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Rezafungin Activity against *Candida* spp. and *Aspergillus* spp. Isolates Causing Invasive Infections Worldwide in 2021

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INTRODUCTION

- Echinocandins are the mainstay treatment for candidemia and invasive candidiasis in both neutropenic and non-neutropenic patients as well as critically ill patients.
- Additionally, echinocandins are recommended as salvage therapy in patients with invasive aspergillosis.
- Rezafungin is a next generation echinocandin with a long half-life and front-loaded drug exposure that allows for once-weekly intravenous administration instead of the once-daily intravenous administration required by anidulafungin, caspofungin, and micafungin.
- Rezafungin has recently completed a Phase 3 trial for the treatment of candidemia and invasive candidiasis (ReSTORE, NCT03667690) and is under evaluation for the prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp. in allogeneic blood and marrow transplant recipients (ReSPECT, NCT04368559).
- The study objective was to evaluate the *in vitro* activity of rezafungin and comparator antifungal agents against a contemporaneous worldwide collection of fungal isolates causing invasive infections.

METHODS

- A total of 868 fungal isolates were collected as part of the 2021 SENTRY Antifungal Surveillance Program.
- A single isolate per patient was collected from 48 medical centers located in Europe (38.8% of isolates; 17 sites in 13 countries), North America (32.9%; 18 sites in 1 country; 9 US Census Regions), Asia-Pacific (15.0%; 7 sites in 4 countries), and Latin America (13.2%; 6 sites in 5 countries).
- Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the program.
- Fungal isolates were identified by MALDI-TOF MS (Bruker Daltonics, Billerica, Massachusetts USA) or by DNA sequencing analysis when an acceptable identification was not achieved by mass spectrometry.
- Antifungal susceptibility testing was performed by broth microdilution following CLSI guidelines (M27, M38) for all isolates.
  - Panels were made by dispensing 10 µL of a 20x drug stock solution into wells that contained 90 µL of RPMI and then mixing well contents.
- Isolates included *C. albicans* (329 isolates), *C. glabrata* (170), *C. parapsilosis* (154), *C. tropicalis* (89), *C. krusei* (25), *C. dubliniensis* (21), *Cryptococcus neoformans* (10), *A. fumigatus* (58), and *A.* section *Flavi* (12).
- Bloodstream infection (61.1%) was the most common infection type, followed by pneumonia in hospitalized patients (12.7%), skin and skin structure (10.0%), urinary tract (2.1%), and intra-abdominal infections (2.0%; Figure 1).
- CLSI interpretative criteria and epidemiological cutoff values (ECV) were applied, including the recently approved rezafungin provisional breakpoints against *Candida* spp. (M57S, M27M44S, and M38M51S; Table 1).
- *Candida* spp. isolates showing any echinocandin MIC values above the ECV were submitted to whole genome sequencing.

Figure 1. Frequency of infection types caused by fungal isolates

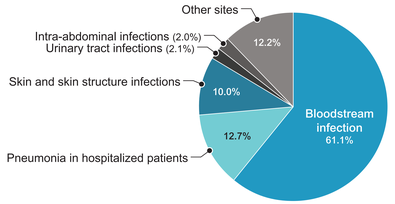


Table 1. Rezafungin CLSI provisional epidemiological cutoff values and clinical breakpoints criteria

Organism	Rezafungin CLSI criteria[a] (mg/L)	
	Epidemiological cutoff value	Susceptible breakpoint
C. albicans	0.06	≤0.25
C. glabrata	0.12	≤0.5
C. parapsilosis	4	≤2
C. krusei	0.12	≤0.25
C. tropicalis	0.12	≤0.25
C. dubliniensis	0.12	≤0.12
C. auris	0.5	≤0.5

[a] ECV and BP criteria published in CLSI M57S (2022) and M27M44S (2022), respectively. Values are considered tentative for one year from the document publication date and are open for comment.

Table 2. Antimicrobial activity of rezafungin and comparator agents tested against *Candida* spp.

Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a]			ECV[a]	
			%S	%I	%R	%WT	%NWT
C. albicans (n=329)							
Rezafungin	0.03	0.06	99.7	—	—	99.7	0.3
Anidulafungin	0.03	0.06	99.7	0.0	0.3	99.7	0.3
Caspofungin	0.015	0.03	99.7	0.0	0.3	—	—
Micafungin	0.015	0.015	99.7	0.0	0.3	99.7	0.3
Fluconazole	0.12	0.25	99.4	0.3 [b]	0.3	98.2	1.8
C. glabrata (n=170)							
Rezafungin	0.03	0.06	97.6	—	—	95.9	4.1
Anidulafungin	0.06	0.12	95.3	0.6	4.1	95.9	4.1
Caspofungin	0.03	0.06	95.9	1.2	2.9	—	—
Micafungin	0.015	0.03	95.9	0.6	3.5	95.3	4.7
Fluconazole	4	8	—	94.1 [b]	5.9	90.0	10.0
C. parapsilosis (n=154)							
Rezafungin	1	2	100.0	—	—	100.0	0.0
Anidulafungin	2	4	87.0	13.0	0.0	100.0	0.0
Caspofungin	0.25	0.25	100.0	0.0	0.0	100.0	0.0
Micafungin	1	1	100.0	0.0	0.0	100.0	0.0
Fluconazole	0.5	16	80.5	5.8 [b]	13.6	80.5	19.5
C. tropicalis (n=89)							
Rezafungin	0.03	0.06	100.0	—	—	100.0	0.0
Anidulafungin	0.03	0.06	100.0	0.0	0.0	100.0	0.0
Caspofungin	0.03	0.03	100.0	0.0	0.0	—	—
Micafungin	0.03	0.03	100.0	0.0	0.0	100.0	0.0
Fluconazole	0.25	1	97.8	0.0 [b]	2.2	94.4	5.6
C. krusei (n=25)							
Rezafungin	0.03	0.03	100.0	—	—	100.0	0.0
Anidulafungin	0.06	0.12	100.0	0.0	0.0	100.0	0.0
Caspofungin	0.12	0.12	100.0	0.0	0.0	—	—
Micafungin	0.12	0.12	100.0	0.0	0.0	100.0	0.0
Fluconazole	32	64	—	—	—	—	—
C. dubliniensis (n=21)							
Rezafungin	0.06	0.06	95.2	—	—	95.2	4.8
Anidulafungin	0.06	0.06	—	—	—	100.0	0.0
Caspofungin	0.03	0.03	—	—	—	—	—
Micafungin	0.015	0.03	—	—	—	100.0	0.0
Fluconazole	0.12	0.25	—	—	—	100.0	0.0

[a] Clinical interpretive criteria published in CLSI M27M44S (2022). ECV criteria published in CLSI M57S (2022).
[b] Intermediate is interpreted as susceptible-dose dependent.
"—", Criteria not available.

Table 3. Summary of Fks alterations detected in echinocandin-NWT *Candida* spp. isolates

Organism	State and/or Country	MIC according to CLSI method (mg/L):				1,3-β-D-glucan synthase alterations:			
		RZF	ANF	CSF	MCF	Fks1 HS1	Fks1 HS2	Fks2 HS1	Fks2 HS2
C. albicans	Germany	0.5	1	2	2	S645P	WT	NT	NT
C. dubliniensis	Germany	0.25	0.12	0.25	0.12	WT	WT	NT	NT
C. glabrata	USA, MA	1	4	4	1	S629P	WT	WT	WT
C. glabrata	USA, WA	2	2	4	1	WT	WT	S663P	WT
C. glabrata	USA, KS	1	2	1	1	WT	WT	S663P	WT
C. glabrata	USA, TX	0.5	1	0.5	1	WT	WT	S663P	WT
C. glabrata	USA, NJ	1	2	2	0.5	S629P	WT	WT	WT
C. glabrata	USA, CO	0.12	0.25	0.12	0.25	WT	WT	WT	WT
C. glabrata	Australia	0.5	1	0.25	0.12	WT	WT	S663P	WT
C. glabrata	USA, VA	0.25	0.5	0.25	0.06	WT	WT	F659Y	WT

RZF, rezafungin; ANF, anidulafungin; CSF, caspofungin; MCF, micafungin; WT, wildtype; NT, not tested

RESULTS

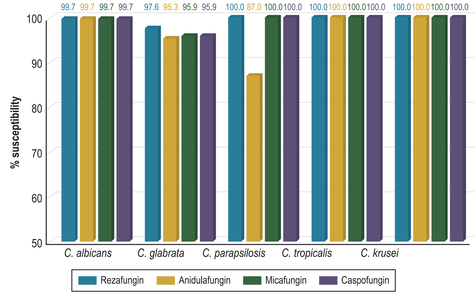
- Rezafungin inhibited 99.7% of *C. albicans*, 97.6% of *C. glabrata*, 95.2% of *C. dubliniensis*, and 100% of *C. parapsilosis*, *C. tropicalis*, and *C. krusei* at the susceptibility (S) breakpoint (Table 2).
- Rezafungin had similar activity to the other echinocandins against *C. albicans* (99.7%S), *C. glabrata* (95.3–95.9%S), *C. tropicalis* (100.0%S), and *C. krusei* (100.0%S; Figure 2).
- Compared to other echinocandins ($MIC_{50/90}$ range, 0.015–0.06/0.03–0.06 mg/L), rezafungin showed similar $MIC_{50/90}$ values (0.06/0.06 mg/L) against *C. dubliniensis*.
- Although caspofungin displayed lower $MIC_{50/90}$ values (0.25/0.25 mg/L) than rezafungin ($MIC_{50/90}$, 1/2 mg/L), micafungin ($MIC_{50/90}$, 1/1 mg/L), or anidulafungin ($MIC_{50/90}$, 2/4 mg/L) against *C. parapsilosis*, all echinocandins but anidulafungin (87.0%S) inhibited 100% of *C. parapsilosis* isolates at their respective breakpoints.
- Only 1 *C. albicans* (Germany), 1 *C. dubliniensis* (Germany), and 4 *C. glabrata* (US) were non-susceptible (NS) to rezafungin.
  - Rezafungin-NS *C. albicans* and 4 *C. glabrata* isolates were resistant to caspofungin, anidulafungin, and micafungin.
- A total of 29 isolates were non-susceptible to anidulafungin, including 1 *C. albicans* (Germany), 8 *C. glabrata* (7 US, 1 Australia), and 20 *C. parapsilosis* (6 US, 4 Australia, 3 Spain, 2 Italy, and 1 each from Argentina, Belgium, Chile, Germany, and Greece).
- 8 out of 10 echinocandin non-wildtype (NWT) *Candida* spp. isolates displayed Fks alterations, including 8 of 9 rezafungin-NWT isolates (Table 3).
- Limited activity was noted for all echinocandins against *C. neoformans* isolates ($MIC_{50/90}$, >4/>4 mg/L).
- All *A. fumigatus* isolates were inhibited by rezafungin at ≤0.06 mg/L ($MEC_{50/90}$, 0.03/0.06 mg/L) and anidulafungin, micafungin, and caspofungin at ≤0.12 mg/L ($MEC_{50/90}$ range, 0.008–0.03/0.015–0.06 mg/L; Table 4).
- Rezafungin (MEC range, 0.008–0.06 mg/L) and the other echinocandins (MEC range, 0.008–0.12 mg/L) were also active against 6 voriconazole-NS *A. fumigatus* isolates (1 France, 1 Germany, 1 Turkey, and 3 US).
- Rezafungin and other echinocandins inhibited all *A.* section *Flavi* isolates at ≤0.06 mg/L (Table 4).

Table 4. Antimicrobial activity of rezafungin and comparator agents tested against *Aspergillus* spp.

Antimicrobial agent	MEC_{50}/ MIC_{50}	MEC_{90}/ MIC_{90}	CLSI[a]			ECV[a]	
			%S	%I	%R	%WT	%NWT
Aspergillus fumigatus (n=58)							
Rezafungin	0.03	0.06	—	—	—	—	—
Anidulafungin	0.03	0.06	—	—	—	—	—
Caspofungin	0.03	0.06	—	—	—	100.0	0.0
Micafungin	0.008	0.015	—	—	—	—	—
Itraconazole	1	2	—	—	—	82.8	17.2
Posaconazole	0.5	0.5	—	—	—	—	—
Voriconazole	0.5	1	89.7	8.6	1.7	98.3	1.7
Amphotericin B	1	1	—	—	—	100.0	0.0
Aspergillus section *Flavi* (n=12)							
Rezafungin	0.015	0.03	—	—	—	—	—
Anidulafungin	0.015	0.03	—	—	—	—	—
Caspofungin	0.03	0.03	—	—	—	100.0	0.0
Micafungin	0.015	0.03	—	—	—	—	—
Itraconazole	1	1	—	—	—	100.0	0.0
Posaconazole	0.5	0.5	—	—	—	100.0	0.0
Voriconazole	0.5	1	—	—	—	100.0	0.0
Amphotericin B	1	2	—	—	—	100.0	0.0

[a] Criteria published by CLSI M38M51S (2022). ECV criteria published in CLSI M57S (2022).
"—", Criteria not available.

Figure 2. Susceptibility rates of rezafungin and comparator agents tested against *Candida* spp.



CONCLUSIONS

- Rezafungin was very active against *Candida* spp. isolates known to cause invasive infections worldwide (99.2%S overall *Candida* spp.).
- Alterations in *FKS* genes were detected in 8 of 10 echinocandin-NWT *Candida* spp. isolates (7 *C. glabrata* and 1 *C. albicans*).
- Rezafungin was also active against *A. fumigatus* and *A.* section *Flavi* isolates, including voriconazole-NS *A. fumigatus* isolates.
- Limited activity was noted by all echinocandins against *C. neoformans*.

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https://www.jmilabs.com/data/posters/IDWeek2022_RezafunginVsInvasive.pdf