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“Ear” on the Side of Caution: Tracking *Candida auris*

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Disclosure

I do not have (nor does any immediate family member have) a vested interest in or affiliation with any corporate organization offering financial support or grant monies **for this continuing education activity**, or any affiliation with an organization whose philosophy could potentially bias my presentation.

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Pharmacist Objectives

- Discuss *C. auris* epidemiology and its emergence as a concerning pathogen, including challenges to microbiological identification
- Describe risk factors for *C. auris* colonization and developing invasive disease
- Examine important infection control measures to manage *C. auris* outbreaks and prevent further spread
- Evaluate current antifungal options and resistance patterns to determine appropriate treatment for patients

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Technician Objectives

- Describe *C. auris* and its emergence as a concerning pathogen
- Examine important infection control measures to manage *C. auris* outbreaks and prevent further spread
- Recognize current antifungal options for the treatment of *C. auris* infections

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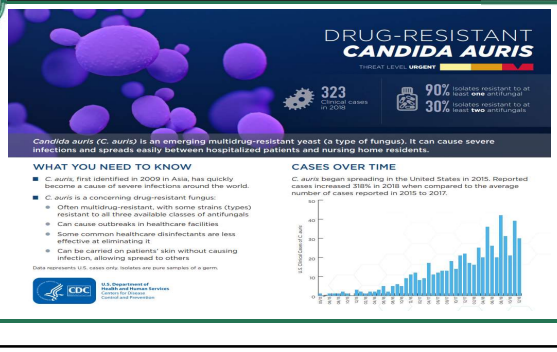

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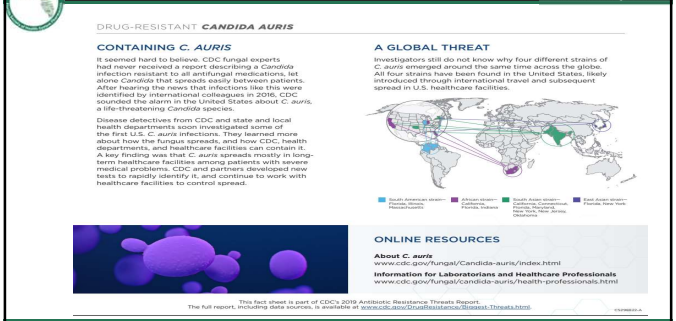

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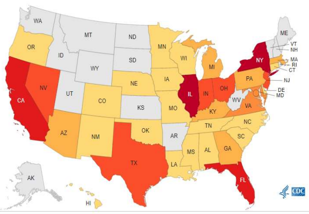
Tracking *Candida auris:* 2013-2022



- Clinical cases include both confirmed and probable cases
  - 5,654
  - Florida = 683
- 13,163 screening cases

CDC: Tracking Candida auris, https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html

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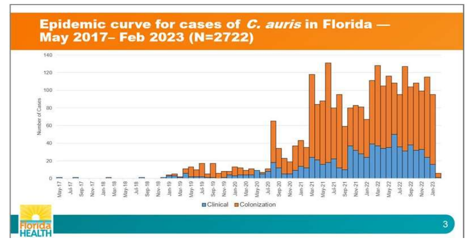
Tracking *Candida auris*- Florida



2722 Total Cases

- 1930 colonized
- 792 clinical
- Mean Age: 66.26

Source: Florida Department of Health, Health Care Associated Infection Prevention Program

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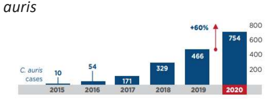
COVID-19 Pandemic and Impact on *C. auris*

- Hospitals saw increase in outbreaks associated with *C. auris*
  - COVID-19 units
- 60% increase in 2020 compared to 2019
- Significant decline in colonization screening
  - Limited resources to perform



COVID-19: U.S. Impact on Antimicrobial Resistance, Special Report 2022

Morbidity and Mortality Weekly Report

Candida auris Outbreak in a COVID-19 Specialty Care Unit — Florida, July–August 2020

Christopher Prestel, MD[1,2]; Erica Anderson, MPH[2]; Kaitlin Forsberg, MPH[3]; Meghan Lyman, MD[3]; Marie A. de Perio, MD[4,5]; David Kuhar, MD[1]; Kendra Edwards[6]; Maria Rivera, MPH[2]; Alicia Shugart, MA[1]; Maroya Walters, PhD[1]; Nychie Q. Dotson, PhD[2]

2022 Special Report COVID-19: U.S. Impact on Antimicrobial Resistance. CDC, 2022. https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf
Prestel C, Anderson E, Forsberg K, Lyman M, de Perio MA, Kuhar D, Edwards K, Rivera M, Shugart A, Walters M, Dotson NQ. Candida auris Outbreak in a COVID-19 Specialty Care Unit - Florida, July-August 2020. MMWR Morb Mortal

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Typically affects patients who are sickest of the sick

- Risk Factors Include
  - Tracheostomies, central venous catheters, feeding tubes, indwelling urinary catheters
  - Ventilator dependent
  - Recent surgery
  - Diabetes
  - Frequent healthcare encounters
  - Recent exposure to broad spectrum antibiotics and antimicrobials
  - Co-colonization with other multi-drug resistant organisms
  - ICU admission
  - Immunocompromised
  - Malignancy
  - Total Parenteral nutrition
  - Chronic Kidney Disease
  - HIV/AIDs

CDC: Candida auris, https://www.cdc.gov/fungal/candida-auris/candida-auris-qanda.html#:~:text=Limited%20data%20suggest%20that%20the,spectrum%20antibiotic%20and%20antifungal%20use.
Al-Rashdi A, Al-Maani A, Al-Wahaibi A, Alqayoudhi A, Al-Jardani A, Al-Abri S. Characteristics, Risk Factors, and Survival Analysis of Candida auris Cases: Results of One-Year National Surveillance Data from Oman. J Fungi (Basel). 2021 Jan 7;7(1):31. doi: 10.3390/jof7010031. PMID: 33430221; PMCID: PMC7825686.
Watkins RR, Gowen R, Lionakis MS, Ghannoum M. Update on the Pathogenesis, Virulence, and Treatment of Candida auris. Pathog Immun. 2022 Oct 21;7(2):46-65. doi: 10.20411/pai.v7i2.535. PMID: 36329818; PMCID: PMC9620957.

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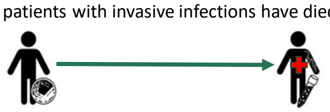
Invasive Infections

- 5-10% of colonized patients develop bloodstream infections
- 30-60% of patients with invasive infections have died



- Reported mortality of invasive infections
  - *39% within the first 30 days*
  - *58% within first 90 days*

Adams E, Quinn M, Tsay S, et al. Candida auris in Healthcare Facilities, New York, USA, 2013–2017. *Emerg Infect Dis*. 2018;24(10):1816-1824.

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Prevention of Invasive Infections

- Patients with *C. auris* generally have invasive devices.
  - Serve as portals of entry for invasive infection
  - Require strict adherence to recommended insertion and maintenance practices (CLABSI, CAUTI bundles)
    - Continually assess need for device and ensure prompt removal when no longer necessary

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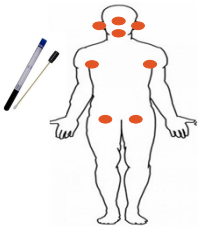
Colonization

- Often indefinite, remaining persistent for many months. Patients often remain colonized even after treatment for clinical infection.
- May lead to:
  - Transmission to others
  - Invasive infection
- Primarily on skin
  - Recommend screening by swabbing axilla/groin
  - Nares and other body sites also can become colonized
- No known decolonization strategies



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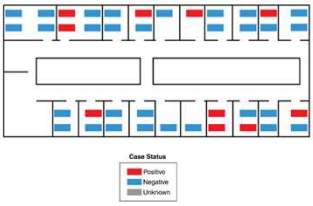
C. auris Spread

Doesn't just spread to roommates—all other patients on the unit are at risk



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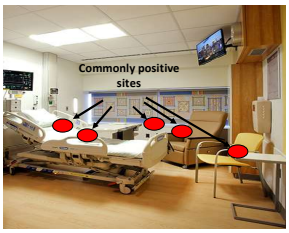
C. auris Spread, Environment

- Persistent in the environment
  - Survival >1 month
- Some common disinfectants (quaternary ammonia compounds) not effective



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C. auris Spread, Shared Equipment

- May be transmitted via shared, mobile equipment that is not properly cleaned and disinfected between patients

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Early Detection and Containment

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Identification of *C. auris*

- Misidentification may occur with different diagnostic methods used for yeast
  - Often misidentified as *Candida haemulonii*
  - Important to understand your lab detection methods
- At Risk: Yeast not identified to species level
  - If *C. auris* has been identified at your facility, consider identifying to species level from both sterile and non-sterile sites
  - Yeast from urine usually tossed out because not considered an infection
  - Only about 50% of clinical cases are from blood
- Missed detection of colonization cases without screening

Identification Method	Organism *C. auris* can be misidentified as
Vitek 2 YST®	*Candida haemulonii* *Candida duobushaemulonii*
API 20C	*Rhodotorula glutinis* (characteristic red color not present) *Candida sake*
API ID 32C	*Candida intermedia* *Candida sake* *Saccharomyces kluyveri*
BD Phoenix yeast identification system	*Candida haemulonii* *Candida catenulata*
MicroScan	*Candida famata* *Candida guilliermondii*[1] *Candida lusitaniae*[1] *Candida parapsilosis*[1]
RapID Yeast Plus	*Candida parapsilosis*[1]

CDC. Identification of Candida auris, https://www.cdc.gov/fungal/candida-auris/identification.html

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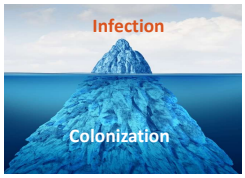
Early Detection

- Allows for earlier infection control precautions
- Strategies to consider for early identification
  - Species identification of all *Candida* specimens
  - Screening high risk patients*
  - Periodic point prevalence surveys in high-risk facilities, even those without known cases



*From facilities/areas with high *C. auris* burden or outbreaks, healthcare abroad, healthcare contacts of cases

CDC Containment Strategy, https://www.cdc.gov/hai/mdro-guides/containment-strategy.html#:~:text=Goal%20of%20Initial%20containment%20response,(Tier%201%202).

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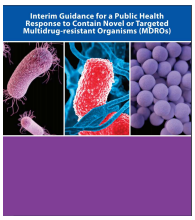
Standardized Response: Containment Strategy

- Offers a systematic response to emerging resistance
- Aggressive and rapid response to targeted, organisms of public health significance
- Objective is to focus on identifying transmission and preventing spread
- Consists of three tiers of organisms, guiding response activities
- Coordinated approach with public health



Guidance Available at: https://www.cdc.gov/hai/containment/index.html

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Containment strategies before the first *C. auris* case

- Assess infection control and ensure good IPC practices
- Use a disinfectant effective against *C. auris*
- Ensure communication (interfacility and intrafacility) about *C. auris* for transferred patients
- Species identification of yeast from any body site, not just invasive specimens
- Consider targeted screening

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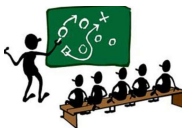
Containment steps ***after*** a case of *C. auris* is found

- Report to health department
- Infection control & staff education
- Screen patients with healthcare contact or high-risk patients
- Lab surveillance
- Consider other connected facilities



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You have Identified a Patient with *Candida auris*

Immediately Implement
Contact Precautions
Ensure disinfectant with EPA-registered claim for *C. auris* (List P) If List P product not available, utilize a disinfectant effective against *Clostridioides difficile* spores (List K)
Perform thorough cleaning and disinfection of shared medical equipment Glucometers, nursing cart, temperature probes
Perform thorough routine and terminal cleaning of patient's room and in areas where they receive care Radiology, surgery, therapy
Education for patient and healthcare provider

While the patient remains in the facility, Continue
Communication of MDRO status (history) during transfer of care
Enhanced hand hygiene and PPE audits to monitor compliance
Contact Precautions Work with your public health partners in reassessment of colonization

Coordinate Containment Response
In collaboration with public health partners

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Meet our Patient

PMH	65 year old male with history of hypertension, gastritis, hyperlipidemia, and alcoholic liver cirrhosis
Chief Complaint	Admitted to the hospital for abdominal distension and jaundice. Found to have MELD Score of 46.
HPI	Underwent liver and kidney transplant and developed *Candida auris* fungemia two weeks later while still hospitalized

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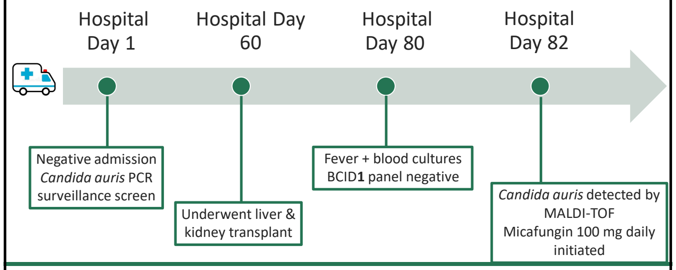
Infectious Work-up



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Rapid Diagnostics

- Rapid identification of *C.auris* is essential to jumpstart treatment and prevent further spread
- Gold standards = MALDI-TOF, The GenMark ePlex Blood Culture Identification Fungal Pathogen (BCID-FP) Panel, BioFire FilmArray BCID2
- **Do not wait for culture growth!**

BCID1	BC ID Candida albicans	Not Detected
	BC ID Candida glabrata	Not Detected
	BC ID Candida krusei	Not Detected
	BC ID Candida parapsilosis	Not Detected
	BC ID Candida tropicalis	Not Detected
BCID2	BC ID Candida albicans	Not Detected
	BC ID Candida auris	Detected * (!)
	BC ID Candida glabrata	Not Detected
	BC ID Candida krusei	Not Detected
	BC ID Candida parapsilosis	Not Detected
	BC ID Candida tropicalis	Not Detected

Rapid turnaround time!

CDC. Identification of Candida auris. https://www.cdc.gov/fungal/candida-auris/identification.html.

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Treatment

- Three classes of antifungal agents are active against *C.auris*: azoles, echinocandins, and polyenes
  - In the United States, >90% of *C. auris* isolates have been resistant to fluconazole, ~30% have been resistant to amphotericin B, and <5% have been resistant to echinocandins
- Echinocandins are considered first-line based on lowest frequency of resistance, however this is increasing
- *C. auris* is the first *Candida* species to be classified as multidrug resistant (MDR)
  - Exhibits resistance to ≥2 different classes of antifungal agents

CDC. Antifungal Susceptibility Testing and Interpretation. https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html.

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Multidrug-Resistant *Candida auris*

- According to a CDC report, 331 isolates taken from infected patients were resistant to fluconazole (99.7%), amphotericin B (63.4%), and echinocandins (3.9%)
- In a study by Lockhart et al., 54 isolates were collected from patients in Pakistan, South Africa, and Venezuela
  - 93% were resistant to fluconazole, 35% to amphotericin B, and 7% to echinocandins
  - 41% were resistant to 2 antifungal classes and 4% were resistant to all 3 classes (pan-resistant)

Ostrowsky B, et al. *MMWR Morb Mortal Wkly Rep*. 2020;69:6-9.
Lockhart SR, et al. *Clin Infec Dis*. 2017;64(2):134-40.

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Pan-Resistant

- Rare
- Resistant to all three antifungal classes (azoles, echinocandins, polyenes)
- Cases reported in NY, TX, DC
- Resistance develops from antifungal pressure, however transmission of resistance strains has been increasingly reported in the absence of echinocandin exposure

CIDRAP
NEWS TOPICS & PROJECTS PODCASTS NEWSLETTERS ABOUT

Three cases of worrisome pan-resistant C auris found in New York

Chris Dall | News Reporter | CIDRAP News, January 9, 2020
Topics: Candida auris

Notes from the Field: Transmission of Pan-Resistant and Echinocandin-Resistant *Candida auris* in Health Care Facilities — Texas and the District of Columbia, January–April 2021

Weekly / July 23, 2021 / 70(29);1022–1023

Meghan Lyman, MD[1]; Kaitlin Forsberg, MPH[1]; Jacqueline Reuben, MHS[2]; Thi Dang, MPH[3]; Rebecca Free, MD[1]; Emma E. Seagle, MPH[1]; D. Joseph Sexton, PhD[1]; Elizabeth Soda, MD[4]; Heather Jones, DNP[4]; Daryl Hawkins, MSN[2]; Adonna Anderson, MSN[2]; Julie Bassett, MPH[3]; Shawn R. Lockhart, PhD[1]; Enyinnaya Merengwa, MD, DrPH[3]; Preetha Iyengar, MD[2]; Brendan R. Jackson, MD[1]; Tom Chiller, MD[1] (VIEW AUTHOR AFFILIATIONS)

Lyman M, et al. *MMWR Morb Mortal Wkly Rep*. 2021;70(29):1022–3.

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Clade Resistance

- Knowing clade information could help guide treatment because different clades differ in their antifungal resistance profiles.
- Antifungal resistance is widespread in *C. auris* South Asia Clade I isolates. These isolates are overwhelmingly resistant to fluconazole, are variably resistant to amphotericin B, and acquire resistance to echinocandins.
- Clade II is known to exhibit less resistance than other clades.
- South Africa Clade III isolates are commonly resistant to azoles.
- South America Clade IV includes isolates with variable resistance to amphotericin B.

Maphanga TG, et al. *Antimicrob Agents Chemother*. 2021;65(9):e0051721.
Jacobs SE, at al. *Antimicrob Agents Chemother*. 2022;66(7):e0005322.

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Resistance Mechanisms

Antifungal Class	Mechanism of Resistance
Azoles	Overexpression of drug efflux pumps belonging to ATP Binding Cassette (ABC) and Major Facilitator Superfamily (MFS) transporters, and alterations of the ergosterol synthesis pathway (overexpression of *ERG11*, and point mutations in *ERG11*, i.e., Y132F)
Echinocandins	Mutations of *FKS1*, a gene that codes the enzyme responsible for the key fungal cell wall component, β(1,3)D-glucan.
Polyenes (e.g., amphotericin)	Single nucleotide polymorphisms in genes related to the ergosterol synthesis pathway leading to altered sterol composition
Nucleoside analogs (e.g., flucytosine)	Amino acids substitution in the *FUR1* gene (i.e., F211I)

Chaabane F, et al. *Front Microbiol*. 2019;10:2788

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Do we have Treatment Guidelines?

Southern African Journal of Infectious Diseases
ISSN: (Online) 2313-1810, (Print) 2312-0053
Page 1 of 17 Guideline
AOSIS

Federation of Infectious Diseases Societies of Southern Africa guideline: Recommendations for the detection, management and prevention of healthcare-associated *Candida auris* colonisation and disease in South Africa

CDC Centers for Disease Control and Prevention
Candida auris
< Candida auris Home

Treatment and Management of *C. auris* Infections and Colonization

IDSA Practice Guidelines

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Recommendation 4.1: What are the suggested treatment regimens for confirmed or strongly suspected invasive *Candida auris* disease in adults and children?

1. In the vast majority of adults, an echinocandin is recommended as first-line treatment. Amphotericin B deoxycholate is an alternative agent in settings where echinocandins are unavailable and is recommended for central nervous system, urinary tract or eye infections.
2. Among children aged < 2 months, the initial treatment of choice is amphotericin B deoxycholate 1 mg/kg daily,
3. Among children aged > 2 months, an echinocandin is recommended for the initial treatment.

Govender NP, et al. *S Afr J Infect Dis*. 2019;34(1):163.

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Recommendation 4.2: How should the source of infection be identified and controlled in adults and children?

TABLE 8: Source control and risk factor modification measures.

Source/risk factor	Suggested intervention
Indwelling venous/arterial catheters	Remove or replace
Urinary catheter	Remove or replace
Infected prosthetic material	Remove or replace
Collections/abscesses	Drain surgically or insert pigtail
Antibiotics	Stop/de-escalate/use only if deemed absolutely necessary
Corticosteroids	Stop/wean
Immunosuppressants	Stop/wean/modify
Total parenteral nutrition	Change to enteral nutrition, if possible

Govender NP, et al. *S Afr J Infect Dis*. 2019;34(1):163.

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CDC Guidance (Last updated December 2022)

Adults and children ≥ 2 months of age
- An echinocandin is recommended as initial therapy for the treatment of *C. auris* infections.
- Switching to a liposomal amphotericin B (5 mg/kg daily) could be considered if the patient is clinically unresponsive to echinocandin treatment or has persistent fungemia for >5 days.

Neonates and infants <2 months of age
The initial treatment of choice for this age group is amphotericin B deoxycholate, 1 mg/kg daily. If unresponsive to amphotericin B deoxycholate, liposomal amphotericin B, 5mg/kg daily, could be considered.

CDC does not recommend treatment of *C. auris* identified from noninvasive sites (such as respiratory tract, urine, and skin colonization) when there is no evidence of infection.

CDC. Treatment and Management of *C.auris* Infections and Colonization. https://www.cdc.gov/fungal/candida-auris/c-auris-treatment.html

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CDC Tentative Breakpoints

Antifungal	Considered as Non-susceptible/resistant	Comments
Fluconazole	MIC ≥ 32 mg/L	Isolates with MICs ≥32 were shown to have a resistance mutation in the *Erg11* gene, making them unlikely to respond to fluconazole
Caspofungin **Anidulafungin** **Micafungin**	MIC ≥ 2 mg/L MIC ≥ 4 mg/L MIC ≥ 4 mg/L	
Amphotericin B	MIC ≥ 2 mg/L	If using E-test, MIC=1.5 should be rounded up to 2
Voriconazole	N/A	Isolates that are resistant to fluconazole may respond to other triazoles. Some studies have used MIC ≥ 2 or 4 as their breakpoint
Flucytosine	N/A	Some studies have used MIC ≥ 8 as their breakpoint

CDC. Antifungal Susceptibility Testing and Interpretation. https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html.
Lockhart SR, et al. *Clin Infect Dis*. 2017;64(2):134-40.
Vu CA, et al. *Transpl Infect Dis*. 2022;24(5):e13919.
Jacobs SE, et al. *Antimicrob Agents Chemother*. 2022;66(7):e0005322.

Treatment Summary

Confirmed *Candida auris* infections

Source Control

Echinocandins
Micafungin
Caspofungin
Anidulafungin
Generally 1st line

Amphotericin
Amphotericin lipid complex
Liposomal amphotericin B
Conventional amphotericin
Preferred if CNS, urine, or eye involvement

Alternative agents
Flucytosine
Voriconazole
Fosmanogepix
Ibrexafungerp

Back to our Patient

- Micafungin was started two days after positive blood cultures for. *C.auris*
- Suspected sources of infection: **line vs. collections**
  - Right upper extremity PICC removed and new left upper extremity PICC was placed
  - Subhepatic collection underwent drainage
  - Perirenal collection also underwent drainage
  - Repeat imaging shows residual collections but smaller
- Despite source control attempts, patient remains fungemic

PICC: Peripherally inserted central catheter

Strategies for treating persistent fungemia

- Source control issue? **Most likely**
- Switching to a liposomal amphotericin B (5 mg/kg daily) could be considered if the patient is clinically unresponsive to echinocandin treatment or has persistent fungemia for >5 days
- Repeat susceptibility testing
  - Are MICs increasing?
- Explore synergy combinations
- Consider alternative novel agents

Addition of Flucytosine (5FC)

- **Nine** *C. auris* isolates resistant to amphotericin, AMB-5FC yielded 100% inhibition.
- **Six** *C. auris* isolates resistant to three echinocandins. Addition of 5FC to caspofungin, micafungin, anidulafungin yielded 100% inhibition.
- **Thirteen** *C.auris* isolates with a high voriconazole MIC were 100% inhibited by VRC-5FC.

O'Brien B, et al. *Antimicrob Agents Chemother*. 2020;64(4):e02195-19.

Echinocandin + Triazole

TABLE 1 *In vitro* interactions of caspofungin with fluconazole and voriconazole against *Candida auris*

	CAS + FLU[a]				CAS + VRC[b]			
	MIC (μg/ml)				MIC (μg/ml)			
Strain no.	CAS	FLU	CAS/FLU	FICI/INT	CAS	VRC	CAS/VRC	FICI/INT
VPCI 482/P/13[a]	2	≥64	1/32	0.75/IND	2	2	1/0.5	0.75/IND
VPCI 1132/P/13[a]	2	32	1/8	0.75/IND	2	0.5	1/0.063	0.62/IND
VPCI 1133/P/13[a]	4	≥64	2/64	1/IND	4	1	2/0.25	0.75/IND
VPCI 265/P/14[a]	4	32	2/32	1.5/IND	4	8	2/0.25	0.75/IND
VPCI 1510/P/14[a]	0.5	32	0.5/32	2/IND	0.5	4	0.5/4	2/IND
VPCI 1514/P/14[a]	1	≥64	0.5/32	0.75/IND	1	0.5	1/0.25	1.5/IND
VPCI 266/P/14[a]	2	≥64	1/32	0.75/IND	2	0.5	1/0.25	1/IND
VPCI 267/P/14[a]	2	32	1/8	0.75/IND	2	0.5	2/0.063	0.62/IND
VPCI 487/P/14[a]	1	≥64	0.5/8	0.56/IND	1	1	0.5/0.125	0.62/IND
VPCI 518/P/14[a]	0.5	≥64	0.25/8	0.56/IND	0.5	1	0.25/0.25	0.75/IND

[a]Fluconazole-resistant isolates (n = 10).
[b]CAS, caspofungin; FLU, fluconazole; VRC, voriconazole; FICI, fractional inhibitory concentration index; IND, indifference; SYN, synergy; INT, interpretation.

TABLE 2 *In vitro* interactions of micafungin with fluconazole and voriconazole against *Candida auris*

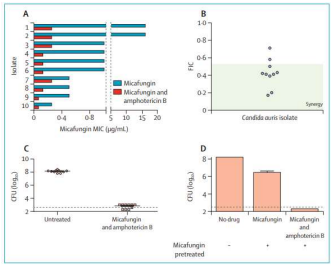
	MFG + FLU[a]				MFG + VRC[a]			
	MIC (μg/ml)				MIC (μg/ml)			
Strain no.	MFG	FLU	MFG/FLU	FICI/INT	MFG	VRC	MFG/VRC	FICI/INT
VPCI 482/P/13[a]	0.25	≥64	0.25/64	1.5/IND	0.25	2	0.016/0.5	0.31/SYN
VPCI 1132/P/13[a]	0.5	32	0.25/4	0.62/IND	0.5	0.5	0.016/0.125	0.28/SYN
VPCI 1133/P/13[a,b]	8	≥64	4/32	0.75/IND	8	1	2/0.25	0.5/SYN
VPCI 265/P/14[a]	0.5	32	0.5/8	1.25/IND	0.5	8	0.063/1	0.25/SYN
VPCI 1510/P/14[a]	0.125	32	0.063/8	0.75/IND	0.125	4	0.016/0.25	0.19/SYN
VPCI 1514/P/14[a,b]	8	≥64	8/16	1.12/IND	8	0.5	1/0.125	0.37/SYN
VPCI 266/P/14[a]	0.25	≥64	0.25/32	1.25/IND	0.25	0.5	0.008/0.125	0.28/SYN
VPCI 267/P/14[a,b]	8	32	8/8	1.25/IND	8	0.5	1/0.125	0.37/SYN
VPCI 487/P/14[a]	4	≥64	4/32	1.25/IND	4	1	0.5/0.125	0.25/SYN
VPCI 518/P/14[a]	0.5	≥64	0.25/64	1/IND	0.5	1	0.016/0.125	0.15/SYN

[a]Fluconazole-resistant isolates (n = 10).
[b]Micafungin-resistant isolates (n = 3).
[c]MFG, micafungin; FLU, fluconazole; VRC, voriconazole; FICI, fractional inhibitory concentration index; IND, indifference; SYN, synergy; INT, interpretation.

Most effective combination was micafungin + voriconazole, as synergy was observed against all 10 MDR isolates belonging to the South Asian clade

Badaili H, et al. *Open Forum Infectious Diseases*. 2017;4(suppl_1):S82.

Micafungin + Amphotericin



Jagavarapu S, et al. *The Lancet*. 2020;1(8):e314-5.

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Back to our Patient

Treatment Day 1	Treatment Day 8	Treatment Day 18
Micafungin 100 mg daily	Micafungin 100 mg daily + Voriconazole 6 mg/kg load followed by 4 mg/kg BID	Micafungin 150 mg daily + Amphotericin lipid complex 5 mg/kg daily

Treatment Day 25, perirenal collection drained again → positive for *C.auris*

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Ibrexafungerp (formerly SCY-078) – Phase 3

Outcomes of Oral Ibrexafungerp in the Treatment of 18 Patients with *Candida auris* Infections, from the CARES Study

NE Azie[1], TR Kirst[1], T Chen[1], DA Angulo[1]
[1]SCYNEXIS, Inc., Jersey City, NJ

MSG ERC Mycoses Study Group

BACKGROUND
- *Candida auris* is a multi-drug resistant fungus associated with high mortality, has been implicated in healthcare setting outbreaks, and subsequently was added as an Urgent Threat Pathogen to the CDC Antimicrobial Resistance Threat Report 2019.
- Ibrexafungerp is an IV/oral, first-in-class triterpenoid, broad-spectrum fungicidal β-D-glucan synthase inhibitor (similar to the echinocandins).
- Ibrexafungerp has activity against *Candida*, *Aspergillus*, *Fusarium*, *Pneumocystis* spp., and dimorphic fungi, including azole- and echinocandin-resistant strains.
- Ibrexafungerp also has high tissue penetration into organ and tissue compartments commonly associated with invasive fungal infections and is in development for life-threatening infections due to those pathogens.

CARES DESIGN
- CARES is currently in recruitment (for this cohort, see patient locations in map on the left).
- Eligible patients have a documented *Candida auris* infection and receive a loading dose of oral ibrexafungerp 750 mg BID on the Day 1 days, then subsequent oral ibrexafungerp 750 mg QD up to 90 days and are followed for 6 weeks post-therapy.
- An Independent Data Review Committee (IDRC) provided an assessment of treatment response for 18 patients who enrolled and completed therapy by October 2021.
- Outcome data from IDRC assessments are reported here.

PATIENT CHARACTERISTICS

Baseline Fungal Disease	Number of patients	Mean Patient Age	% Female	Mean days on Ibrexafungerp
Candidemia	12	59	25	54
Lower Urinary Tract	5	62	60	27
Intra-abdominal	1	64	0	1
OVERALL	18	60	33%	38

- Of the 18 enrolled patients, 11 had received prior antifungal therapy for their infection, and 7 were treatment-naïve.

OUTCOMES BY BASELINE FUNGAL DISEASE

	Complete/ Partial Response	Stable Response	Disease Progression	Death	Indeterminate
Candidemia	8	2	0	1	1
Lower Urinary	5	0	0	0	0
Intraabdominal	1	0	0	0	0
Totals	14	2	0	1	1

FUNGAL MECHANISM OF ACTION

Scanning electron microscopy — Before IBX / After IBX

Transmission electron microscopy — Before IBX / After IBX

Fungicidal action of ibrexafungerp (IBX) against cells of *Candida auris* (SEM and TEM images)
- abnormalities in cell division (fused cells),
- thickening of the cell wall with disappearance of the cell membrane,
- leakage of cytoplasmic matrix, and
- destruction of cytoplasmic organelles.

(Images from Larkin, et al. AAC 2017.)

GLOBAL DISEASE, GLOBAL STUDY

As of the latest interim data analysis (October 2021), CARES has enrolled 18 patients from areas where *Candida auris* outbreaks have occurred: South Africa, South Asia, and North America.

RESULTS DETAILS
- Mean patient age: 56.3 years; 11 males, 7 females enrolled.
- Ibrexafungerp median duration of therapy was 18 days.
- The most frequent treatment-related adverse event were gastrointestinal in nature including diarrhea, nausea and abdominal pain.

CONCLUSIONS

These cases provide continued evidence of the potential clinical utility of ibrexafungerp in the treatment of invasive candidiasis and candidemia caused by *Candida auris*.

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Fosmanogepix (formerly APX001) – Phase 2

Ongoing open-label non-comparative *in vivo* study evaluating the efficacy of fosmanogepix for the treatment of *C. auris* invasive candidiasis

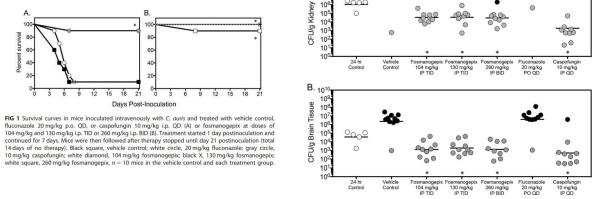

FIG 1 Survival curves in mice inoculated intravenously with *C. auris* and treated with vehicle control, fluconazole 20 mg/kg p.o. QD, or caspofungin 10 mg/kg i.p. QD (A) or fosmanogepix at doses of 104 mg/kg and 130 mg/kg i.p. TID or 260 mg/kg i.p. BID (B). Treatment started 1 day postinoculation and continued for 7 days. Mice were then followed after therapy stopped until day 21 postinoculation (total 14 days of no therapy). Black square, vehicle control; white circle, 20 mg/kg fluconazole; gray circle, 10 mg/kg caspofungin; white diamond, 104 mg/kg fosmanogepix; black X, 130 mg/kg fosmanogepix; white square, 260 mg/kg fosmanogepix. *n* = 10 mice in the vehicle control and each treatment group.

Wiederhold NP, et al. *Antimicrob Agents Chemother.* 2019;63(11):e01120-19.

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Back to our Patient

Treatment	Antifungal regimen
Day 1	Micafungin
Day 8	Micafungin + Voriconazole
Day 18	Micafungin + Amphotericin
Day 30	Micafungin + Amphotericin + Ibrexafungerp
Day 50	**Biopsies from transplanted liver and kidney resulted positive for yeast A few weeks later, TTE revealed mitral valve mass, suggestive of fungal endocarditis**
Day 52	Micafungin + Amphotericin + Voriconazole
Day 81	Micafungin + Amphotericin + Voriconazole + Terbinafine
Day 92	Micafungin + Amphotericin + Isavuconazole + Terbinafine + Flucytosine

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Did MICs increase?

- Antifungal pressure drives the evolution of resistance to all major classes of antifungals
- For our patient, we observed increasing MICs to both micafungin and amphotericin after prolonged treatment

	Index Culture	Treatment Day 37	Treatment Day 80	Treatment Day 88	Tentative CDC Breakpoints
Fluconazole	128	256	256	256	MIC ≥ 32 mg/L
⇨ **Micafungin**	0.25	0.5	2	4	MIC ≥ 4 mg/L
⇨ **Amphotericin**	--	0.25	--	2	MIC ≥ 2 mg/L
Voriconazole	1	1	2	1	N/A

Ostrowsky B, et al. *MMWR Morb Mortal Wkly Rep.* 2020;69:6-9.
Jacobs SE, et al. *Antimicrob Agents Chemother.* 2022;66(7):e0053322.

#FSHP2023 Momentum

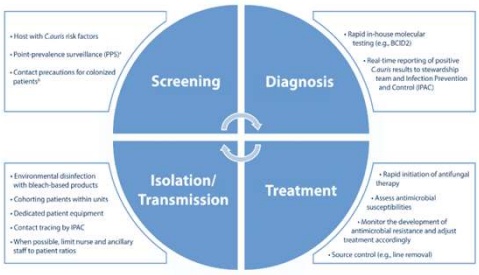
Lessons Learned

- Importance of rapid diagnostics (our hospital has since upgraded to BCID2 to be able to detect *C. auris* quicker)
- Try to avoid putting in a new line when patient is actively fungemic. But sometimes this is not always feasible!
- Methodically plan out escalation of treatment. Send out for synergy testing?
- Low threshold to escalate treatment with combination therapy or novel agents in the setting of persistent fungemia (>5 days)
- Antifungals will not treat infection without SOURCE CONTROL

Is there a role for *C.auris* stewardship?

- Pharmacists play a key role
  - Timely initiation of treatment
  - Choice of antifungals (initial and/or escalation)
  - Monitoring for increasing MICs
- Collaborate with laboratory to implement rapid diagnostics
- Remove unnecessary sources of infection (e.g., central lines, medical devices)
- Protect the gut
  - Exposure to broad-spectrum antimicrobials is an independent risk factor for invasive candidiasis
- Explore new antifungal stewardship initiatives!
  - Example: Create *C. auris* antibiogram and monitor echinocandin resistance to determine the best empiric regimen for your institution

The Role of Stewardship



Vu CA, et al. *Transpl Infect Dis.* 2022;24(5):e13919.

Resources

- Infection Prevention and Control: https://www.cdc.gov/fungal/candida-auris/c-auris-infection-control.html
- Laboratory Identification: https://www.cdc.gov/fungal/candida-auris/identification.html
- CDC Antifungal Susceptibility Testing and Interpretation: https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html.
- Federation of Infectious Diseases Societies of Southern Africa guideline: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8377779/

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THANK YOU!