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1 **Isavuconazole MICs distribution of 29 yeast species responsible for invasive infections**
2 **(2015-2017)**

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22 **Abstract**

23 **Objectives**

24 Isavuconazole is a recent extended-spectrum triazole with activity against yeasts. However,
25 few data are available on the *in vitro* activity on rare yeast species. We report minimum
26 inhibitory concentration (MIC) distribution of isavuconazole compared to fluconazole for a
27 large collection of common or rare yeasts.

28 **Methods**

29 Isavuconazole and fluconazole MICs were determined using the EUCAST method for 1457
30 clinical isolates, mainly recovered from invasive infections, belonging to 29 species. They
31 were sent to the National Reference Center for Invasive Mycoses & Antifungals between
32 January 2015 and October 2017 and species identification was performed by polyphasic
33 approach (MALDI-TOF and molecular method).

34 **Results**

35 Isavuconazole had effective *in vitro* activity against *Cryptococcus neoformans*
36 (MIC₉₀<0.25mg/L), the five most common *Candida* spp. (MIC₉₀≤0.5mg/L for *Candida*
37 *albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis* and, *Candida krusei*)
38 and also against the majority of rare species, including *Candida kefyr* and *Candida lusitanae*.
39 A few isolates of *C. albicans* (0.7%, 3/404), *C. glabrata* (2.7%, 5/184), *C. tropicalis* (1.0%,
40 1/96) and *C. parapsilosis* (0.8%, 1/127) exhibited MIC ≥4 mg/L. All were also resistant to
41 fluconazole according to the EUCAST breakpoints. Some isolates with isavuconazole MIC
42 ≥4 mg/L were also observed among rarer species: *Meyerozyma guilliermondii* (8.7%, 2/23),
43 *Wickerhamomyces anomalus* (10.0%, 1/10). Other rare species *Saprochaete clavata*,
44 *Magnusiomyces capitatus* and *Rhodotorula mucilaginosa* had high MIC₅₀ (≥1mg/L) and
45 MIC₉₀ (≥4mg/L) and could be considered as resistant to isavuconazole.

46 **Conclusions**

47 We confirmed the good *in vitro* activity of isavuconazole against common *Candida*,
48 *Cryptococcus* species and majority of the rare yeast species studied.

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72 **Introduction**

73 Isavuconazole is part of the triazoles antifungal agents which exert antifungal activity through
74 the inhibition of sterol 14- α -demethylase. It is currently approved as one of the first line
75 therapy for human invasive aspergillosis and mucormycosis (1-4). *In vitro* activity of
76 isavuconazole against *Cryptococcus* spp. is also reported (5) and a prospective clinical trial
77 enrolling patients with candidemia or invasive candidiasis failed to demonstrate the non-
78 inferiority with caspofungin (6). *In vitro*, isavuconazole is active against common *Candida*
79 species with higher MIC value for *Candida glabrata* and *Candida krusei* than for *Candida*
80 *albicans* (7-9). Few data are available for rare yeast species.

81 We here reported minimal inhibitory concentrations (MICs) of isavuconazole using EUCAST
82 method for a large collection of yeast species recovered mainly from blood culture during a
83 prospective multicenter surveillance program. We compared the results with those of
84 fluconazole for which breakpoints (BP) exist for several *Candida* species and given that
85 fluconazole is one of the first option for treating invasive yeast infections. The objective was
86 to know whether isavuconazole could be proposed as an option for also treating yeast
87 infection in case of concomitant mold infection, justifying using an extended spectrum azole.

88 **Methods**

89 **Isolates and species identification**

90 As part of its missions of expertise and surveillance, the National Reference Center for
91 Invasive Mycoses & Antifungals (NRCMA) received clinical isolates involved in invasive
92 infections from hospitals in France. Yeast isolates received between January 2015 and
93 October 2017 were checked for purity on chromogenic medium BBL Chromagar™ *Candida*
94 (BD) or Niger seed medium for *Cryptococcus* species and identified at the species level by
95 phenotypic method and mass spectrometry (MALDI-TOF, Bruker Biotyper, Bruker Daltonic,
96 Germany). For *C. albicans* and *Candida dubliniensis*, a duplex PCR was performed (10). For

97 rare species, D1D2 and ITS regions of ribosomal DNA were amplified and sequenced with
98 panfungal primers (NL1/NL4 and V9D/LS266, respectively). In addition, actin gene (for
99 *Candida lusitanae*), *RPBI* gene (for *Meyerozyma guilliermondii*, *Meyerozyma caribbica*,
100 primer forward 5'-AGGGTTTGCGAGTGTGTTTGT-3', primer reverse 5'-
101 CGTCAAGCTCCAATCTCTGC-3') and IGS1 region (for *Trichosporon* spp.) were
102 sequenced (11). *Cryptococcus neoformans* serotypes were determined by amplification of
103 *PAK1* and *GPA1* genes with serotype-specific primers and ploidy by flow cytometry (12).

104 **Minimal Inhibitory Concentration (MIC) determination**

105 Isavuconazole and fluconazole MICs were determined in parallel according to the EUCAST
106 standardized broth microdilution method (13). The concentrations tested ranged between
107 0.007 mg/L to 4 mg/L and between 0.125 mg/L to 64 mg/L for isavuconazole and
108 fluconazole, respectively. For MIC determination, tissue culture testplate with F-bottom,
109 sterilized by radiation, were used (TPP®, Switzerland, Ref 92096). Quality control strains
110 (ATCC22019, ATCC6258) were included in each set. The concentrations that inhibited 50%
111 (MIC₅₀) and 90% (MIC₉₀) of the isolates were determined for isavuconazole and
112 fluconazole for each species represented by at least 10 isolates. Results were analysed using
113 EUCAST BP (resistance when MIC >4mg/L for *C. albicans*, *Candida tropicalis*, *Candida*
114 *parapsilosis* >32mg/L for *C. glabrata*) (14). Rare species without defined BP and exhibiting
115 fluconazole MIC₅₀>4mg/L (non-species related BP determined by EUCAST is R>4mg/L)
116 were considered as intrinsically resistant to fluconazole or at least less susceptible.

117 **Results**

118 The 1457 isolates analysed belonged to 29 species (23 ascomycetous and 6 basidiomycetous)
119 including the five most frequent species involved in candidemia (*C. albicans*, *C. glabrata*, *C.*
120 *tropicalis*, *C. parapsilosis*, and *C. krusei*) and three serotypes of *Cryptococcus neoformans*
121 (Table 1). Isolates were mostly (93%, 1351/1457) recovered from blood cultures (n=1133),

122 cerebrospinal fluids (n=89) or other site of invasive infections (n=129). Isolates were sent
123 mainly (52.5%, 765/1457) in the context of the active surveillance of all yeasts fungemia in
124 the Paris area (YEASTS program). Other isolates were sent in the context of the French
125 Surveillance Network of Invasive Fungal Infections (RESSIF) but only in case of abnormal
126 antifungal susceptibility profiles and/or rare species.

127 For 17 species among the 29 studied here, isavuconazole MIC₉₀ varied between <0.007 and 2
128 mg/L with 14/17 having an MIC₉₀ <0.5 mg/L. Of note, *C. neoformans* serotype D exhibited
129 lower MIC₅₀ and MIC₉₀ for isavuconazole and fluconazole than serotype A and hybrid AD
130 isolates. Three species exhibited an MIC₉₀ of 0.5 mg/L (*C. glabrata*, *Saccharomyces*
131 *cerevisiae*) and 2 mg/L (*Meyerozyma guilliermondii*). Finally, *Saprochaete clavata*,
132 *Magnusiomyces capitatus* and *Rhodotorula mucilaginosa* had high MIC₉₀ (≥ 4 mg/L).

133 MICs were also determined for 9 rare yeast species (7 Ascomycetous and 2 Basidiomycetous)
134 (Table 1) for which less than ten isolates were studied. For four species, the MIC values were
135 low (<0.25mg/L) whereas MIC distribution was heterogeneous for the others (Table S1).

136 Analysis of the MIC distributions showed that for 11 species, some isolates (2.5%-10.0%) had
137 a MIC above the MIC₉₀ (Table 1 and Table S1). Of those with MICs ≥ 4 mg/L were found
138 isolates of *C. albicans* (n=3), *C. glabrata* (n=5), *C. tropicalis* (n=1), *C. parapsilosis* (n=1), *M.*
139 *guilliermondii* (n=2), and *Wickerhamomyces anomalus* (n=1). All these isolates were
140 considered resistant to fluconazole according to the EUCAST BP.

141 In the absence of BP and epidemiological cut-off values defined for isavuconazole, Astvad *et*
142 *al* (17) categorized isolates as wild-type (wt) and non-wild-type (non-wt) based on a wild-type
143 upper limit value (wtUL). The wtUL corresponds to two dilutions above the MIC₅₀, or to the
144 lowest concentration tested in case all the isolates of a given species exhibit MICs less than or
145 equal to the lowest concentration tested (*C. dubliniensis* in our study). In case of species
146 exhibiting an MIC₅₀ equal to the highest concentration tested (*S. clavata* and *M. capitatus* in

147 our study), the wtUL is impossible to determine. Comparable to the published wtUL values,
148 only minor differences (maximum two-fold dilutions) were detected here for some species.
149 The percentage of isolates with MIC>wtUL ranged from 1.3% to 5.2% for common *Candida*
150 species, a proportion similar to that of the fluconazole-resistant isolates (2.72% to 6.3%, Table
151 1). This proportion ranged between 0 and 13% for rare species, except for *S. cerevisiae* that
152 reached almost 44% (7/16) of non-wt with a very heterogeneous MIC distribution (Table S1).
153 Looking at cross-resistance (9), among the 12 non-wt isolates of *C. albicans*, 11 were resistant
154 to fluconazole (MIC>4mg/L). For the 5 non-wt isolates of *C. tropicalis*, 3 were resistant to
155 fluconazole (MIC>4mg/L). All the 6 non-wt isolates of *C. parapsilosis* and the 7 non-wt
156 isolates of *C. glabrata* were also resistant to fluconazole (MIC>4mg/L and MIC>32mg/L,
157 respectively). Similarly, all isolates of *C. albicans* (11/404, 2.7%) resistant to fluconazole
158 were non-wt for isavuconazole. For *C. glabrata* (11/184, 5.9%), *C. tropicalis* (3/96, 3.1%)
159 and *C. parapsilosis* (8/127, 6.3%) resistant to fluconazole, the majority (7/11, 2/3 and 6/8,
160 respectively) were non-wt for isavuconazole.

161 **Discussion**

162 We here confirmed that isavuconazole is active *in vitro* against *C. neoformans* and the most
163 common *Candida* species (7, 8). Of note, *C. glabrata* and *C. krusei* which are considered as
164 less susceptible or intrinsically resistant to fluconazole, respectively, had isavuconazole
165 MIC₉₀≤0.5 mg/L which is higher than for *C. albicans* but suggest a good *in vitro* activity (7,
166 9). We also observed a low percentage of isolates of common *Candida* species categorized as
167 fluconazole resistant or with high MIC for isavuconazole. But mainly, isolates resistant to
168 fluconazole were also nonwt for isavuconazole. The proportion of isavuconazole non-wt
169 isolates was comparable to that obtained by Marcos-Zambrano *et al.* for *C. albicans* [2.97%
170 (12/404) vs. 2.3%] but higher for *C. glabrata* [3.8% (7/184) vs. 1.1%], *C. parapsilosis* [4.7%
171 (6/127) vs. 1.5%] and *C. tropicalis* [5.2% (5/96) vs. 0%] (19). Our data suggest that

172 isavuconazole is also active *in vitro* against the majority of rare yeast species studied, except
173 for species already considered as intrinsically resistant to fluconazole such as *S. cerevisiae*, *M.*
174 *guilliermondii*, *S. clavata*, *M. capitatus* and *R. mucilaginosa* (11, 15, 16). These results are in
175 accordance with data reviewed by Miceli *et al.* and Astvad *et al.*, except for *M. capitatus* and
176 *R. mucilaginosa* previously reported with low MICs (17, 18). In conclusion, except for *C.*
177 *krusei*, MIC distributions of isavuconazole and fluconazole were comparable for common and
178 rare yeast species. .

179 Preliminary results were presented at the 28th European Congress of Clinical Microbiology
180 and Infectious Diseases, (21-24 April 2018, Madrid, Spain; abstract number 7965).

181 **Conflict of interests**

182 SB: consultancy (Gilead), honorarium for educational programs (Astellas), congress
183 symposium (Gilead, Bio-Rad), and travel grants (Pfizer).

184 OL: member of speaker's bureau Merck, Pfizer, Astellas, Gilead; consultant for Gilead

185 MDO, AB, CG and FD: nothing to declare

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Table 1: Isavuconazole and Fluconazole susceptibility of the 20 yeast species with more than 10 isolates studied (France, 2015-2017)

| Species (current name) | n | % of isolates from blood culture or CSF (nb of isolates) | Isavuconazole | | | | | | Fluconazole | | | |
|--|-----|--|---------------|--------------|------------------|--|-------------|---|--------------|--------------|------------------|--|
| | | | MIC50 (mg/L) | MIC90 (mg/L) | MIC range (mg/L) | % isolates with MIC > MIC90 (nb of isolates) | wtUL (mg/L) | % isolates with MIC>wtUL (nb of isolates) | MIC50 (mg/L) | MIC90 (mg/L) | MIC range (mg/L) | % of isolates Resistant*(nb of isolates) |
| <i>Candida albicans</i> | 404 | 91.8% (371) | ≤0.007 | ≤0.007 | ≤0.007-≥4 | 4.95 (20) | 0.03 | 2.97 (12) | ≤0.125 | 0.25 | ≤0.125 -≥64 | 2.72 (11) |
| <i>Candida dubliniensis</i> | 34 | 97.1 (33) | ≤0.007 | ≤0.007 | ≤0.007-≤0.007 | 0 (0) | ≤0.007 | 0 | ≤0.125 | 0.25 | ≤0.125 -0.5 | NA |
| <i>Candida tropicalis</i> | 96 | 89.6% (86) | ≤0.007 | 0.03 | ≤0.007-≥4 | 5.21 (5) | 0.03 | 5.21 (5) | 0.25 | 1 | ≤0.125 -≥64 | 3.16 (2) |
| <i>Candida parapsilosis</i> | 127 | 85.8% (109) | 0.015 | 0.03 | ≤0.007-≥4 | 5.51 (7) | 0.06 | 4.72 (6) | 0.5 | 2 | ≤0.125 -≥64 | 6.3 (8) |
| <i>Candida orthopsilosis</i> | 10 | 100% (10) | 0.015 | 0.06 | ≤0.007-0.25 | 10 (1) | 0.06 | 10.0 (1) | 0.5 | 16 | 0.25 - 16 | 20 (2) |
| <i>Candida metapsilosis</i> | 11 | 72.7% (8) | 0.015 | 0.015 | ≤0.007-0.015 | 0 (0) | 0.06 | 0 | 1 | 1 | 1 - 2 | 0 |
| <i>Candida glabrata</i> | 184 | 91.3% (168) | 0.25 | 0.5 | 0.03-≥4 | 7.07 (13) | 1 | 3.80 (7) | 8 | 16 | 1 - ≥64 | 5.98 (11) |
| <i>Saccharomyces cerevisiae</i> | 16 | 100% (16) | ≤0.007 | 0.5 | 0.03-0.5 | 0 (0) | 0.03 | 43.75 (7) | 8 | 32 | ≤0.125 -32 | 56.25 (9) |
| <i>Candida lusitanae</i> (<i>Clavispora lusitanae</i>) | 55 | 96.4% (53) | ≤0.007 | 0.015 | ≤0.007-0.5 | 5.45 (3) | 0.03 | 3.64 (2) | 0.25 | 0.5 | ≤0.125 -16 | 3.64 (2) |
| <i>Candida guilliermondii</i> (<i>Meyerozyma guilliermondii</i>) | 23 | 91.3% (21) | 0.25 | 2 | 0.03-≥4 | 8.7 (2) | 1 | 13.04 (3) | 4 | 16 | 1 -≥64 | NA |
| <i>Candida krusei</i> (<i>Pichia kudriavzevii</i>) | 76 | 90.8% (69) | 0.125 | 0.25 | 0.015-1 | 6.58 (5) | 0.5 | 1.32 (1) | 32 | 64 | 16 -≥64 | NA |
| <i>Candida kefyr</i> (<i>Kluyveromyces marxianus</i>) | 41 | 80.5%(33) | ≤0.007 | ≤0.007 | ≤0.007-0.015 | 4.88 (2) | 0.03 | 0 | 0.25 | 0.5 | ≤0.125 -1 | 0 |
| <i>Candida pelliculosa</i> (<i>Wickerhamomyces anomalus</i>) | 10 | 60% (6) | 0.06 | 0.06 | 0.03-4 | 10 (1) | 0.25 | 10.0 (1) | 2 | 4 | 1-8 | 20 (2) |
| <i>Pichia ohmeri</i> (<i>Kodamaea ohmeri</i>) | 11 | 100%(11) | 0.015 | 0.03 | ≤0.007-0.25 | 9.09 (1) | 0.06 | 9.09 (1) | 4 | 4 | 2-64 | 9.09 (1) |
| <i>Geotrichum clavatum</i> (<i>Saprochaete clavata</i>) | 64 | 45.3%(29) | 4 | ≥4 | 0.25-≥4 | 0 (0) | NA | NA | 16 | 32 | 0.25-32 | 81.25 (52) |
| <i>Geotrichum capitatum</i> (<i>Magnusiomyces capitatus</i>) | 25 | 48% (12) | 4 | ≥4 | 0.125-≥4 | 0 (0) | NA | NA | 4 | 16 | 0.25-32 | 48 (12) |
| <i>Cryptococcus neoformans</i> var. <i>grubii</i> (A) | 158 | 70.9% (112) | 0.06 | 0.25 | ≤0.007-0.5 | 2.53 (4) | 0.25 | 2.53 (4) | 2 | 8 | ≤0.125 -16 | 11.39 (18) |
| <i>Cryptococcus neoformans</i> var. <i>neoformans</i> (D) | 25 | 60% (15) | 0.015 | 0.03 | ≤0.007-0.125 | 8 (2) | 0.06 | 4.0 (1) | 1 | 2 | 0.25-2 | 0 |
| <i>Cryptococcus neoformans</i> AD hybrid | 26 | 73.1% (19) | 0.03 | 0.125 | ≤0.007-0.25 | 7.69 (2) | 0.125 | 7.69 (2) | 2 | 8 | ≤0.125 -16 | 15.38 (4) |
| <i>Rhodotorula mucilaginosa</i> | 16 | 93.8% (15) | 1 | 4 | 0.125-4 | 0 (0) | 4 | 25.0 (4) | ≥64 | ≥64 | 1-≥64 | 93.75 (15) |
| <i>Candida auris</i> | 2 | 50% (1) | NA | NA | 0.015 | NA | NA | NA | NA | NA | 16-64 | 100 (2) |
| <i>Candida inconspicua</i> | 8 | 75%(6) | 0.06 | NA | 0.06-0.25 | NA | NA | NA | 16 | NA | 4-32 | 87.5 (7) |
| <i>Candida nivariensis</i> | 3 | 100%(3) | NA | NA | ≤0.007-0.5 | NA | NA | NA | NA | NA | 2-4 | 0 |
| <i>Candida utilis</i> (<i>Cyberlindnera jadinii</i>) | 5 | 80%(4) | 0.03 | NA | 0.015-0.03 | NA | NA | NA | 1 | NA | 1-2 | 0 |
| <i>Geotrichum candidum</i> (<i>Galactomyces candidus</i>) | 7 | 0% (0) | 0.25 | NA | ≤0.007-2 | NA | NA | NA | 16 | NA | 0.5-≥64 | 85.71 (6) |
| <i>Candida fermentati</i> (<i>Meyerozyma caribbica</i>) | 3 | 66.7%(2) | NA | NA | 0.06-≥ 4 | NA | NA | NA | NA | NA | 4-≥64 | 66.67 (2) |
| <i>Yarrowia lipolytica</i> | 5 | 40% (2) | 0.125 | NA | 0.125-0.25 | NA | NA | NA | 2 | NA | ≤0.124-16 | 20 (1) |
| <i>Trichosporon asahii</i> | 9 | 66.7% (6) | 0.25 | NA | 0.06-1 | NA | NA | NA | 2 | NA | 0.25-8 | 11.11 (1) |
| <i>Trichosporon dermatis</i> (<i>Cutaneotrichosporon dermatis</i>) | 3 | 66.7%(2) | NA | NA | 0.06-2 | NA | NA | NA | NA | NA | 2-4 | 0 |

*EUCAST BP were used for categorized isolates as resistant. Non-species related BP (R>4mg/L) was used for all species without any BP.