UWTASP tele-antimicrobial stewardship program | echo

March 12, 2024

A Candid Review of *Candida* Treatment

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Project ECHO

Patient Case

JC is a 63-year-old female with past medical history of type 2 diabetes, hyperlipidemia, and Crohn's disease receiving TPN presents with new onset of general weakness and fevers. Blood cultures are positive for ***Candida glabrata***.

Patient Case – Audience Response

What initial therapy would you choose to treat the patient's candidemia?

- Fluconazole 400 mg IV daily
- Micafungin 100 mg IV daily
- Liposomal Amphotericin B 3 mg/kg IV daily
- I'm not sure

What is *Candida*?

HEALTH NEWS

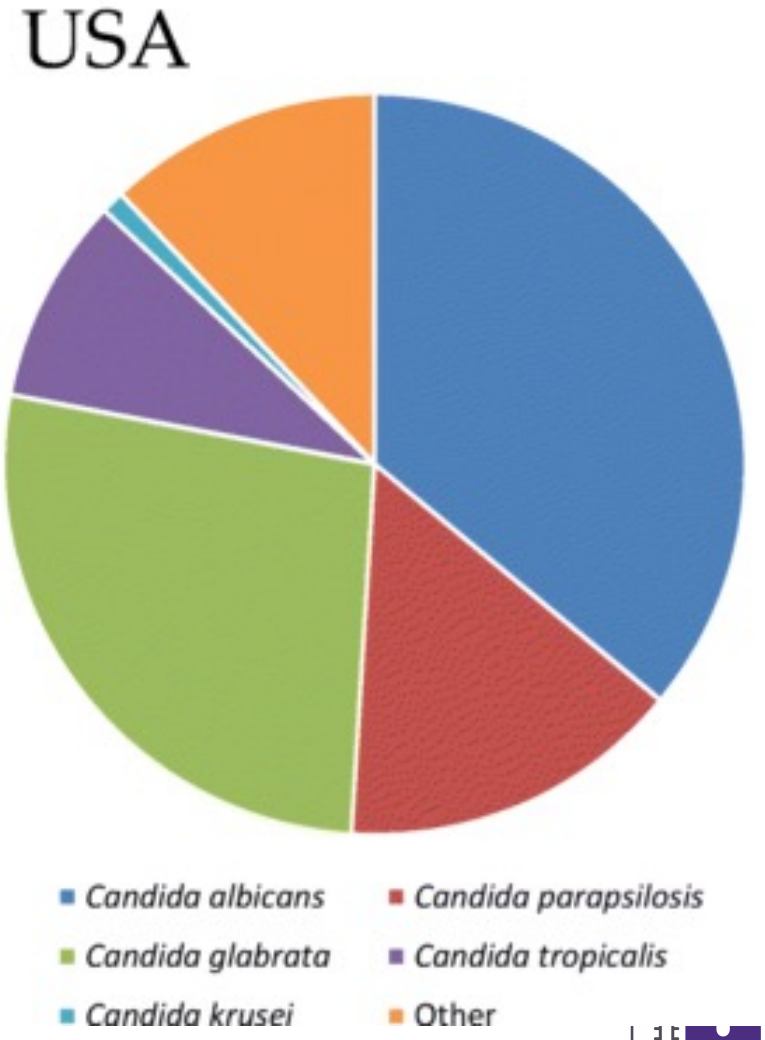
Washington state faces first outbreak of a deadly fungal infection that's on the rise in the U.S.

Cases of Candida auris have increased every year since 2016. Experts say it's only a matter of time before they're reported in every state.

Bendix, A; NBCNews.com. 31 Jan 2024.

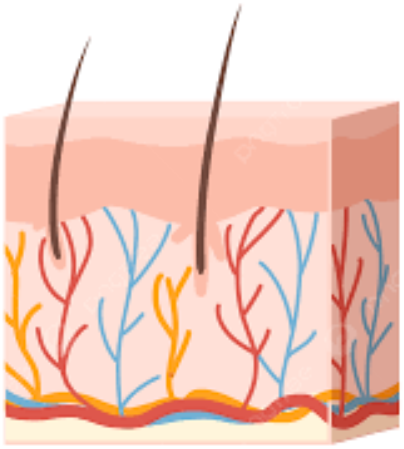
What is *Candida*?

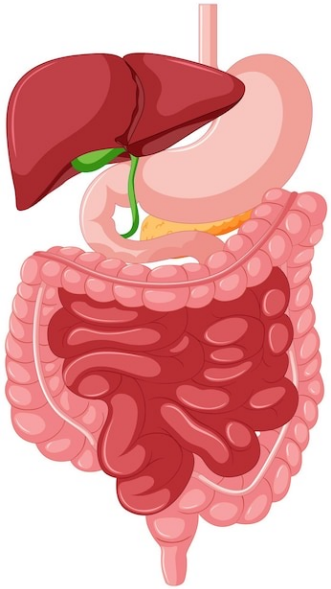
- *Candida* organisms = yeast
- > 150 species of *Candida*
- Ubiquitous to the environment (commensal)
- Pathogenic potential



Edwards et.al. Elsevier, Inc.; 2022; 256, 3087-3102.e4.
World Health Organization; 2022. License: CC BY-NC-SA 3.0 IGO.
Quindos et.al. International Micro; 2018. 21. 10.1007/s10123-018-0014-1.

What is *Candida*?





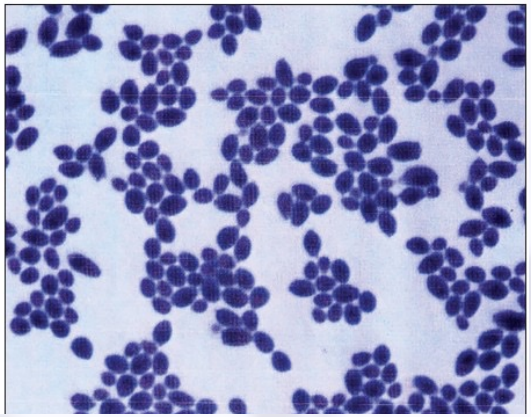
Edwards et.al. Elsevier, Inc.; 2022; 256, 3087-3102.e4.
Image: https://pngtree.com/freepng/skin-tissue-hair_6746653.html.
Image: https://www.freepik.com/free-photos-vectors/gastrointestinal
Image: https://www.freepik.com/premium-vector/open-mouth-with-health-throat-human-healthy-throat-tonsils_69838379.htm

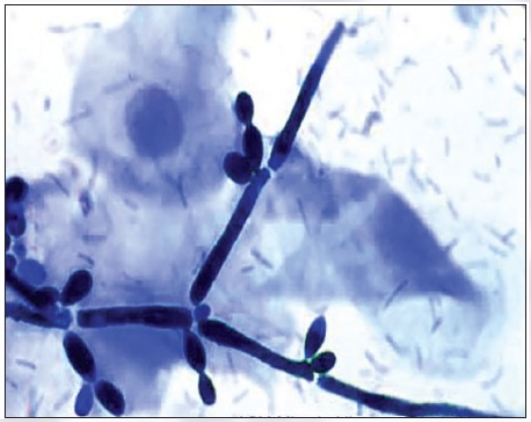
How to Identify *Candida*?

Back to our case…

JC is a 63-year-old female with past medical history of type 2 diabetes, hyperlipidemia, and Crohn's disease receiving TPN presents with new onset of general weakness and fevers. Blood cultures are positive for ***Candida glabrata***.

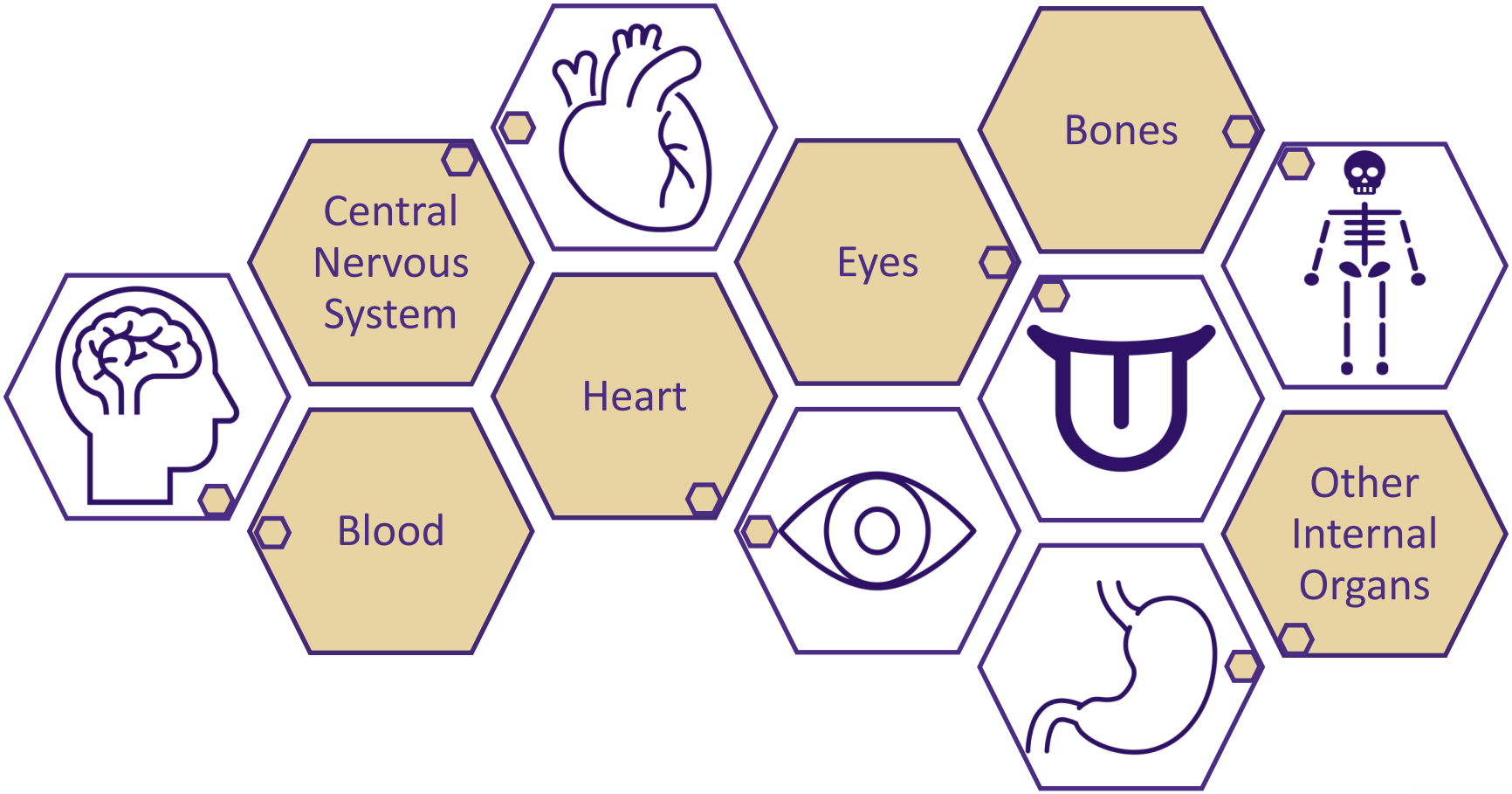
How to Identify *Candida*?





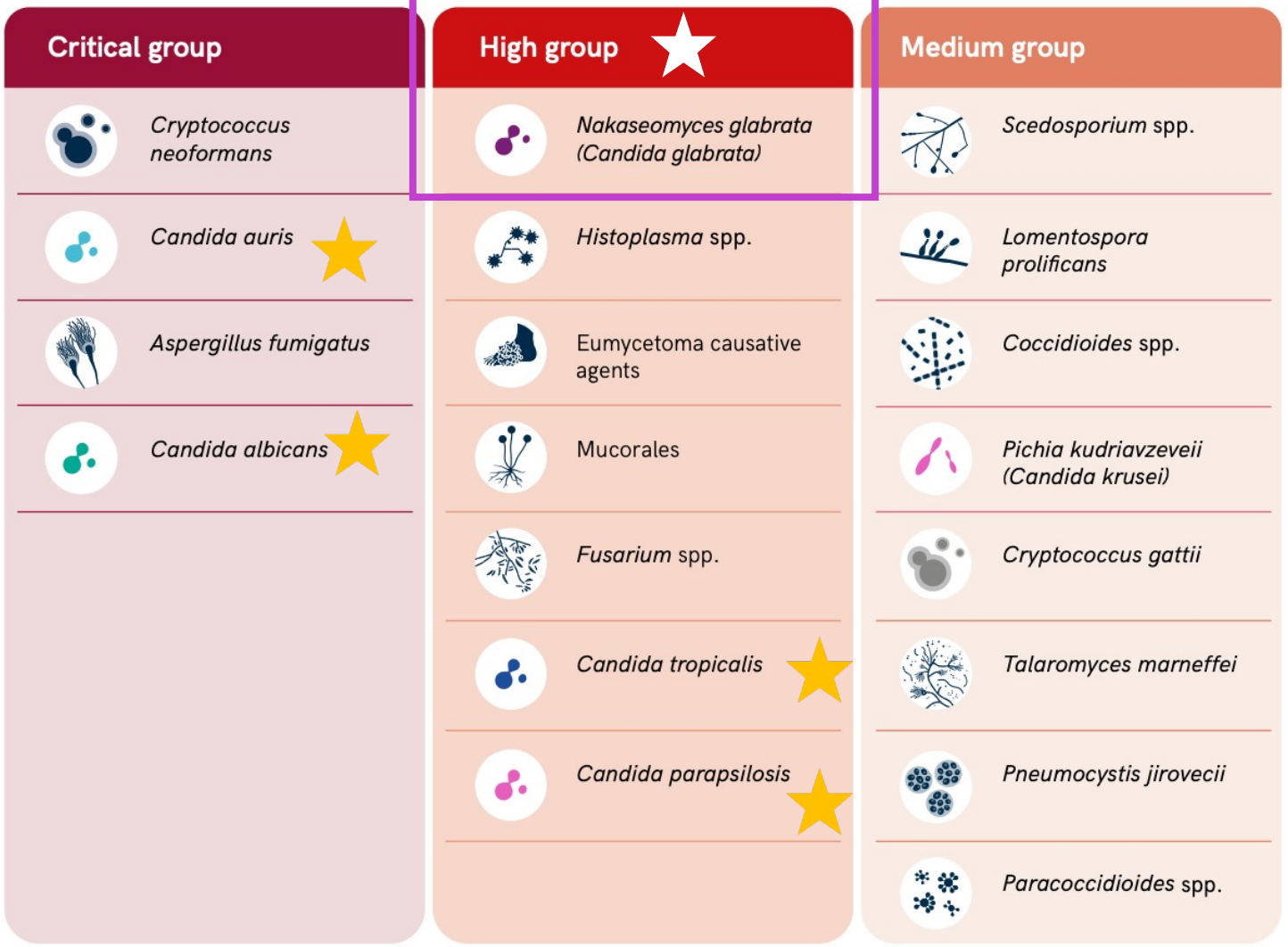
Edwards et.al. Elsevier, Inc.; 2022; 256, 3087-3102.e4.
Thairu et. al. Sub-Saharan Afr J Med 2014;1:168-74.
Image: https://www.medical-labs.net/morphologic-features-of-yeast-colonies-2818/

Clinical Manifestations



Edwards et.al. Elsevier, Inc.; 2022; 256, 3087-3102.e4.

WHO Fungal Priority Pathogens List



Epidemiology

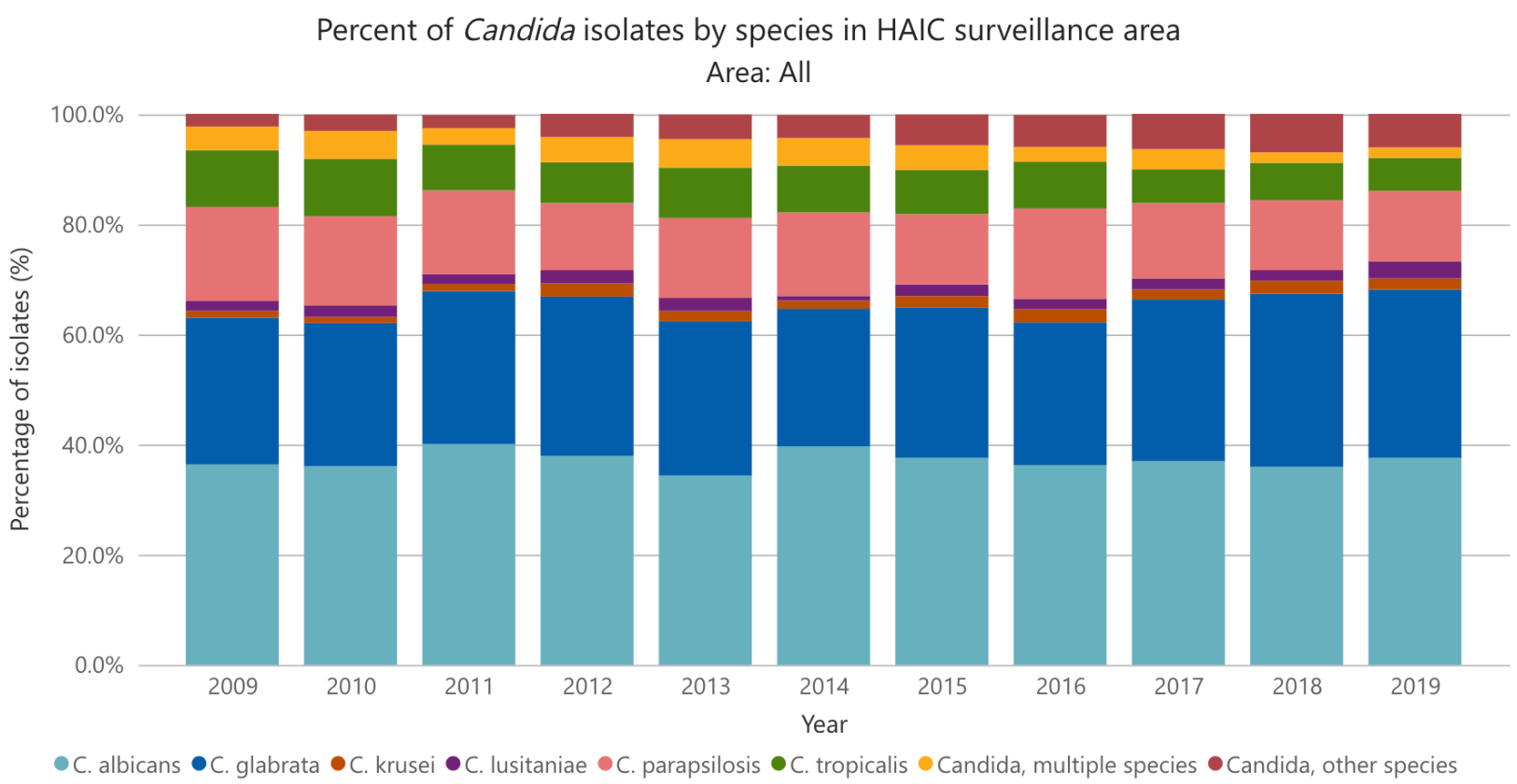
- Candidemia is one of the **most common bloodstream infections** in the United States, with estimated incidence ~ 9 per 100,000 people (2013-2017).

- All-cause mortality among patients with candidemia is ~ 25%.

- Each case of candidemia is estimated to add 3 to 13 days of hospitalization and $6,000 to $29,000 in healthcare costs.

Center for Disease Control and Prevention; Invasive Candidiasis Statistics; Jan 2023.

Epidemiology



Note: Surveillance areas have changed over time. To learn more about the surveillance areas, **click here**.

Data last updated: 3/16/2023 | **Accessibility:** Right click on the graph area to show as a table

Center for Disease Control and Prevention; Healthcare-Associated Infections – Community Interface (HAIC). 2021.

Risk Factors for Infection

Compromised immunity	Exposure to broad-spectrum antibiotics	Indwelling IV catheters	Prolonged hospitalization
Total parenteral nutrition	Colonization of *Candida*	Gastrointestinal surgery	Thoracic surgery
	Burn patients	IV drug use	

Edwards et.al. Elsevier, Inc.; 2022; 256, 3087-3102.e4.
Fidel et.al. Clin Microbiol Rev. 1999 Jan;12(1):80-96.
Isenberg et.al. J Clin Microbiol. 1989 Nov;27(11):2426-8.
Vazquez et.al. J Infect Dis. 1993 Jul;168(1):195-201.

Treating *Candida*

Clinical Infectious Diseases

IDSA GUIDELINE

Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America

Peter G. Pappas,[1] Carol A. Kauffman,[2] David R. Andes,[3] Cornelius J. Clancy,[4] Kieren A. Marr,[5] Luis Ostrosky-Zeichner,[6] Annette C. Reboli,[7] Mindy G. Schuster,[8] Jose A. Vazquez,[9] Thomas J. Walsh,[10] Theoklis E. Zaoutis,[11] and Jack D. Sobel[12]

Pappas et.al. Clin Infect Dis. 2016 Feb 15;62(4):e1-50.

Treating Candidemia

- An echinocandin is recommended as initial therapy (*strong recommendation; high-quality evidence*)
- Fluconazole IV or PO 800 mg (12 mg/kg) loading dose, then 400 mg (6 mg/kg) daily is an acceptable alternative in selected patients – not critically ill, unlikely to have fluconazole-resistant *Candida* species (*strong recommendation; high-quality evidence*)
- Transition from echinocandin to fluconazole if clinically stable with negative repeat blood cultures, and isolates are susceptible (*strong recommendation; moderate-quality evidence*)

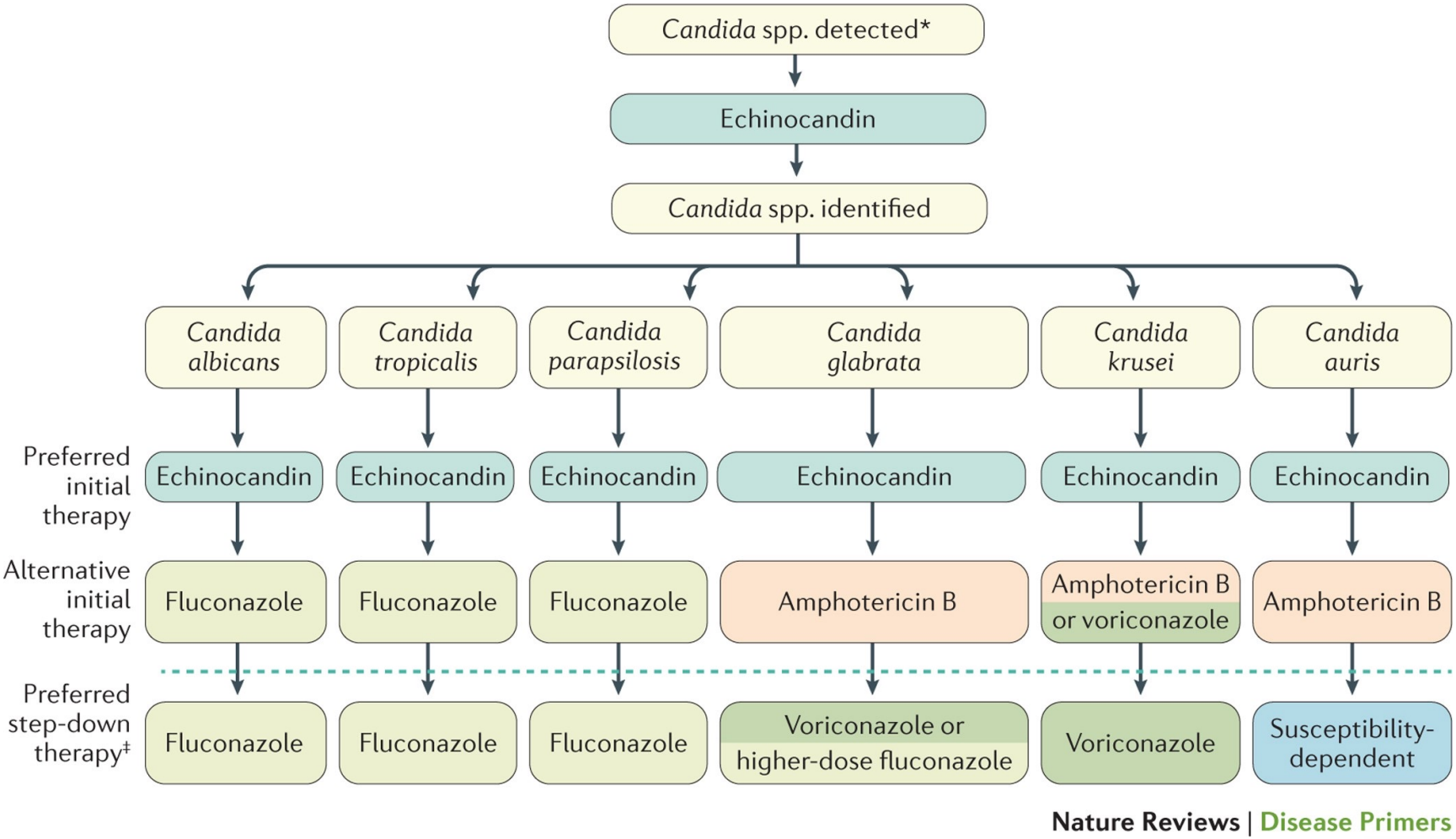
Pappas et.al. Clin Infect Dis. 2016 Feb 15;62(4):e1-50.

Treating *Candida*

- Recommended duration (without complications) = 2 weeks from documented bloodstream clearance
- Central venous catheters should be removed as soon as possible
- Ophthalmological exam?

Pappas et.al. Clin Infect Dis. 2016 Feb 15;62(4):e1-50.

Treating Candidemia



Pappas et.al. Clin Infect Dis. 2016 Feb 15;62(4):e1-50.
Pappas et. al. Nat Rev Dis Primers. 2018 May 11; https://doi.org/10.1038/nrdp.2018.26

Back to Our Patient!

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Susceptibility

	Candida glabrata YEAST MIC (MCG/ML)
Amphotericin	0.06
Fluconazole	16
Micafungin	0.03

Audience Response

What antifungal agents do you have on formulary?

- Echinocandin
  (micafungin, caspofungin, or anidulafungin)
- Amphotericin B
  (liposomal, deoxycholate, or lipid formulation)
- Neither
- I'm not sure

Interpreting the Fluconazole MIC

Antifungal Agent		MIC Breakpoints and Interpretive Categories (mcg/mL)			
		S	I	SDD	R
Candida spp. (Except *C. krusei*)	Fluconazole	≤ 8	-	16-32	≥ 64

2012

Antifungal Agent		MIC Breakpoints and Interpretive Categories (mcg/mL)			
		S	I	SDD	R
C. albicans	Fluconazole	≤ 2	-	4	≥ 8
C. glabrata	Fluconazole	-	-	≤ 32	≥ 64

S = susceptible, I = intermediate, SDD = susceptible-dose dependent, R = resistant

CLSI M27M44S ED3:2022.

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JC's Isolate

	Candida glabrata YEAST MIC (MCG/ML)
Amphotericin	0.06
Fluconazole	16
Micafungin	0.03

CLSI M27M44S ED3:2022.

Susceptible Dose-Dependent

Clinical and Laboratory Standards Institute (CLSI)

Fluconazole

- Breakpoints based on clinical experience with mucosal and invasive infections
- Susceptibility depends on achieving maximum blood level

→ doses higher than the standard 6 mg/kg/day may be needed

- "Clinician should determine whether fluconazole is appropriate in the specific clinical context"
- **Recommend use of "maximum dosage regimen" for all C. glabrata**

  → such as 12 mg/kg/day

CLSI M27M44S ED3:2022.

Susceptible Dose-Dependent

Infectious Diseases Society of America (IDSA)

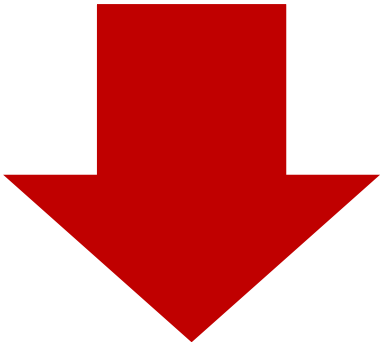
Clinical Practice Guideline for the Management of Candidiasis: 2016 Update

For infection due to *C. glabrata*, transition to **higher-dose fluconazole 800 mg (12 mg/kg) daily** or voriconazole 200-300 (3-4 mg/kg) twice daily should only be considered among patients with fluconazole-susceptible or voriconazole-susceptible isolates

(strong recommendation; low-quality evidence)

Pappas et.al. Clin Infect Dis. 2016 Feb 15;62(4):e1-50.

Risks vs Benefits



- Increased risk of <u>adverse effects</u>

→ Can affect adherence

- Increased magnitude of CYP3A4 inhibition

- Elevated LFTs
- Nausea, vomiting, diarrhea
- Abdominal pain
- Headache
- Prolonged QT interval
- Alopecia (at high doses)
- Severe hepatotoxicity (rare)

- Higher probability of target attainment
- Decrease risk of emerging resistance

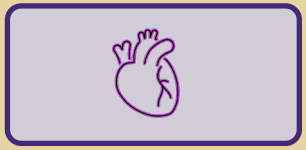
Rex et.al. Clin Infect Dis. 1997 Feb;24(2):235-47.
Fluconazole [package insert]. 2023 Aug.

Remember the Big Picture

Factors other than *in vitro* susceptibility that affect outcomes of infection

Drug pharmacokinetics: dosing, penetration to infection site, protein binding, drug interactions

Host factors: inflammatory response, antibody response, underlying disease



Site of infection: source control, presence of foreign body

Pathogen: toxin production or virulence factors, evasion of host response

Rex et.al. Clin Infect Dis. 1997 Feb;24(2):235-47.

Take-Aways

- *Candida* infections are a common cause of morbidity and mortality in the United States.
- Based on IDSA Clinical Guidelines, echinocandin agents are recommended 1st line for treatment of candidemia with the option for oral fluconazole step-down.
- *Candida glabrata* is unique in that it has a susceptible dose-dependent breakpoint, requiring higher daily fluconazole doses.
- Treatment success depends on many factors beyond microbiological data.

Thank You!

Questions?

Darrad@uw.edu

Appendix: PK/PD and Fluconazole Dosing

Predictive PD Parameter = *f*AUC/MIC → **~25-50**

~ 1:1 relationship for Dose:AUC

Dose/MIC can be used as a surrogate for AUC/MIC

From Our Patient Case: *C. glabrata* isolated with **MIC 16**

- CLSI Interpretation: susceptible-dose dependent

High-Dose $\frac{fAUC}{MIC} \approx \frac{Dose}{MIC} = \frac{800\ mg}{16} = 50$

vs

Standard Dose $\frac{fAUC}{MIC} \approx \frac{Dose}{MIC} = \frac{400\ mg}{16} = 25$