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

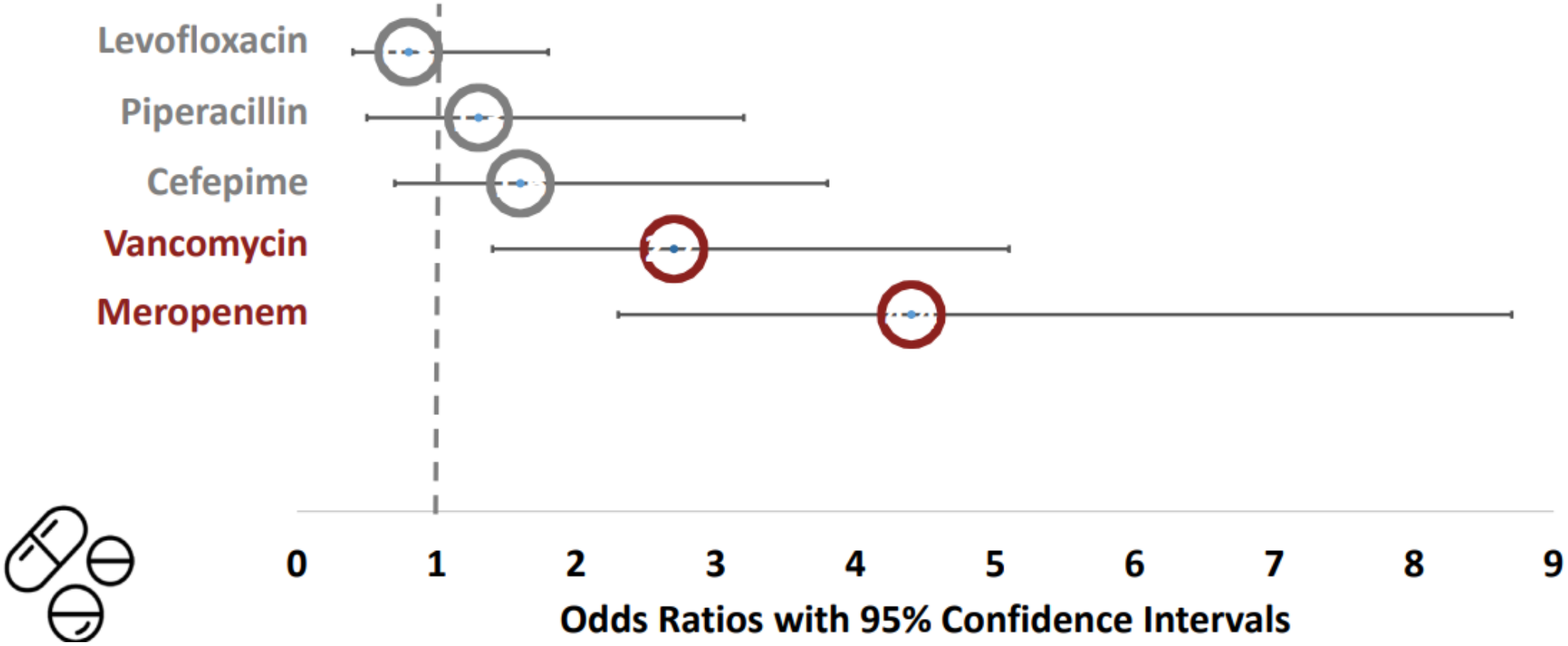
Ventilator-dependent/ Tracheostomies

Colonized with other MDROs

High-acuity, long length of stay facilities

Recently received antibiotics and antifungals

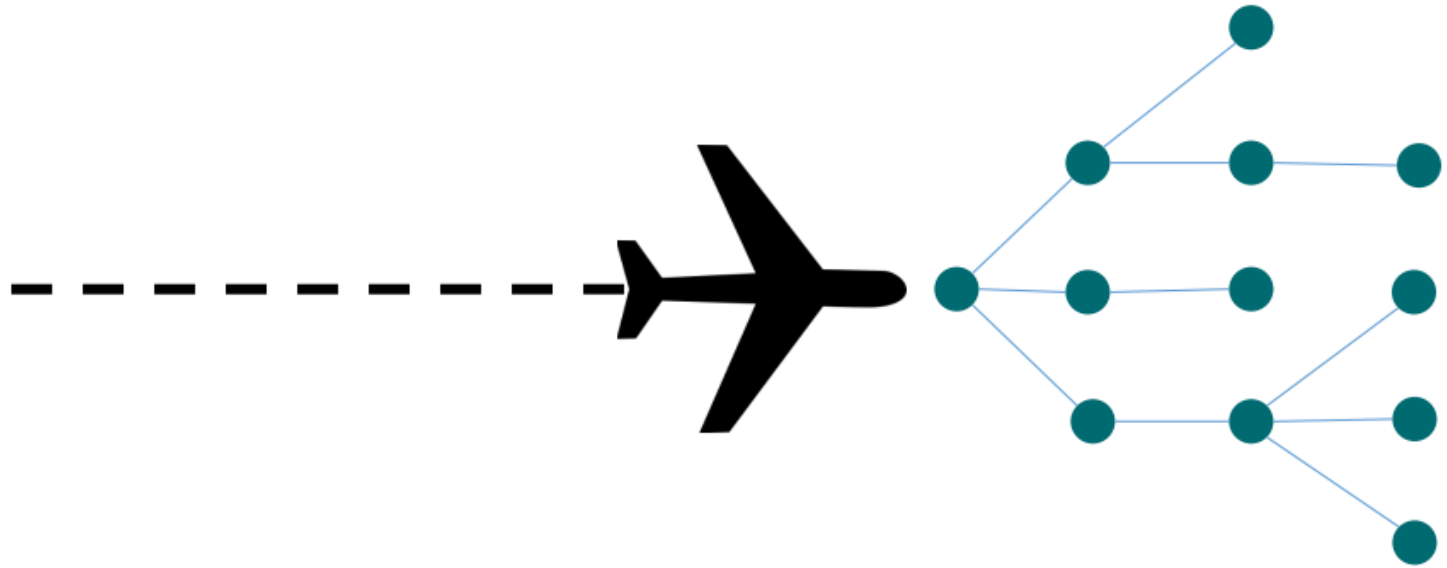
Certain broad-spectrum antibiotics were associated with *C. auris* colonization



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This map is no longer being updated given how widespread *C. auris* has become.

https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html

Virginia Reporting Requirements (since Nov 2018)

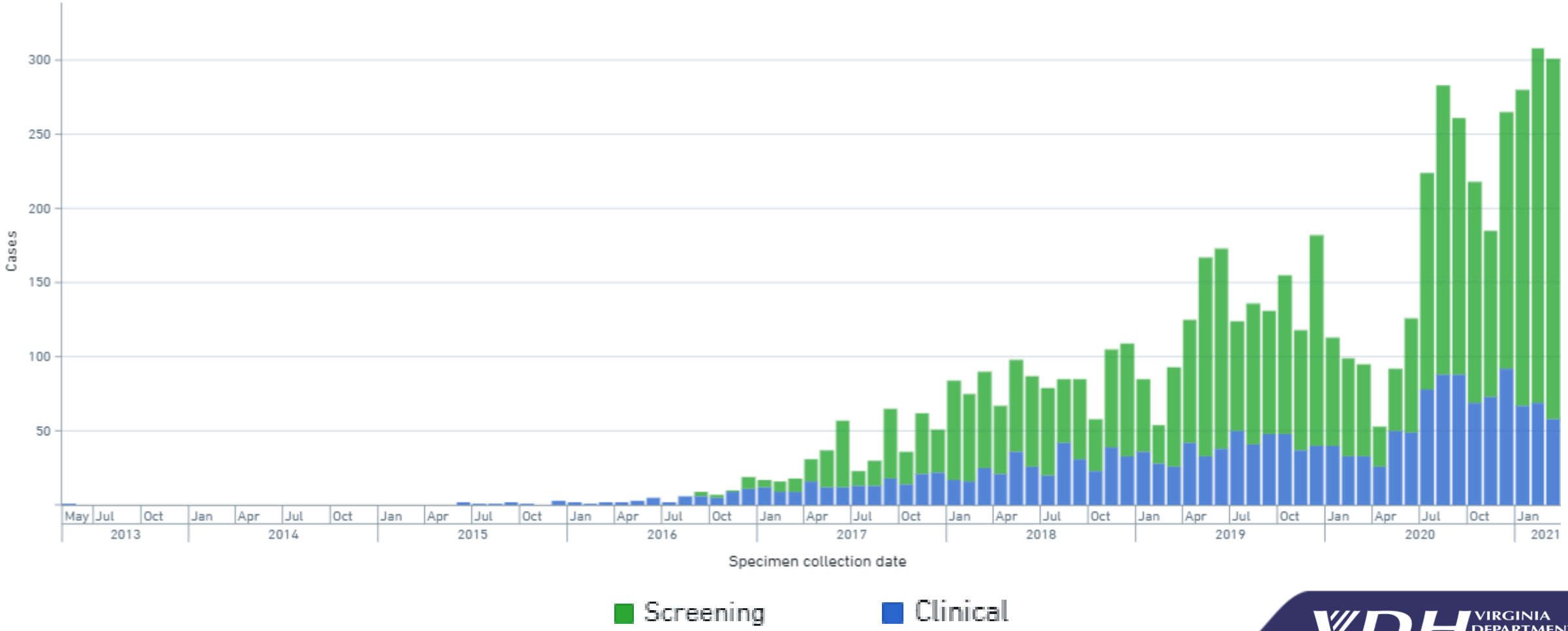
Virginia Reportable Disease List	Virginia Isolate Submission List
Report suspected or confirmed *C. auris*, infection or colonization. Include available antifungal susceptibility testing (AFST) results.	Submit any of the following isolates to DCLS using the DCLS Clinical Microbiology/Virology Request 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.

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)**

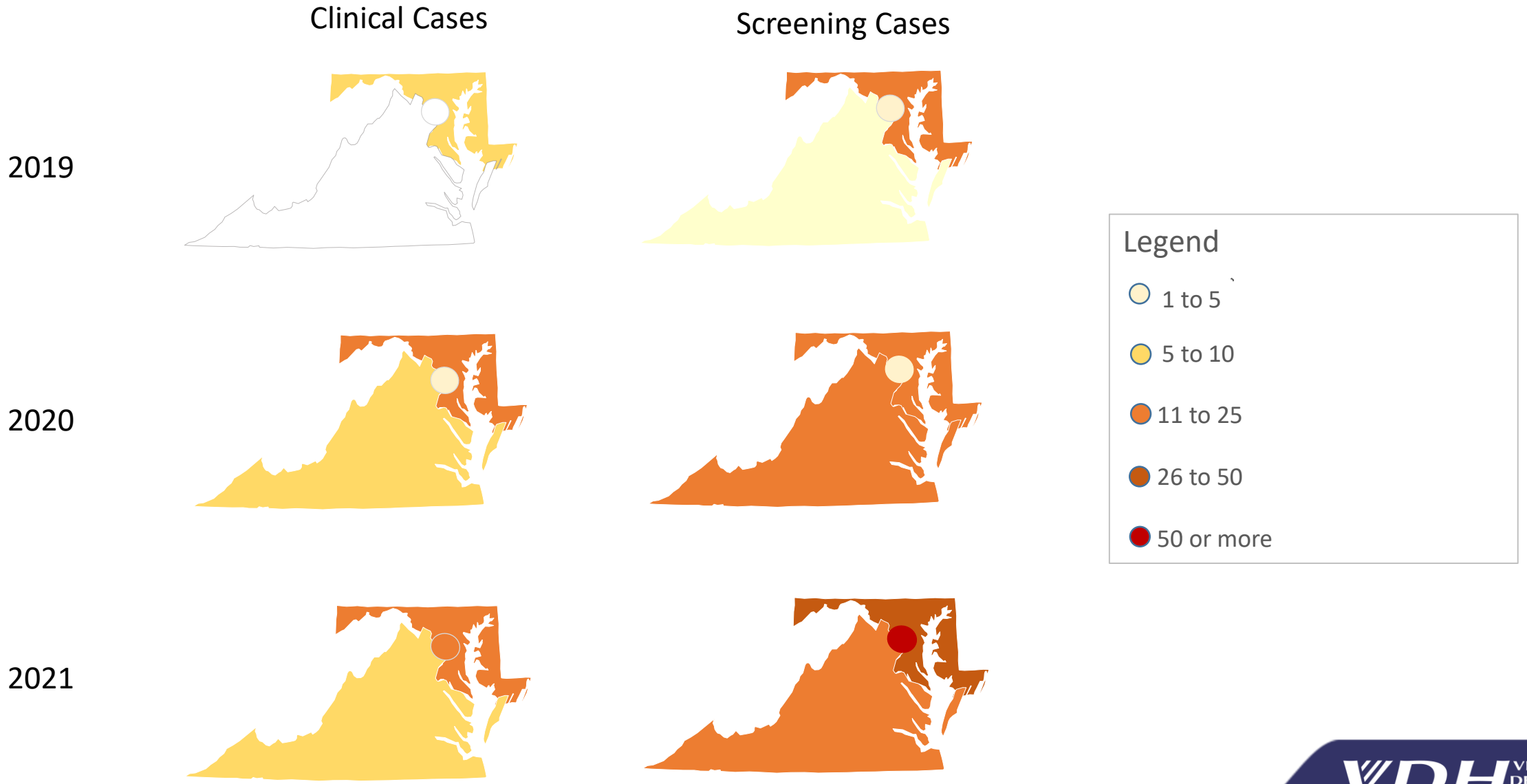
- **Colonized/Screening case: A person with *C. auris* identified at a laboratory from a swab collected for the purpose of determining if they are colonized**
  - ***C. auris:* primarily skin**

Increasing transmission of *C. auris* in the United States



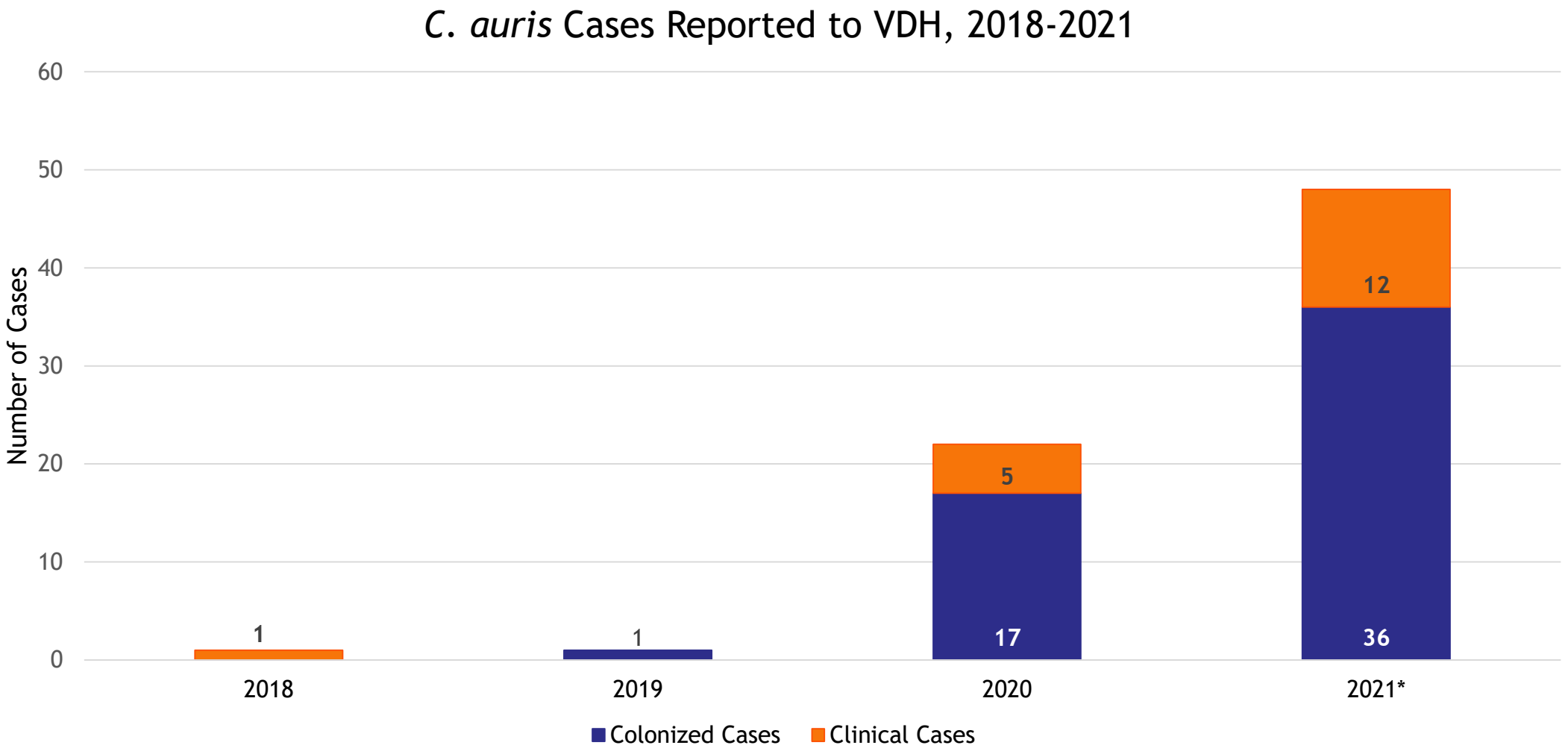
C. auris in the Mid-Atlantic Region

Data through August 2021



Slide courtesy MD AR Lab Network

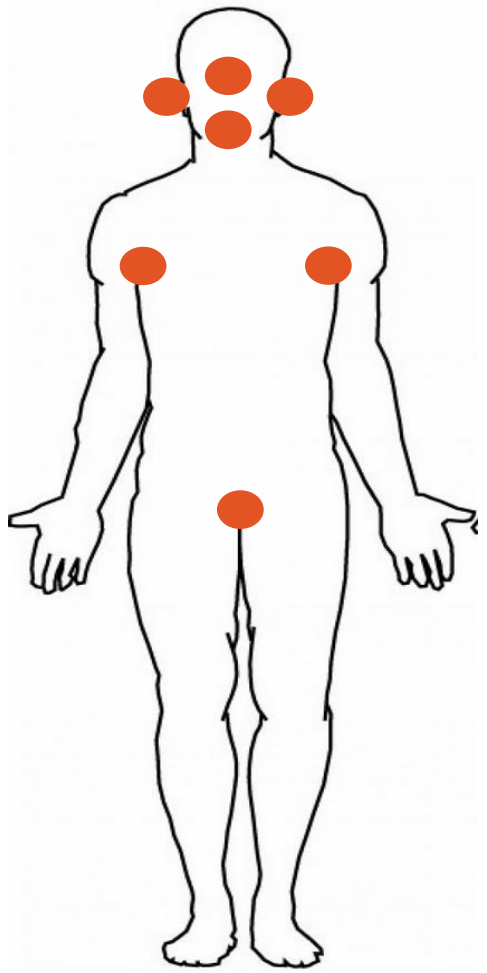
Virginia *C. auris* Case Counts



*Data reported to VDH as of November 1, 2021

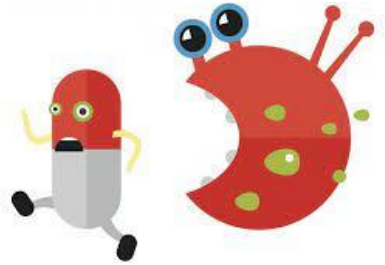
C. auris Colonization Duration

- **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

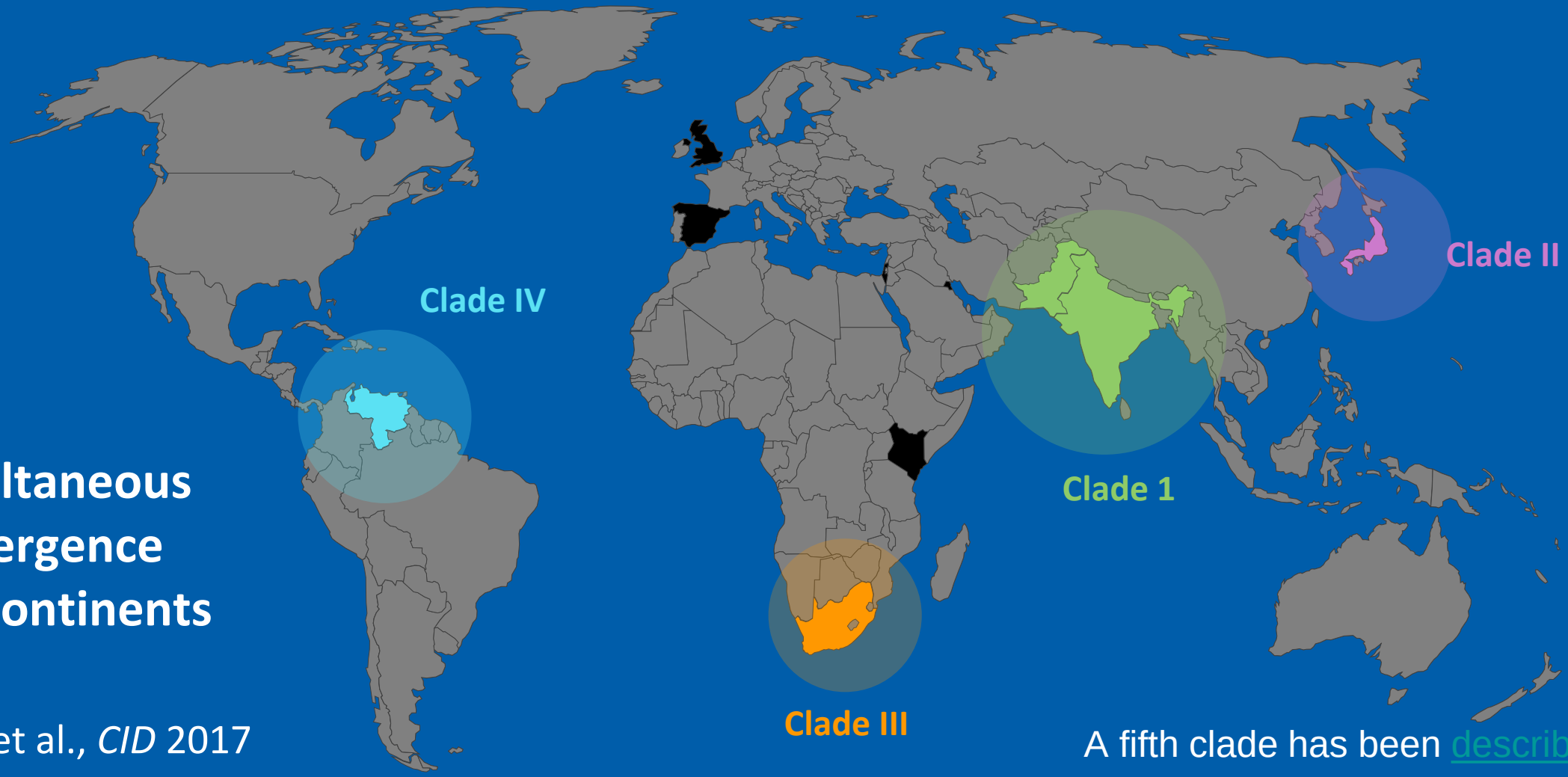
Difficult to identify (improving)

***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

Azoles

99%

National: 85%

Polyenes

64%

National: 33%

Echinocandins

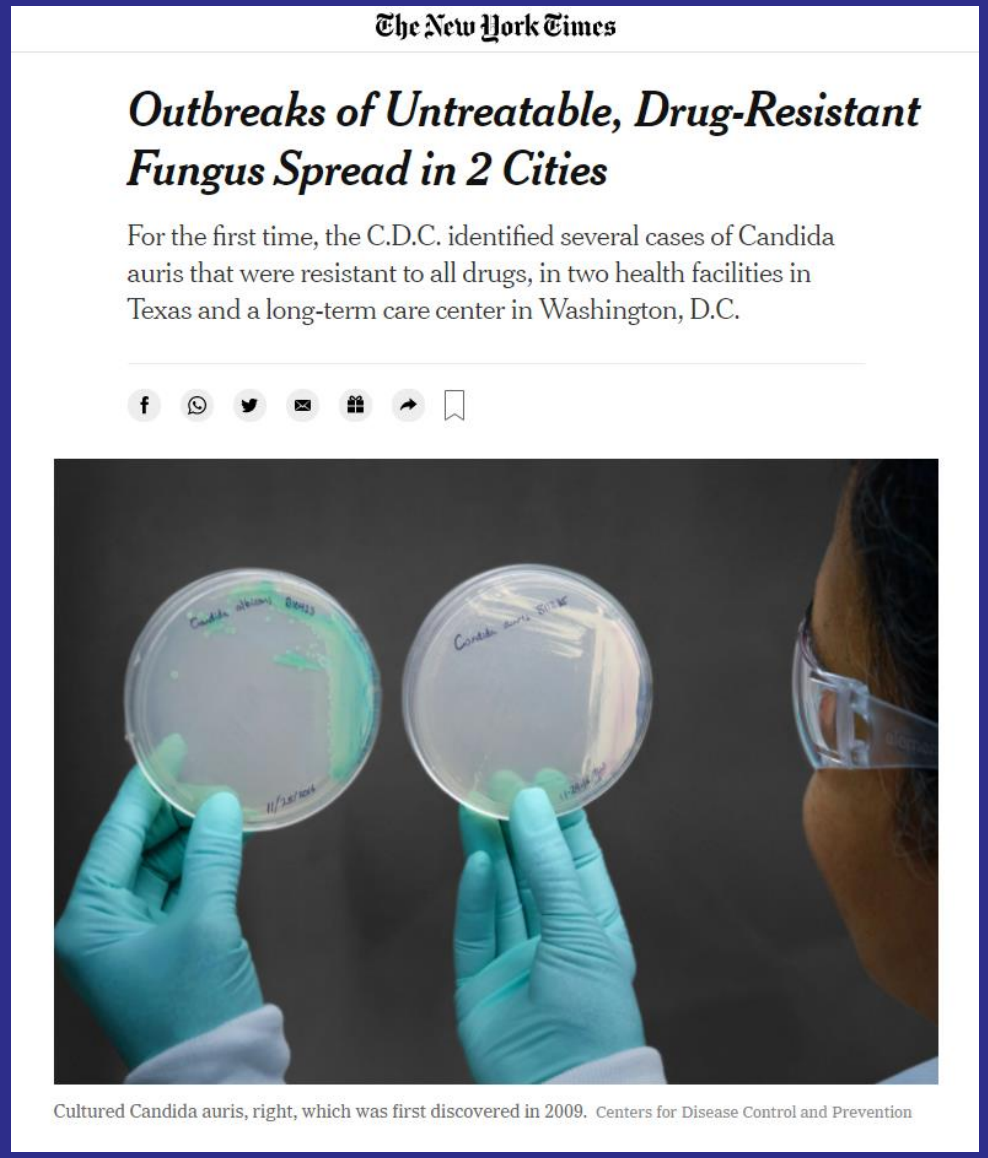
4%

National: 2%

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

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*



The New York Times

Outbreaks of Untreatable, Drug-Resistant Fungus Spread in 2 Cities

For the first time, the C.D.C. identified several cases of Candida auris that were resistant to all drugs, in two health facilities in Texas and a long-term care center in Washington, D.C.

Cultured Candida auris, right, which was first discovered in 2009. Centers for Disease Control and Prevention

TREATMENT OF *CANDIDA AURIS*

Laura Cwengros, PharmD, BCIDP

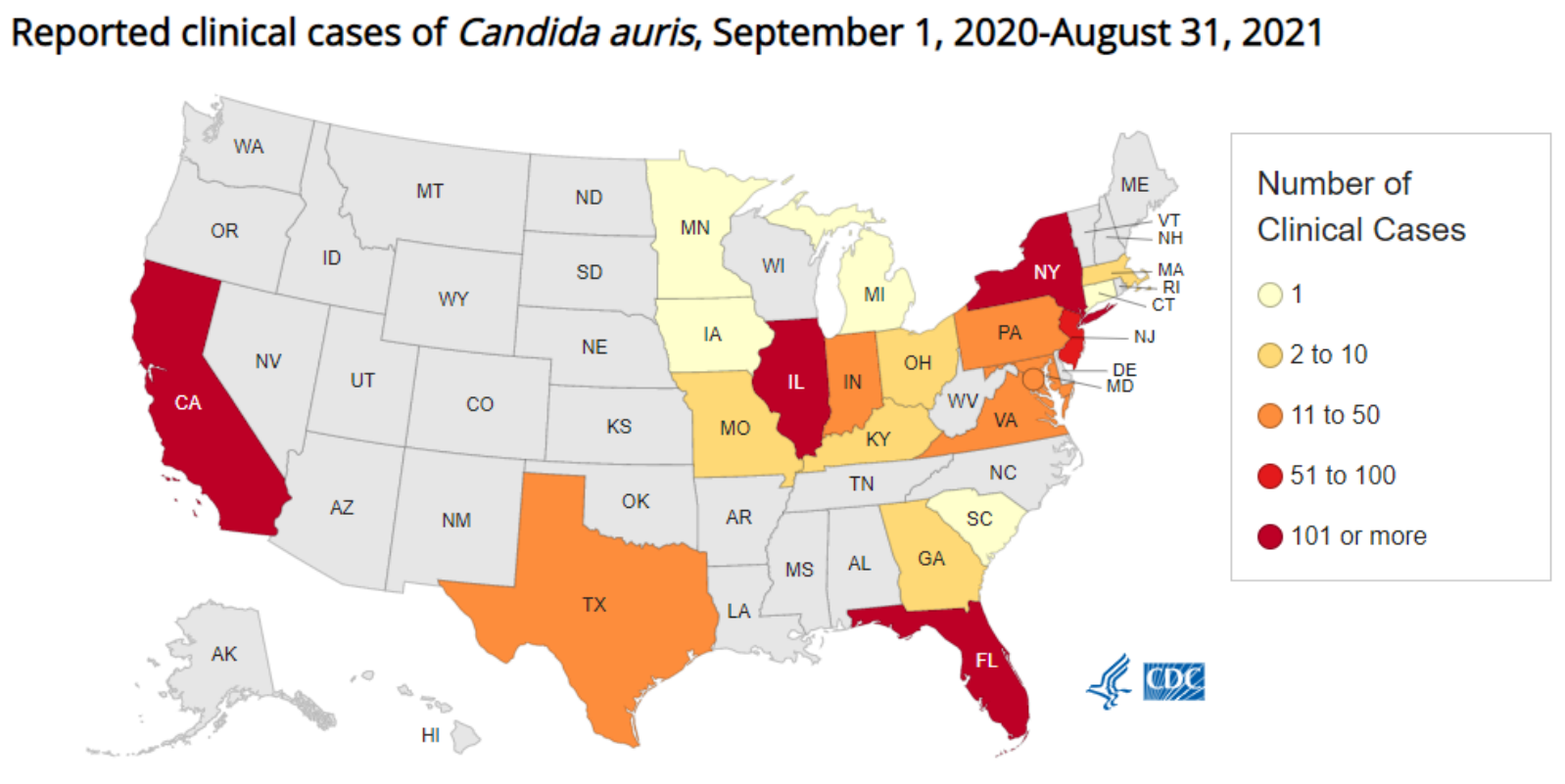
Clinical Infectious Diseases Manager

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

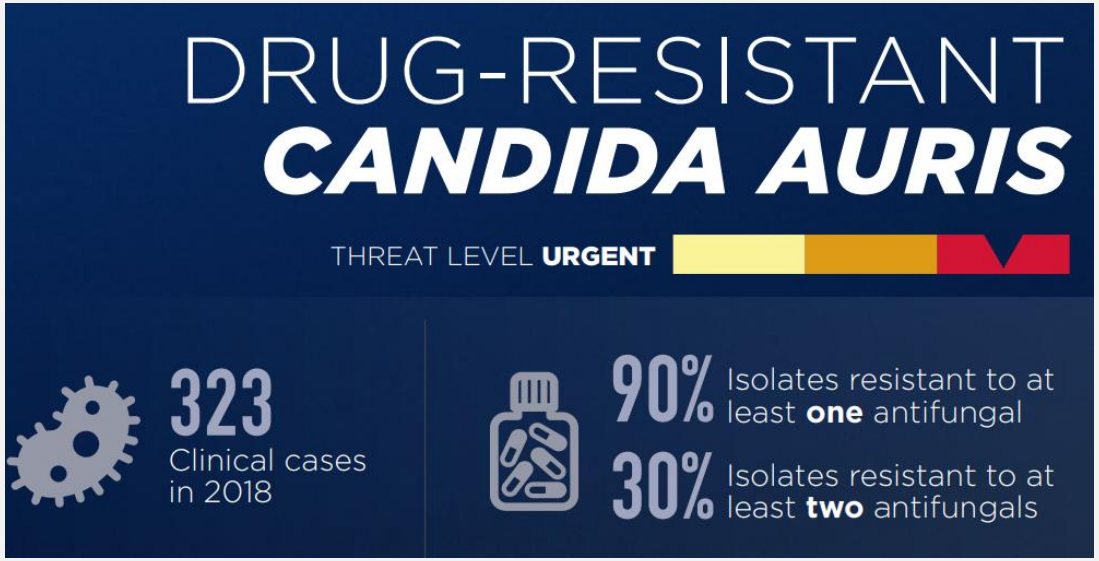


- Clinical cases include confirmed and probably cases
- Targeted screening has identified an additional 3,043 patients colonized with *C. auris*

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

CDC CONCERNS REGARDING *C. AURIS*

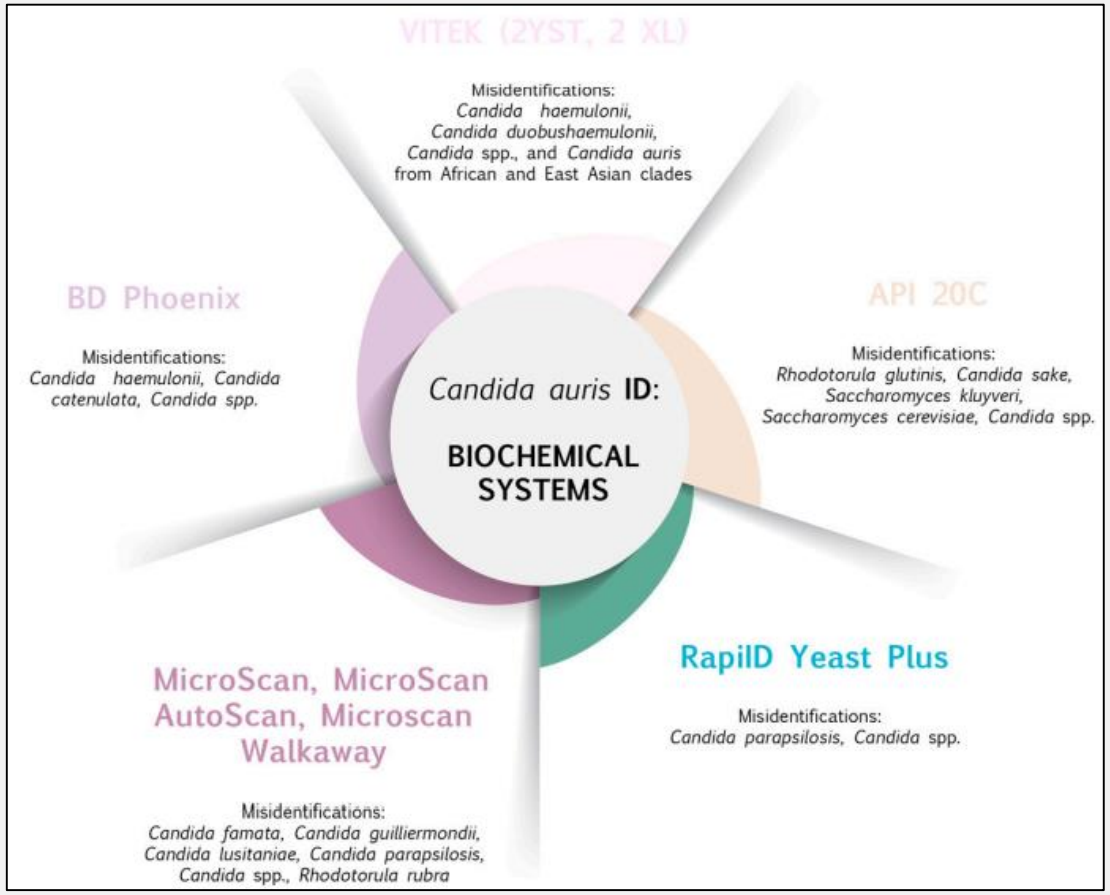
- Often multidrug-resistant
- Difficult to identify with standard laboratory methods
- Has caused outbreaks in healthcare settings



- 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*



Cernakova et al. Int. J. Mol. Sci. 2021, 22, 4470

ANTIFUNGAL "BREAKPOINTS"

Drugs	Tentative MIC Breakpoints (µg/mL)	Comments
Anidulafungin	≥ 4	Tentative breakpoints are based on the modal distribution of echinocandin MICs of approximately 100 isolates from diverse geographic locations
Caspofungin	≥ 2	
Micafungin	≥ 4	
Amphotericin B	≥ 2	Recent pharmacokinetic/pharmacodynamic mouse model of *C. auris* indicates that under standard dosing, the breakpoint for amphotericin B should be 1 or 1.5, similar to what has been determined for other *Candida* species. Therefore, **isolates with an MIC of ≥2** should now be considered resistant. **If using Etest for amphotericin B and an MIC of 1.5 is determined, that value should be rounded up to 2.**
Fluconazole	≥ 32	Isolates with MICs ≥ 32 were shown to have a resistance mutation in the *Erg11* gene
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

https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html

Ong CW et al. *Intern Med J.* 2019; 49(10): 1229-43.
ElBaradei A et al. *Eur J Clin Microbiol Infect Dis.* 2020; 39:1617-27.

NOTES FROM THE FIELD

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)

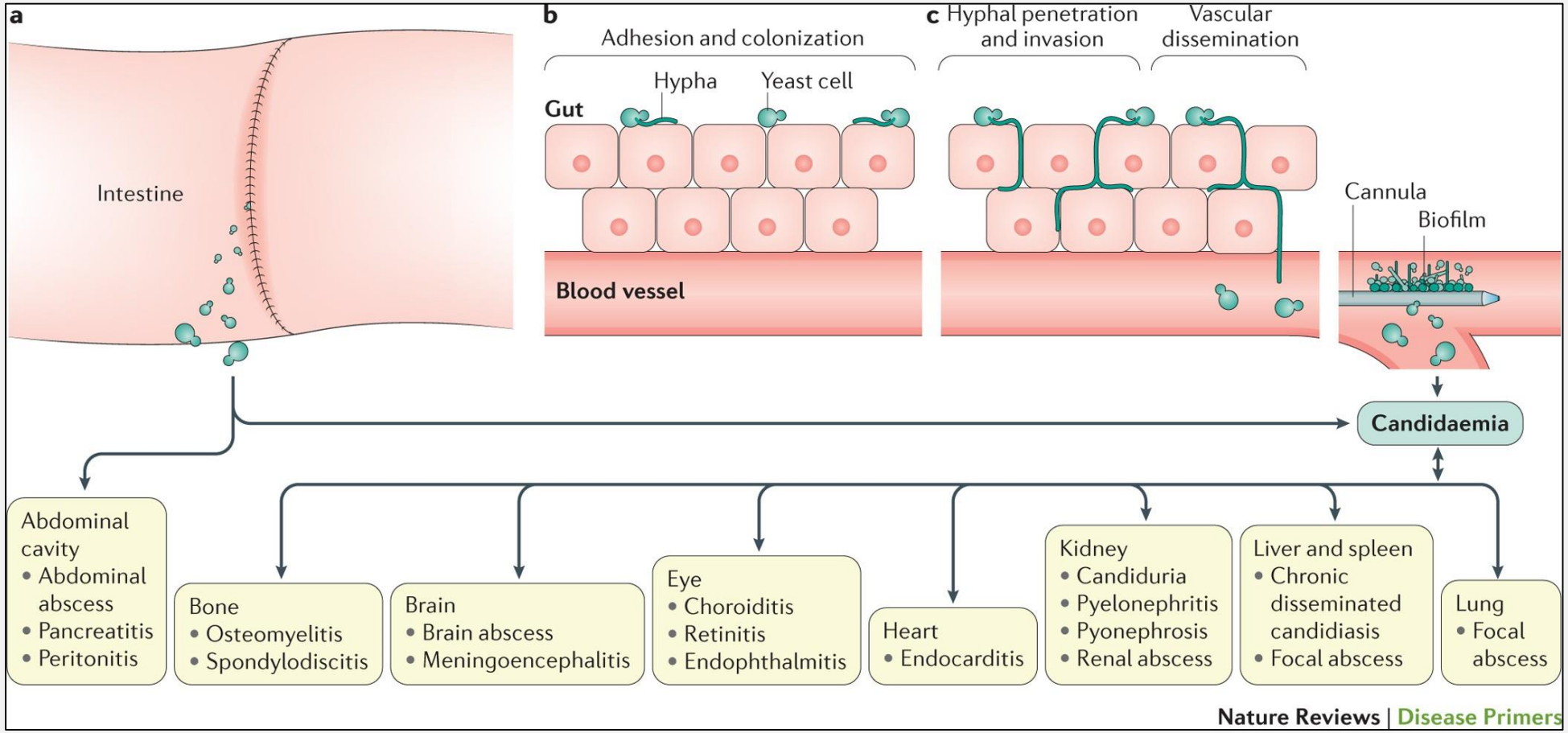
Considerations to prevent clusters

- 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.
Tsay et al. *Clin Infect Dis.* 2018; 66(2): 306-11.

INVASIVE CANDIDIASIS



Pappas PG et al. *Nat Rev Dis Primers*. 2018; 4. 18026.

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

Drugs	U.S. resistance rate
Fluconazole	90%
Amphotericin B	30%
Echinocandins	< 5%

Adults and children ≥ 2 months of age	• Echinocandins
Neonates and infants < 2 months of age	• Amphotericin B deoxycholate (1 mg/kg daily)

Ong, C et al. Intern. Med. J. 2019, 49, 1229–1243
Cernakova et al. Int. J. Mol. Sci. 2021, 22, 4470
https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html

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 → de-escalate based on susceptibilities?
- Lack of improvement:
  - Combination treatment?
  - Investigational drugs?

Pappas PG et al. *Clin Infect Dis*. 2016; 62(4): e1-50.
https://www.cdc.gov/fungal/candida-auris/c-auris-treatment.html

SYNERGY OR ANTAGONISM OF COMBINATIONS?

			Type of interaction *N* (%)[a]		
N of isolates	Compound A	Compound B	SYN	IND	ANT
15	5-Flucytosine	Amphotericin B	1 (7)	14 (93)	
		Micafungin	1 (7)	14 (93)	
		Voriconazole		15 (100)	
10	Caspofungin	Fluconazole		10 (100)	
		Voriconazole		10 (100)	
	Micafungin	Fluconazole		10 (100)	
		Voriconazole	10 (100)		

SYN = synergy; IND = indifferent; ANT = antagonism

Gharehbolagh SA et al. *Mycoses*. 2021; 64(1308-16).
Bidaud AL et al. *Antimicrob Agents Chemother*. 2019; e01383-19.
Fakhim H et al. *Antimicrob Agents Chemother*. 2017; 61: e01056-17.

C. AURIS RESISTANCE MECHANISMS

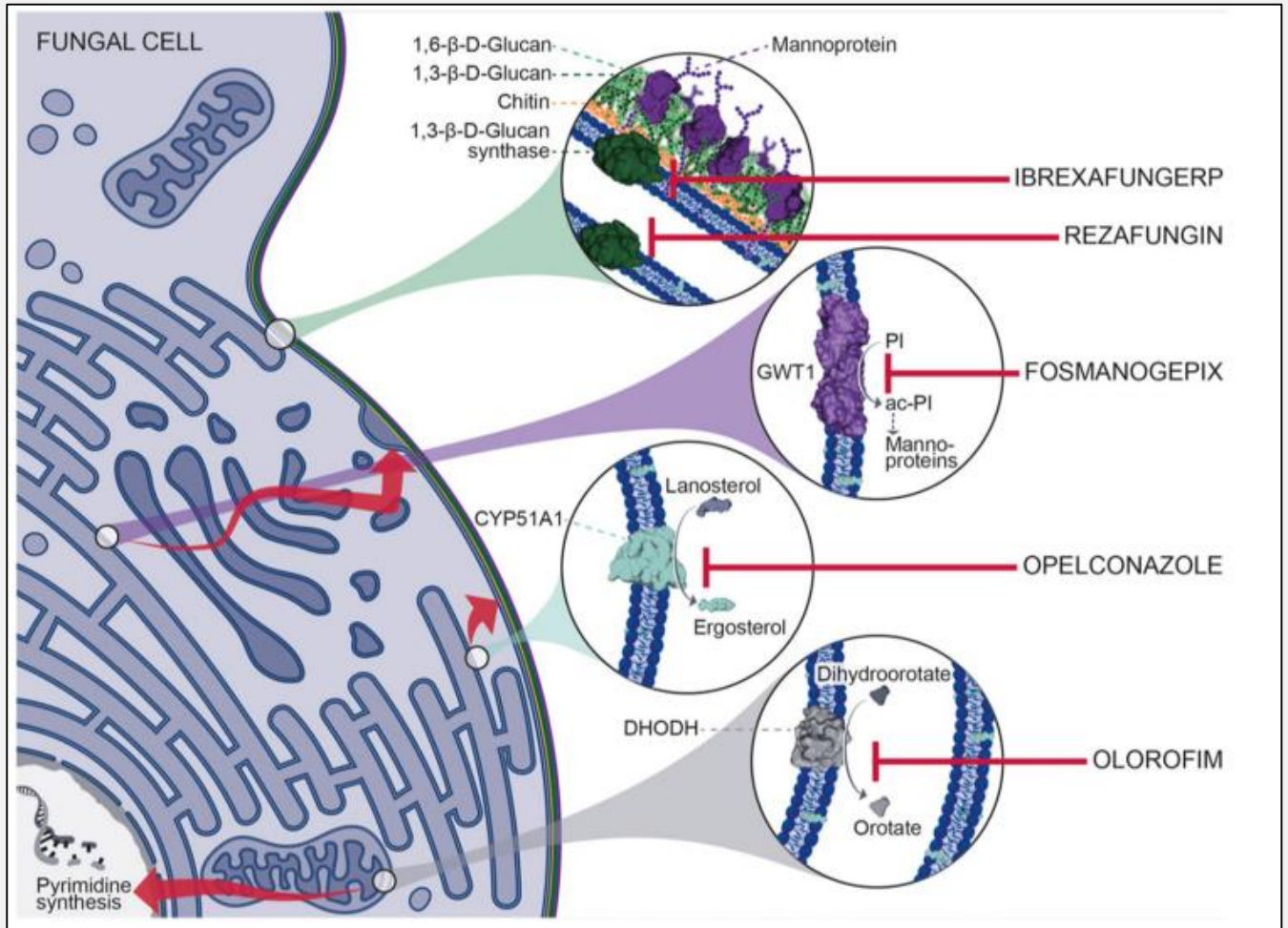
Class	Target of class	Resistance mechanism
Echinocandins	Inhibit 1,3-β-D-glucan synthetase (encoded by *FKS1* and *FKS2)*	*FKS1* gene mutation
Azoles	Inhibits lanosterol 14 α-demethylase (LDM) → converts lanosterol to ergosterol (key fungal membrane component) *ERG11* encodes LDM	*ERG11* mutation Efflux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

ElBaradei A et al. *Eur J Clin Microbiol Infect Dis*. 2020; 39:1617-27.

PATIENT SCENARIO #2

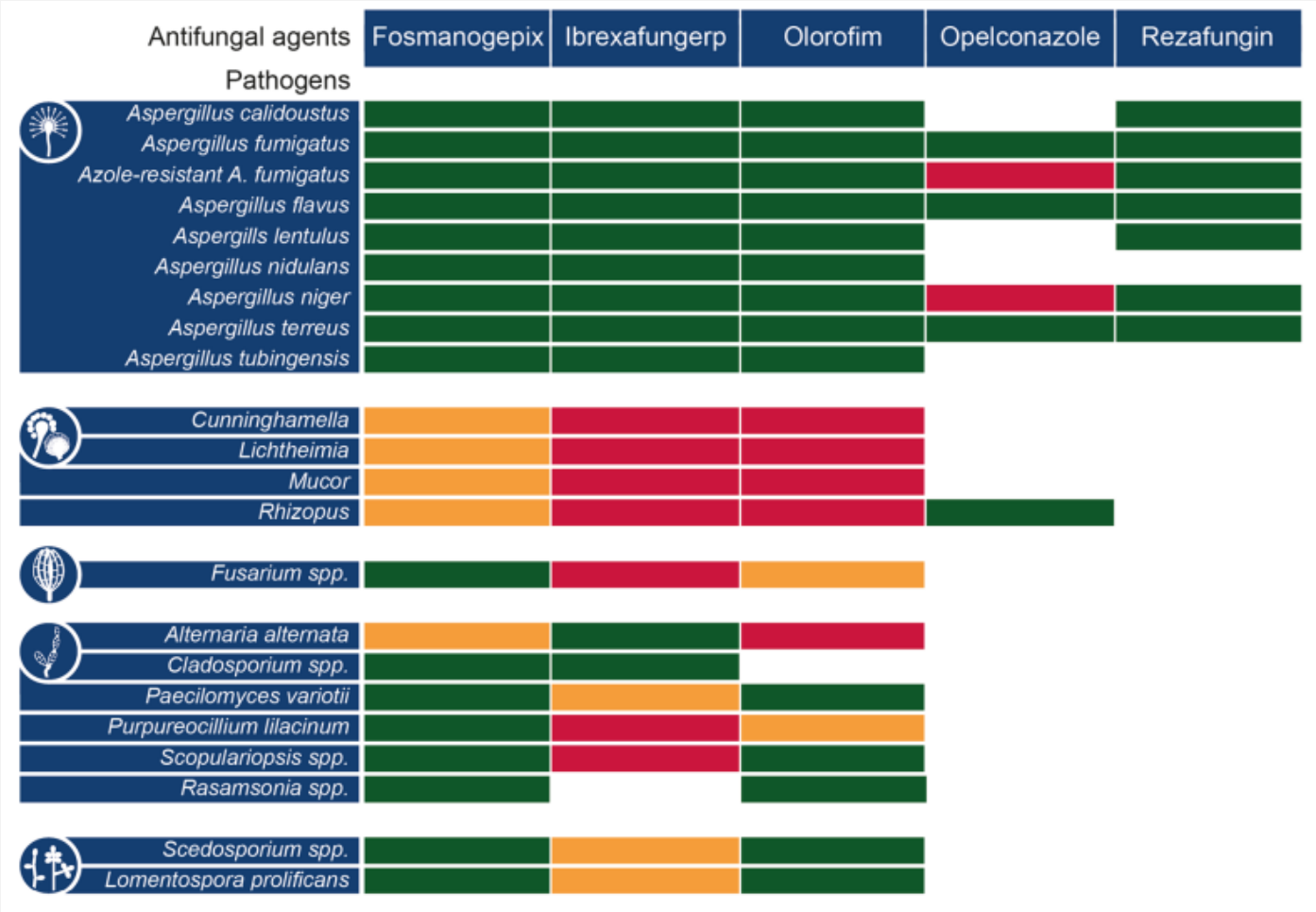
- One week later, the patient's blood cultures return, identified as *C. auris*. Cultures are resistant to fluconazole and there may be concern for *FKS1* mutation. Patient remains on pressors with persistent positive blood cultures.
- What antifungal treatment should the patient be transitioned to?
  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

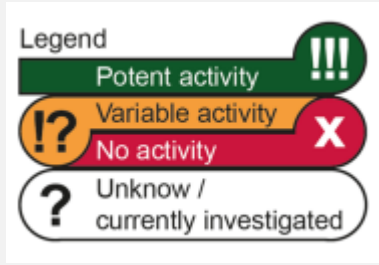
THE ANTIFUNGAL PIPELINE



Hoenigl M et al. *Drugs*. 2021; 81: 1703-29.

PIPELINE DRUGS & SPECTRUM OF ACTIVITY





Giacobbe DR et al. *Expert Rev Clin Pharmacol*. 2021; 14(10): 1205-20.

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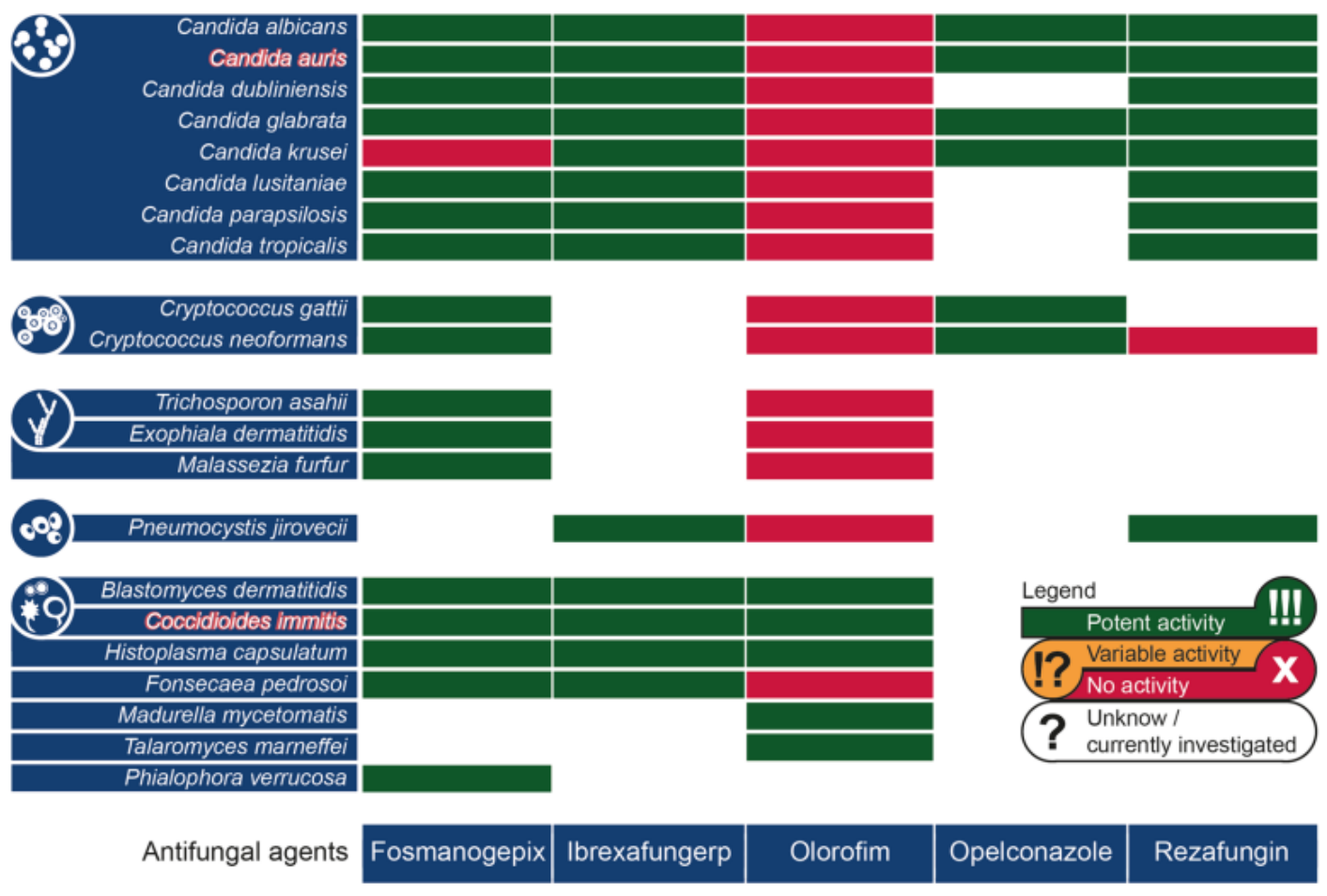
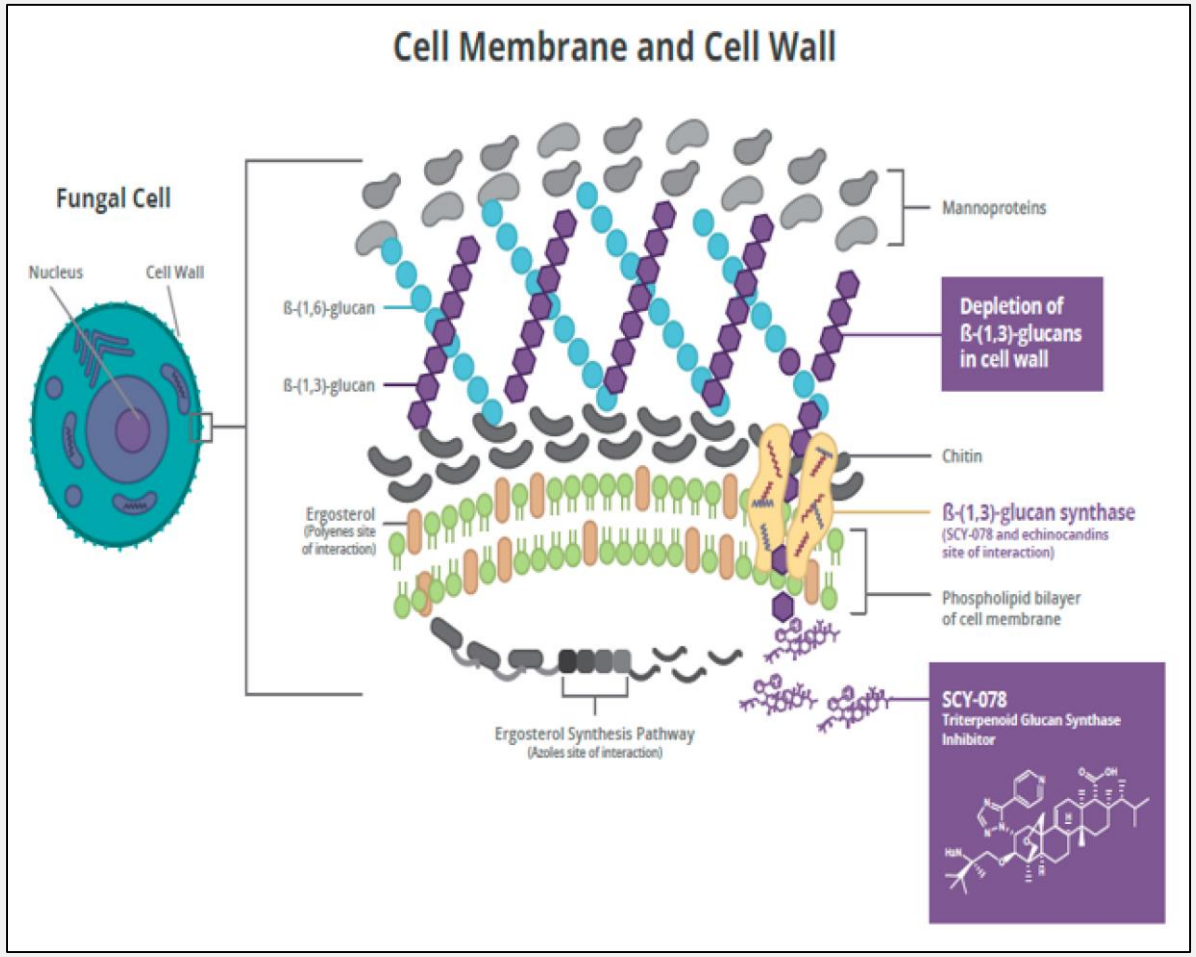


Giacobbe DR et al. *Expert Rev Clin Pharmacol*. 2021; 14(10): 1205-20.

IBREXAFUNGERP (FORMERLY SCY-08)

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



Giacobbe DR et al. *Expert Rev Clin Pharmacol*. 2021; 14(10): 1205-20.
Ghannoum M et al. *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 every12 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)

Giacobbe DR et al. *Expert Rev Clin Pharmacol*. 2021; 14(10): 1205-20.

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

https://www.scynexis.com/news-media/press-releases/detail/233/scynexis-announces-positive-results-from-interim-analyses

PATIENT SCENARIO #3

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

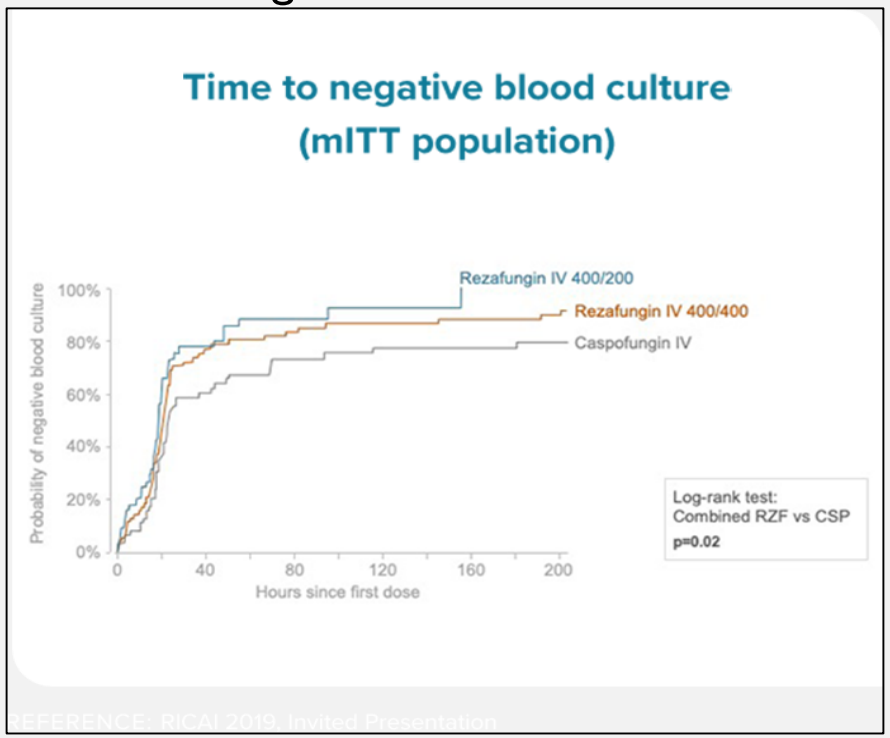
- Compassionate use for oral ibrexafungerp is being considered, what dose should be used?

  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)

Pathogen	CDC Threat Level	Rezafungin
Candida auris	Urgent Threat	✓
Drug resistant *Candida*	Serious Threat	✓
Azole-resistant *Aspergillus fumigatus*	Watch List	✓

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



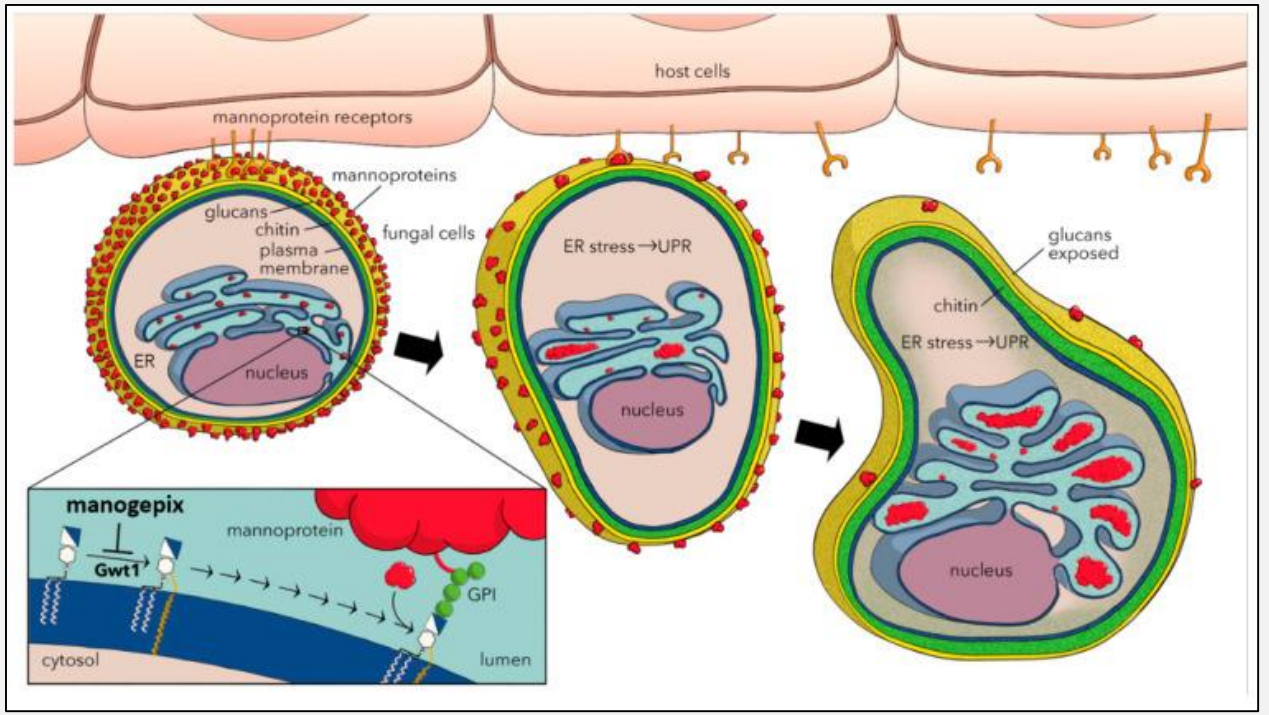
https://www.cidara.com/rezafungin/

CDC, Report on Antibiotic Resistant Threats. Updated Dec 2019.

Giacobbe DR et al. *Expert Rev Clin Pharmacol*. 2021; 14(10): 1205-20.

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



Shaw KJ et al. *J Fungi (Basel).* 2020; 6(4): 239.
Giacobbe DR et al. *Expert Rev Clin Pharmacol.* 2021; 14(10): 1205-20.

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
  - *PDR*1-mediated drug efflux transporters

Giacobbe DR et al. *Expert Rev Clin Pharmacol*. 2021; 14(10): 1205-20.
Schell WA et al. *Antimicrob Agents Chemother*. 2017; 61: e01817-7.
Shubitz LF et al. *Antimicrob Agents Chemother*. 2017; 61: e00111-7.

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

https://www.f2g.com/access_olorofim
https://clinicaltrials.gov/ct2/show/NCT03583164
Hoenigl M et al. *Drugs.* 2021; 81: 1703-29.

OPELCONAZOLE (PC945)

- 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 ?

Hoenigl M et al. *Drugs.* 2021; 81: 1703-29.

FINAL THOUGHTS