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Rezafungin Activity against Invasive Candidiasis Isolates Globally: Results from the 2022 Rezafungin Surveillance Program

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Introduction

- Rezafungin is a new echinocandin approved by the US FDA to treat candidemia and invasive candidiasis.
- Rising fluconazole resistance rates is a concern to treat invasive candidiasis, and echinocandins are often used as first-line therapy.
- Rezafungin is a once-weekly echinocandin with a long half-life and front-loaded drug exposure that differs from the usual daily regimen of other echinocandins.
- We evaluated the *in vitro* activity of rezafungin, caspofungin, micafungin, anidulafungin, and azoles against a global collection of 500 *Candida* isolates causing invasive candidiasis worldwide.

Methods

- A total of 500 *Candida* isolates causing invasive infections were collected in 2022 from 52 medical centers located in Europe (*n*=203; 19 centers), North America (*n*=167; 14 centers), Asia-Pacific (*n*=63; 8 centers), and Latin America (*n*=67; 7 centers).
- Invasive candidiasis is defined as any serious infection caused by *Candida* species.
- Candidemia was the most prevalent infection (59.2%), followed by skin and skin structure (6.6%), pneumonia in hospitalized patients (4.4%), urinary tract (3.8%), and intra-abdominal infections (1.8%).
- The site of infection was not reported for 24.2% of isolates.
- Only 1 isolate per patient was included.
- Organisms included 233 C. albicans (46.6%), 102 C. glabrata (20.4%), 82 C. parapsilosis (16.4%), 41 C. tropicalis (8.2%), 18 C. krusei (3.6%), 15 C. dubliniensis (3.0%), and 9 C. auris (1.8%) isolates.
- Isolates were identified by MALDI-TOF MS and/or sequencing and susceptibility tested by CLSI broth microdilution.
- CLSI breakpoints (BP) were applied where available in the M27M44S document, including rezafungin susceptible only clinical BPs (Table 1).
- CLSI BP and CDC tentative BPs were used for rezafungin and other echinocandins against C. *auris*, respectively.

Results

C. albicans

- Rezafungin exhibited activity against *C. albicans* inhibiting 99.1% of the 233 isolates overall, and 98.6%, 99.0%, 100%, and 100% of isolates from North America, Europe, Asia-Pacific, and Latin America, respectively (Table 2).
- Only 1 C. albicans isolate (from US) displayed a fluconazole MIC value within the susceptible-dose dependent (SDD) category but was susceptible to rezafungin and other echinocandins (Table 3).
- Caspofungin, anidulafungin, and micafungin showed susceptibility rates of 99.1% against C. albicans.

C. glabrata

- All but 1 C. glabrata isolate was susceptible to rezafungin (99.0% susceptible). – The rezafungin-non susceptible *C. glabrata* isolate was resistant to all echinocandins.
- C. glabrata susceptibility rates to caspofungin, anidulafungin, and micafungin were 98.0%, 98.0%, and 97.1%, respectively.

C. parapsilosis

Rezafungin and other echinocandins inhibited all 10 fluconazole-resistant isolates (9 from Europe and 1 from US; Table 3).

Other Candida species

- echinocandins.
- to voriconazole.

- (66.7% susceptible).

Conclusions

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Fluconazole resistance was detected in 3.9% (4) of *C. glabrata* isolates. All 4 fluconazole-resistant C. glabrata isolates were susceptible to rezafungin and 2/4 isolates were also susceptible to other echinocandins (Table 3).

• All C. *parapsilosis* isolates were susceptible to rezafungin, caspofungin, and micafungin. • However, a total of 13 isolates (15.9%) were non-susceptible to fluconazole, 10 of them were resistant to fluconazole (12.2%).

All C. tropicalis and C. krusei isolates were susceptible to rezafungin and other

All C. tropicalis were also susceptible to azoles, and 94.4% of C. krusei were susceptible

Rezafungin is the only echinocandin with clinical breakpoints available by CLSI against C. dubliniensis (86.7% susceptibility).

• All C. auris isolates (9 total; 4 from Europe, 3 North America, and 2 Latin America) were fluconazole-resistant (Table 3).

2 C. *auris* isolates were non-susceptible to rezafungin (77.8% susceptible) by the CLSI susceptible only criteria of ≤0.5 mg/L. One of the 2 isolates was resistant to all echinocandins and carried R1354G alteration in Fks1-HS2 sequence.

- 1 C. auris isolate was resistant to anidulafungin ($\geq 4 \text{ mg/L}$), caspofungin ($\geq 2 \text{ mg/L}$), and micafungin (\geq 4 mg/L) per CDC tentative breakpoint (88.9% susceptible). - 3 *C. auris* isolates were resistant to amphotericin B per CDC tentative breakpoint

Rezafungin demonstrated potent *in vitro* activity against invasive candidiasis isolates from North America, Europe, Asia-Pacific and Latin America medical centers.

Rezafungin and other echinocandins remained active against fluconazole-resistant C. parapsilosis and C. glabrata isolates.

Most of the fluconazole-resistant *C. auris* isolates were susceptible to echinocandins. Based on MIC₅₀ and MIC₉₀ results, rezafungin has similar activity to the other echinocandins overall.

Acknowledgments

Table 1. CLSI clinical breakpoints and CDC tentative breakpoints applied in this study

	•								
Candida species	Susceptible / Resistant breakpoint criteria (CLSI, 2022) ^a								
	Rezafungin	Anidulafungin	Caspofungin	Micafungin	Fluconazole	Voriconazole			
C. albicans	≤0.25 / NA	≤0.25 / ≥1	≤0.25 / ≥1	≤0.25 / ≥1	≤2 ^b /≥8	≤0.12/≥1			
C. glabrata	≤0.5/NA	≤0.12 / ≥0.5	≤0.12/≥0.5	≤0.06 / ≥0.25	≤32 ^b /≥64	NA			
C. parapsilosis	≤2 / NA	≤2/≥8	≤2/≥8	≤2/≥8	≤2 ^b /≥8	≤0.12/≥1			
C. tropicalis	≤0.25 / NA	≤0.25 / ≥1	≤0.25 / ≥1	≤0.25 / ≥1	≤2 ^b /≥8	≤0.12/≥1			
C. krusei	≤0.25 / NA	≤0.25 / ≥1	≤0.25 / ≥1	≤0.25 / ≥1	NA	≤0.5 / ≥2			
C. dubliniensis	≤0.12/NA	NA	NA	NA	NA	NA			
C. auris	≤0.5 / NA	NA/≥4	NA / ≥2	NA / ≥4	NA/≥32	NA			
NA not available									

^aCDC tentative breakpoints were applied for all antifungal agents against C. auris but rezafungin. CDC tentative breakpoints are available at https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.htm Susceptible-dose dependent

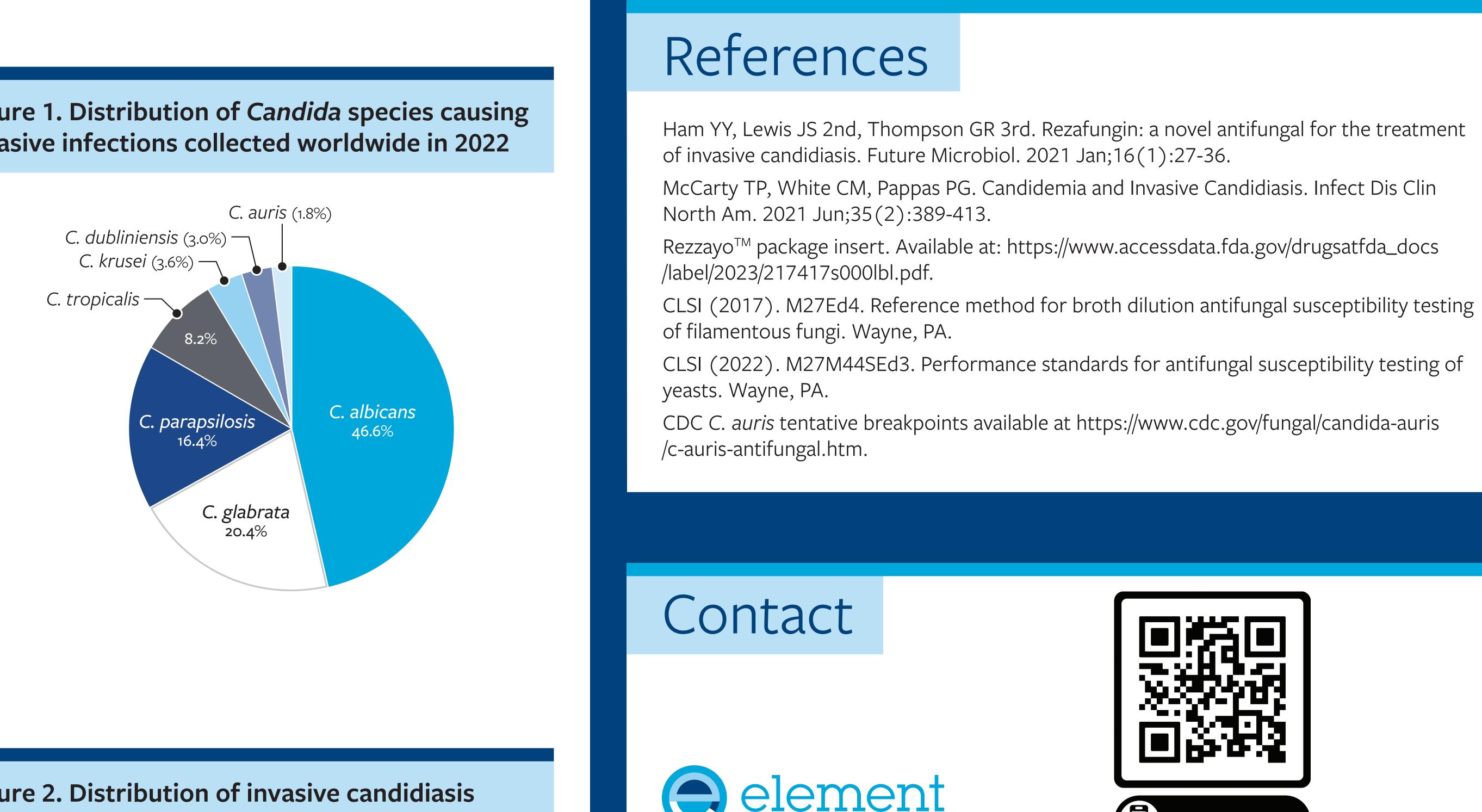
Table 2. Activity of rezafungin and comparator agents against worldwide collection of Candida isolates causing invasive infection in 2022

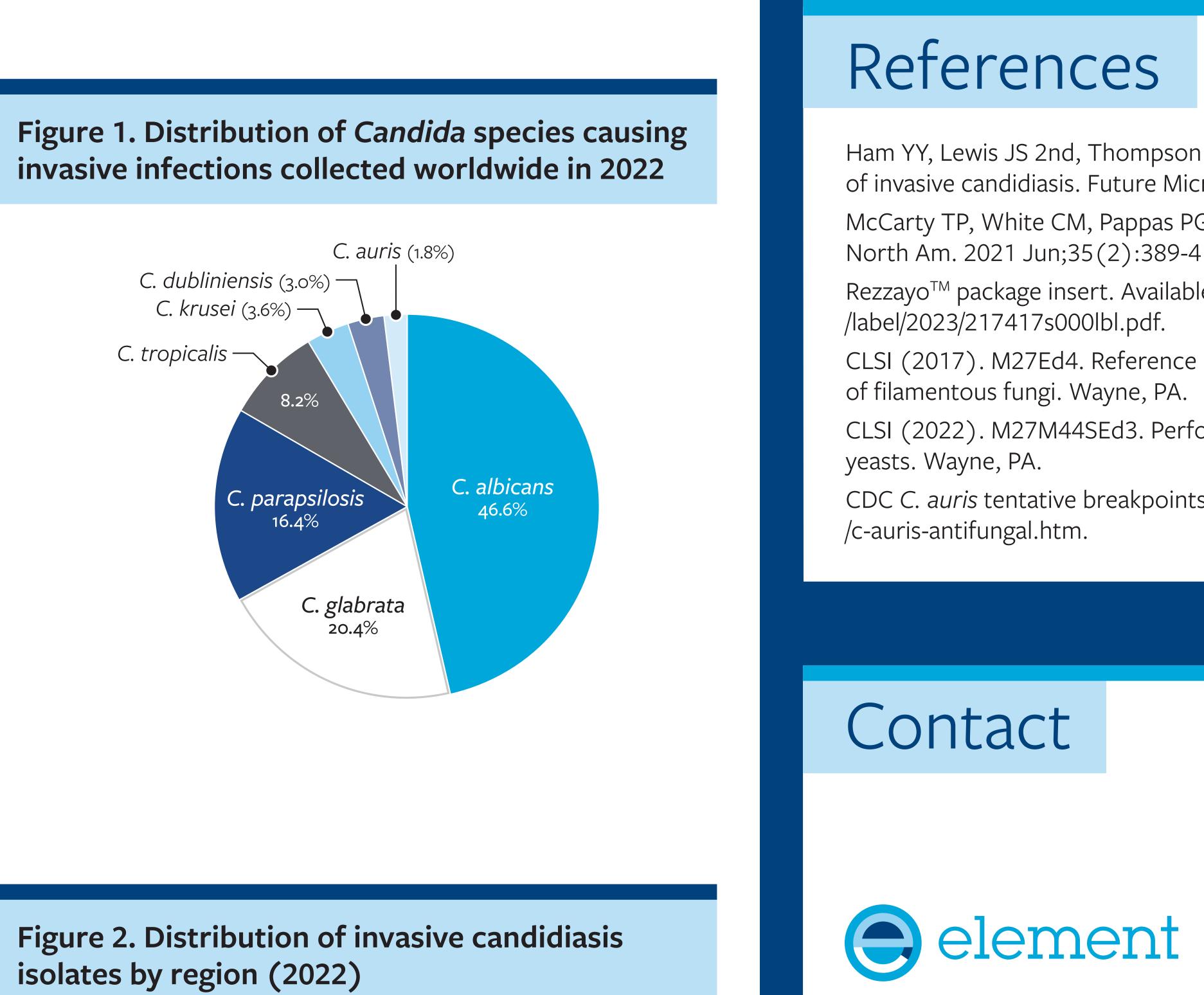
Organism (no of isolates)	MIC ₅₀ /MIC ₉₀ ; CLSI ^a %S								
Organism (no. of isolates)	RZF	ANF	CSF	MCF	FLC	VRC			
C albicana (222)	0.015/0.06	0.015/0.03	0.015/0.03	0.015/0.015	0.12/0.25	0.004/0.008			
C. albicans (233)	99.1	99.1	99.1	99.1	99.6	99.6			
C alphrata (102)	0.03/0.06	0.06/0.06	0.03/0.06	0.015/0.03	4/8	0.06/0.12			
C. glabrata (102)	99.0	98.0	98.0	97.1	96.1 ^b	NA			
C parapeilogie (92)	1/2	2/2	0.25/0.25	1/1	0.5/8	0.008/0.12			
C. parapsilosis (82)	100.0	96.3	100.0	100.0	84.1	93.9			
$\Gamma \mid C \mid D \mid C \mid P \mid P$	1/2	2/2	0.25/0.5	1/1	16/32	0.12/0.5			
FLC-R C. parapsilosis (10)	100.0	100.0	100.0	100.0	0.0	50.0			
(tranicalic (11)	0.015/0.03	0.015/0.03	0.015/0.03	0.015/0.03	0.25/0.5	0.015/0.03			
C. tropicalis (41)	100.0	100.0	100.0	100.0	100.0	100.0			
C krucci (10)	0.015/0.03	0.03/0.06	0.12/0.12	0.12/0.12	32/64	0.25/0.5			
C. krusei (18)	100	100	100	100	NA	94.4			
C dubliniancia (1E)	0.03/0.5	0.03/0.5	0.03/1	0.015/1	0.12/0.25	0.004/0.008			
C. dubliniensis (15)	86.7	NA	NA	NA	NA	NA			
C puris (0)	0.5/—	0.5/—	0.12/—	0.25/—	>128/—	1/—			
C. auris (9)	77.8	88.9	88.9	88.9	0.0	NA			

^a CLSI (2022) breakpoint was applied, including RZF breakpoint against C. *auris* CDC tentative breakpoints were applied to all other antifungal agents. Breakpoints are available at https://www.cdc.gov/fungal/candida-auris /c-auris-antifungal.html. Susceptible-dose-dependent.

Table 3. Activity of rezafungin and other echinocandins against worldwide fluconazolenonsusceptible Candida isolates causing invasive infections (2022)

				N	IIC (mg/L)	; Catego	ory of sus	ceptibili	ty ^a	
Organism C. albicans	Continent	Country USA	Rezafungin		Anidulafungin		Caspofungin		Micafungin	
	North America		0.004	S	0.008	S	0.008	S	0.015	S
C. auris	North America	USA	1	NS	1	S	0.06	S	0.25	S
C. auris	Latin America	Panama	>4	NS	4	R	>4	R	4	R
C. auris	North America	USA	0.5	S	0.25	S	0.12	S	0.12	S
C. auris	North America	USA	0.5	S	0.5	S	0.12	S	0.25	S
C. auris	Europe	Greece	0.5	S	0.25	S	0.25	S	0.25	S
C. auris	Europe	Greece	0.5	S	0.5	S	0.25	S	0.25	S
C. auris	Europe	Israel	0.5	S	0.5	S	0.06	S	0.12	S
C. auris	Latin America	Panama	0.25	S	0.25	S	0.06	S	0.12	S
C. auris	Europe	Greece	0.25	S	0.25	S	0.25	S	0.12	S
C. glabrata	North America	USA	0.25	S	0.25	I	0.25	I	0.06	S
C. glabrata	Europe	Germany	0.06	S	0.06	S	0.06	S	0.03	S
C. glabrata	Europe	Spain	0.06	S	0.12	S	0.12	S	0.12	I
C. glabrata	Europe	Israel	0.03	S	0.06	S	0.06	S	0.03	S
C. parapsilosis	North America	USA	1	S	1	S	0.12	S	0.5	S
C. parapsilosis	Europe	Israel	1	S	1	S	0.25	S	1	S
C. parapsilosis	Latin America	Brazil	2	S	2	S	0.5	S	1	S
C. parapsilosis	Europe	Italy	1	S	2	S	0.25	S	1	S
C. parapsilosis	Europe	Italy	1	S	2	S	0.25	S	1	S
C. parapsilosis	Europe	Italy	1	S	2	S	0.25	S	1	S
C. parapsilosis	Europe	Spain	1	S	2	S	0.5	S	1	S
C. parapsilosis	Europe	Italy	1	S	1	S	0.25	S	1	S
C. parapsilosis	Europe	Spain	1	S	2	S	0.5	S	1	S
C. parapsilosis	Europe	Spain	2	S	2	S	0.25	S	1	S
C. parapsilosis	North America	USA	2	S	2	S	0.25	S	2	S
C. parapsilosis	Europe	Turkey	1	S	2	S	0.25	S	1	S
C. parapsilosis	Europe	Turkey	0.5	S	1	S	0.25	S	1	S





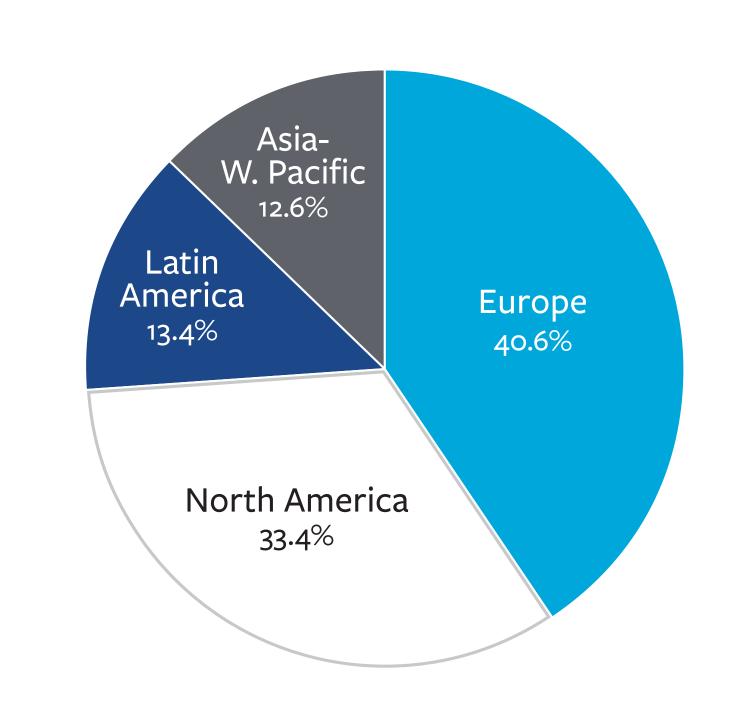
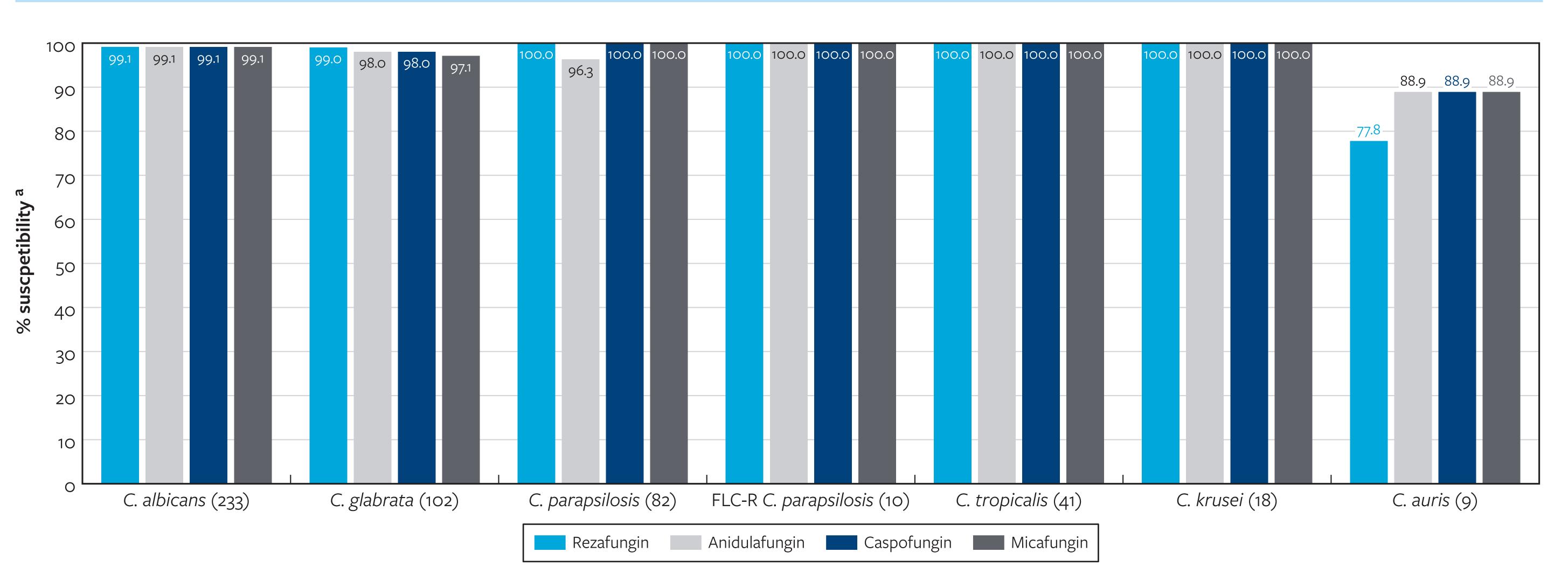


Figure 3. Activity of rezafungin and other echinocandins against invasive candidiasis isolates (2022)



^a CLSI (2022) breakpoint was applied, where available including RZF breakpoint against C. auris. C. auris CDC tentative breakpoints were applied to all other antifungal agents.

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