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Echinocandin susceptibility patterns and genetic changes in nonsusceptible *Candida glabrata* with non-hotspot FKS alterations

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Introduction

- Rezafungin is a long-acting echinocandin with a pharmacodynamic/pharmacokinetic profile allowing a higher concentration in the bloodstream and at sites of infection.
  - CLSI breakpoints are 2–3 doubling dilutions higher than for other echinocandins.
- *Candida glabrata* is a common causative *Candida* species in invasive infections.
  - Echinocandin resistance is rising in *C. glabrata*.
- Echinocandin resistance is often due to alterations in the hotspot (HS) regions of FKS1 and FKS2 proteins in *Candida* spp.
  - Little is known about the effects of non-HS alterations on echinocandin susceptibility patterns.
- We looked at the activity of rezafungin and other echinocandins against *C. glabrata* isolates with non-HS FKS alterations.

Methods

- A total of 1,663 *C. glabrata* isolates were collected from 2014–2023 in 42 different hospitals in all 9 US Census regions (1,602 isolates) and Canada (61 isolates) (Figure 1).
- 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) were applied for rezafungin and comparator agents.
- Nonsusceptible criteria was defined as an MIC of >0.12 mg/L for anidulafungin and caspofungin, 0.06 mg/L for micafungin, and 0.5 mg/L for rezafungin.
- Isolates that met criteria as nonsusceptible to any echinocandins were submitted to whole genome sequencing (WGS) and analyzed for alterations in FKS1 and FKS2.

Results

- 99 *C. glabrata* isolates were nonsusceptible to one or more echinocandins (Figure 2 and Table 1) and 97 of these had WGS performed.
- By WGS, 74 of the isolates had FKS hotspot (HS) alterations.
  - 30 of these also had non-HS alterations (Table 2).
- By WGS, 10 isolates only had non-HS alterations (Table 3).
- 11 isolates had no FKS alterations (wildtype population).
  - Further work is needed to understand echinocandin resistance in these isolates.
- Of the 10 isolates with only non-HS alterations, 100% were susceptible to rezafungin, 30% were susceptible to anidulafungin, 90% were susceptible to caspofungin, and 40% were susceptible to micafungin.
- Of the 30 isolates with both HS and non-HS alterations, 53.3% (16/30) were nonsusceptible to rezafungin, 96.7% (29/30) were nonsusceptible to anidulafungin, 90.0% were nonsusceptible to micafungin (27/30), and 90.0% (27/30) were nonsusceptible to caspofungin.
- The most common non-HS alterations were FKS1 G14S in combination with FKS2 T926P, which was seen in 17 isolates with non-HS alterations (56.7%) and 5 isolates without HS alterations (50%).
- ST3 was the most prevalent multilocus sequence type (MLST) in the study and has been associated with higher mortality among clinical infections.

Conclusions

- 41.2% (40/97) of sequenced echinocandin-nonsusceptible *C. glabrata* isolates contain non-HS FKS alterations.
- Rezafungin had the highest susceptibility rate of all echinocandins against these isolates.
  - This is presumed to be due to the PK/PD properties of rezafungin that allow it to overcome elevated MICs better than other echinocandins.
- Non-HS FKS1 G14S and FKS2 T926P substitutions are prevalent in echinocandin-nonsusceptible *C. glabrata* isolates.
  - These alterations warrant further study to understand their contribution to reduced echinocandin susceptibility.
- Rezafungin represents a promising treatment for *C. glabrata* isolates nonsusceptible to other echinocandins both with HS and non-HS FKS alterations.

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Figure 1. Map of geography of collected isolates

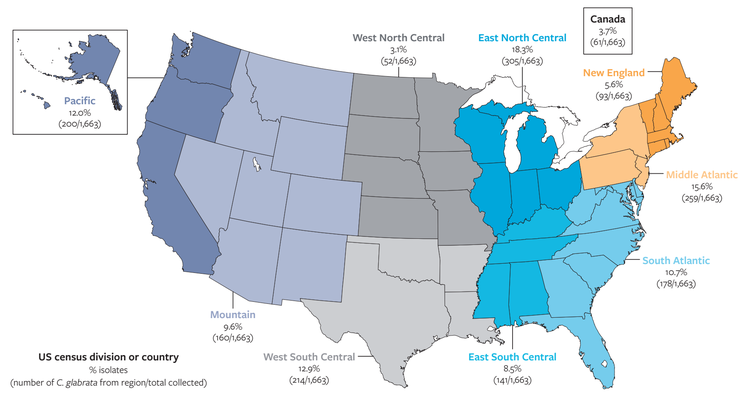

Figure 2. Distribution of echinocandin MIC values tested against the 1,663 *C. glabrata* isolates collected from 2014–2023

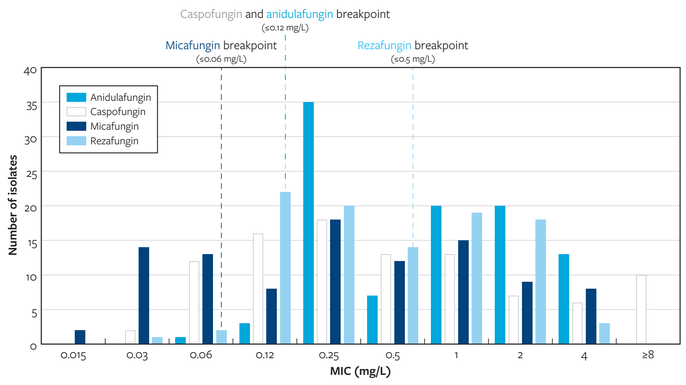

Table 1. Cumulative MICs, $MIC_{50/90}$s, and percentage nonsusceptible (NS) for CLSI testing of echinocandins against *C. glabrata* isolates nonsusceptible to one or more agents

Antimicrobial Agent	Dilution (mg/L)										Isolates tested	MIC_{50} (mg/L)	MIC_{90} (mg/L)	% NS
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	≥8				
Rezafungin (CLSI)	0	1	2	22	20	14	19	18	3		99	0.5	2	40.4%
	0.00%	1.00%	3.00%	25.30%	45.50%	59.60%	78.80%	97.00%	100.00%					
Anidulafungin (CLSI)		0	1	3	35	7	20	20	13		99	1	4	96%
		0.00%	1.00%	4.00%	39.40%	46.50%	66.70%	86.90%	100.00%					
Caspofungin (CLSI)	0	2	12	16	18	13	13	7	6	10	97	0.5	>4	69.1%
	0.00%	2.10%	14.40%	30.90%	49.50%	62.90%	76.30%	83.50%	89.70%	100.00%				
Micafungin (CLSI)	2	14	13	8	18	12	15	9	8		99	0.25	2	70.7%
	2.00%	16.20%	29.30%	37.40%	55.60%	67.70%	82.80%	91.90%	100.00%					

Table 2. *C. glabrata* isolates from 2014–2023 nonsusceptible (NS) to ≥1 echinocandin with both HS and non-HS FKS alterations

Year	US Census Division	MIC by CLSI methodology (mg/L)				HS alterations	non-HS alterations	MLST
		RZF	AND	CAS	MCF			
2014	2: Middle Atlantic	0.12	0.25	0.5	0.03	FKS2 P667T	FKS1 G14S, FKS2 T926P	3
2016	2: Middle Atlantic	1	1	1	1	FKS2 S663P	FKS2 F30V	2
2016	8: Mountain	0.12	0.25	0.25	0.12	FKS2 P667H	FKS1 G14S, FKS2 T926P	3
2016	8: Mountain	1	1	1	0.25	FKS2 F659S	FKS1 G14S, FKS2 T926P	3
2016	2: Middle Atlantic	0.25	0.25	0.06	0.12	FKS2 S629P	FKS1 G14S, FKS2 T926P	3
2016	9: Pacific	2	2	8	2	FKS2 S663P	FKS1 G14S, FKS2 T926P, A1436V	3
2016	9: Pacific	1	2	4	1	FKS2 S663P	FKS1 G14S, FKS2 T926P	3
2017	3: East North Central	2	2	1	1	FKS2 S663P	FKS2 A122V	58-like
2017	9: Pacific	0.5	1	0.5	0.25	FKS1 S629P+ FKS2 R665G	FKS2 S481P	8
2018	3: East North Central	0.03	0.06	0.03	0.06	FKS1 I634V	FKS1 K1323E	15
2018	2: Middle Atlantic	1	1	0.25	0.5	FKS2 S663P	FKS2 N120K	10-like
2018	5: South Atlantic	2	4	4	4	FKS2 S663P	FKS1 A597_ins	8
2018	3: East North Central	0.5	1	0.5	0.25	FKS2 S663P	FKS1 G14S, FKS2 T926P	3
2019	6: East South Central	1	2	1	0.5	FKS2 S663P	FKS1 G14S, FKS2 T926P	3
2019	8: Mountain	0.25	0.25	0.25	0.25	FKS2 F659 deletion	FKS1 G14S, FKS2 T926P	3
2019	8: Mountain	0.25	0.25	0.12	0.06	FKS2 F659 deletion	FKS1 G14S, FKS2 T926P	19
2020	3: East North Central	0.5	1	1	0.25	FKS1 D632E	FKS1 D892E, FKS2 Q388X	16
2020	2: Middle Atlantic	1	2	4	1	FKS1 S629P	FKS2 G1284R	16
2020	9: Pacific	2	4	>4	4	FKS1 S629P	FKS2 1704X	182
2020	2: Middle Atlantic	2	4	>4	4	FKS2 S663P	FKS1 G14S, Y477H, F1727C, FKS2 T926P	3
2020	9: Pacific	1	2	0.5	0.5	FKS2 S663P	FKS1 G14S, FKS2 T926P	3
2021	4: West North Central	1	2	1	1	FKS2 S663P	FKS1 G14S, FKS2 T926P	3
2021	6: East South Central	0.5	1	0.5	0.25	FKS2 S663P	FKS1 G14S, FKS2 T926P	3
2021	6: East South Central	0.5	2	0.5	0.5	FKS2 S663P	FKS1 G14S, FKS2 T926P	3
2021	6: East South Central	0.5	1	0.5	0.25	FKS2 S663P	FKS1 G14S, FKS2 T926P	3
2021	1: New England	1	4	4	1	FKS2 S629P	FKS1 F1335L, FKS2 W1495X	15
2021	6: East South Central	0.5	1	0.5	0.25	FKS2 S663P	FKS1 G14S, FKS2 T926P	3
2021	8: Mountain	0.12	0.25	0.25	0.06	FKS1 R635G+ FKS2 I661F	FKS1 A1633T	16
2022	7: West South Central	2	4	4	≥4	FKS1 S629P+ FKS2 S663P	FKS1/2 recombination, FKS2 P1150Q, T1155S, K1164N	15
2022	6: East South Central	1	1	0.25	0.25	FKS2 S663P	FKS1 G14S, FKS2 T926P	3-like

Shading indicates NS isolate/drug combinations per CLSI breakpoint criteria
RZF, rezafungin; AND, anidulafungin; CAS, caspofungin; MCF, micafungin; HS, hotspot; MLST, multilocus sequence type

Table 3. MICs for rezafungin, anidulafungin, caspofungin, and micafungin against ≥1 echinocandin-nonsusceptible *C. glabrata* isolates with non-HS FKS alterations

Study year	US Census Division	MIC by CLSI methodology (mg/L)				Non-HS alterations	MLST
		RZF	AND	CAS	MCF		
2015	2: Middle Atlantic	0.25	0.25	0.12	0.03	FKS1 E1047G	19
2016	2: Middle Atlantic	0.03	0.06	0.06	0.12	FKS2 F30V	2
2017	3: East North Central	0.25	0.25	0.06	0.06	FKS2 F384Y	83/75*
2017	1: New England	0.25	0.25	0.12	0.06	FKS1 G14S, FKS2 T926P	3
2017	7: West South Central	0.12	0.12	0.06	0.06	FKS1 G14S, FKS2 T926P	174
2018	7: West South Central	0.25	0.25	0.12	0.06	FKS1 G14S, FKS2 T926P	3
2020	5: South Atlantic	0.12	0.12	0.06	0.25	FKS1 G14S, FKS2 T926P, K1357E	3
2020	7: West South Central	0.12	0.25	0.12	0.5	FKS2 W715L	19
2021	8: Mountain	0.12	0.25	0.12	0.25	FKS2 K1357E	15
2023	8: Mountain	0.12	0.25	0.25	1	FKS1 K1323E, FKS2 W639X	10
% susceptible		100%	30%	90%	50%		

Shading indicates NS MIC values per CLSI breakpoint criteria
RZF, rezafungin; AND, anidulafungin; CAS, caspofungin; MCF, micafungin; HS, hotspot; MLST, multilocus sequence type
* ST83 and ST75 are identical (Lott *et al.* 2012 (PMID 21838617))

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