

Characterization of *Candida auris* (*Candidozyma auris*) from a worldwide surveillance program over 12 years

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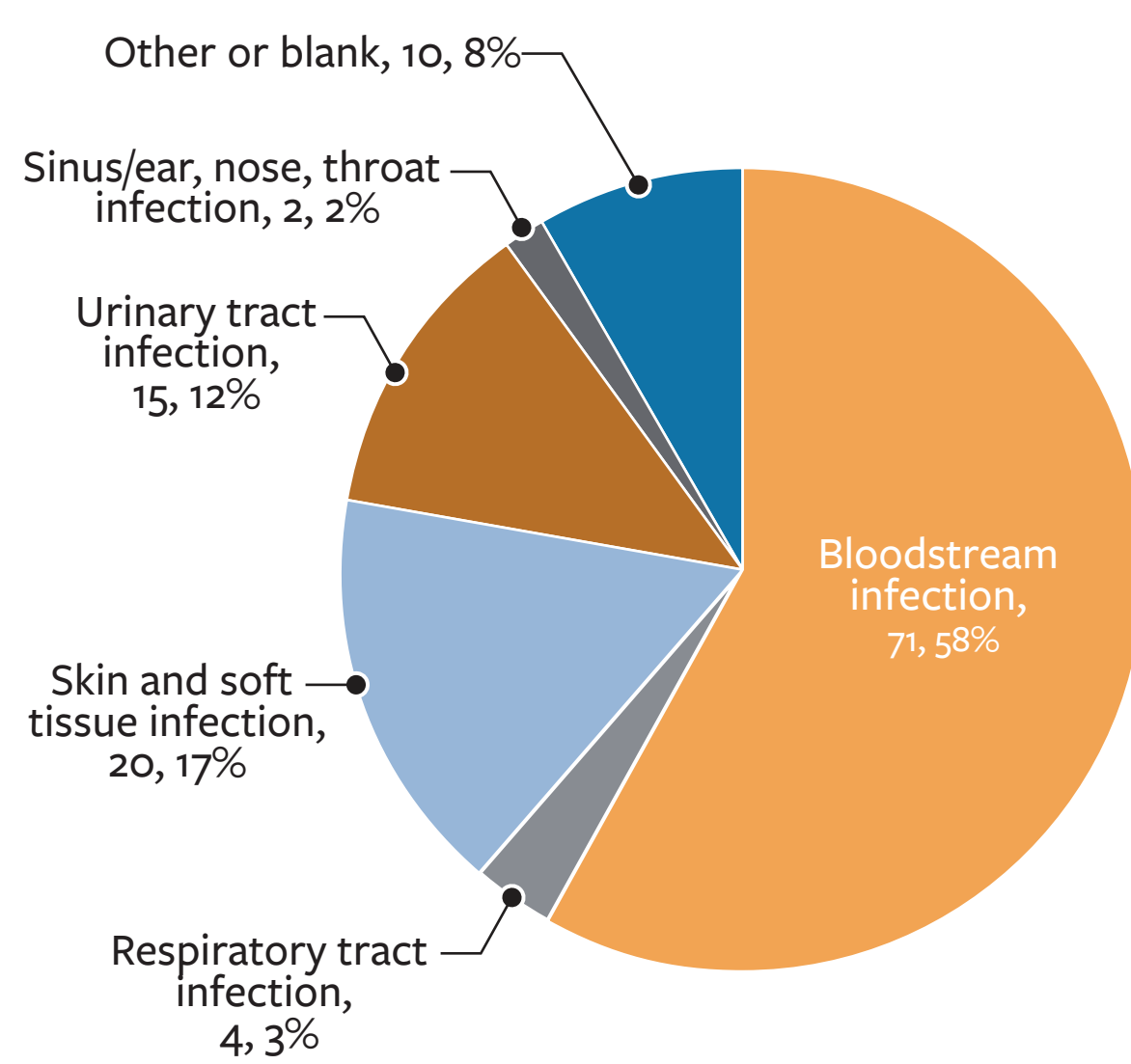
Introduction

- The World Health Organization (WHO) defines *Candida auris* (*Candidozyma auris*) as a critical priority pathogen due to its public health implications and multidrug-resistant properties
- 80-90% of *C. auris* isolates are fluconazole-resistant, 15-50% are resistant to amphotericin B, and approximately 1% are resistant to echinocandins in surveillance studies when minimum inhibitory concentrations (MICs) are interpreted by resistant-only US CDC breakpoints
 - No breakpoints are defined for triazoles outside of fluconazole
- The mortality rate of *C. auris* infections is >40%
- Additional information about *C. auris* susceptibility patterns, resistance markers, and genetic background is needed to understand optimal management of infections due to this organism
- To better understand antifungal resistance in *C. auris*, we performed antifungal susceptibility testing and comparative genomics on *C. auris* isolates collected as part of the SENTRY Antifungal Surveillance program

Methods

- C. auris* isolates ($n = 122$; 1 isolate per patient episode) were collected globally from 2013-2024 in 10 different countries (21 medical centers) from diverse infection sources (Figure 1)
- All isolates were initially identified by MALDI and were tested by CLSI reference broth microdilution method (M27); CDC resistant-only breakpoints were applied for anidulafungin, micafungin, amphotericin B, and fluconazole (<https://www.cdc.gov/candida-auris/hcp/laboratories/antifungal-susceptibility-testing.html>), no breakpoints were available for isavuconazole MIC interpretation
- Genome sequencing was performed on all clinical isolates
- Isolate FASTQs were quality trimmed and filtered with Sickel. Publicly available references for Clades I-VI were downloaded from the National Centre for Biotechnology Information. Variant calling was performed with Snippy; only unique, intraclade alterations are reported. Phylogeny was determined using the generalized time-reversible model in FastTree and the visualized using iTOL v7.4.2.

Figure 1. Infection sources of *C. auris* isolates



Results

- There has been an exponential increase in isolate numbers since 2013 ($n = 1$) to 2024 ($n = 46$)
- Clade I (South Asian, 59.8%), Clade III (South African, 23.0%), and Clade IV (South American, 17.2%) were recovered
- Clade-specific susceptibility patterns were observed (Table 1)
 - 98.6% of Clade I isolates were resistant to fluconazole, 68.5% were resistant to amphotericin B, and 0.0% were resistant to echinocandins
 - 100.0% of Clade III isolates were resistant to fluconazole, 7.1% were resistant to amphotericin B, and 7.1% were resistant to echinocandins
 - 85.7% of Clade IV isolates were resistant to fluconazole, 14.3% were resistant to amphotericin B, and 4.8% were resistant to echinocandins
- Overall, 90.2% of isolates had MICs ≤ 0.5 mg/L for isavuconazole
 - 8.2% of Clade I, 3.6% of Clade III, and 28.6% of Clade IV isolates had isavuconazole MICs ≥ 1 mg/L
- There were 3 isolates resistant to fluconazole and echinocandins (2 in Clade III, 1 in Clade IV)
 - Isavuconazole MICs in these isolates were 0.004, 0.03, and 0.03 mg/L
- Genetic characterization revealed that the majority of isolates had ERG11 alterations, but the predominant amino acid substitutions in fluconazole-resistant isolates differed among clades (Figure 2)
 - Y132F and K143R in Clade I, V125A/F126L in Clade III, and K143R and V447F in Clade IV
- CDR1 alterations were seen in most Clade I and 5 Clade IV isolates while only 2 Clade III isolates had CDR1 alterations; MDR1 could not be identified in one Clade III and IV isolate
 - These alterations were not associated with particular susceptibility patterns

Conclusions

- Twelve years of surveillance has shown a rising prevalence of *C. auris* worldwide among diverse infection sources
- >90% of isolates were non-resistant to echinocandins and had MICs <1 mg/L for isavuconazole
- >90% of all isolates were resistant to fluconazole and 7.1 to 68.5%, by clade, were resistant to amphotericin B
- There were no clear relationships observed between alterations in ERG11, MDR1, or CDR1 and susceptibility patterns

References

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Figure 2. Phylogenetic tree of *C. auris* isolates with Clade I in blue, Clade III in green, and Clade IV in yellow. Continent of origin (NA, North America; LATAM, Latin America; APAC, Asia-Pacific; EUR, Europe), isavuconazole (ISA), fluconazole (FLC), anidulafungin (AND), and amphotericin B (AMB) MIC indicated by respective colors, ERG11, CDR1, and MDR1 alterations also indicated in respective colors. Abbreviations: ND, not detected; del, deletion.

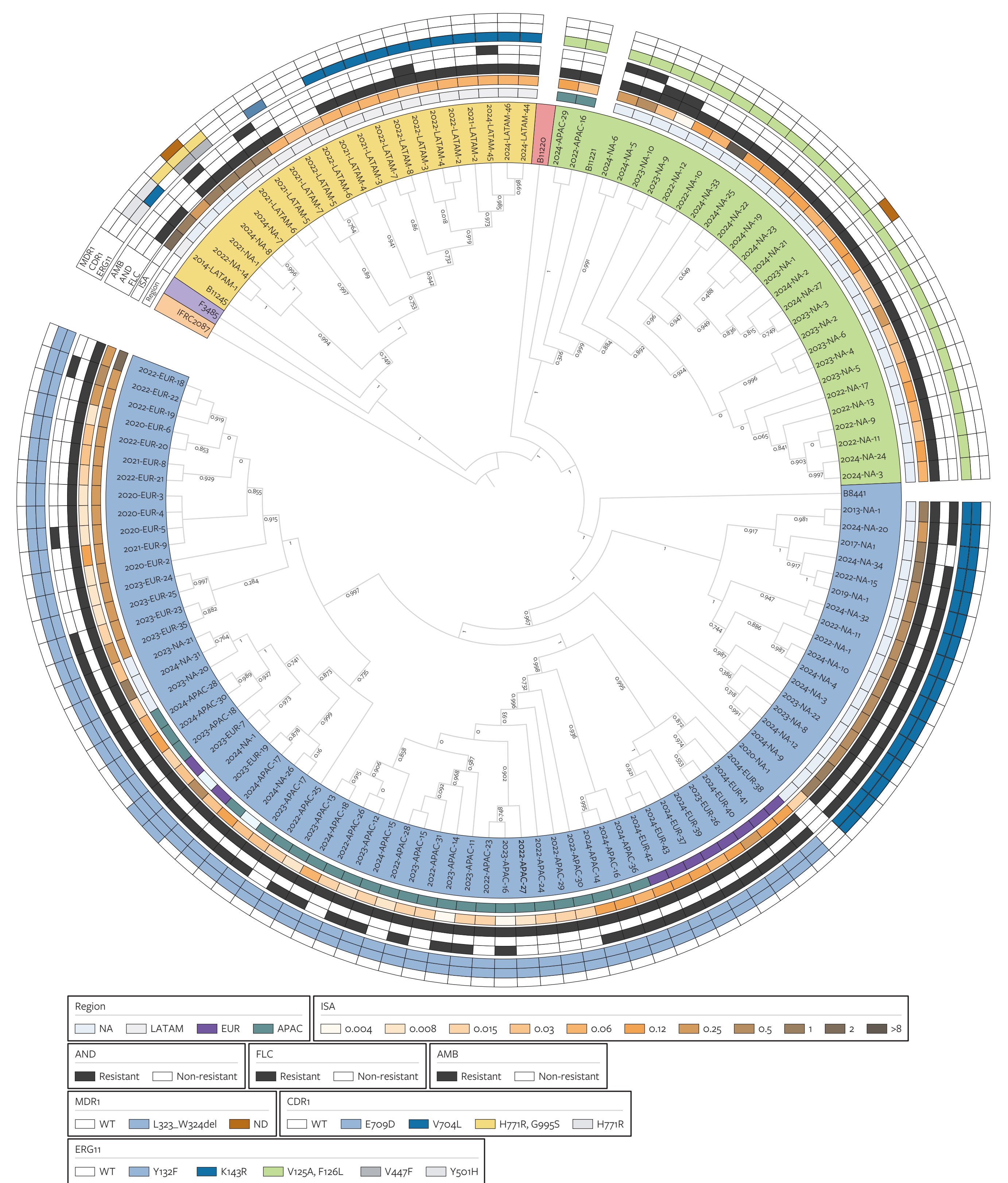


Table 1. *C. auris* isolates divided by clade and geographic region with MIC distributions

Clade (no. of isolates in all years)	MIC ₅₀ /MIC ₉₀ (mg/L) (CDC %NR ¹)				
	AND	MCF	ISA	FLC	AMB
I (73)	0.25/0.5 (100.0)	0.25/0.25 (100.0)	0.06/0.5	128/>128 (1.4)	2/2 (31.5)
North America (22)	0.5/1 (100.0)	0.25/0.5 (100.0)	0.5/1	>128/>128 (4.5)	2/2 (9.1)
Europe (26)	0.25/0.5 (100.0)	0.25/0.25 (100.0)	0.03/0.25	128/>128 (0.0)	2/2 (46.2)
APAC (25)	0.25/0.5 (100.0)	0.12/0.25 (100.0)	0.015/0.12	64/>128 (0.0)	2/2 (36.0)
III (28)	0.5/1 (92.9)	0.25/1 (92.9)	0.06/0.25	>128/>128 (0.0)	0.5/1 (92.9)
North America (26)	0.5/1 (92.3)	0.25/1 (92.3)	0.06/0.25	>128/>128 (0.0)	0.5/1 (92.3)
APAC (2)	0.25/NA* (100.0)	0.12/NA* (100.0)	0.03/NA*	128/NA* (0.0)	1/NA* (100.0)
IV (21)	0.5/0.5 (95.2)	0.12/0.25 (95.2)	0.06/1	64/128 (14.3)	1/2 (85.7)
North America (4)	0.25/NA* (100.0)	0.25/NA* (100.0)	1/NA*	64/NA* (25.0)	1/NA (75.0)
South America (17)	0.5/0.5 (94.1)	0.12/0.25 (94.1)	0.06/1	64/128 (11.8)	1/2 (88.2)

AND, anidulafungin; MCF, micafungin; ISA, isavuconazole; FLC, fluconazole; AMB, amphotericin B; *NA, not applicable as < 10 isolates represented
¹ <https://www.cdc.gov/candida-auris/hcp/laboratories/antifungal-susceptibility-testing.html>

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