May 3, 2022

Antifungal Stewardship Part 1

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Antifungal Stewardship

- Goal: optimize the use of antifungals to achieve the best outcomes while minimizing adverse effects and limiting selection pressures that drive resistance

- 30-50% of antifungal use is inappropriate or suboptimal

- Targeted antifungal stewardship (AFS) interventions are less common

How We Use Antifungal Drugs

Prophylaxis | Empiric | Targeted | Definitive

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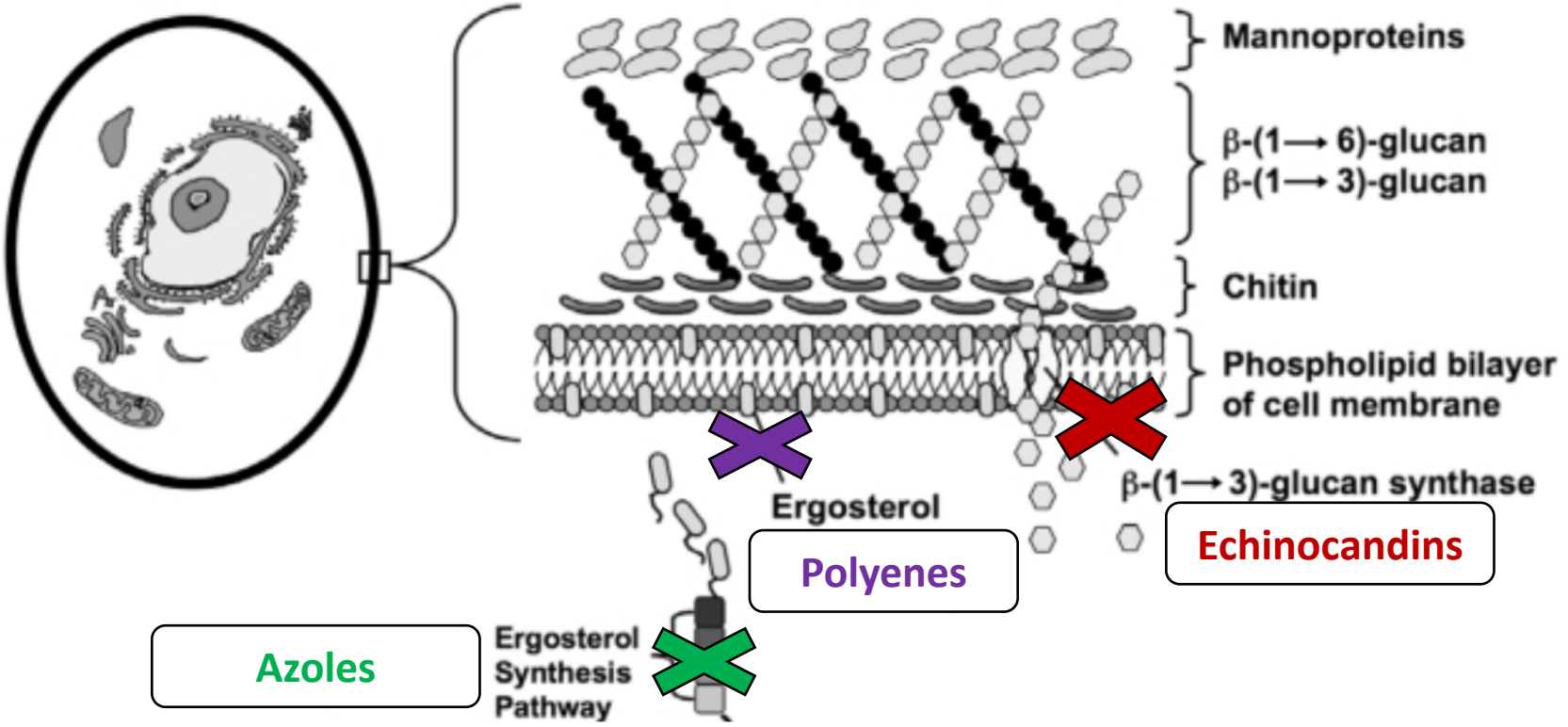
Depend on the host

Antifungal Targets



Case 1a: Candidemia

A 66 yo M is mechanically ventilated in the ICU following a MVA where he sustained abdominal trauma.

On day 9, after two days of high fevers, his blood culture is reportedly growing yeast.

Audience Response Question

What should you start empirically?

- Caspofungin 50 mg IV daily
- Micafungin 100 mg IV daily
- Fluconazole 400 mg IV daily
- Amphotericin B 3-5 mg/kg daily

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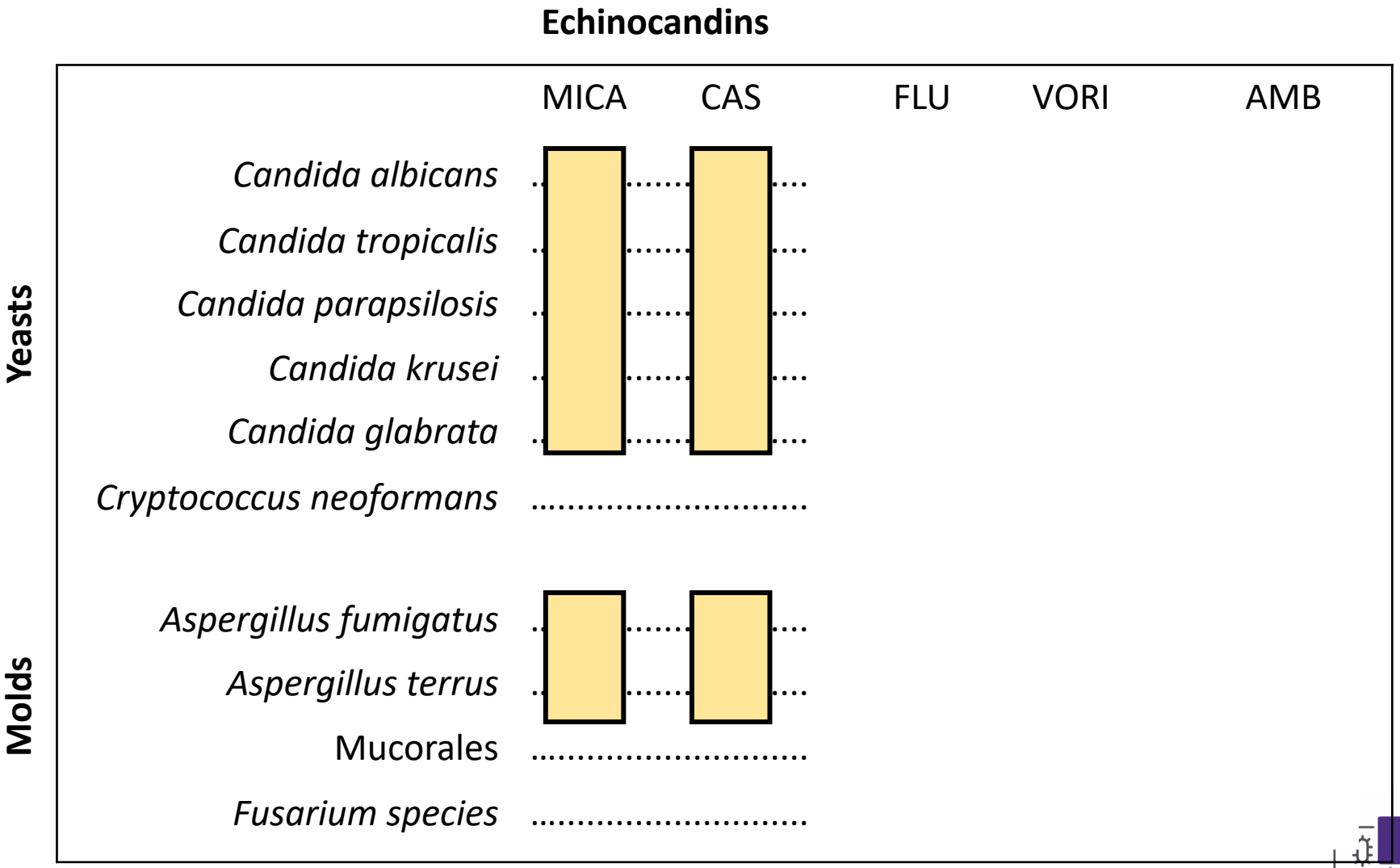
Spectrum of Activity



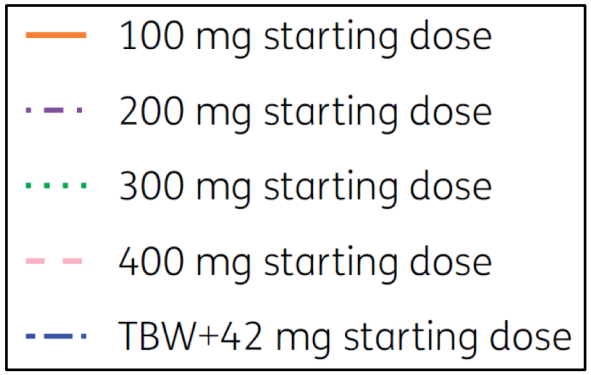
Lewis. Mayo Clin Proc. 2011.

Echinocandins

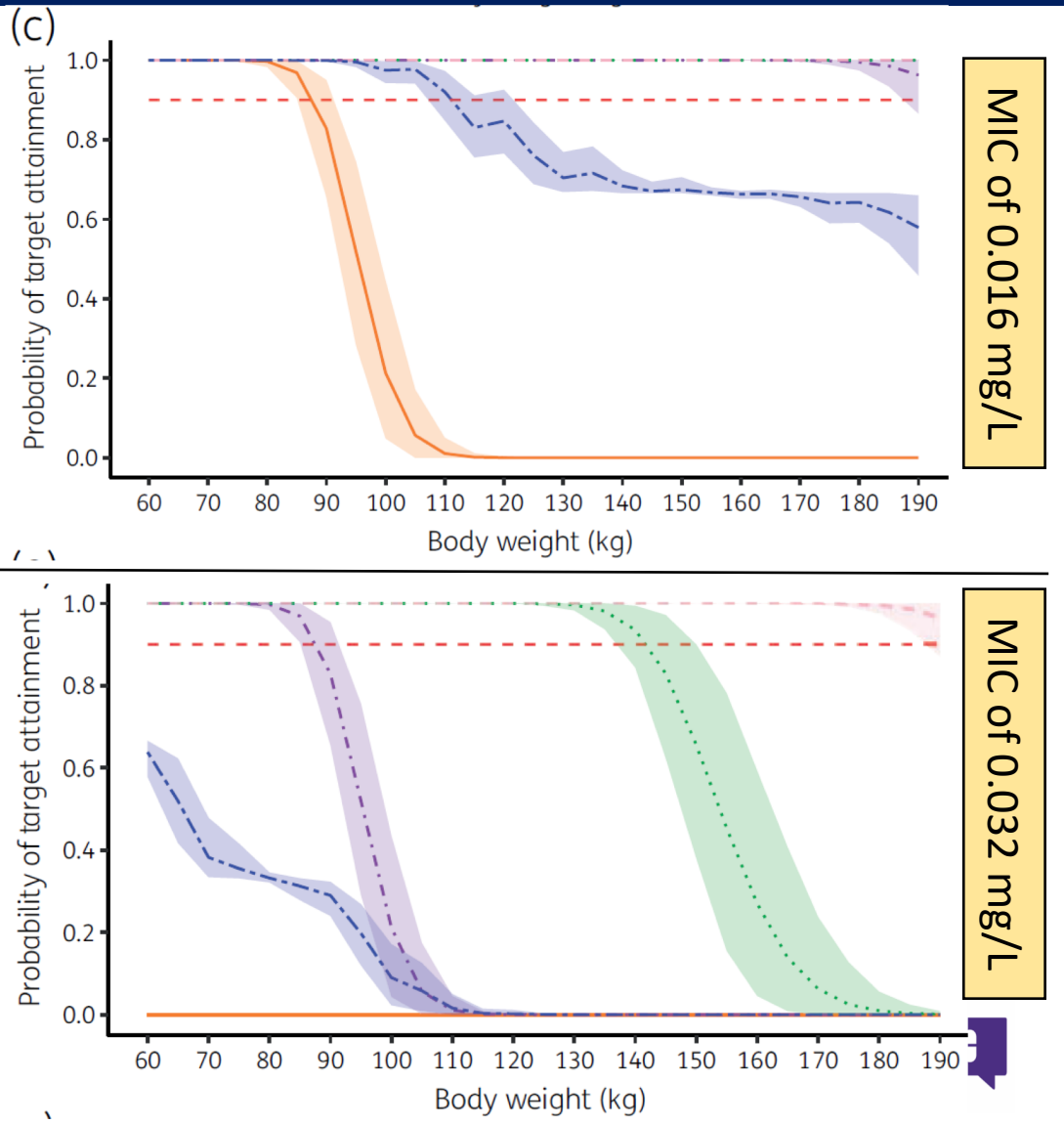
- Administered IV once daily
- Achieve therapeutic concentrations at all infection sites **except for** the eye, CNS, and urine
- No dose adjustment for renal insufficiency or dialysis
- **Few toxicities**
  - Histamine-mediated infusion-related reaction --> slow rate of infusion or premedicate with an antihistamine
- **Monitoring:** weekly LFTs

Pharmacokinetics in Obese

- Probability of target attainment (PTA) for micafungin in normal-weight and morbidly obese adults



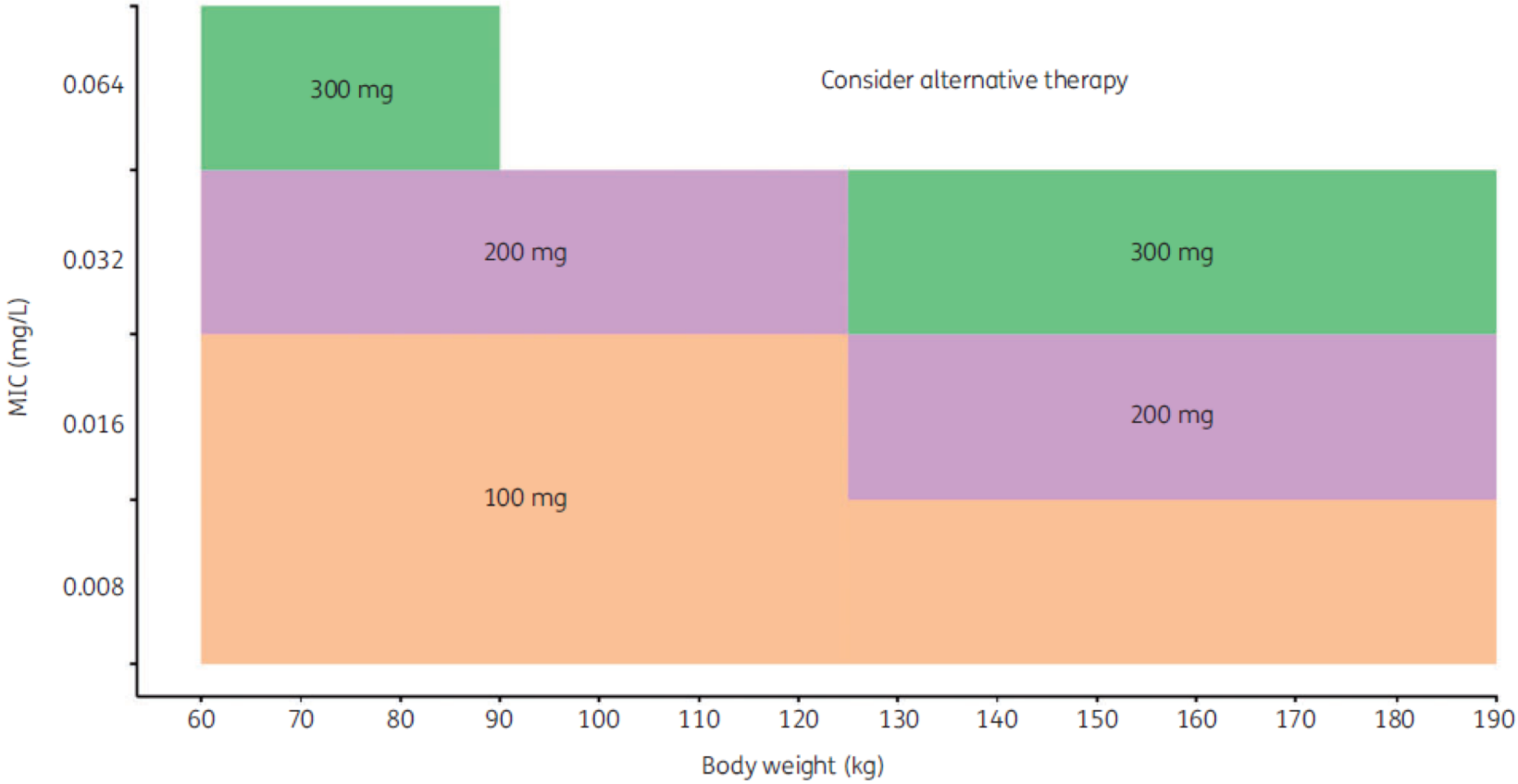
As body weight and MICs increase, higher doses are needed for high PTA



Wasmann. *J Antimicrob Chemother*. 2019.

Pharmacokinetics in Obese

Recommendations for maintenance dose by body weight and MICs



Body weight >125 kg, MIC >0.016, not responding on therapy

Wasmann. *J Antimicrob Chemother*. 2019.

Case 1b: Candidemia

A 66 yo M is mechanically ventilated in the ICU following a MVA where he sustained abdominal trauma. On day 9, after two days of high fevers, his blood culture is reportedly growing yeast.

Four days later, the patient's culture from before grows ***Candida albicans*** susceptible to fluconazole. Repeat blood cultures are clear. Weight=70kg

Audience Response Question

What changes, if any, should you make?

- Continue micafungin 100 mg IV daily
- Switch micafungin to fluconazole 400 mg IV/PO daily
- Switch micafungin to fluconazole 800 mg IV/PO daily

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Case 1c: Candidemia

A 66 yo M is mechanically ventilated in the ICU following a MVA where he sustained abdominal trauma. On day 9, after two days of high fevers, his blood culture is reportedly growing yeast.

Four days later, the patient's culture from before grows ***Candida glabrata*** **susceptible dose dependent to fluconazole**. Repeat blood cultures are clear. Weight=70kg

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- Continue micafungin 100 mg IV daily
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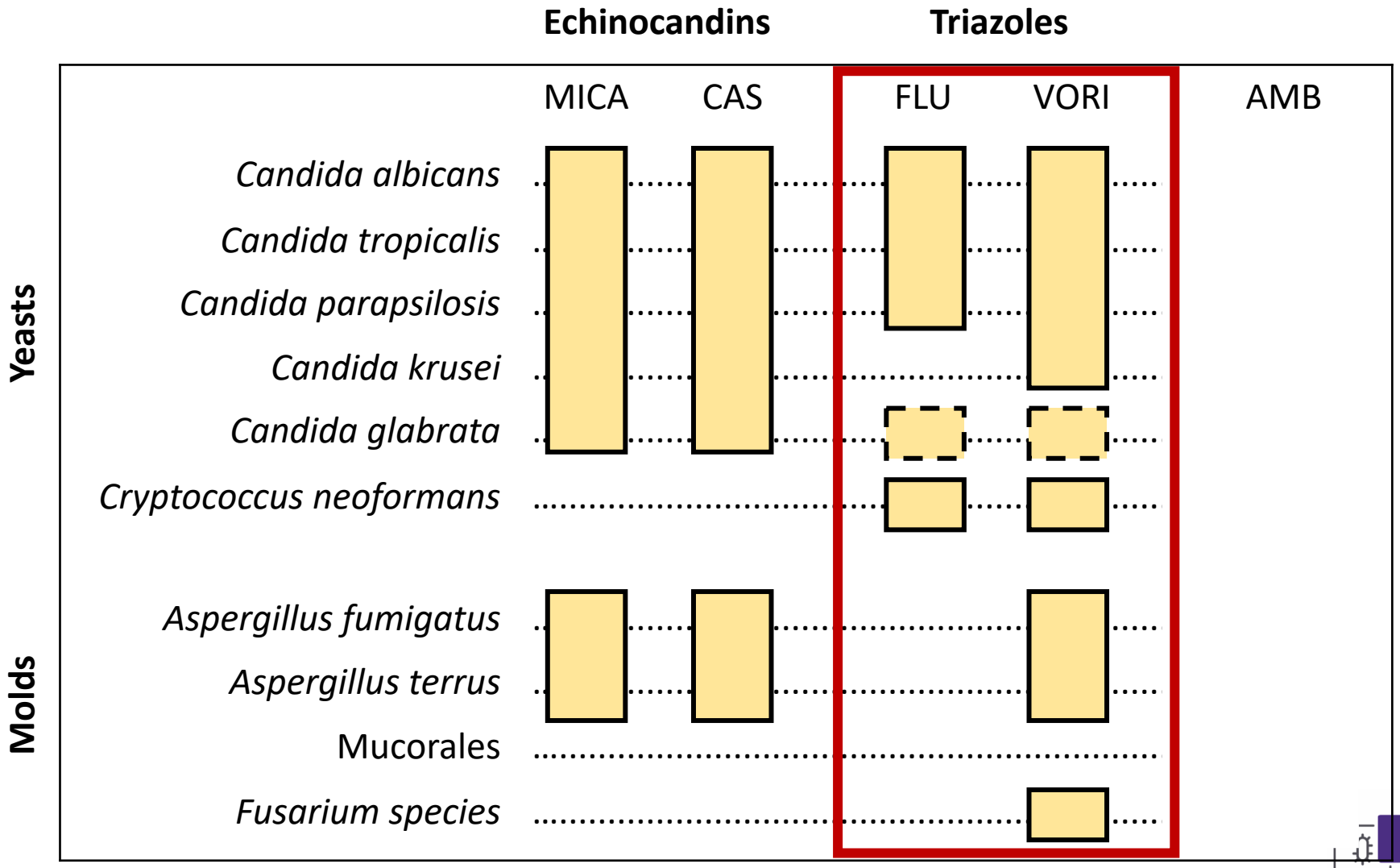
Spectrum of Activity



Lewis. Mayo Clin Proc. 2011.

Fluconazole

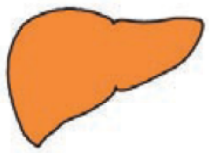
- Excellent oral bioavailability **>90%**
  - Absorption not affected by food or gastric pH
- Intrinsic resistance to ***C. krusei***
- MIC thresholds are higher for ***C. glabrata*** than other *Candida* species
    - "susceptible dose dependent" → higher doses should be used (800 mg or 12 mg/kg/day)
- Only azole renally eliminated
- Cerebrospinal fluid, intraocular, and urine penetration
- **Monitoring:** LFTs twice a month

Voriconazole

- Excellent oral bioavailability >90% **when stomach is empty**
  - Administered on an empty stomach
- **Highly dependent** on metabolism for drug elimination
- Goal voriconazole trough: 1-5.5 mg/L
- Cerebrospinal fluid and intraocular penetration
- **Monitoring:** CBC with differential monthly; Chem-7 + Mg + Ca + Phos twice a month; LFTs weekly

Azole Toxicities

Fluconazole

Hepatic 

QT prolongation 

Lewis. Mayo Clin Proc. 2011.

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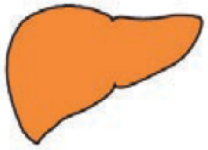
Hepatic 

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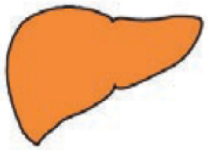
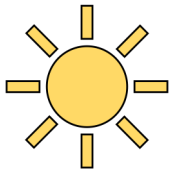
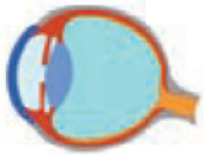
Hepatic 

QT prolongation 

CNS 

Cutaneous 

Photopsia 

Lewis. Mayo Clin Proc. 2011.

Case 1d: Candidemia

The 66 yo M who was found to have ***Candidia krusei*** candidemia **resistant to fluconazole and susceptible to voriconazole**. Goal voriconazole trough: 1-5.5 mg/L.

Other medications:

- Warfarin
- Sirolimus
- Atorvastatin
- Digoxin
- Omeprazole

Audience Response Question

Patient's voriconazole trough resulted at 7.2 mg/L one week after starting therapy. Could any of the patient's medications be contributing?

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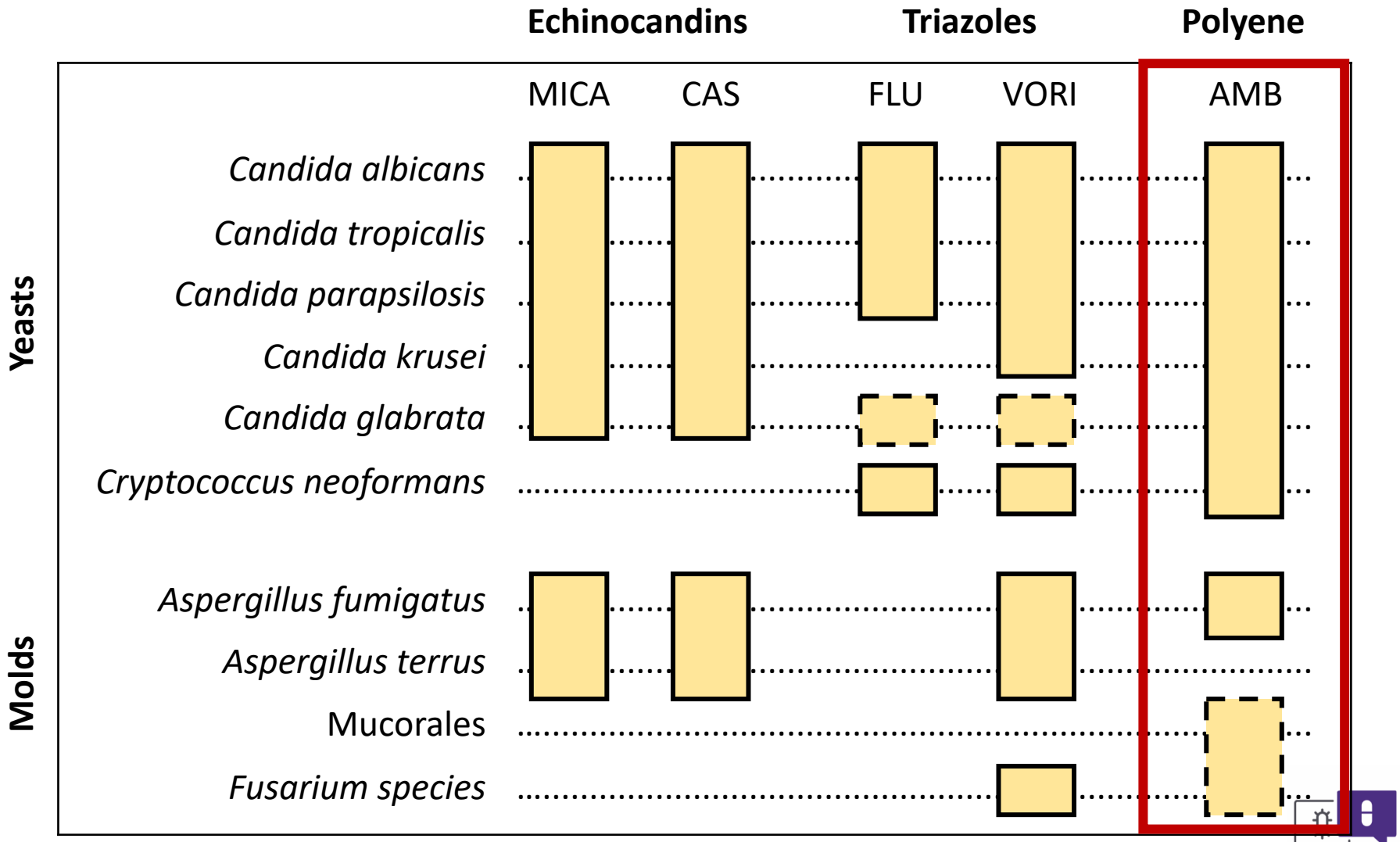
Anticipating Drug Interactions

Cytochrome P450 (CYP) Inhibition Profile of Triazole Antifungal Agents				
Mechanism	**FLU**	**VORI**	**POSA**	**ITRA**
Inhibitor				
CYP2C19	+	+++	--	--
CYP2C9	++	++	--	+
CYP3A4	++	++	+++	+++
Substrate				
CYP2C19	--	+++	--	--
CYP2C9	--	+	--	--
CYP3A4	+	+	--	+++

-- = no activity; + = minimal activity; ++ moderate activity; +++ = strong activity

Lewis. Mayo Clin Proc. 2011.

Spectrum of Activity



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Amphotericin B

	AmB Deoxycholate	Lipid AmB
Formulation	IV only	IV only
Typical dosing	0.5-1 mg/kg daily	3-5 mg/kg daily
Penetration		
Eye	Previously used; poor levels in vitreous	Limited data
CNS	++	+++
Urine	+	---
Toxicity		
Nephrotoxicity	+++	+
Infusion reaction	+++	+
Electrolyte wasting	↓ K, ↓ Mg, ↑ Cl	↓ K, ↓ Mg, ↑ Cl

Monitoring: Chem-7 + Mg twice weekly; CBC with differential + LFTs weekly

Conclusion

- Inappropriate antifungal use is prevalent and can lead to drug-resistant fungi, expose patients to adverse drug events, and increase healthcare costs
- Need for antifungal experts
- Need for targeted antifungal stewardship interventions

Thank you!

Questions?

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