

Rezafungin Activity against *Candida* and *Aspergillus* Isolates Causing Invasive Infections in European Medical Centres (2019–2021)

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INTRODUCTION

- The US FDA recently approved rezafungin for the treatment of candidemia and invasive candidiasis in adults.
- In addition, rezafungin is in development to prevent invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* spp.
- We evaluated the *in vitro* activity of rezafungin, caspofungin, micafungin, and anidulafungin against European fungal isolates causing invasive infection.

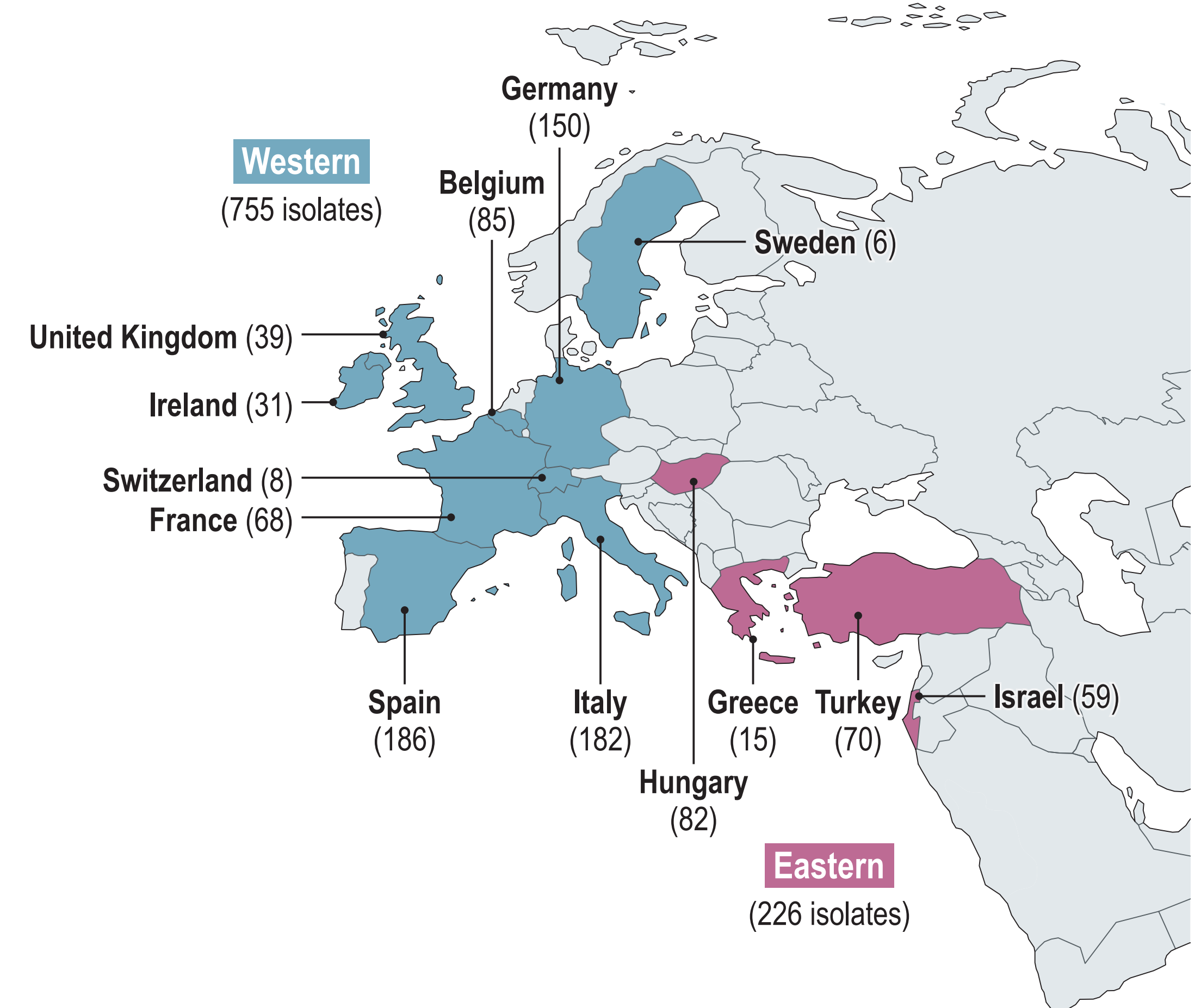
MATERIALS AND METHODS

- A total of 981 isolates were collected (1/patient) in 2019–2021 from 19 medical centres located in Western Europe (W-EU; n=755; 15 centres; 9 countries) and Eastern Europe (E-EU; n=226; 4 centres; 4 countries; Figure 1).
- Isolates were identified by MALDI-TOF and/or sequencing and tested by CLSI broth microdilution.
- CLSI breakpoints (2022) were applied, including susceptible-only provisional breakpoints for rezafungin.
- Rezafungin-nonsusceptible isolates were submitted to FKS sequencing by whole genome sequencing.

RESULTS

- Isolates included *Candida albicans* (403 isolates), *Candida parapsilosis* (173), *Candida glabrata* (155), *Candida tropicalis* (80), *Candida krusei* (27), *Candida dubliniensis* (12), *Aspergillus fumigatus* (115), and *Aspergillus* section *Flavi* (16).
- Rezafungin inhibited all *C. parapsilosis*, *C. tropicalis*, and *C. krusei* regardless of the region, 99.7%/100% of *C. albicans* from W-EU/E-EU, and 88.9%/100% of *C. dubliniensis* at their susceptibility breakpoints.
- Rezafungin had similar activity to the other echinocandins against *C. albicans* (99.7%S), *C. glabrata* (99.1%S), *C. parapsilosis* (100.0%S), *C. tropicalis* (100.0%S), *C. krusei* (100.0%S), and *C. dubliniensis* (MIC₅₀ range, 0.015–0.03 mg/L) from W-EU.
- Except for caspofungin against *C. glabrata* (97.8%S) and anidulafungin against *C. parapsilosis* (95.2%S), echinocandins inhibited all *Candida* isolates from E-EU at their respective susceptible breakpoints.
- Out of all *Candida* spp. isolates tested, only 1 *C. albicans* (Germany), 1 *C. dubliniensis* (Germany), and 1 *C. glabrata* (Spain), were nonsusceptible to rezafungin (Table 2).
 - The *C. albicans* and *C. glabrata* nonsusceptible strains were resistant to all echinocandins and displayed an S645P alteration in Fks1 or an S663P alteration in Fks2, respectively.
 - No CLSI breakpoints are published for caspofungin, anidulafungin, or micafungin against *C. dubliniensis*, and no FKS gene mutations were observed in this strain.
- All *A. fumigatus* isolates were inhibited by rezafungin at ≤0.06 mg/L.
- Anidulafungin, micafungin, and caspofungin inhibited all *A. fumigatus* at ≤0.12 mg/L.
- A total of 10 (8.7%) voriconazole-nonsusceptible *A. fumigatus* isolates (9 W-EU, 1 E-EU) were observed (Table 1).
 - Rezafungin (MEC range, 0.015–0.03 mg/L) and all other echinocandins (MEC range, 0.004–0.06 mg/L) displayed activity against the voriconazole-nonsusceptible *A. fumigatus* isolates.
- Rezafungin and all other echinocandins inhibited all *A. section Flavi* isolates at ≤0.06 mg/L.

Figure 1. Distribution of 981 fungal isolates included in this study split by European region and country



CONCLUSIONS

- Rezafungin was very active against contemporary *Candida* spp. isolates causing invasive infections in European medical centres.
- Only 3 *Candida* isolates were nonsusceptible to rezafungin and other echinocandins (*C. albicans* carrying an S645P alteration in Fks1, *C. glabrata* carrying an S663P alteration in Fks2, and *C. dubliniensis* that was FKS-wildtype)
- Rezafungin was also very active against *A. fumigatus* and *A. section Flavi* isolates causing invasive infections, including voriconazole-nonsusceptible *A. fumigatus* isolates.

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Table 1. Activity of rezafungin and other echinocandins against *Candida* spp. and *Aspergillus* spp. isolates causing invasive infections in Western and Eastern Europe

Organism (no. of isolates from W-EU/E-EU)	MIC ₅₀ /MIC ₉₀ or MEC ₅₀ /MEC ₉₀ (mg/L)							
	W-EU				E-EU			
	RZF	ANF	CSF	MCF	RZF	ANF	CSF	MCF
<i>C. albicans</i> (329/74)	0.03/0.06	0.03/0.06	0.015/0.03	0.015/0.03	0.03/0.06	0.03/0.06	0.015/0.03	0.015/0.015
	99.7	99.7	99.7	99.7	100	100	100	100
<i>C. glabrata</i> (109/46)	0.06/0.06	0.06/0.12	0.03/0.06	0.015/0.03	0.06/0.06	0.06/0.12	0.03/0.06	0.015/0.03
	99.1	99.1	99.1	99.1	100	100	97.8	100
<i>C. parapsilosis</i> (131/42)	1/2	2/4	0.25/0.5	1/1	1/1	2/2	0.25/0.5	1/1
	100	86.3	100	100	100	95.2	100	100
<i>C. tropicalis</i> (57/23)	0.03/0.06	0.03/0.06	0.015/0.03	0.03/0.06	0.03/0.06	0.03/0.06	0.03/0.06	0.03/0.06
	100	100	100	100	100	100	100	100
<i>C. dubliniensis</i> (9/3)	0.03/-	0.03/-	0.03/-	0.015/-	0.06/-	0.12/-	0.03/-	0.03/-
	88.9	NA	NA	NA	100	NA	NA	NA
<i>C. krusei</i> (19/8)	0.03/0.06	0.06/0.12	0.12/0.12	0.12/0.12	0.03/-	0.06/-	0.06/-	0.06/-
	100	100	100	100	100	100	100	100
<i>A. fumigatus</i> (94/21)	0.015/0.03	0.03/0.06	0.015/0.03	0.008/0.015	0.03/0.06	0.03/0.06	0.015/0.06	0.008/0.008
	NA	NA	NA	NA	NA	NA	NA	NA
VRC-NS AF (9/1)	0.015/-	0.03/-	0.015/-	0.008/-	0.03/-	0.03/-	0.03/-	0.008/-
	NA	NA	NA	NA	NA	NA	NA	NA
<i>A. section Flavi</i> (7/9)	0.008/-	0.008/-	0.015/-	0.015/-	0.015/-	0.015/-	0.008/-	0.008/-
	NA	NA	NA	NA	NA	NA	NA	NA

S, susceptible; RZF, rezafungin; ANF, anidulafungin; CSF, caspofungin; MCF, micafungin; VRC-NS, voriconazole-nonsusceptible; AF, *Aspergillus fumigatus*; NA, not available; "-", MIC₉₀ not calculated due to the low number of isolates (<10 isolates).

Table 2. Characterization of 3 *Candida* spp. isolates nonsusceptible to rezafungin per CLSI provisional breakpoints

Organism	Study Year	Country	Infection Type	MIC (mg/L)				Fks sequence	
				Rezafungin	Anidulafungin	Caspofungin	Micafungin	Fks1 HS1	Fks2 HS1
<i>Candida albicans</i>	2021	Germany	Bloodstream infection	0.5	1	2	2	S645P	WT
<i>Candida dubliniensis</i>	2021	Germany	Bloodstream infection	0.25	0.12	0.25	0.12	WT	WT
<i>Candida glabrata</i>	2019	Spain	Bloodstream infection	2	2	>4	1	WT	S663P

HS1, hot spot 1; WT, wildtype

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