasts: 4th informational supplement. Clinical and Laboratory Standards Institute, Wayne, PA.
71. Pfaller MA, Diekema DJ. 2012. Progress in antifungal susceptibility testing of *Candida* spp. by use of Clinical and Laboratory Standards Institute broth microdilution methods, 2010 to 2012. J Clin Microbiol 50:2846–2856. https://doi.org/10.1128/JCM.00937-12.
72. Espinel-Ingroff A, Pfaller MA, Bustamante B, Canton E, Fothergill A, Fuller J, Gonzalez GM, Lass-Florl C, Lockhart SR, Martin-Mazuelos E, Meis JF, Melhem MS, Ostrosky-Zeichner L, Pelaez T, Szeszs MW, St-Germain G, Bonfietti LX, Guarro J, Turnidge J. 2014. Multilaboratory study of epidemiological cutoff values for detection of resistance in eight Candida species to fluconazole, posaconazole, and voriconazole. Antimicrob Agents Chemother 58:2006–2012. https://doi.org/10.1128/AAC.02615-13.
73. Espinel-Ingroff A, Diekema DJ, Fothergill A, Johnson E, Pelaez T, Pfaller MA, Rinaldi MG, Canton E, Turnidge J. 2010. Wild-type MIC distributions and epidemiological cutoff values for the triazoles and six *Aspergillus* spp. for the CLSI broth microdilution method (M38-A2 document). J Clin Microbiol 48:3251–3257. https://doi.org/10.1128/JCM.00536-10.
74. Howard SJ, Cerar D, Anderson MJ, Albarrag A, Fisher MC, Pasqualotto AC, Laverdiere M, Arendrup MC, Perlin DS, Denning DW. 2009. Frequency and evolution of azole resistance in *Aspergillus fumigatus* associated with treatment failure. Emerg Infect Dis 15:1068–1076. https://doi.org/10.3201/eid1507.090043.
75. Rodriguez-Tudela JL, Alcazar-Fuoli L, Mellado E, Alastruey-Izquierdo A, Monzon A, Cuenca-Estrella M. 2008. Epidemiological cutoffs and cross-resistance to azole drugs in *Aspergillus fumigatus*. Antimicrob Agents Chemother 52:2468–2472. https://doi.org/10.1128/AAC.00156-08.
76. Espinel-Ingroff A, Aller AI, Canton E, Castanon-Olivares LR, Chowdhary A, Cordoba S, Cuenca-Estrella M, Fothergill A, Fuller J, Govender N, Hagen F, Illnait-Zaragozi MT, Johnson E, Kidd S, Lass-Florl C, Lockhart SR, Martins MA, Meis JF, Melhem MS, Ostrosky-Zeichner L, Pelaez T, Pfaller MA, Schell WA, St-Germain G, Trilles L, Turnidge J. 2012. *Cryptococcus neoformans-Cryptococcus gattii* species complex: an international study of wild-type susceptibility endpoint distributions and epidemiological cutoff values for fluconazole, itraconazole, posaconazole, and voriconazole. Antimicrob Agents Chemother 56:5898–5906. https://doi.org/10.1128/AAC.01115-12.