# 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.

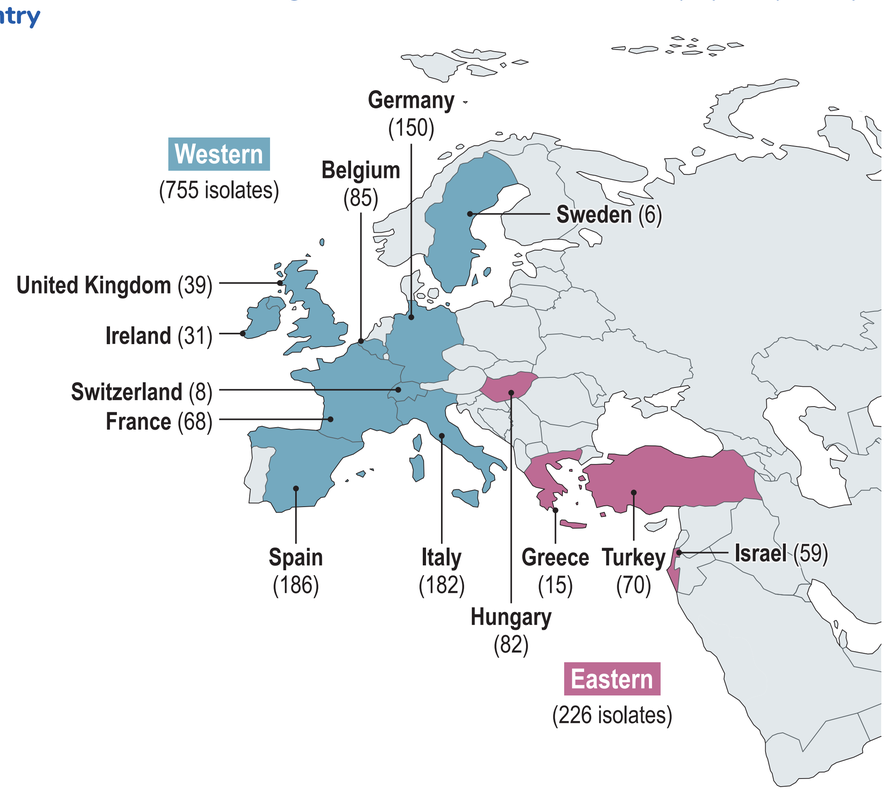
## MATERIALS AND METHODS

- 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* ($MIC_{50}$ 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.

## CONTACT

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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) CLSI %S | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | W-EU | | | | E-EU | | | |
| | RZF | ANF | CSF | MCF | RZF | ANF | CSF | MCF |
| *C. albicans* (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 |
| *C. glabrata* (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 |
| *C. parapsilosis* (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 |
| *C. tropicalis* (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 |
| *C. dubliniensis* (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 |
| *C. krusei* (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 |
| *A. fumigatus* (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 |
| *A.* section *Flavi* (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; "-", $MIC_{90}$ 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 |
| *Candida albicans* | 2021 | Germany | Bloodstream infection | 0.5 | 1 | 2 | 2 | S645P | WT |
| *Candida dubliniensis* | 2021 | Germany | Bloodstream infection | 0.25 | 0.12 | 0.25 | 0.12 | WT | WT |
| *Candida glabrata* | 2019 | Spain | Bloodstream infection | 2 | 2 | >4 | 1 | WT | S663P |

HS1, hot spot 1; WT, wildtype

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