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Activity of rezafungin against clinical isolates of uncommon species of *Candida* spp.

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Introduction

- Rezafungin is a long-acting echinocandin approved by the United States Food and Drug Administration for the treatment of candidemia and invasive candidiasis (C/IC).
- Rezafungin has pharmacokinetic and pharmacodynamic properties distinct from other echinocandins.
  - This includes a prolonged half-life and stable molecular structure allowing once weekly dosing, high front-loaded therapeutic drug exposures, significant post-antifungal effect, widespread distribution to and penetration at sites of infection, and prevention and treatment of Candida biofilms.
- Rezafungin was noninferior to caspofungin in phase 2 (STRIVE) and phase 3 (ReSTORE) trials for efficacy and safety in the treatment of invasive candidiasis (C/IC) or candidemia.
- Rezafungin breakpoints are published for *Candida albicans*, *C. auris*, *C. dubliniensis*, *C. glabrata*, *C. krusei*, *C. parapsilosis*, and *C. tropicalis* but susceptibility results against other *Candida* spp. are scarce.
- We evaluated the *in vitro* activity of rezafungin and comparator agents against a global collection of less common *Candida* spp. collected from C/IC infections in 2020–2022 as a part of a global surveillance study.

Methods

- 590 less common *Candida* spp. were collected from IC infections in prevalence-based surveillance as a part of the SENTRY program.
- 80 medical centers provided isolates including 31 in North America, 29 in Europe, 14 in Asia-Pacific, and 6 in Latin America (Figure 1).
- Only 1 isolate per patient was included.
- Isolate identification was performed by MALDI-TOF MS and/or molecular analysis.
- Susceptibility testing was performed by broth microdilution according to CLSI standards.
- Breakpoints or epidemiological cutoff values (ECVs) were applied where available for specific species/drug combinations and CDC tentative breakpoints were used for *C. auris* for all agents except rezafungin (Table 1).
- $MIC_{50/90}$ were calculated for any species with more than 10 isolates.

Results

- 28 different *Candida* spp. were tested (Figure 2).
- MICs were similar for rezafungin and other echinocandins for all tested species (Table 2).
- For isolates with defined breakpoints, rezafungin susceptibility rates were > 95% (Figure 3).
  - Against *C. dubliniensis* (n = 175) 97.7% of isolates were susceptible to rezafungin.
  - Against *C. auris* (n = 65) 95.4% of isolates tested susceptible to rezafungin.
- For isolates without breakpoints or ECVs for rezafungin, MIC_{90} was similar to that of other echinocandins (Table 2) and the majority of isolates were susceptible or wildtype for anidulafungin, caspofungin, and/or micafungin where defined values were present.
  - For *C. lusitaniae* (n = 107), MIC_{90} for rezafungin was 0.25 mg/L and 100% of isolates were wildtype to anidulafungin, caspofungin, and micafungin (MIC_{90} 0.12–0.5 mg/L).
  - For *C. kefyr* (n = 51) MIC_{90} for rezafungin was 0.06 and 100% of isolates were wildtype to anidulafungin, caspofungin, and micafungin (MIC_{90} 0.015–0.012 mg/L).
  - For *C. guilliermondii* (n = 33) MIC_{90} for rezafungin was 1 mg/L and 87.9% of isolates were wildtype to anidulafungin while 100% were wildtype to caspofungin and micafungin (MIC_{90} of 4, 0.5, and 1 mg/L, respectively).
  - For *C. orthopsilosis* (n = 49) MIC_{90} for rezafungin was 1 mg/L and 100% of isolates were wildtype to anidulafungin, caspofungin, and micafungin (MIC_{90} 0.5–2 mg/L).
  - For *C. metapsilosis* (n = 25) MIC_{90} for rezafungin was 0.5 mg/L and 100% of isolates were wildtype to anidulafungin, caspofungin, and micafungin (MIC_{90} 0.12–0.5 mg/L).
  - For *C. pelliculosa* (n = 10) MIC_{90} for rezafungin was 0.03 mg/L and 100% of isolates were wildtype to micafungin with MIC_{90} of 0.06 mg/L (no ECV for caspofungin or anidulafungin).
  - For species with less than 10 isolates (combined, n=58), MIC_{90} for rezafungin was 0.5 mg/L and MIC_{90} for other echinocandins was 0.25–0.5 mg/L.
- Fluconazole susceptibility rates were <90% for most organisms (10.8% [*C. auris*], 69.7% [*C. guilliermondii*], and 85.7% [*C. orthopsilosis*]).

Conclusions

- Rezafungin has potent activity against a large collection of less common *Candida* spp.
- Rezafungin MICs were similar to other echinocandins which were highly active against our population by breakpoints and/or ECVs.
- Fluconazole activity was significantly lower than echinocandins against less common *Candida* spp.
- Rezafungin may be a good alternative to other echinocandins for treatment of C/IC caused by less common *Candida* spp. based on the MIC profile and weekly dosage schedule.

Table 1. Defined ECVs and breakpoints for *Candida* spp. according to CLSI M27M44S 3rd Ed and CLSI M57S 4th Ed

Candida spp.	Rezafungin			Anidulafungin				Caspofungin				Micafungin			
	S	I	R	S	I	R	WT	S	I	R	WT	S	I	R	WT
C. albicans	≤0.25			≤0.25	0.5	≥1		≤0.25	0.5	≥1		≤0.25	0.5	≥1	
C. glabrata	≤0.5			≤0.12	0.3	≥0.5		≤0.12	0.3	≥0.5		≤0.06	0.1	≥0.25	
C. tropicalis	≤0.25			≤0.25	0.5	≥1		≤0.25	0.5	≥1		≤0.25	0.5	≥1	
C. parapsilosis	≤2			≤2	4	≥8		≤2	4	≥8		≤2	4	≥8	
C. krusei	≤0.25			≤0.25	0.5	≥1		≤0.25	0.5	≥1		≤0.25	0.5	≥1	
C. guilliermondi				≤2	4	≥8		≤2	4	≥8		≤2	4	≥8	
C. dubliniensis	≤0.12						≤0.12								≤0.12
C. auris	≤0.5					≥4[a]	≤1			≥2[a]	≤0.5			≥4[a]	≤0.5
C. duobushaemulonii							≤1				≤0.25				≤0.5
C. haemulonii							≤0.5								≤0.5
C. kefyr							≤0.25								≤0.12
C. lusitaniae							≤1				≤1				≤0.5
C. metapsilosis							≤0.5				≤0.25				≤1
C. orthopsilosis							≤2				≤1				≤1
C. pelliculosa															≤0.12

[a]Tentative CDC breakpoints
S (susceptible), I (intermediate), R (resistant), WT (wildtype)

Figure 1. Geographic makeup of tested isolates

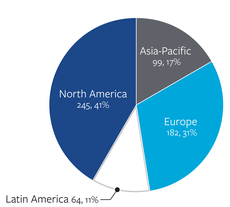


Figure 2. Species of tested less common *Candida* spp.

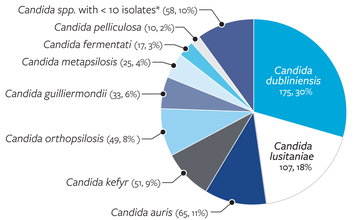
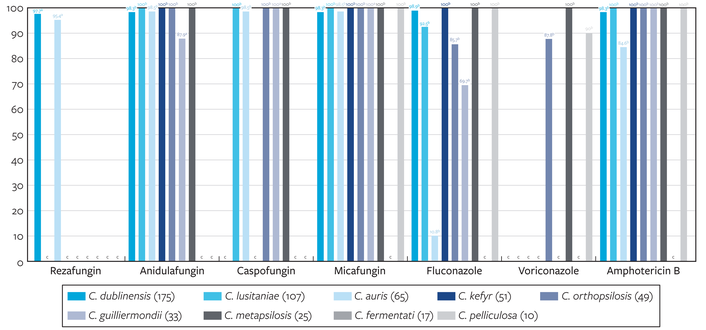


***Table 3. Breakdown of *Candida* spp. with < 10 isolates**

Candida fabianii	7
Candida utilis	6
Candida bracarensis	5
Candida lipolytica	5
Candida inconspicua	5
Candida haemulonii	4
Candida duobushaemulonii	4
Candida pararugosa	4
Candida rugosa	4
Candida nivariensis	3
Candida norvegensis	2
Candida theae	2
Candida digboiensis	1
Candida intermedia	1
Candida mengyuniae	1
Candida sojae	1
Candida spencermartinsiae	1
Candida sphaerica	1
Unspeciated *Candida*	1

Figure 3. Rezafungin and comparator agents with percent of organisms susceptible by breakpoint or wildtype by ECV



[a] CLSI M27M44S 3rd edition, 2022
[b] CLSI M57S 4th edition, 2022
[c] Antifungal/organism combinations without bars have no breakpoint or ECV defined.

Table 2. Tested organisms with MIC_{50} and MIC_{90} values

Organism (no. of isolates)	MIC_{50}/MIC_{90}						
	RZF	AND	CAS	MCF	FLC	VRC	AMB
C. dublinensis (175)	0.03/0.06	0.06/0.12	0.03/0.03	0.015/0.03	0.12/0.25	0.004/0.008	0.25/0.5
C. lusitaniae (107)	0.25/0.25	0.25/0.5	0.12/0.25	0.12/0.12	0.25/1	0.008/0.015	0.25/0.5
C. auris (65)	0.25/0.5	0.25/0.5	0.12/0.25	0.12/0.25	128/>128	0.5/2	1/2
C. kefyr (51)	0.03/0.06	0.06/0.12	0.015/0.015	0.06/0.06	0.5/0.5	0.008/0.015	1/1
C. orthopsilosis (49)	0.5/1	0.5/2	0.12/0.5	0.25/0.5	0.5/32	0.015/0.5	0.5/0.5
C. guilliermondii (33)	1/1	2/4	0.25/0.5	0.5/1	2/>128	0.06/4	0.5/0.5
C. metapsilosis (25)	0.12/0.5	0.25/0.25	0.06/0.12	0.25/0.5	1/2	0.015/0.03	0.5/0.5
C. fermentati (17)	0.5/1	1/2	0.25/0.5	0.25/0.5	2/32	0.12/0.5	0.5/1
C. pelliculosa (10)	0.015/0.03	0.015/0.06	0.03/0.03	0.03/0.06	2/8	0.12/0.25	0.5/1
Other *Candida* spp. (58)	0.06/0.5	0.12/0.5	0.06/0.25	0.06/0.5	2/16	0.03/0.12	0.5/1

MIC (minimum inhibitory concentration) in mg/L, RZF (rezafungin), AND (anidulafungin), CAS (caspofungin), MCF (micafungin), FLC (fluconazole), VRC (voriconazole), AMB (amphotericin B)

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https://www.cdc.gov/candida-auris/hcp/laboratories/antifungal-susceptibility-testing.html

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