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Rezafungin Activity Against Echinocandin–Nonwildtype *Candida glabrata* Clinical Isolates Collected in European countries (2014–2021)

Mariana Castanheira, Paul R Rhomberg, Lalitagauri M Deshpande, Cecilia G. Carvalhaes‡

Element Materials Technology (JMI Laboratories), North Liberty, Iowa, USA; ‡ New affiliation: bioMerieux, Hazelwood, Missouri, USA

Introduction

- Echinocandins are often used as first-line therapy against *C. glabrata* infections due to the high fluconazole resistance rates in this species.
- Resistance to echinocandins has been reported in *C. glabrata* isolates and is associated with mutations in hot spots (HS) regions of the Fks1- and Fks2-encoding genes
- Rezafungin is a long-acting echinocandin approved by the US FDA to treat candidemia and invasive candidiasis
- The activity of rezafungin and other echinocandins was evaluated against a collection of echinocandin–nonwildtype (NWT) *C. glabrata* isolates

Methods

- A total of 1,257 *C. glabrata* isolates were collected in 2014–2022 from 41 European hospitals from 2014–2022.
- Only 1 isolate per patient episode was included.
- All isolates were identified by MALDI-TOF MS and/or DNA sequencing.
- Isolates were tested by CLSI reference broth microdilution method (M27).
- CLSI breakpoints (M27M44S) and epidemiological cut-off values (M57S) were applied, including recently approved rezafungin breakpoints (≤0.5 mg/L for susceptible).
- Echinocandin-NWT isolates were submitted to *FKS* analysis by PCR or whole genome sequencing as previously described.

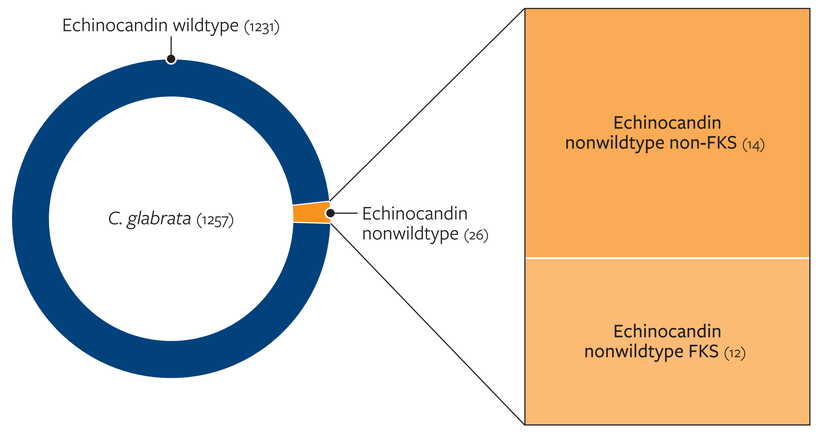
Results

- Among 1,257 *C. glabrata* isolates, 26 (2.1%) were NWT to the echinocandins (Figure 1).
- 12 NWT isolates displayed Fks alterations (46.2% of echinocandin-NWT isolates; 0.9% overall)
  - 11 isolates exhibited Fks2 HS1 alterations (7 S663F and 4 F659Y/deletion) and 1 isolate displayed a Fks1 HS1 L630Q amino acid change
- Rezafungin displayed similar activity to other echinocandins against the overall *C. glabrata* isolates, inhibiting 99.4% at ≤0.5 mg/L (Figure 2).
- Anidulafungin, caspofungin, and micafungin susceptibility rates were 98.0%, 98.8%, and 99.0%, respectively.
- Rezafungin was active against 73.1% of the 26 echinocandin-NWT *C. glabrata*.
- The susceptibility rates to anidulafungin, caspofungin, and micafungin were 46.2%, 65.4%, and 57.7%, respectively.
- Rezafungin was active against 41.7% of the echinocandin-NWT isolates that carried Fks alterations while anidulafungin, caspofungin, and micafungin were active against 8.3%, 25.0%, and 25.0% of these isolates.
- Against echinocandin-NWT isolates that did not carry *FKS* mutations (non-*FKS*), the activity of rezafungin, anidulafungin, caspofungin, and micafungin was 100.0%, 78.6%, 100.0%, and 85.7%, respectively.
- Fluconazole susceptibility rates ranged from 50.0% to 95.9% and was lowest among non-*FKS* echinocandin-NWT isolates.

Conclusions

- Rezafungin and other echinocandins demonstrated potent *in vitro* activity against *C. glabrata* isolates collected in European hospitals from 2014 to 2022.
- Rezafungin remained active against 73.1% of the most isolates of the *C. glabrata* displaying an echinocandin-NWT phenotype with or without Fks alterations.
- Rezafungin favourable PK/PD profile allow for the activity against some echinocandin-NWT phenotype with or without Fks alterations.

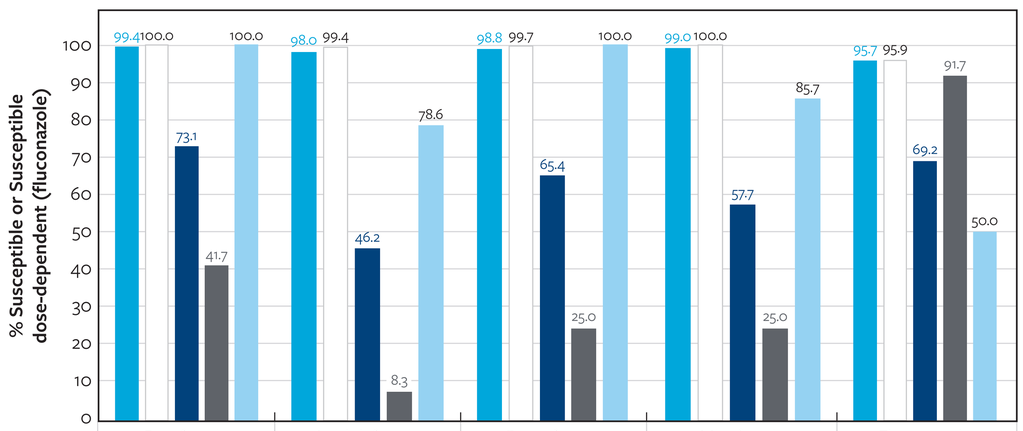
Figure 1. Echinocandin NWT and Fks alteration among *C. glabrata* isolates collected in European hospitals from 2014 to 2022



Echinocandin nonwildtype FKS (12)

	MIC (mg/L)				
Country	**Rezafungin**	**Anidulafungin**	**Caspofungin**	**Micafungin**	**Fks alteration**
Italy	0.12	0.25	0.06	0.03	Fks1 HS1 L630Q
Hungary	1	1	1	0.5	Fks2 HS1 F659 deletion
Spain	1	1	0.25	0.25	Fks2 HS1 F659 deletion
Spain	0.5	1	0.5	0.25	Fks2 HS1 F659 deletion
Slovenia	0.5	1	0.25	0.06	Fks2 HS1 F659Y
France	1	2	0.5	0.5	Fks2 HS1 S663P
Ireland	2	4	2	0.5	Fks2 HS1 S663P
Ireland	0.25	0.5	0.12	0.12	Fks2 HS1 S663P
Ireland	0.06	0.12	0.12	0.06	Fks2 HS1 S663P
Turkey	1	2	1	1	Fks2 HS1 S663P
Spain	1	2	>4	1	Fks2 HS1 S663P
Greece	1	2	4	1	Fks2 HS1 S663P

Figure 2. Activity of echinocandins and fluconazole against *C. glabrata* isolates collected in European hospitals from 2014 to 2022



	Rezafungin		Anidulafungin		Caspofungin		Micafungin		Fluconazole	
	$MIC_{50/90}$	**%S**	**$MIC_{50/90}$**	**%S**	**$MIC_{50/90}$**	**%S**	**$MIC_{50/90}$**	**%S**	**$MIC_{50/90}$**	**%SDD**
C. glabrata (1,257)	0.03/0.12	99.4	0.06/0.12	98.0	0.03/0.06	98.8	0.015/0.03	99.0	4/8	95.7
Echinocandin-wildtype (1,231)	0.03/0.06	100.0	0.06/0.12	99.4	0.03/0.06	99.7	0.015/0.03	100.0	4/8	95.9
Echinocandin-nonwildtype (26)	0.25/1	73.1	0.25/2	46.2	0.12/2	65.4	0.06/1	57.7	16/128	69.2
Echinocandin-nonwildtype FKS (12)	1/2	41.7	1/2	8.3	0.5/4	25.0	0.25/1	25.0	4/16	91.7
Echinocandin-nonwildtype non-FKS (14)	0.25/0.5	100.0	0.25/0.5	78.6	0.06/0.25	100.0	0.06/0.12	85.7	64/128	50.0

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Contact

element

Mariana Castanheira, Ph.D., FIDSA, FAAM
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: mariana.castanheira@element.com

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