4 – Core Concepts: Antifungal Drugs

Speaker: John Bennett, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 17-21, 2024

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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- **Royalties (Chapter Author):** UpToDate

Agenda

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

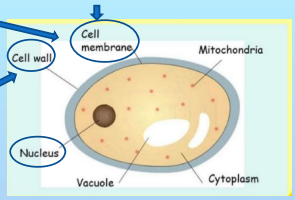
Antifungal Drugs

Amphotericin makes cell membrane leak

Azoles stops sterol synthesis for the cell membrane

Echinocandins block cell wall synthesis (glucan fibers)

Flucytosine blocks DNA synthesis in nucleus



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 fks1, fks2)
- 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 lusitaniae, 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 voricoazole, but more activity against Mucorales
- Echinocandin resistance: *Cryptococcus, Trichosporon, Rhodotorula*

CLSI. Epidemiological Cutoff Values for Antifungal Susceptibility testing. 4th ed. CLSI supplement M57S. Clinical and Laboratory Standards Institute; 2022.

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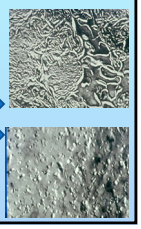
Amphotericin B

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 soluable 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

4 – Core Concepts: Antifungal Drugs

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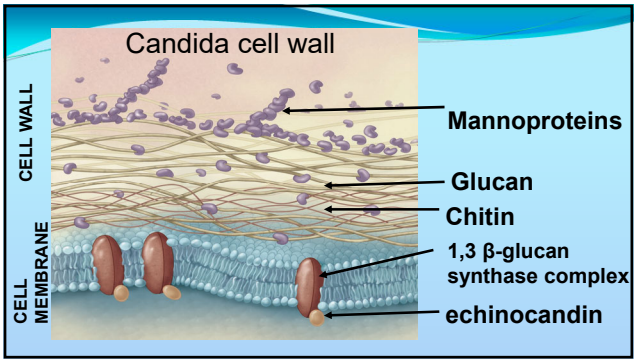
Posaconazole THE FUNDAMENTALS

- 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 wwith amphoB 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

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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 lusitaniae*. 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 #2 (continued)

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

A. Itraconazole
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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

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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.

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 #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 #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 #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.

Question #7 (continued)

Which of the following would be preferred?

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

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 wm 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

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 lusitaniae, 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

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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

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.
- **Encochleated amphotericin B**: PO. low absorption.
- **Opelconazole**: aerosol for chronic aspergillosis

Thank You

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