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Activity Profile In Vitro of Micafungin against Spanish Clinical Isolates of Common and Emerging Species of Yeasts and Molds[▽]

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A collection of 2,278 isolates belonging to 86 different fungal species was tested with micafungin and eight other drugs using the EUCAST procedures. Micafungin was active against species of *Candida* and *Aspergillus* (even azole-resistant species) as well as *Penicillium* spp., *Scedosporium apiospermum*, and *Acremonium* spp. It was inactive for species of *Basidiomycota* and *Mucorales* and for multiresistant species such as those of *Fusarium*.

Micafungin is a new drug that belongs to the echinocandin class of antifungal agents. Its mechanism of action is by means of the inhibition of 1,3-β-D-glucan synthesis in the fungal cell wall (10).

Micafungin has been recently approved in Europe and the United States for the treatment of candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses, esophageal candidiasis, and recently for the prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation.

The in vitro activity of micafungin against most common species of *Candida* is well known (4, 11–13). However, information is limited for uncommon species of yeasts as well as for molds.

The aim of this study is to analyze the in vitro activity of micafungin and eight other antifungal agents against a collection of clinical isolates of yeasts and molds from human beings using the methods approved by AFST-EUCAST.

The strains were recovered from 115 Spanish hospitals through a period of 3 years, from 2005 to 2007. A total of 2,278 clinical isolates were included in the analysis. Isolates were identified by morphological and biochemical methods and sequencing of DNA targets if necessary. They belonged to 86 different species of common and emerging fungal pathogens. The isolates were obtained from blood (559; 24.5%), biopsies and other deep sites (217; 9.5%), respiratory tract specimens (751; 33%), skin samples (180; 7.9%), and other locations (707; 25.1%).

The following drugs were used: amphotericin B (range, 16.0 to 0.03 μg/ml; Sigma-Aldrich Quimica S.A., Madrid, Spain), flucytosine (64.0 to 0.12 μg/ml; Sigma-Aldrich), fluconazole (64.0 to 0.12 μg/ml; Pfizer S.A. Madrid, Spain), itraconazole (8.0 to 0.015 μg/ml; Janssen S.A., Madrid, Spain), voriconazole (8.0 to 0.015 μg/ml; Pfizer S.A.), posaconazole (8.0 to 0.015 μg/ml; Schering-Plough, Kenilworth, NJ), caspofungin (16.0 to 0.03 μg/ml; Merck & Co., Inc., Rahway, NJ), micafungin (16.0 to 0.03 μg/ml; Astellas Pharma Inc., Tokyo, Japan), and anidulafungin (16.0 to 0.03 μg/ml; Pfizer S.A.).

Susceptibility testing was performed by using broth microdilution. For *Candida* species, MICs were determined using the reference procedure for testing fermentative yeasts described by AFST-EUCAST (7, 17). For *Cryptococcus neoformans* and other species of nonfermentative yeasts, such as *Trichosporon* and *Rhodotorula* spp., susceptibility testing strictly followed the recommendations by the EUCAST with a minor modification in order to improve the growth of microorganisms (3). For filamentous fungi, broth microdilution testing was performed following the AFST-EUCAST reference method (18). For testing echinocandins against molds, the MIC was defined as the lowest drug concentration resulting in aberrant hyphal growth by examination with an inverted microscope, that is, the minimum effective concentration (MEC) (2).

Tables 1 and 2 display the susceptibility results obtained when the collection of clinical isolates was tested.

Micafungin exhibited a potent activity in vitro against *Candida* spp. That activity was somehow better than the in vitro activity of caspofungin and similar to that of anidulafungin. AFST-EUCAST has not yet proposed breakpoints to read the susceptibility testing of echinocandins. CLSI and others have published that *Candida* isolates exhibiting MICs of echinocandins of >2 μg/ml can be considered nonsusceptible in vitro (14). Following that criterion, only one isolate out of 20 *Candida guilliermondii* clinical isolates tested (1/20; 5%) had a MIC of micafungin of >2 μg/ml. That isolate exhibited cross-resistance in vitro to both caspofungin and anidulafungin.

A total of 15.3% of the *Candida* isolates analyzed (160/1,043; 61 *Candida glabrata*, 53 *Candida krusei*, 25 *Candida albicans*, 8 *Candida tropicalis*, 7 *C. guilliermondii*, 3 *Candida parapsilosis*, 1 *Candida lusitaniae*, 1 *Candida norvegensis*, and 1 *Candida rugosa*) were resistant in vitro to fluconazole according to AFST-EUCAST criteria (fluconazole MIC, >4 μg/ml) (19). In addition, 7.9% of the isolates (82/1,043; 36 *C. glabrata*, 18 *C. krusei*, 16 *C. albicans*, 7 *C. tropicalis*, 4 *C. guilliermondii*, and 1 *C. parapsilosis*) were also resistant in vitro to voriconazole (MIC, >0.12 μg/ml by EUCAST criteria) (20). All azole-re-

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TABLE 1. Summary of susceptibility results of antifungal agents tested in vitro against yeast species[a]

Species	*n*	Amphotericin B		Flucytosine		Fluconazole		Itraconazole		Voriconazole		Posaconazole		Caspofungin		Anidulafungin		Micafungin	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Candida species																			
Candida albicans	393	0.06	0.12	0.12	0.50	0.12	0.25	0.02	0.03	0.02	0.02	0.02	0.02	0.06	0.12	0.03	0.03	0.03	0.03
Candida parapsilosis	225	0.12	0.25	0.12	0.25	0.50	1.0	0.02	0.03	0.02	0.02	0.02	0.03	1.0	1.0	1.0	2.0	0.5	1.0
Candida tropicalis	105	0.12	0.25	0.12	0.25	0.25	2.0	0.02	0.06	0.03	0.12	0.02	0.03	0.12	0.25	0.03	0.03	0.03	0.03
Candida glabrata	182	0.12	0.25	0.12	0.25	4.0	32.0	0.25	1.0	0.12	1.0	0.25	1.0	0.12	0.25	0.03	0.03	0.03	0.03
Candida krusei	53	0.50	0.50	4.0	8.0	32.0	>64.0	0.25	0.25	0.25	0.50	0.12	0.25	0.25	0.50	0.03	0.06	0.03	0.06
Candida guilliermondii	20	0.06	0.50	0.12	0.25	4.0	>64.0	0.25	>8.0	0.12	>8.0	0.12	>8.0	0.50	1.0	1.0	8.0	0.12	1.0
Candida lusitaniae	21	0.06	0.12	0.12	16.0	0.25	1.0	0.02	0.03	0.02	0.02	0.02	0.02	0.50	1.0	0.03	0.12	0.03	0.03
Candida kefyr	15	0.25	0.50	0.50	4.0	0.25	0.50	0.02	0.06	0.02	0.02	0.03	0.06	0.06	0.12	0.03	0.03	0.03	0.03
Other *Candida* spp.[b]	29	0.12	1.0	0.25	16.0	8.0	>64.0	0.12	>8.0	0.12	>8.0	0.03	>8.0	0.06	0.50	0.06	0.25	0.03	0.12
Other *Ascomycota* yeasts																			
Dipodascus capitatus	30	0.50	0.50	0.12	1.0	16.0	32.0	0.25	0.50	0.50	1.0	0.50	0.50	>16.0	>16.0	2.0	4.0	>16.0	>16.0
Saccharomyces cerevisiae	25	0.12	0.25	0.12	0.50	4.0	>64.0	0.50	2.0	0.06	0.50	0.25	0.50	0.50	1.0	0.12	0.25	0.03	0.06
Yarrowia lipolytica	10	0.50	0.50	>64.0	>64.0	8.0	>64.0	0.50	>8.0	0.50	2.0	0.25	2.0	0.50	1.0	0.06	0.12	0.03	1.0
Galactomyces geotrichum	10	0.25	0.50	0.12	0.25	64.0	>64.0	0.50	2.0	0.50	1.0	0.50	0.50	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Basidiomycota yeasts																			
C. neoformans var. *neoformans*	35	0.12	2.0	16.0	32.0	16.0	>64.0	0.12	0.50	0.12	0.50	0.12	0.50	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Trichosporon asahii	13	8.0	>16.0	32.0	>64.0	16.0	>64.0	0.50	>8.0	0.25	>8.0	0.25	>8.0	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Rhodotorula mucilaginosa	11	0.12	0.50	0.25	1.0	>64.0	>64.0	8.0	>8.0	4.0	>8.0	2.0	>8.0	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Trichosporon inkin	10	0.12	1.0	64.0	>64.0	4.0	4.0	0.12	0.25	0.06	0.12	0.06	0.12	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Other *Basidiomycota* yeasts[c]	35	0.50	8.0	16.0	>64.0	16.0	>64.0	0.50	>8.0	0.50	>8.0	0.25	>8.0	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0

[a] MIC_{50} and MIC_{90} values (μg/ml) were calculated for those species with 10 or more isolates.

[b] "Other *Candida* species" includes the following species with less than 10 isolates: *Candida rugosa* (4), *Candida famata* (4), *Candida pelliculosa* (4), *Candida colliculosa* (3), *Candida norvegensis* (2), *Candida intermedia* (2), *Candida inconspicua* (2), *Candida metapsilosis* (2), *Candida orthopsilosis* (2), *Candida pintolopesii* (2), and *Candida zeylanoides* (2).

[c] "Other *Basidiomycota* yeasts" includes the following species with less than 10 isolates: *Trichosporon ovoides* (5), *Trichosporon dermatis* (5), *Trichosporon jirovecii* (4), *Cryptococcus albidus* (3), *Ustilago* spp. (3), *Rhodotorula glutinis* (3), *Cryptococcus laurentii* (2), *Trichosporon domesticum* (2), *Trichosporon mycotoxinivorans* (2), and *Trichosporon* spp. (6).

TABLE 2. Summary of susceptibility results of antifungal agents tested in vitro against mold species[a]

Species	*n*	Amphotericin B		Itraconazole		Voriconazole		Posaconazole		Caspofungin		Anidulafungin		Micafungin	
		MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Aspergillus spp.															
Aspergillus fumigatus	299	0.25	0.50	0.25	0.50	0.50	1.0	0.06	0.25	0.25	0.50	0.03	0.03	0.03	0.03
Aspergillus terreus	155	1.0	4.0	0.25	0.50	1.0	2.0	0.06	0.12	1.0	2.0	0.03	0.03	0.03	0.03
Aspergillus flavus	81	1.0	2.0	0.25	0.50	1.0	2.0	0.12	0.25	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Aspergillus niger	83	0.25	0.25	1.0	>8.0	1.0	2.0	0.25	0.50	0.25	0.50	0.03	0.03	0.03	0.06
Aspergillus nidulans	29	1.0	4.0	0.25	0.50	0.25	1.0	0.06	0.25	0.50	>16.0	0.03	0.25	0.03	>16.0
Aspergillus sydowii	28	1.0	2.0	0.50	>8.0	1.0	2.0	0.25	0.50	0.25	1.0	0.03	0.03	0.03	0.03
Aspergillus versicolor	12	1.0	2.0	0.50	1.0	1.0	2.0	0.25	0.50	0.25	2.0	0.03	0.03	0.03	0.06
Other *Aspergillus* spp.[b]	18	0.50	>16.0	0.50	>8.0	0.25	>8.0	0.12	>8.0	0.12	0.50	0.06	0.25	0.06	0.25
Other hyaline fungi															
Penicillium spp.	72	0.50	2.0	0.50	>8.0	2.0	>8.0	0.25	4.0	0.25	8.0	0.03	0.03	0.03	0.06
Fusarium solani	32	1.0	2.0	>8.0	>8.0	>8.0	>8.0	>8.0	>8.0	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Fusarium proliferatum	19	2.0	4.0	>8.0	>8.0	8.0	>8.0	>8.0	>8.0	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Fusarium oxysporum	17	1.0	2.0	>8.0	>8.0	4.0	>8.0	4.0	>8.0	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Fusarium verticillioides	11	2.0	4.0	>8.0	>8.0	8.0	>8.0	2.0	>8.0	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Paecilomyces variotii	17	0.03	0.50	0.06	0.25	1.0	8.0	0.03	0.25	0.50	4.0	0.03	0.03	0.03	0.03
Paecilomyces lilacinus	10	>16.0	>16.0	>8.0	>8.0	0.50	4.0	0.25	0.50	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Acremonium spp.	10	4.0	>16.0	>8.0	>8.0	4.0	8.0	8.0	>16.0	0.50	1.0	0.03	0.03	0.12	0.25
Other hyaline fungi[c]	26	0.50	>16.0	>8.0	>8.0	4.0	>8.0	4.0	>8.0	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Black fungi															
Scedosporium apiospermum	36	4.0	>16.0	1.0	>8.0	0.50	2.0	1.0	8.0	2.0	>16.0	0.50	4.0	0.03	>16.0
Scedosporium prolificans	17	>16.0	>16.0	>8.0	>8.0	>8.0	>8.0	>8.0	>8.0	8	>16.0	4.0	>16.0	8.0	>16.0
Alternaria alternata	11	0.50	>16.0	0.50	>8.0	4.0	>8.0	1.0	>8.0	4.0	>16.0	0.06	>16.0	0.25	>16.0
Alternaria infectoria	10	0.06	>16.0	2.0	>8.0	2.0	>8.0	0.50	>8.0	>16.0	>16.0	2.0	>16.0	>16.0	>16.0
Other black fungi[d]	14	0.25	1.0	0.12	>8.0	0.06	>8.0	0.06	>8.0	0.25	1.0	0.03	0.06	0.03	0.06
Mucorales															
Mycocladus corymbiferus	16	0.12	0.25	1	>8.0	>8.0	>8.0	0.50	>8.0	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Rhizopus oryzae	11	0.50	2.0	4.0	>8.0	>8.0	>8.0	2.0	>8.0	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Mucor spp.	11	0.12	1.0	>8.0	>8.0	>8.0	>8.0	4.0	>8.0	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0
Other *Mucorales* species[e]	11	2.0	>16.0	>8.0	>8.0	>8.0	>8.0	4.0	>8.0	>16.0	>16.0	>16.0	>16.0	>16.0	>16.0

[a] MIC_{50} and MIC_{90} values (μg/ml) were calculated for those species with 10 or more isolates.

[b] "Other *Aspergillus* spp." includes the following species with less than 10 isolates: *Aspergillus ochraceus* (5), *Aspergillus ustus* (4), *Aspergillus niveus* (3), *Aspergillus sclerotiorum* (2), *Aspergillus glaucus* (2), and *Aspergillus* spp. (2).

[c] "Other hyaline fungi" includes the following species with less than 10 isolates: *Scopulariopsis brevicaulis* (6), *Trichoderma* spp. (5), *Phialemonium curvatum* (5), *Hormographiella aspergillata* (3), *Fusarium equiseti* (2), *Fusarium reticulatum* (2), *Hormographiella verticillata* (1), *Chrysonilia sitophila* (1), and *Beauveria bassiana* (1).

[d] "Other black fungi" includes the following species with less than 10 isolates: *Exophiala dermatitidis* (4), *Exophiala jeanselmei* (3), *Aureobasidium pullulans* (2), *Hortae werneckii* (1), *Cladosporium* spp. (1), *Cladophialophora bantiana* (1), *Scytalidium hyalinum* (1), and *Lecythophora hoffmannii* (1).

[e] "Other *Mucorales* species" includes the following species with less than 10 isolates: *Cunninghamella bertholletiae* (6), *Rhizopus microsporus* (2), *Rhizomucor* spp. (2), and *Saksenaea vasiformis* (1).

sistant *Candida* strains exhibited low MICs of micafungin and other echinocandins.

Micafungin and the other echinocandins were inactive in vitro against *Dipodascus capitatus* and *Galactomyces geotrichum* and against species of all genera belonging to *Basidiomycota*, such as *Cryptococcus*, *Trichosporon*, and *Rhodotorula*. The echinocandins were active in vitro against some non-*Candida Ascomycota* species, such as *Saccharomyces cerevisiae* and *Yarrowia lipolytica*.

Regarding *Aspergillus* spp., micafungin exhibited a good activity in vitro against most of the *Aspergillus* isolates. Notably, the echinocandin seemed to be inactive in vitro against *Aspergillus flavus* and a number of *Aspergillus nidulans* clinical isolates as others have reported before (1, 9). Micafungin and the other echinocandins were active in vitro (MEC, ≤ 2μg/ml) against 11 strains of *Aspergillus* spp. (1.6%; 11/705; 7 *Aspergillus niger*, 2 *Aspergillus fumigatus*, and 2 *Aspergillus ustus*) that had MICs of itraconazole of ≥8 μg/ml.

Micafungin also inhibited in vitro some other species of hyaline fungi, such as *Penicillium* spp., *Paecilomyces variotii*, and *Acremonium* spp. In addition, it exhibited activity against some isolates of black fungi as the echinocandin had low MEC values (MEC, ≤ 2μg/ml) for 32 out of 36 (88.9%) isolates of *Scedosporium apiospermum*, 7/11 (63.6%) isolates of *Alternaria alternata*, and for most of the *Exophiala* strains tested.

On the contrary, micafungin and the other two echinocandins were inactive in vitro against some species of molds, such *Fusarium* spp., *Paecilomyces lilacinus*, *Scopulariopsis* spp., and *Trichoderma* spp. which are characterized by their resistance to other antifungal families. The echinocandins were inactive against *Mucorales* species as well.

These results of in vitro activity match published data by other authors for *Candida* and *Aspergillus* species (5, 6, 8, 9, 21), including the good activities of the three echinocandins against azole-resistant isolates (15, 16). There again, this study collects susceptibility data on species of fungal pathogens that have not been published before, such as non-*Candida Ascomycota* yeasts and some species of hyaline and black molds. Notably, micafungin showed activity in vitro against most of the strains of *S. apiospermum* tested. Zeng et al. reported that that species is resistant in vitro to echinocandins when the MIC is defined as total inhibition of growth (22). However, as a criterion of the MIC definition, we use the lowest drug concentration resulting in aberrant hyphal growth by examination with an inverted microscope (MEC). Following that, micafungin exhibited activity in vitro against 89% of the clinical isolates analyzed.

In summary, micafungin is a broad-spectrum antifungal agent with a good profile of activity in vitro which is comparable to those of caspofungin and anidulafungin. It exhibits activity against *Candida* and *Aspergillus* spp. except for *A. flavus*. The echinocandin also inhibits *Candida* isolates with resistance to both fluconazole and voriconazole and *Aspergillus* strains with resistance in vitro to itraconazole. It must be noted that micafungin and the other echinocandins are inactive in vitro against *Basidiomycota* spp., *Mucorales* spp., and some species of multiresistant fungi, such as *Fusarium* spp.

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