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Activity of Manogepix and Comparator Antifungal Agents Against Yeast Isolates Collected from Invasive Infections in Intensive Care Unit (ICU) and Non-ICU Settings

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Introduction

- The occurrence of invasive candidiasis among patients hospitalized in Intensive Care Units (ICUs) can be as high as 50%.
- Despite its high clinical impact, relatively few studies describe the species distribution of *Candida* and the antifungal resistance profiles associated with invasive candidiasis in ICU settings compared to non-ICU settings, highlighting the need for surveillance data and comparative analyses.
- We evaluated the species distribution according to ICU versus non-ICU location in a global yeast collection, and the associated resistance profiles for the contemporary echinocandin and azole antifungal agents and compared them to the activity of manogepix.

Materials and Methods

- 7,266 non-duplicate yeast isolates deemed as cause of invasive infections were collected in 91 hospitals during 2017–2024.
- All isolates were identified by MALDI-TOF MS and/or ITS and 28S sequencing.
- All isolates were tested by the CLSI reference broth microdilution method following the M27 guidelines.
- Breakpoints used for antifungal susceptibility interpretation were applied according to the CLSI M27M44S document.
- Epidemiological cutoff values (ECVs) were obtained from the CLSI M57 document.

Table 1. Activity of clinically available antifungals against main yeast species in ICU and non-ICU settings

Antifungal agent[a]	ICU[b]		Non-ICU[b]	
	%R[c]	%NWT[d]	%R[c]	%NWT[d]
Candida albicans	N=828		N=1297	
Micafungin	0.2	0.7	0.4	0.8
Caspofungin	0.2		0.4	
Fluconazole	0.1	2.2	0.4	2.8
Voriconazole	0.1	1.1	0	1.5
Amphotericin B		0		0
Candida glabrata	N=666		N=1017	
Micafungin	3	5	1.7	3
Caspofungin	2.3		1.3	
Fluconazole	7.5	11.6	6.2	11.2
Voriconazole		10.2		9.5
Amphotericin B		0		0
Candida parapsilosis	N=433		N=787	
Micafungin	0	0	0	0
Caspofungin	0	0.2	0	0
Fluconazole	15.2	18.9	8.8	11.6
Voriconazole	3	19.6	1.5	12.3
Amphotericin B		0.5		0.4
Candida tropicalis	N=276		N=497	
Micafungin	0	0.4	0	1.4
Caspofungin	0		0	
Fluconazole	5.1	8	2.6	4.6
Voriconazole	4	5.8	1.4	2.8
Amphotericin B		0		0
Candida dubliniensis	N=92		N=143	
Micafungin		2.2		0.7
Fluconazole		0		3.5
Amphotericin B		0		1.4
Candida krusei	N=87		N=131	
Micafungin	0	0	0.8	0.8
Caspofungin	0		0.8	
Voriconazole	1.1	3.4	0	1.5
Amphotericin B		0		0
Candida lusitaniae	N=68		N=90	
Micafungin		0		0
Caspofungin		0		0
Fluconazole		10.3		13.3
Amphotericin B		0		0
Candida auris	N=61		N=72	
Micafungin	6.6	9.8	1.4	2.8
Caspofungin	13.1	13.1	6.9	8.3
Fluconazole	90.2		93.1	
Amphotericin B	45.9		37.5	
Candida orthopsilosis	N=34		N=46	
Micafungin		0		0
Caspofungin		0		0
Fluconazole		14.7		6.5
Voriconazole		14.7		2.2
Amphotericin B		0		0
Candida guilliermondii	N=10		N=30	
Micafungin	0	0	0	0
Caspofungin	0	0	0	3.4
Fluconazole		40		16.7
Amphotericin B		0		0

[a] Representative antifungal agents with established breakpoints and/or ECV criteria are shown
[b] Values in red display difference of ±0.5 when comparing ICU and non-ICU isolates
[c] Breakpoint criteria published by CLSI M27M44S (2022)
[d] ECV criteria published in CLSI M57S (2022)

Results

- A total of 2,744 isolates from ICU and 4,522 from non-ICU were evaluated.
- The frequency of different species by ICU versus non-ICU displayed minor differences.
- In both cases 83–84% of the infections were caused by the top 5 species—*C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. dubliniensis*.
- The 10 most common species are displayed in Figure 1.
- Resistance to echinocandins was uncommon and similar in ICU and non-ICU settings for *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. orthopsilosis* and *C. guillermondii* (≤0.4%; Table 1).
- Echinocandin resistance rates were higher overall and increased in the ICU setting for *C. glabrata* (3.0% vs. 1.7% for micafungin in the ICU vs. non-ICU) and *C. auris* (6.6% vs. 1.4%).
- Fluconazole resistance was noted among *C. glabrata* (7.5% vs. 6.2%), *C. parapsilosis* (15.2% vs. 8.8%), *C. tropicalis* (5.1% vs. 2.6%) and *C. orthopsilosis* (14.7% vs. 6.5%) with higher rates in ICU vs. non-ICU isolates.
- *C. auris* isolates displayed high fluconazole-resistance rates in both settings (90.2–93.1%) and resistance to amphotericin B was higher among ICU (45.9%) compared to non-ICU isolates (37.5%).
- Manogepix (MIC_{50}, 0.004–0.03 mg/L and MIC_{90}, 0.008–0.25 mg/L) was very active against the main *Candida* spp. isolates tested regardless of ICU status (Figure 2) for all species but *C. krusei* and *Trichosporon asahii* ($MIC_{50/90}$, ≥1/>2 mg/L).

Conclusions

- Yeast species distributions were similar between ICU and non-ICU settings.
- Among species displaying resistance to echinocandins and/or fluconazole, rates were higher among ICU compared to the non-ICU isolates.
- Manogepix activity was unchanged by ICU status, and this evidence supports the further development of this agent.

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Figure 1. Distributions of 10 most common yeast species in ICU and non-ICU settings

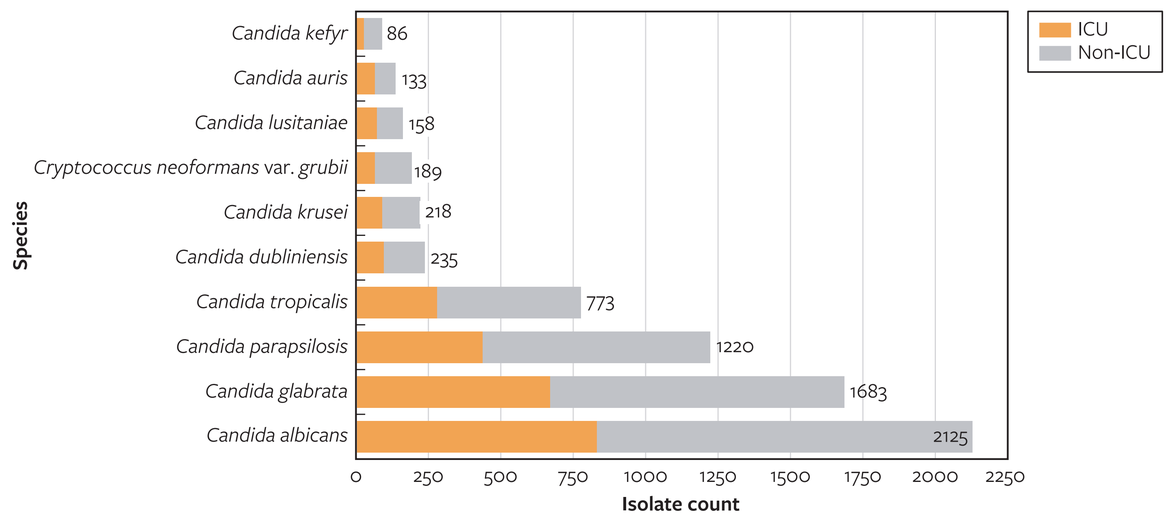

Figure 2. Activity of manogepix tested against main yeast species and *C. auris* from ICU vs non-ICU