Treatment of *Candida auris*
Background and Data

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Candida auris

- Type of yeast first described in 2009
- Mortality is >45% for clinical infections within the first 30 days
- Can cause bloodstream, wound, and ear infections
- It also has been isolated from respiratory and urine specimens, but it is unclear if it causes infections in the lung or bladder
- CDC does not recommend treatment of C. auris identified from noninvasive sites when there is no evidence of infection
Typically affects the sickest of the sick

- Ventilator-dependent/Tracheostomies
- Colonized with other MDROs
- High-acuity, long length of stay facilities
- Recently received antibiotics and antifungals
Certain broad-spectrum antibiotics were associated with *C. auris* colonization.

Slide courtesy CDC
Role of International Healthcare Exposure

- Majority of Virginia cases don’t have direct links to healthcare abroad
- Cases are a result of introductions from abroad followed by local transmission

Obtaining healthcare exposure history is still important…….
Countries from which *Candida auris* cases have been reported, as of February 15, 2021

This map is no longer being updated given how widespread *C. auris* has become.

**Virginia Reporting Requirements (since Nov 2018)**

<table>
<thead>
<tr>
<th>Virginia Reportable Disease List</th>
<th>Virginia Isolate Submission List</th>
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</thead>
</table>
| Report suspected or confirmed *C. auris*, infection or colonization. | Submit any of the following isolates to DCLS using the [DCLS Clinical Microbiology/Virology Request Form](#) and including AFST results with submission:  
1. All confirmed *C. auris* and *Candida haemulonii* isolates from any specimen source. OR  
2. Yeast isolates from any specimen source when unable to identify species after identification is attempted per laboratory policies. OR  
3. Suspected *C. auris* isolates from any specimen source. *C. auris* can be misidentified if your laboratory uses certain yeast identification methods.  
| Include available antifungal susceptibility testing (AFST) results. | |
Public Health Terminology: Clinical vs Colonized

• Clinical case: A person with *C. auris* identified through microbiological cultures obtained for routine care.
  • Ex. Blood or urine cultures (doesn’t have to represent a “true” infection)

• Colonized/Screening case: A person with *C. auris* identified at a laboratory from a swab collected for the purpose of determining if they are colonized
  • *C. auris*: primarily skin
Increasing transmission of *C. auris* in the United States
C. auris in the Mid-Atlantic Region
Data through August 2021

Clinical Cases

Screening Cases

Legend
- 1 to 5
- 5 to 10
- 11 to 25
- 26 to 50
- 50 or more

2019

2020

2021

Slide courtesy MD AR Lab Network
Virginia *C. auris* Case Counts

*C. auris* Cases Reported to VDH, 2018-2021

*Data reported to VDH as of November 1, 2021*
C. auris Colonization Duration

- Colonization can persist for many months
- Many different body sites can be colonized with C. auris
- 5-10% of patients colonized with C. auris develop invasive infections
- Currently, no well-established decolonization strategies for C. auris

Slide courtesy CDC
Why are we concerned about *Candida auris*?

- **Highly drug-resistant**
- **Patients can become colonized and develop invasive infections**
- **Spreads in healthcare settings**
- **Can persist on surfaces in healthcare environments**
- **Difficult to identify (improving)**

*C. auris* resources

- AFST Interpretation
- Tracking
- Infection Prevention
- EPA List P
- Identification
Strong phylogeographic structure – 4 clades

*Virginia has identified all 4 clades*

Simultaneous emergence on 3 continents

Lockhart et al., *CID* 2017

A fifth clade has been described
C. auris Resistant Isolates in DC, MD, and VA
301 isolates through 8/12/2021

- 65% multidrug-resistant (National: 33%)
- Multiple pan-resistant cases reported in US since 2020

Azoles
99%
National: 85%

Polyenes
64%
National: 33%

Echinocandins
4%
National: 2%

Preliminary data courtesy CDC AR Lab Network
The Mid-Atlantic is one of the 2 areas of the country experiencing transmission of echinocandin-resistant *C. auris*
TREATMENT OF CANDIDA AURIS

Laura Cwengros, PharmD, BCIDP
Clinical Infectious Diseases Manager
CJW Medical Center
OBJECTIVES

1. Identify first-line therapy for *Candida auris* infections

2. Understand the resistance mechanisms from *Candida auris*

3. Review salvage therapy & pipeline drugs for persistent infection
**CANDIDA AURIS: EMERGING THREAT**

Reported clinical cases of *Candida auris*, September 1, 2020-August 31, 2021

- Clinical cases include confirmed and probably cases
- Targeted screening has identified an additional 3,043 patients colonized with *C. auris*

https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html#recent
 Often multidrug-resistant

Difficult to identify with standard laboratory methods

Has caused outbreaks in healthcare settings

• Healthcare facilities or laboratories that suspect infection with C. auris should contact state or local public health authorities and CDC

https://www.cdc.gov/fungal/candida-auris/index.html
IDENTIFICATION NUANCES FOR C. AURIS
# Antifungal “Breakpoints”

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Tentative MIC Breakpoints (µg/mL)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anidulafungin</td>
<td>≥ 4</td>
<td>Tentative breakpoints are based on the modal distribution of echinocandin MICs of approximately 100 isolates from diverse geographic locations</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>≥ 2</td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>≥ 4</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>≥ 2</td>
<td>Recent pharmacokinetic/pharmacodynamic mouse model of <em>C. auris</em> indicates that under standard dosing, the breakpoint for amphotericin B should be 1 or 1.5, similar to what has been determined for other <em>Candida</em> species. Therefore, <strong>isolates with an MIC of ≥2 should now be considered resistant</strong>. If using Etest for amphotericin B and an <strong>MIC of 1.5 is determined</strong>, that value should be rounded up to 2.</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>≥ 32</td>
<td>Isolates with MICs ≥ 32 were shown to have a resistance mutation in the <em>Erg11</em> gene</td>
</tr>
</tbody>
</table>
| Voriconazole and other second generation triazoles | N/A                               | - Consider using fluconazole susceptibility as a surrogate for susceptibilities  
- Isolates resistant to fluconazole may respond to other triazoles occasionally                                                             |

Transmission of pan-resistant and echinocandin-resistant strains

• Since January 2021, independent clusters of pan-resistant or echinocandin-resistance cases in Texas and the District of Columbia (DC)
  • Involved common health care encounters
  • No known previous echinocandin exposures
• January – April 2021
  • Pan-resistance strains: 3 (DC), 2 (Texas)
  • Resistant to both echinocandins and fluconazole: 5 (Texas)

Considerations to prevent clusters

• Measures to contain further spread:
  • Surveillance
  • Public health reporting
  • Infection control measures
  • Consider early antifungal susceptibility testing

In the U.S., cases of *C. auris* had average of 3 healthcare facility encounters in 90 days preceding diagnosis; majority admitted to high-acuity long-term care facility

Lyman et al. MMWR. 2021; 70(29). 1022-3.
INVASIVE CANDIDIASIS

Abdominal cavity
- Abdominal abscess
- Pancreatitis
- Peritonitis

Bone
- Osteomyelitis
- Spondyloitis

Brain
- Brain abscess
- Meningoencephalitis

Eye
- Choroiditis
- Retinitis
- Endophthalmitis

Kidney
- Candiduria
- Pyelonephritis
- Pyonephrosis
- Renal abscess

Liver and spleen
- Chronic disseminated candidiasis
- Focal abscess

Lung
- Focal abscess

Nature Reviews | Disease Primers

PATIENT SCENARIO #1

- Patient presents to the hospital with septic shock from a long-term care facility. CC: altered mental status and fevers. Blood cultures obtained in the ED (+) for yeast with no identified source.

- What antifungal treatment do you start for fungemia?
  A. Fluconazole 6 mg/kg loading dose, then 400 mg PO/IV daily
  B. Micafungin 100 mg IV daily
  C. Liposomal amphotericin B 3 mg/kg IV daily
  D. Ibrexafungerp 300 mg PO every 12 hours
### FIRST-LINE TREATMENT

<table>
<thead>
<tr>
<th>Drugs</th>
<th>U.S. resistance rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>90%</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>30%</td>
</tr>
<tr>
<td>Echinocandins</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>

- Adults and children ≥ 2 months of age: 
  - Echinocandins

- Neonates and infants < 2 months of age: 
  - Amphotericin B deoxycholate (1 mg/kg daily)

TACKLING CANDIDA AURIS

Empiric
- Start echinocandin (consider source of infection)
- Obtain source control
- Repeat blood cultures (if fungemic)

Escalation
- If clinically unresponsive to echinocandin treatment OR has persistent fungemia (>5 days): start liposomal amphotericin B

Additional Treatment
- Rapid improvement $\rightarrow$ de-escalate based on susceptibilities?
- Lack of improvement:
  - Combination treatment?
  - Investigational drugs?

SYNERGY OR ANTAGONISM OF COMBINATIONS?

<table>
<thead>
<tr>
<th>N of isolates</th>
<th>Compound A</th>
<th>Compound B</th>
<th>Type of interaction N (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>5-Flucytosine</td>
<td>Amphotericin B</td>
<td>SYN: 1 (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IND: 14 (93)</td>
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<tr>
<td></td>
<td></td>
<td>Micafungin</td>
<td>SYN: 1 (7)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>IND: 14 (93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voriconazole</td>
<td>SYN: 15 (100)</td>
</tr>
<tr>
<td>10</td>
<td>Caspofungin</td>
<td>Fluconazole</td>
<td>SYN: 10 (100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IND: 10 (100)</td>
</tr>
<tr>
<td></td>
<td>Micafungin</td>
<td>Fluconazole</td>
<td>SYN: 10 (100)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>IND: 10 (100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Voriconazole</td>
<td>SYN: 10 (100)</td>
</tr>
</tbody>
</table>

SYN = synergy; IND = indifferent; ANT = antagonism

## C. AURIS RESISTANCE MECHANISMS

<table>
<thead>
<tr>
<th>Class</th>
<th>Target of class</th>
<th>Resistance mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echinocandins</td>
<td>Inhibit 1,3-β-D-glucan synthetase (encoded by FKS1 and FKS2)</td>
<td>FKS1 gene mutation</td>
</tr>
<tr>
<td>Azoles</td>
<td>Inhibits lanosterol 14 α-demethylase (LDM) → converts lanosterol to ergosterol (key fungal membrane component)</td>
<td>ERG11 mutation</td>
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<tr>
<td></td>
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<td>Efflux pumps</td>
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<tr>
<td></td>
<td></td>
<td>ERG11 duplication</td>
</tr>
<tr>
<td>Polyenes</td>
<td>Binds to ergosterol → alters cell membrane permeability → leakage of cell components → cell death</td>
<td>Poorly understood</td>
</tr>
<tr>
<td>5-Flucytosine</td>
<td>Converted to fluorouracil by uracil phosphoribosyl transferase (encoded by FUR1) → competes with uracil interfering with fungal RNA</td>
<td>FUR1 gene mutation</td>
</tr>
</tbody>
</table>

One week later, the patient’s blood cultures return, identified as *C. auris*. Cultures are resistant to fluconazole and there may be concern for *FKSI* mutation. Patient remains on pressors with persistent positive blood cultures.

What antifungal treatment should the patient be transitioned to?

A. Fluconazole 6 mg/kg loading dose, then 400 mg PO/IV daily
B. Micafungin 100 mg IV daily
C. Liposomal amphotericin B 5 mg/kg IV daily
D. Ibrexafungerp 300 mg PO every 12 hours
THE ANTIFUNGAL PIPELINE
PIPEDLINE DRUGS & SPECTRUM OF ACTIVITY

<table>
<thead>
<tr>
<th>Antifungal agents</th>
<th>Fosmanogepix</th>
<th>Ibrexafungerp</th>
<th>Olorofim</th>
<th>Opelconazole</th>
<th>Rezafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus calidolusius</td>
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<tr>
<td>Aspergillus fumigatus</td>
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<tr>
<td>Azole-resistant A. fumigatus</td>
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<tr>
<td>Aspergillus flavus</td>
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<td>Aspergillus niger</td>
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<td>Aspergillus terreus</td>
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<tr>
<td>Aspergillus niger</td>
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<tr>
<td>Cunninghamella</td>
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<td>Lichtheimia</td>
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<td>Mucor</td>
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<tr>
<td>Rhizopus</td>
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<tr>
<td>Fusarium spp</td>
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<tr>
<td>Alternaria alternata</td>
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<tr>
<td>Gladosporium spp</td>
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<tr>
<td>Pessicillomyces variotii</td>
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<tr>
<td>Purpureocillium lilacinum</td>
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<tr>
<td>Scopulariopsis spp.</td>
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<td>Rasamsonia spp.</td>
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<tr>
<td>Scedosporium spp.</td>
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<tr>
<td>Lomentospora prolificans</td>
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</table>

Legend:
- **Potent activity**
- **Variable activity**
- **No activity**
- **Unknown / currently investigated**

IBREXAFUNGERP
(FORMERLY SCY-08)

- First antifungal from the triterpenoid class
- Novel enfumafungin-derived inhibitor of \((1,3)\)-\(\beta\)-D-glucan synthase (inhibits cell wall synthesis)
- Retains activity \textit{in vitro} against azole-resistant and echinocandin-resistant strains, stable against \textit{FKS} gene mutations
- High tissue concentration, minimal distribution to CNS

Ghannoum M et al. \textit{Antibiotics.} 2020; 9(9): 539.
IBREXAFUNGERP

- FDA approved: vulvovaginal candidiasis (VVC)
- Dosage: 300 mg (two 150 mg tablets) every 12 hours
- Use with strong CYP3A inhibitors: reduce dose to 150 mg every 12 hours
- Administration:
  - Can crush and administer with 8 oz/240 mL water. Close tube 1 hour before and after (flush) to ensure tube functionality
  - Bioavailability increases with food
- Well tolerated
  - Largest side effect in clinical studies: GI disturbance (nausea/vomiting/upset stomach)

ONGOING OPEN-LABELED STUDIES

**FURI**
- Salvage treatment: difficult-to-treat mucocutaneous & invasive fungal infections
- Refractory to, intolerant of current standards of care, or require a non-azole oral step-down therapy for azole-resistant species
- Total response: 87% (64/74)

**CARES**
- Hospitalized patients with invasive candidiasis caused by *C. auris*
- Total response: 80% (8/10)

- Enrolled patients with candidemia or *C. auris* infection: ibrexafungerp 750 mg (3 x 250 mg tablets) orally twice daily x 48 hours, then 750 mg orally once daily
- In combination with azoles: 500 mg orally twice daily x 48 hrs, then 500 mg orally once daily

PATIENT SCENARIO #3

• Patients blood cultures with *C. auris* continue to persist. TEE positive for endocarditis. Current treatment: micafungin 150 mg IV daily + liposomal amphotericin B 5 mg/kg.

• Compassionate use for oral ibrexafungerp is being considered, what dose should be used?
  A. Ibrexafungerp 150 mg twice daily every 12 hours
  B. Ibrexafungerp 300 mg twice daily every 12 hours
  C. Ibrexafungerp 750 mg twice daily x 48 hours, then 750 mg daily
  D. Ibrexafugerp 500 mg twice daily x 48 hrs, then 500 mg daily
REZAFUNGIN
(FORMERLY CD101)

- Prolonged half-life (> 130 hours) = once weekly dosing
- *In vitro* MIC\textsubscript{90} \(C\) \textit{auris}: 0.25-1 mcg/mL (AUC/MIC adequate for > 90% \(C.\) \textit{auris})
- Reduced activity against strains carrying \textit{FKS1} and \textit{FKS2} genes

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>CDC Threat Level</th>
<th>Rezafungin</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{Candida auris}</td>
<td>Urgent Threat</td>
<td>✔️</td>
</tr>
<tr>
<td>Drug resistant \textit{Candida}</td>
<td>Serious Threat</td>
<td>✔️</td>
</tr>
<tr>
<td>Azole-resistant \textit{Aspergillus fumigatus}</td>
<td>Watch List</td>
<td>✔️</td>
</tr>
</tbody>
</table>
FOSMANOGEPIX (APX001)

- Prodrug of manogepix
- Inhibits Gwt1; targets GPI-anchored protein maturation
- Dosing for invasive infection:
  - 1000 mg IV twice daily for one day, then 600 mg IV daily for at least two days, followed by 600 mg IV daily or 700 mg orally daily
- Has CNS penetration
- Potent: MIC against *C. auris* < 0.0005-0.03 mcg/mL
  - *In vitro* activity vs. pan-resistant *C. auris*
  - No activity vs. *C. krusei*
- Phase 2 open-label study for candidemia/invasive candidiasis caused by *C. auris* (NCT04148287) – terminated early due to COVID-19

OTESECONAZOLE (VT-1161)

- Tetrazole class (new generation of oral lanosterol 14α-demethylase inhibitors)
- Selective inhibition of fungal CYP51A
  - Less drug-drug interactions and adverse events
- In vitro activity against Candida spp. resistant to fluconazole and echinocandins
- Early evidence of possible cross-resistance between triazoles and tetrazoles
  - Target enzyme modification or overexpression
  - PDR1-mediated drug efflux transporters

OLOROFIM (FORMERLY F901318)

- Orotomide class
- Inhibits dihydroorotate dehydrogenase (targets pyrimidine synthesis)
- Treatment of invasive infection: 150 mg orally twice daily for one day, then 90-150 mg orally twice daily
- NCT03583164: Phase 2 open-label single-arm of F901318 as treatment of invasive fungal infections due to Lomentospora prolificans, Scedosporium spp., Aspergillus spp., and other resistant fungi which are susceptible to F901318 in patients with limited treatment options
  - 30 mg tablets, maximum daily dose of 300 mg with dose adjustments (CYP interactions and plasma level monitoring)
- Compassionate use or expanded access: rare and difficult-to-treat mold infections
- No published reports describing clinical efficacy
• Triazole with inhaled administration
• *In vitro* synergy with posaconazole and voriconazole for Aspergillus
• Clinical setting:
  • intolerance to high systemic azole concentrations
  • prophylaxis in lung transplants, ICU setting
• Treatment of invasive infection: 5 mg nebulized daily
• Efficacy vs. C. auris?
FINAL THOUGHTS

Appropriate identification & susceptibility testing

Antifungal treatment (site of infection, clinical response, adverse events)

Source control (line removal, debridement, etc.)

Infection control (patient isolation, surveillance swabbing, and reporting)

“Effective” management of C. auris