

IDWEEK 2023

P#1947

Session: Surveillance for New Agents

Friday, Oct 13, 2023

Session time: 1:45 pm

Session location: 102 AB



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Activity of Rezafungin against Echinocandin–Non-wildtype *C. glabrata* Clinical Isolates from the Rezafungin Surveillance Program (2014–2021)

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Transparency Statement

JMI Laboratories was contracted to perform services in 2022 for AbbVie, Inc., AimMax Therapeutics, Amicrobe, Inc., Appili Therapeutics, Armata Pharmaceuticals, Astellas Pharma, Inc., Basilea Pharmaceutica AG, Becton, Dickinson and Company, bioMérieux, Biosergen AB, Bugworks, Cerba Research NV, Cidara Therapeutics, Cipla USA Inc., ContraFect Corporation, CorMedix Inc., Crestone, Inc., Curza Global, LLC, Diamond V, Discuva Ltd., Entasis Therapeutics, Enveda Biosciences, Evopoint Biosciences, Fedora Pharmaceuticals, Fox Chase Chemical Diversity Center, Genentech, Gilead Sciences, Inc., GSK plc, Institute for Clinical Pharmacodynamics, Iterum Therapeutics plc, Janssen Biopharma, Johnson & Johnson, Kaleido Biosciences, LifeMine Therapeutics, Medpace, Inc, Lysovant Sciences, Inc, Meiji Seika Pharma, Melinta Therapeutics, Menarini Group, Merck & Co., MicuRx Pharmaceutical Inc., Mundipharma International Ltd., Mutabilis, Nabriva Therapeutics, National Cancer Institute, National Institutes of Health, Ohio State University, Omnix Medical Ltd., Paratek Pharmaceuticals, Pfizer, PolyPid Ltd., PPD, Prokaryotics, Inc., Pulmocide Ltd, Qpex Biopharma, Revagenix, Roche Holding AG, Roivant Sciences, Scynexis, Inc., SeLux Diagnostics, Shionogi & Co., Ltd., Sinovent Pharmaceuticals, Inc., Spero Therapeutics, Sumitovant Biopharma, Inc., TenNor Therapeutics, ThermoFisher Scientific, U.S. Food and Drug Administration, VenatoRx Pharmaceuticals, Washington University, Watershed Medical, LLC, Wockhardt, and Zoetis, Inc.

INTRODUCTION



- Fluconazole resistance is a concern for *C. glabrata*
 - 8.6% per CDC population-based surveillance for candidemia (2012-2016)
 - 12.2% reported by SENTRY Program (2016-2018)
- Echinocandins are the established first-line therapy in patients with candidemia and other forms of invasive candidiasis
- Acquired echinocandin resistance in *Candida* spp. is reported, most notably for *C. glabrata*.
- Resistance to echinocandins has been associated with FKS1 and FKS2 alterations in the hot spot (HS) regions

Pfaller *et al.*, Antimicrob Agents Chemother. 2020
Toda *et al.*, MMWR Surveill Summ. 2019
Rogers *et al.*, J Antimicrob Chemother. 2022

INTRODUCTION



- Rezafungin is a new echinocandin approved by the US FDA to treat candidemia and invasive candidiasis in patients aged ≥ 18 years who have limited or no alternative treatment options.
- Rezafungin exhibits optimized pharmacokinetics providing an extended half-life and once-weekly dosing by intravenous infusion.
- Rezafungin is also being investigated for the prevention of invasive fungal diseases in blood and marrow transplant recipients:
 - Study of Rezafungin Compared to Standard Antimicrobial Regimen for Prevention of Invasive Fungal Diseases in Adults Undergoing Allogeneic Blood and Marrow Transplantation (ReSPECT); NCT04368559.

OBJECTIVES



To evaluate the activity of rezafungin against a large collection of echinocandin non-wildtype (NWT) *C. glabrata* isolates

To evaluate the comparative activity of caspofungin, micafungin, anidulafungin, and fluconazole

To evaluate the epidemiology of echinocandin NWT- *C. glabrata*

MATERIALS & METHODS



- 1,045 *C. glabrata* isolates evaluated (1/patient) between 2014–2021 as part of the SENTRY Surveillance program
- Isolates from 58 medical centers located in:
 - North America (NA; n=459; 20 centers),
 - Europe (EU; n=396; 23 centers),
 - Asia-Pacific (APAC; n=130; 10 centers), and
 - Latin America (LATAM, n=60; 5 centers)

MATERIALS & METHODS

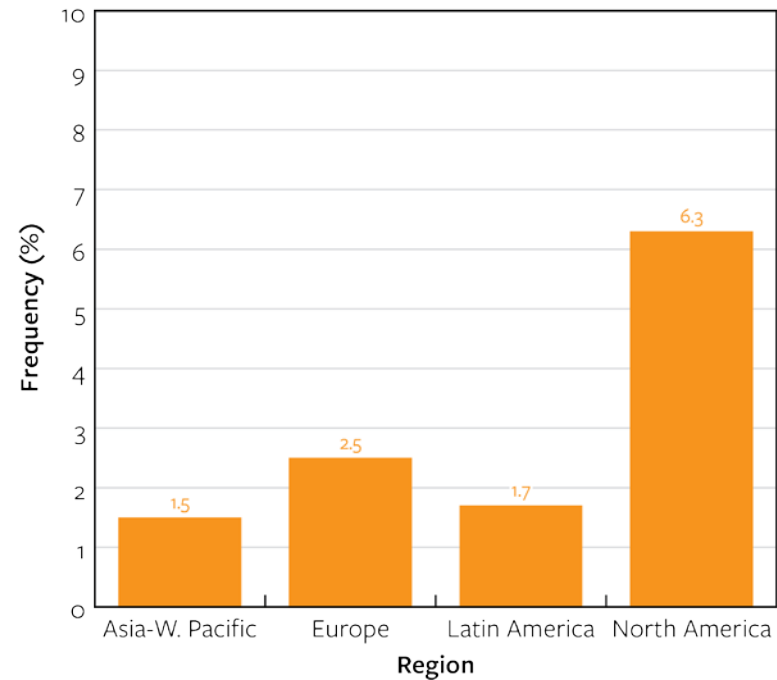


- Isolates were identified by MALDI-TOF and/or sequencing
- Susceptibility tested by CLSI broth microdilution.
- CLSI clinical breakpoints and epidemiological cut-off values were applied.
- Echinocandin-NWT isolates were submitted for FKS analysis by whole genome sequencing (WGS).

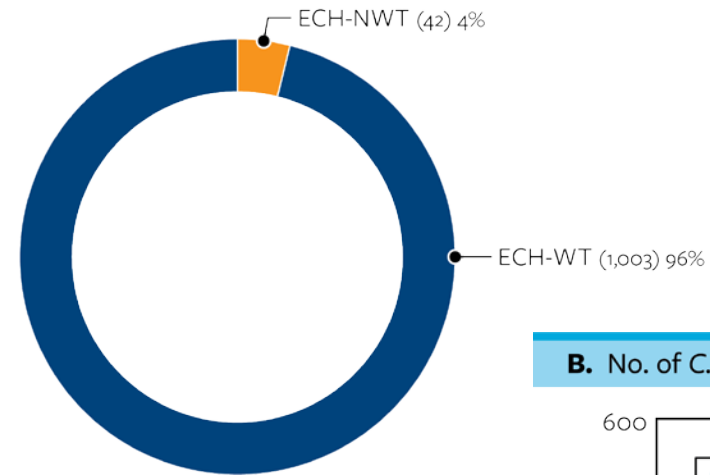
CLSI. M27Ed4, 2017
CLSI. M27M44SEd3, 2022
CLSI M57SEd4, 2022

RESULTS

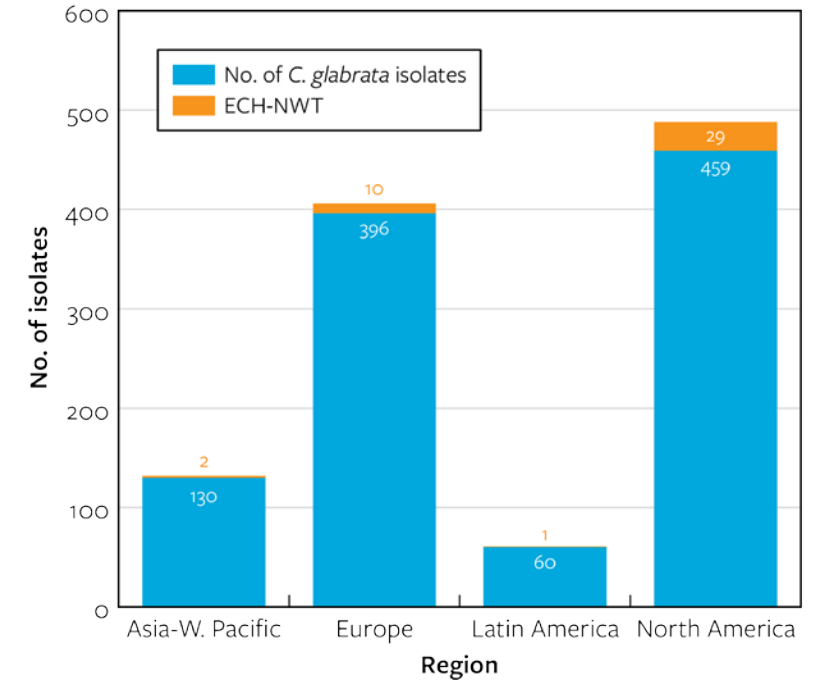
A. ECH-NWT *C. glabrata* rates by region



C. Overall *C. glabrata*

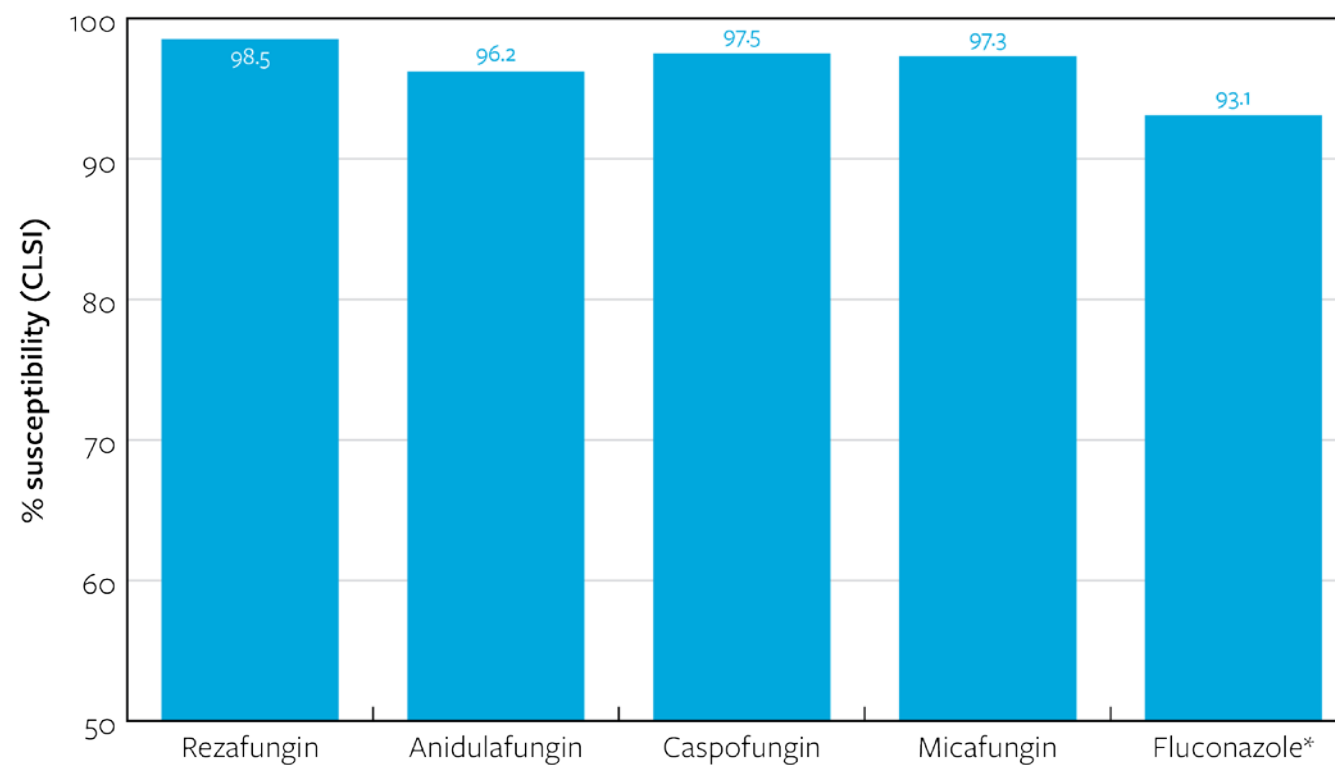


B. No. of *C. glabrata* isolates by region



RESULTS

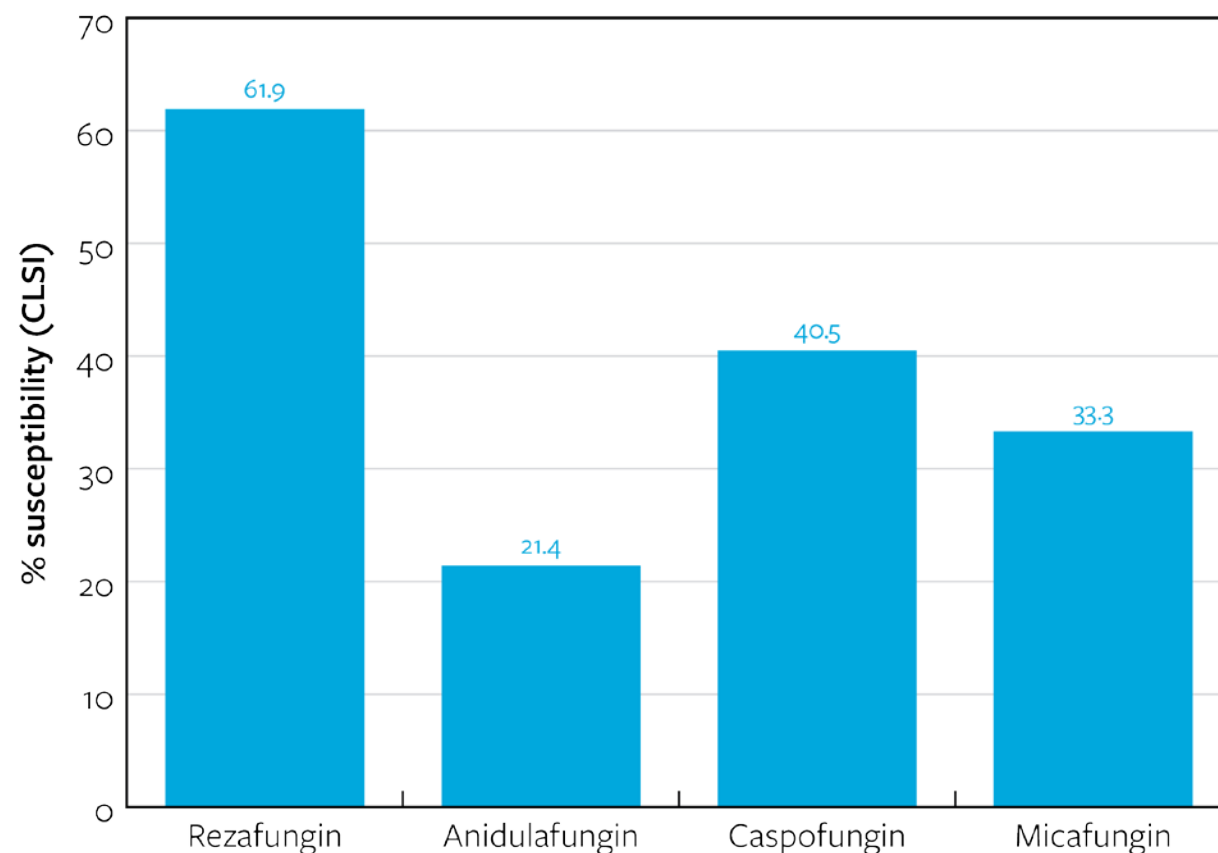
Rezafungin and comparator activity against 1,045 *C. glabrata* isolates



* Susceptible-dose-dependent

RESULTS

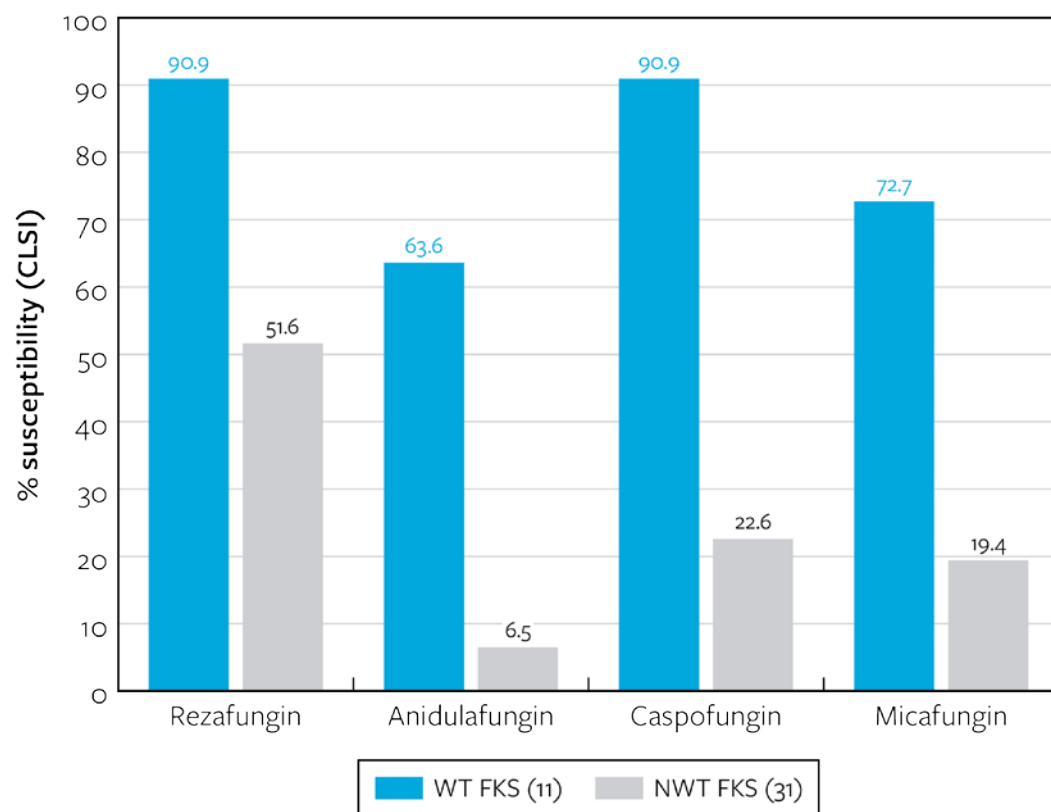
Echinocandin activity against 42 ECH-NWT *C. glabrata* isolates



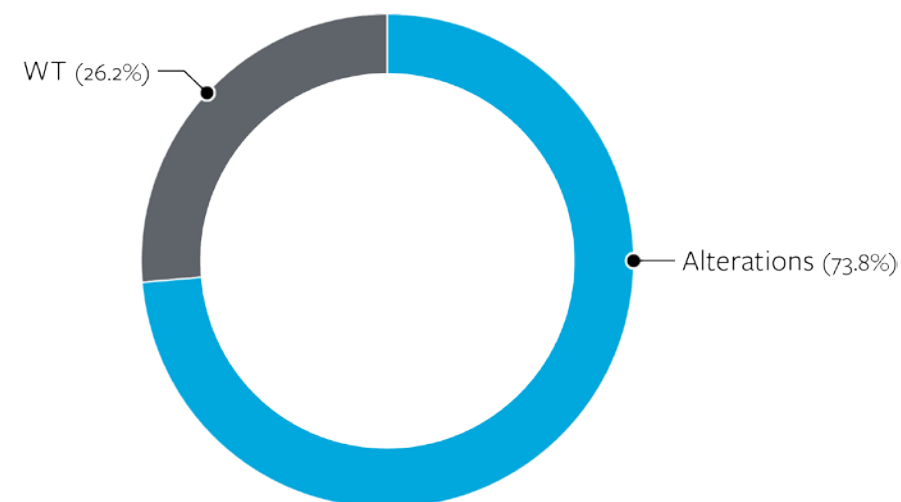
Antifungal	CLSI Susceptible criteria (mg/L)
RZF	≤ 0.5
ANF	≤ 0.12
CSF	≤ 0.12
MCF	≤ 0.06

RESULTS

Echinocandin activity against ECH-NWT *C. glabrata* isolates with and without FKS alterations



FKS Hot Spot alterations in 42 ECH-NWT isolates



RESULTS

FKS alterations in ECH-NWT isolates



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- FKS2-HS1 alterations were more frequently observed
 - 23 isolates (54.8% of ECH-NWT; 74.2% of all FKS alterations)
 - 13 of them displayed S663P/F – 9 from USA, 2 Ireland, 1 Spain, 1 Australia
- FKS1-HS1 alterations
 - 9 isolates (21.4% of ECH-NWT)
 - 7 displayed S629P – all from USA
- FLC-R was observed in 6.9% of *C. glabrata* overall and 16.7% of the ECH-NWT isolates.
 - 60.8% NA; 35.1% EU; 4.1% APAC; 0% LATAM

CONCLUSIONS



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- Rezafungin demonstrated potent *in vitro* activity, and similar to the activity displayed by the other clinically available echinocandins, against ECH-WT *C. glabrata* isolates.
- ECH-NWT isolates were most frequent in NA (6.5%) vs. EU (2.5%), LATAM (1.7%) or APAC (1.5%)

CONCLUSIONS



- Rezafungin remained active against most isolates of *C. glabrata* displaying an ECH-NWT phenotype with or without FKS alterations (51.6%S and 90.9%S, respectively).
- Rezafungin had greater activity than the other available echinocandins against ECH-NWT isolates of *C. glabrata*.
- FKS alterations in *C. glabrata* were more frequently observed in USA isolates.



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THANK YOU