

4 – Core Concepts: Antifungal Drugs

Speaker: John Bennett, MD



Core Concepts: Antifungal Drugs

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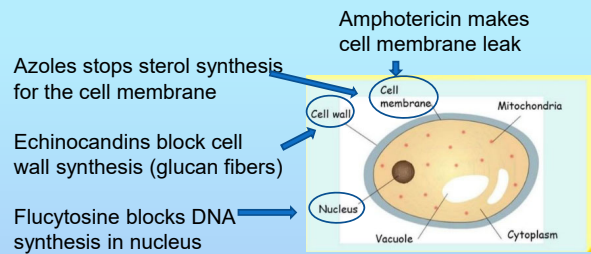
Disclosures of Financial Relationships with Relevant Commercial Interests:

- **Consultant:** Scynexis, GSK, Astellas, Merck, HealthTrackRx, Basilea
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Agenda

1. Review of Antifungals
 - Key points are underlined
2. Questions on antifungals with answers
3. New stuff (not on boards)

Antifungal Drugs



ANTIFUNGAL RESISTANCE

Altered Target Ezymes

AZOLE RESISTANCE IN CANDIDA and ASPERGILLUS

- Fungus modifies the drug target, C14 ergosterol demethylase (gene *cyp51A*)
- Azoles no longer block synthesis of ergosterol, which is necessary for cytoplasmic membrane function
- Cross resistance varies with azole

ECHINOCANDIN RESISTANCE IN CANDIDA

- Fungus modifies the drug targets, glucan synthase, (genes *fts1*, *fts2*)
- Echinocandins no longer block synthesis of beta-D- glucan, which is necessary for cell wall synthesis
- Cross resistance between echinocandins is usual

Antifungal Resistant Species



- **Amphotericin B resistant:** *Scedosporium apiospermum* complex, *Lomentosporum prolificans*, *Aspergillus terreus*; variable in *Candida lusitanae*, *Candida auris*, *Fusarium species*
- **Fluconazole resistant:** All molds, *Rhodotorula species*, *Candida krusei*, *Candida auris*, *Candida haemulonii*, some *Candida glabrata*
- **Voriconazole resistant:** Mucorales; higher MIC's for cryptic *Aspergillus* species (*lentulus*, *ustus*, *calidoustus*)
- **Posaconazole, Isavuconazole resistance:** Similar to voriconazole, but more activity against Mucorales
- **Echinocandin resistance:** *Cryptococcus*, *Trichosporon*, *Rhodotorula*

CLSI. Epidemiological Cutoff Values for Antifungal Susceptibility testing. 4th ed. CLSI supplement M77S. Clinical and Laboratory Standards Institute; 2022.

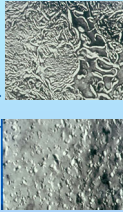
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Amphotericin B

Azotemia (less with saline loading), hypokalemia, renal tubular acidosis, anemia (erythropoietin loss)

- Amph B deoxycholate (conventional)
- Lipid formulations are less toxic
 - Ampho B Lipid Complex (ABLC) – flakes
 - Liposomal Ampho B (LAMB)- tiny particles



Azoles

All azoles teratogenic; CYP3A4 drug interactions

- Fluconazole: *Candida*, *Cryptococcus*, *Coccidioides*
 - Good concentration in urine
- Itraconazole: *Histoplasma*, *Blastomyces*, ringworm
 - Check blood levels
- Voriconazole: *Aspergillus*, molds other than *Mucorales*, *Candida*
 - Check blood levels
- Posaconazole: *Aspergillus*, variable *Mucorales*
 - Check blood levels
- Isavuconazole: *Aspergillus*, variable *Mucorales*
 - Fewer drug interactions, less QTc Prolongation than other azoles
 - Water soluble so no cyclodextrin (which can accumulate in renal dysfunction)

Voriconazole: THE FUNDAMENTALS

- Invasive *Candida*; Invasive *Aspergillus*; *Scedosporium apiospermum* complex & *Fusarium* in pts with refractory dz or intolerant of other therapy.
- Metabolism: Children are rapid metabolizers; Japanese 20% slower (2C19)
- Distribution: Good CSF levels, none in urine
- Formulations: IV contains sulphobutylether-B-cyclodextrin which accumulates in azotemia (use oral if CrCl <50 mL/min)
- Drug interactions: increases many other drug levels: cyclosporine, tacrolimus, serolimus, steroids (budesonide, fluticasone), etc.
- Side effects: hallucinations, hepatitis, photosensitivity, visual changes, peripheral neuropathy
 - After many months of Rx: skin cancer, periostitis

Voriconazole Side Effects

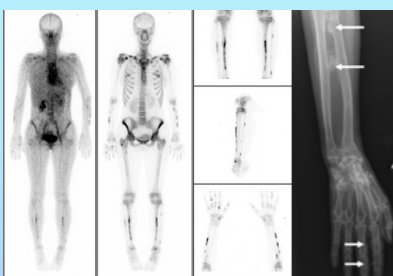
Photosensitivity: Skin cancer after months of sun:



Voriconazole Side Effects

Periostitis:

- Bone pain
- Months of Rx
- Alk phos high
- Plasma fluoride high (fluorosis)
- Bone scan
- Exostoses



Wermers, et al. CID 2011
Rossier, et al. Eur J Nuc Med Mol Imag 2011

Isavuconazole THE FUNDAMENTALS

- Approved for: Invasive Aspergillosis (noninferior to vori); *Mucorales* (use is controversial)
- Inferior to caspofungin for candidemia
- No good data on prophylaxis
- Distribution: no drug in CSF or urine; long half life (5.4 days)
- Drug interactions: fewer than vori or posa; teratogenic
- Isavuconazonium 372mg = isavuconazole 200 mg
- Load with 200 mg q8h X 6 doses then 200 mg qd, IV or PO
- No dose change for renal or moderate liver failure

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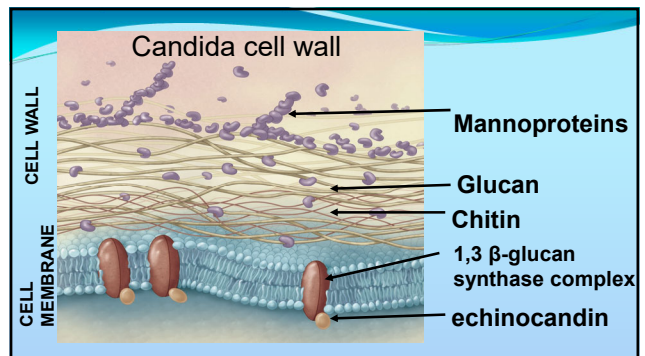
Posaconazole THE FUNDAMENTALS

- **Approved for:** prophylaxis in GVHD or prolonged neutropenia; oral thrush; Invasive Aspergillosis
 - Mucormycosis once patient has responded to amphotericin B
- **Formulations:**
 - Extended release tabs (three 100mg tablets twice daily on day 1, then 300mg daily)
 - IV same dose; contains cyclodextrin (use oral if CrCl <50 mL/min)
- **Pharmacokinetics:** 7-10 days for steady state; check trough levels (target usually 2-5 mcg/ml)
- **Drug Interactions:** increases some drug levels (CYP3A4)
- **Side effects:** Generally well-tolerated; hypertension, hypokalemia

FLUCONAZOLE THE FUNDAMENTALS

- **Approved for:** Candidiasis, Cryptococcosis, Prophylaxis in HSCT
- Also good for Coccidioidal meningitis, ringworm
- **NO MOLD ACTIVITY**
- **Side Effects:** Few; rarely dry skin, alopecia
- **Distribution:** Good penetration into urine and CSF
- Wide dose range; accumulated in renal dysfunction, requires adjustment
- **Drug interactions:** moderate CYP2C9 and CYP3A4
- **TERATOGENIC**

Echinocandins



Caspofungin, Micafungin, Anidulafungin, Rezafungin

- **Indications:** Invasive and Esophageal Candidiasis
 - Febrile neutropenia and refractory aspergillosis (caspofungin only)
 - Prophylaxis of *Candida* in HSCT (micafungin only)
- Resistance in *Candida* can arise during long therapy
- *Cryptococcus*, *Rhodotorula* & *Trichosporon* are intrinsically resistant
- *Aspergillus* and other mold activity is variable
- **Formulations:** IV only, once daily dosing.
 - Rezafungin with prolonged half-life; once weekly dosing
- **Distribution:** No drug in urine; protein binding high; poor penetration into CSF and vitreous humor of eye
- **Drug interactions:** none important

Flucytosine

- **Indications:** Used in combination with amphotericin B in cryptococcal meningitis and invasive candidiasis
- **Distribution:** Bioavailability 100%; good levels in CSF, eye, urine
- **Side Effects:** Accumulates in azotemia: bone marrow depression, hepatitis, colitis
- Measure blood levels/dose adjust
- Drug resistance arises during monotherapy

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Now for a few questions



Question #1



PREVIEW QUESTION

A 47-year-old male with known HIV, poorly compliant with ARV, last CD4 20/mcl, presents with low grade fever and headache. Blood culture is growing a yeast, not yet identified. Starting micafungin would be a poor choice if the isolate is which of the following:

- A. *Candida parapsilosis*
- B. *Cryptococcus gattii*
- C. *Candida auris*
- D. *Candida krusei*
- E. *Candida glabrata*

Question #2

A 72 yr man with diabetes mellitus, renal failure and a central venous catheter developed fever and hypotension. Blood cultures grew *Candida lusitanae*. On day 5 of liposomal amphotericin B 5 mg/kg he remained febrile and his creatinine rose from 4.5 to 6.0 mg/dl.

Question #2 (continued)

In addition to changing his IV catheter, which of the following would be most appropriate?

- A. Itraconazole
- B. Micafungin
- C. Amphotericin B lipid complex
- D. IV Voriconazole
- E. Isavuconazole

Question #3

The echinocandin class of antifungals has which mechanism of action:

- A. inhibits synthesis of membrane sterols
- B. damages cytoplasmic membrane
- C. interferes with synthesis of fungal cell wall glucans
- D. inhibits fungal DNA synthesis
- E. interfere with synthesis of fungal cell wall chitin

Question #4



PREVIEW QUESTION

A 37 yr female with diabetes mellitus is admitted for ketoacidosis, fever and sinus pain. Biopsy of a necrotic area of the middle turbinate shows wide, branching nonseptate hyphae. Serum creatinine is 2.5 mg/dl.

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Question #4 (cont.)



PREVIEW QUESTION

Which of the following would be most appropriate?

- A. Voriconazole
- B. Anidulafungin
- C. Fluconazole
- D. Liposomal amphotericin B
- E. Itraconazole

Question #5

You are asked to advise your hem-onc colleagues as to what prophylactic antifungal agent might be useful in preventing aspergillosis in their patients with prolonged neutropenia or acute graft-vs-host disease.

Question #5 (continued)

According to the IDSA guidelines and literature you recommend:

- A. itraconazole solution
- B. posaconazole
- C. rezafungin
- D. voriconazole
- E. caspofungin

Question #6

45 yr old male 6 weeks post stem cell transplant for myelodysplasia, with a history of chronic hepatitis C was discharged home to Florida on cyclosporine, mycophenylate, prednisone , bactrim (tmp/smz), citalopram and voriconazole. Diffuse nonpruritic erythema developed over his sun exposed skin.

Question #6 (continued)

The most probable cause was:

- A. porphyria cutanea tarda
- B. graft versus host disease
- C. drug interaction
- D. voriconazole
- E. bactrim allergy

Question #7

A 66 yr old male with neutropenia following chemotherapy for lung cancer, serum creatinine 5 mg/dl, and congestive heart failure is found to have a *Scedosporium apiospermum* lung abscess.

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Question #7 (continued)

Which of the following would be preferred?

- A. Anidulafungin
- B. Itraconazole
- C. Micafungin
- D. Oral voriconazole
- E. Liposomal amphotericin B

Question #8

- 65 yr w/m admitted with cryptococcal meningitis, seizures, diabetes mellitus and granulomatosis with polyangiitis. Given conventional amphotericin B, flucytosine, phenytoin, glipizide, prednisone and cyclophosphamide.
- By the end of the first week of treatment, his creatinine had risen from 1.6 to 3 mg/dl.
- By the end of the second week his WBC count had fallen to 1.2K, platelets 60K and diarrhea began.

Question #8 (continued)

The cause of his WBC falling to 1.2K, platelets 60K and copious diarrhea is most likely which of these drugs?

- A. flucytosine
- B. phenytoin
- C. glipizide
- D. cyclophosphamide
- E. cytomegalovirus

Take Home Messages...

- Ampho: not *Scedosporium/Lomentosporum*, *Candida lusitanae*, or *Asperillus terreus*
- Only ampho as first line for mucormycosis
- Fluconazole: not *Candida krusei*, *Candida auris*; +/- *Candida glabrata*
- Echinocandins: not *Trichosporon*, *Rhodotorula* or *Crypto*
- Know mechanisms of action: glucan, sterol, cell membrane, DNA synthesis
- Flucytosine: leuko- and thrombo-cytopenias, diarrhea, hepatitis

Take home, continued...

- Voriconazole: phototoxicity, periostitis, skin cancer hallucinations
- Azole interactions:
 - Increases other drug levels: cyclosporine, tacrolimus, serolimus, warfarin, midazolam, steroids, etc.
 - Decrease azole level: phenytoin, rifampin, etc

New oral antifungals approved for vulvovaginal candidiasis

Ibrexafungerp – novel glucan synthase inhibitor

- Acute infection: two 150 mg tabs 12 hours apart on same day
Cost \$ 475
- Recurrent infection: 300g bid q month for 6 months
Cost \$2,992

Otesaconazole – azole with long half life (drug persists about 2 years)

- FDA approval: recurrent infection in women not breastfeeding or capable of childbearing
- Start with one week of fluconazole or otesaconazole then otesaconazole once a week for 11 weeks.
Cost \$2,966

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Investigational Antifungals in Clinical Trials

- **Olorofim.** Novel drug for *Aspergillus*, *Coccidioides*, some molds including *Scedosporium*, *Lomentospora* (not Mucorales or yeast). PO, ALT rises in 8%
- **Fosmanogepix.** In vitro activity against *Candida* (not *krusei*), *Aspergillus*, *Fusarium*, *Scedosporium*, (not Mucorales). PO, IV.
- **Enochleated amphotericin B:** PO. low absorption.
- **Opelconazole:** aerosol for chronic aspergillosis

Thank You

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