

Rezafungin Activity against Candidemia isolates collected from European medical centres (2019–2021)

ECCMID 2023
#P509



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INTRODUCTION

- Rezafungin is a once weekly echinocandin with a long half-life and front-loaded drug exposure recently approved for the treatment of candidemia and invasive candidiasis by the US FDA.
- Rezafungin is currently under review by the European Medicines Agency and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK.
- We evaluated the *in vitro* activity of rezafungin, caspofungin, micafungin, anidulafungin, and fluconazole against a contemporaneous collection of *Candida* spp. causing bloodstream infection in Europe.

MATERIALS AND METHODS

- A total of 610 isolates were collected (1/patient) in 2019–2021 from 18 medical centres located in Western Europe (W-EU; n=438; 14 centres) and Eastern Europe (E-EU; n=172; 4 centres; Figure 1).
- Isolates were identified by MALDI-TOF MS and/or sequencing and tested by CLSI broth microdilution.
- CLSI breakpoints (2022) were applied, including rezafungin susceptible-only provisional breakpoints for the main *Candida* species.
- Rezafungin-nonsusceptible isolates were submitted to FKS sequencing by whole genome sequencing.

RESULTS

- Isolates included *Candida albicans* (261 isolates), *Candida parapsilosis* (134), *Candida glabrata* (121), *Candida tropicalis* (67), *Candida krusei* (20), and *Candida dubliniensis* (7).
- Figure 1 lists the *Candida* species distribution in Eastern and Western Europe.
- Rezafungin had similar activity to the other echinocandins against *C. albicans* (98.9–100.0%S), *C. glabrata* (97.6–100.0%S), *C. parapsilosis* (100.0%S; except anidulafungin, 89.2–95.1%S), *C. tropicalis* (100.0%S), *C. krusei* (100.0%S), and *C. dubliniensis* (MIC₅₀ range, 0.015–0.12 mg/L), regardless of the region or year (Figure 2, Tables 1 and 2).
- Fluconazole was active against *C. albicans* (100.0%S) and *C. tropicalis* (100.0%S), regardless of the region or year.
- Fluconazole resistance rates against *C. parapsilosis* isolates were 31.2%/17.1% from W-EU/E-EU and 18.9%/27.5%/31.6% for *C. parapsilosis* isolates from 2019/2020/2021, respectively.
- Fluconazole resistance rates against *C. glabrata* isolates were 6.3%/2.4% from W-EU/E-EU and 10.3%/4.4%/2.1% in 2019/2020/2021, respectively.

Figure 1. *Candida* species distribution recovered from bloodstream infection in Eastern and Western Europe

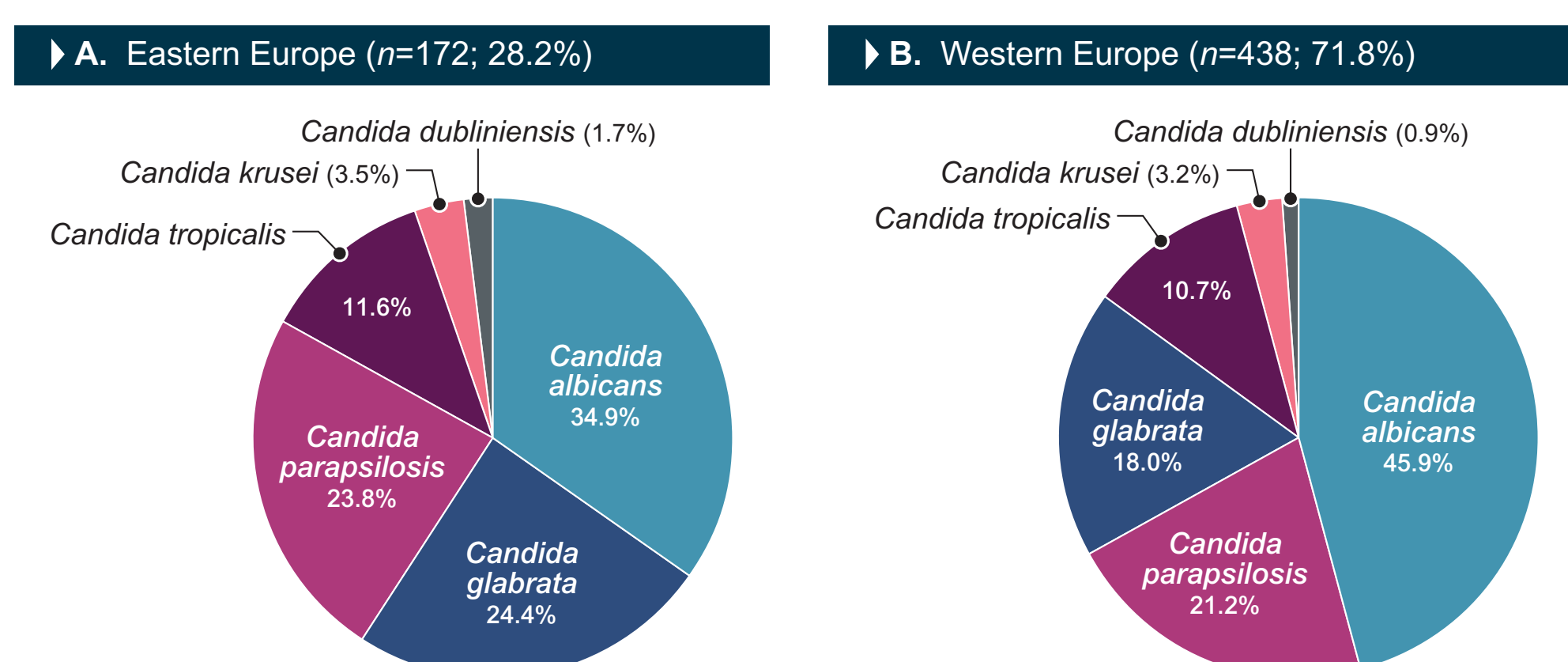
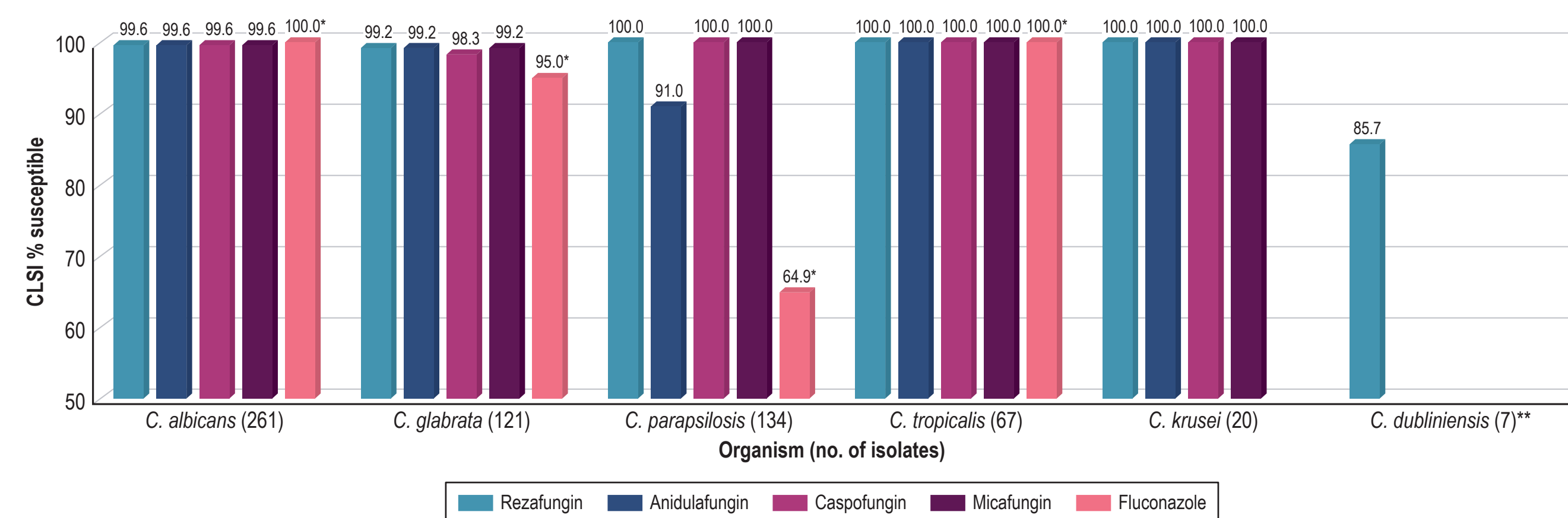


Figure 2. Activity of rezafungin and comparator agents against 610 *Candida* spp. isolates causing bloodstream infections in European medical centres (2019–2021)



*SDD, Susceptible-dose dependent
**No CLSI breakpoints are published for anidulafungin, caspofungin, or micafungin against *C. dubliniensis*.

- Rezafungin inhibited all but 3 *Candida* spp. isolates at the susceptible breakpoint for each species.
- One *C. albicans* carrying an S645P alteration in Fks1 (Germany) and 1 *C. glabrata* carrying an S663P alteration in Fks2 (Spain) were nonsusceptible to rezafungin.
- Rezafungin-nonsusceptible *C. albicans* (MIC, 0.5 mg/L) and *C. glabrata* (MIC, 2 mg/L) strains were resistant to the other echinocandins (MIC range, 1–>4 mg/L)
- One *C. dubliniensis* (Germany) isolate was also nonsusceptible to rezafungin (MIC, 0.25 mg/L) but no FKS gene mutations were observed. Caspofungin, anidulafungin, and micafungin MIC values were 0.25 mg/L, 0.12 mg/L, and 0.12 mg/L, respectively.

CONCLUSIONS

- Rezafungin was very active against *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and *C. dubliniensis* causing candidemia in European medical centres.
- Echinocandins, including rezafungin, displayed similar activity against different *Candida* species.
- Rezafungin and all other echinocandin susceptibility rates were stable over the 3-year period.
- Notably, fluconazole-resistant rates progressively increased against *C. parapsilosis* and decreased against *C. glabrata*.

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Table 1. Activity of rezafungin and comparator agents against candidemia isolates in Western and Eastern Europe (2019–2021)

Organism (no. of isolates from W-EU/E-EU)	MIC ₅₀ /MIC ₉₀ (mg/L); CLSI %S									
	W-EU					E-EU				
	RZF	ANF	CSF	MCF	FLC	RZF	ANF	CSF	MCF	FLC
<i>C. albicans</i> (201/60)	0.03/0.06	0.03/0.06	0.015/0.03	0.015/0.03	0.12/0.25	0.03/0.06	0.03/0.06	0.015/0.03	0.015/0.015	0.12/0.25
	99.5	99.5	99.5	99.5	100*	100	100	100	100	100*
<i>C. glabrata</i> (79/42)	0.06/0.06	0.06/0.12	0.03/0.06	0.015/0.03	4/8	0.06/0.06	0.06/0.12	0.03/0.06	0.015/0.03	4/8
	98.7	98.7	98.7	98.7	93.7*	100	100	97.6	100	97.6*
<i>C. parapsilosis</i> (93/41)	1/1	2/4	0.25/0.5	1/1	0.5/64	1/1	2/2	0.25/0.5	1/1	0.5/8
	100	89.2	100	100	67.7*	100	95.1	100	100	58.5*
<i>C. tropicalis</i> (47/20)	0.03/0.06	0.03/0.06	0.015/0.03	0.03/0.06	0.25/1	0.03/0.06	0.03/0.06	0.015/0.06	0.015/0.06	0.5/0.5
	100	100	100	100	100*	100	100	100	100	100*
<i>C. dubliniensis</i> (4/3)	0.03/-	0.03/-	0.015/-	0.015/-	0.25/-	0.06/-	0.12/-	0.03/-	0.03/-	0.25/-
	75	NA	NA	NA	NA	100	NA	NA	NA	NA
<i>C. krusei</i> (14/6)	0.03/0.06	0.06/0.12	0.06/0.12	0.06/0.12	32/32	0.03/-	0.06/-	0.06/-	0.06/-	32/-
	100	100	100	100	NA	100	100	100	100	NA

*SDD, susceptible-dose dependent; S, susceptible; RZF, rezafungin; ANF, anidulafungin; CSF, caspofungin; MCF, micafungin; FLC, fluconazole; NA, not available. "-", MIC₉₀ not calculated due to the low number of isolates (<10 isolates).

Table 2. Activity of rezafungin and comparator agents against candidemia isolates by study year.

Organism	Year (no. of isolates)	MIC ₅₀ /MIC ₉₀ (mg/L); CLSI %S				
		RZF	ANF	CSF	MCF	FLC
<i>C. albicans</i>	2019 (78)	0.03/0.06	0.03/0.06	0.015/0.03	0.015/0.03	0.12/0.25
		100	100	100	100	100*
	2020 (89)	0.03/0.06	0.03/0.06	0.015/0.03	0.015/0.015	0.12/0.25
		100	100	100	100	100*
	2021 (94)	0.03/0.06	0.03/0.06	0.015/0.03	0.015/0.015	0.12/0.25
		98.9	98.9	98.9	98.9	100*
<i>C. glabrata</i>	2019 (29)	0.06/0.06	0.06/0.12	0.03/0.06	0.015/0.03	4/64
		98.7	98.7	98.7	98.7	89.7*
	2020 (45)	0.06/0.06	0.06/0.12	0.03/0.06	0.015/0.03	4/8
		100	100	97.6	100	95.6*
	2021 (47)	0.06/0.06	0.06/0.12	0.03/0.06	0.015/0.03	4/8
		100	100	97.6	100	97.9*
<i>C. parapsilosis</i>	2019 (37)	1/2	2/4	0.25/0.5	1/1	0.5/64
		100	89.2	100	100	70.3*
	2020 (40)	1/1	2/2	0.25/0.5	1/1	0.5/64
		100	95	100	100	72.5*
	2021 (57)	1/1	2/4	0.25/0.5	1/1	2/64
		100	89.5	100	100	56.1*

*SDD, susceptible-dose dependent; S, susceptible; RZF, rezafungin; ANF, anidulafungin; CSF, caspofungin; MCF, micafungin; FLC, fluconazole; NA, not available. "-", MIC₉₀ not calculated due to the low number of isolates (<10 isolates).

Acknowledgements

This project was supported by Mundipharma Research Limited. CG Carvalhaes, PR Rhomberg, A Klauer, B Hatch, and M Castanheira are employees of JMI Laboratories, which was a paid consultant to Mundipharma Research Limited in connection with the development of this poster.

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