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# Antifungal Resistance Trends of *Candida auris* Clinical Isolates in New York and New Jersey from 2016 to 2020

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**ABSTRACT** About 55% of U.S. *Candida auris* clinical cases were reported from New York and New Jersey from 2016 through 2020. Nearly all New York-New Jersey clinical isolates (99.8%) were fluconazole resistant, and 50% were amphotericin B resistant. Echinocandin resistance increased from 0% to 4% and pan-resistance increased from 0 to <1% for New York *C. auris* clinical isolates but not for New Jersey, highlighting the regional differences.

**KEYWORDS** antifungals, *Candida auris*, minimum inhibitory concentration, epidemiological cutoff

*Candida auris* is a multidrug-resistant fungal pathogen classified as an urgent public health threat by the Centers for Disease Control and Prevention (CDC) (1). First identified in the United States in 2013 and first detected in New York State in 2016 (2), *C. auris* was made nationally notifiable in 2018 (3). *C. auris* infection has caused severe illnesses among hospitalized patients and long-term care residents in the New York metropolitan area (4). As of December 31, 2020, of the 1,678 CDC tracked confirmed clinical cases in the United States, ~55% were reported by New York and New Jersey (3). Additionally, approximately 10% of all colonized cases in New York developed symptomatic *C. auris* infections. A previous study which analyzed 51 clinical case-patients in New York reported that 45% died within 90 days of reporting, and 98% of all clinical isolates were fluconazole resistant (4). As of December 2020, major *C. auris* genotypes comprise South Asia (clade I), East Asia (clade II), Africa (clade III), and South America (clade IV) (5). Recently, a fifth clade was identified based on whole genome sequencing, from a patient in Iran without travel history (6). Clade I was the major genotype (>99%) among clinical isolates reported from New York and New Jersey.

The CDC has tentatively defined MIC breakpoints (CDC-BP) for fluconazole (FLC), amphotericin B (AMB), and echinocandins using values established for other pathogenic *Candida* species (7). In instances where no breakpoints have been established, epidemiological cutoff value (ECV) could be used to find upper limit of the wild type (UL-WT) values, which help to identify non-wild-type strains within a population regardless of their susceptibility (7, 8). ECVs may aid in an early detection of *C. auris* isolates with the possible acquired resistance (7). Although the criteria for both ECV estimation and breakpoint establishment include the determination of MIC/minimum effective concentration (MEC) distribution of the pathogens, the breakpoint is the preferred value for making clinical decisions (7). This study aims to summarize antifungal resistance trends for New York and New Jersey *C. auris* clinical isolates using the recommended CDC-BP criteria and ECVs as an additional information for those antifungals for which CDC-BP are not available.



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**TABLE 1** Resistance and non-wild-type antifungals pattern of New York *C. auris* clinical isolates from 2016 through 2020

| Year and total no. of isolates | | | 2016 (28) | 2017 (141) | 2018 (231) | 2019 (300) | 2020 (448) | |
|---|---|---|---|---|---|---|---|---|
| Antifungal | CDC BP | ECV UL-WT | % (n) resistance/non-wild-type | | | | | *P* value |
| FLC | ≥ 32 | - | 100% (28) | 100% (141) | 100% (231) | 100% (300) | 99.6% (446) | 0.6393 |
| ITC | - | 2 | 0 | 0 | 0 | 0.7% (2) | 0.2% (1) | 0.666 |
| ISA | - | 2 | 0 | 7.1% (10) | 0.9 (2) | 0 | 9.2% (41) | $4.42e^{-12}$ |
| POS | - | 0.5 | 0 | 23.4% (33) | 13.4% (31) | 33% (99) | 42.6% (191) | $2.2e^{-16}$ |
| VRC | - | 4 | 7.4% (2) | 14.2% (20) | 0.9% (2) | 4.3% (13) | 4.9% (22) | $3.94e^{-6}$ |
| AFG | ≥ 4 | - | 0 | 1.4% (2) | 0.4% (1) | 2.3% (7) | 4% (18) | 0.05707 |
| CAS | ≥ 2 | - | 0 | 1.4% (2) | 0.4% (1) | 2.3% (7) | 4% (18) | 0.05707 |
| MFG | ≥ 4 | - | 0 | 1.4% (2) | 0.9% (2) | 1.7% (5) | 3.8% (17) | 0.1549 |
| AMB | ≥ 2 | - | 82.1% (23) | 75.9% (107) | 48.1% (111) | 45.3% (136) | 51.3% (230) | $1.019e^{-9}$ |
| 5-FC | - | 0.125 | 7.1% (2) | 11.3% (16) | 19.4% (31)[a] | - | - | 0.0793 |

[a]160 of 231 *C. auris* isolates were part of testing due to discontinuation of 5-FC Etest strips in 2018.

Wadsworth Center Mycology Laboratory (WCML), New York State Department of Health serves as the Northeast Regional Laboratory in CDC's Antibiotic Resistance Laboratory Network (AR Lab Network) for drug-resistant *Candida* spp. Suspected *C. auris* isolates from New York and New Jersey health care facilities were submitted to WCML and confirmed by Matrix Assisted Laser Desorption Ionization-time of flight mass spectrometry (MALDI-TOF MS) (9). Clinical isolates were defined as *C. auris* isolates from specimens that were collected from anatomical sites other than axilla-groin or nares, including blood, urine, and wounds. Genotyping of *C. auris* was performed by Sanger sequencing of the ribosomal genes (9). Antifungal susceptibility testing (AFST) was performed according to CLSI method M27-A3 for pathogenic yeasts (10). The MICs in $\mu$g/mL for the azoles and echinocandins were determined using the TREK frozen broth microdilution panel (catalog number CML2FCAN; Thermo Fisher Scientific, Marietta, OH, USA) (9, 11). MICs for AMB and 5-flucytosine (5-FC), were determined using Etest strips (AB Biodisk; bioMérieux, Solna, Sweden). AMB MICs of 1.5 $\mu$g/mL were rounded up to 2 $\mu$g/mL when determining susceptibility (12). MICs for 5-FC were only available from 2016 to September 2018 due to limited availability of 5-FC test strips in the United States. The UL-WT for posaconazole (POS), itraconazole (ITC), isavuconazole (ISA), voriconazole (VRC), and 5-FC were determined at the 97.5% estimation level using ECOFFinder (8). For New Jersey, there were $<$100 isolates tested against 5-FC, therefore, the UL-WT for 5-FC was not estimated. The isolates from New Jersey that were evaluated do not accurately represent the number of *C. auris* clinical cases in New Jersey, as only those isolates submitted to WCML for testing were included in this study. Statistical analyses, chi-squared and Fisher's exact test, were performed using R statistical software (v4.1.0; R Core Team, Vienna, Austria).

In total, 1,148 clinical *C. auris* isolates from 697 individuals in New York were evaluated: 28 from 2016, 141 from 2017, 231 from 2018, 300 from 2019, and 448 from 2020. Forty-five percent (512/1,148) of the isolates were recovered from the blood, followed by 23% (260/1,148) from urine, 13% (151/1,148) from respiratory tract, 12% (138/1,148) from other body sites and fluids, and 7% (87/1,148) from wounds (Fig. S1). Isolates with MIC values greater than or equal to the CDC tentative MIC breakpoint or estimated UL-WT were considered resistant or non-wild-type, respectively. All New York isolates were resistant to FLC (100%) during 2016 to 2019, while for 2020 resistance slightly dropped to 99.6% (446/448) (Table 1) with the modal MIC value at $\geq$256 $\mu$g/mL (Table S1). While isolates exhibited no resistance to echinocandins in 2016 (0/28), there was a steady increase in resistance isolates with 0.9% (2/231), 2.3% (7/300), and 4% (18/448) in 2018, 2019, and 2020, respectively (Fig. 1A). AMB resistance decreased significantly ($P < 0.001$) from 82.1% (23/28) in 2016 to 45.3% (136/300) in 2019 (Table 1) with the modal MIC value at the borderline, 1.5 $\mu$g/mL (Table S1). The percentage of isolates non-wild-type to 5-FC increased by year from 7.1% (2/28) in 2016 to 19.4% (31/160) in 2018. While the percentage of isolates non-wild-type to POS, ISA, and VRC fluctuated over time, a higher percentage was non-wild-type to POS (23.4% [33/141] in 2017; 13.4% [31/231] in 2018; 33% [99/300] in 2019; and 42.6% [191/448] in 2020) compared with the other azoles (Table 1 and Fig. 1B). Additionally, there was a noticeable increase in

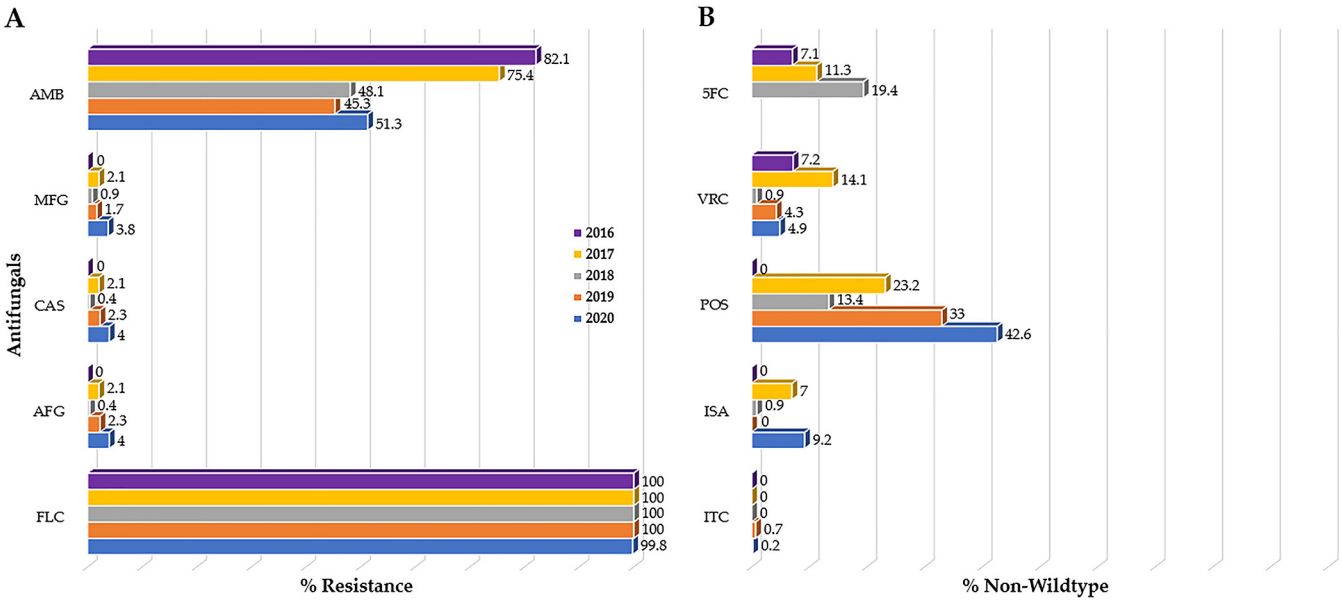


**FIG 1** Antifungal susceptibility pattern of *C. auris* clinical isolates from New York, 2016 to 2020. (A) Percent *C. auris* resistant isolates to antifungals for which CDC tentative MIC breakpoint (CDC-BP) are available. Most of the isolates were resistant to fluconazole (FLC) followed by amphotericin B (AMB), with a small number exhibiting resistance to echinocandins. (B) Percent *C. auris* non-wild-type isolates based on epidemiological cutoff values (ECV). A higher percentage of *C. auris* isolates were non-wild-type to posaconazole (POS) compared with the other azoles and 5-flucytosine (5-FC).

pan-resistance to three major classes of antifungals, from one isolate each in 2017 and 2018 to four isolates each in 2019 and 2020.

In total, 134 clinical *C. auris* isolates from 121 individuals in New Jersey were evaluated, including 12 from 2017, 13 from 2018, 48 from 2019, and 61 from 2020. Thirty-six percent (48/134) of the New Jersey *C. auris* isolates were recovered from urine, followed by 31% (41/134) from blood, 16% (22/134) from respiratory tract, 10% (13/134) from wound, and 7% (10/134) from other body sites and fluids (Fig. S2). All submitted New Jersey *C. auris* isolates were resistant to FLC and susceptible to the echinocandins (Table 2). The modal MIC values for FLC and AMB were ≥256 $\mu$g/mL and 1 $\mu$g/mL, respectively (Table S2). AMB resistance decreased from 66.7% (8/12) in 2017 to 31.1% (19/61) in 2020 (Fig. 2A). Like New York, a higher percentage of New Jersey *C. auris* isolates were non-wild-type to POS 15.4% (2/13) in 2018; 18.7% (9/48) in 2019; and 47.5% (29/61) in 2020 compared with the other azoles (Fig. 2B).

Previous studies of *C. auris* clinical isolates in different parts of the world including New York, have reported FLC resistance, elevated MICs to other azoles and AMB, and low resistance to echinocandins (9, 13, 14). *C. auris* isolates in this study displayed high AMB resistance early in the outbreak which decreased during later years; however, the small sample size does not allow for any strong inference about the presence and evolution of AMB resistant *C. auris* early in the New York and New Jersey outbreak. There was a steady increase in

**TABLE 2** Resistance and non-wild-type antifungals pattern of New Jersey *C. auris* clinical isolates from 2017 through 2020

| Year and total no. of isolates | | | 2017 (12) | 2018 (13) | 2019 (48) | 2020 (61) | |
|---|---|---|---|---|---|---|---|
| Antifungal | CDC BP | ECV UL-WT | % (n) resistance/non-wild-type | | | | *P* value |
| FLC | ≥ 32 | - | 100% (12) | 100% (13) | 100% (48) | 100% (61) | 1 |
| ITC | - | 2 | 0 | 7.7% (1) | 0 | 0 | 0.1852 |
| ISA | - | 2 | 0 | 7.7% (1) | 0 | 14.8% (9) | 0.01613 |
| POS | - | 0.5 | 0 | 15.4% (2) | 18.7% (9) | 47.5% (29) | 0.0002489 |
| VRC | - | 4 | 8.3% (1) | 7.7% (1) | 2.1% (1) | 4.9% (3) | 0.3546 |
| AFG | ≥ 4 | - | 0 | 0 | 0 | 0 | 1 |
| CAS | ≥ 2 | - | 0 | 0 | 0 | 0 | 1 |
| MFG | ≥ 4 | - | 0 | 0 | 0 | 0 | 1 |
| AMB | ≥ 2 | - | 66.7% (8) | 46.2% (6) | 43.7% (21) | 31.1% (19) | 0.1108 |

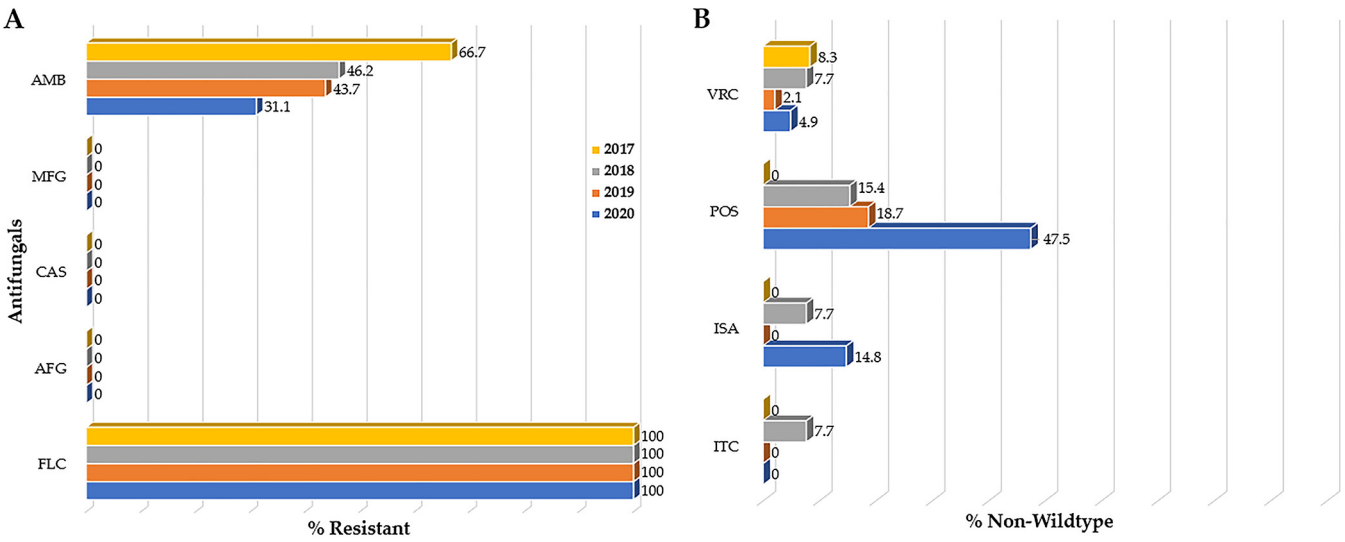


**FIG 2** Antifungal susceptibility pattern of *C. auris* clinical isolates from New Jersey, 2017 to 2020. (A) Percent *C. auris* resistant isolates to antifungals for which CDC tentative MIC breakpoint (CDC-BP) are available. All isolates were resistant to fluconazole (FLC) followed by amphotericin B (AMB), while none showed resistance to echinocandins. (B) Percent *C. auris* non-wild-type isolates based on epidemiological cutoff values (ECV). A higher percentage of *C. auris* isolates was non-wild-type to posaconazole (POS) compared with the other azoles.

echinocandins resistance observed between 2017 and 2020 in New York that was not observed in *C. auris* isolates from New Jersey. Pan-resistance, which was only observed in New York isolates, increased over time, but remained rare in 2020, 4 years into the New York outbreak (15). The precise mechanism(s) behind differences in *C. auris* echinocandin and pan-resistance between New York and New Jersey isolates is not clear from the present study. Previous studies in the U.S. including from New York documented *C. auris* echinocandin resistance in patient isolates after echinocandin therapy (15, 16). The observed resistance pattern might reflect intraregional differences in antifungal treatment practices, but further investigations are needed for confirmation (15). We noticed significant difference in the total submission of clinical *C. auris* isolates submitted from New York and New Jersey. Most likely this reflects a lag in submission from clinical laboratories in New Jersey. It is also likely that initial introduction and local spread were confined to New York health care facilities and surrounding metropolitan areas, including New Jersey, were affected subsequently.

**Conclusions.** This study highlights the antifungal resistance pattern of New York and New Jersey *C. auris* clinical isolates. Nearly all isolates were FLC resistant. Additionally, AMB resistance was high, but decreased significantly for New York in later years compared with earlier years of investigations. Echinocandin resistance was rare initially but increased for New York isolates in later years. Ten New York *C. auris* isolates from eight individuals were identified as pan-resistant.

## SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

**SUPPLEMENTAL FILE 1**, PDF file, 0.2 MB.

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