09 – Core Concepts Antifungal Drugs

Speaker: John Bennett, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Antifungal Drugs

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Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Disclosures Off-Label Use

- **Will be cited as discussed**

Plan of the talk

- 1. review of antifungals
  - Key points are underlined
- 2. questions on antifungals with answers
- 3. Key points

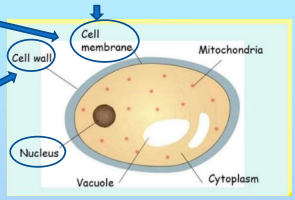
Antifungal drugs

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



DRUG RESISTANCE IN FUNGI: BLOCK TARGET ENZYME

1. ASPERGILLUS AND CANDIDA: AZOLE RESISTANCE IN CYP51A

gene CYP51A ← modified CYP51A =drug resistance

Lanosterol → C14-demethylase → ergosterol in cell membrane

Azole

2. CANDIDA : ECHINOCANDIN RESISTANCE IN FKS1, FKS2

genes FKS1 and FKS2 ← modified gene=drug resistance

Substrates → glucan synthase → glucan fibers in cell wall

Echinocandin

Antifungal resistant species

- Amphotericin B resistant: Scedosporium apiospermum (Pseudallescheria boydii), Aspergillus terreus, Variable in Candida lusitaniae, C. auris
- Fluconazole resistant: All moulds, Candida krusei, Candida auris, Candida haemulonii, some Candida glabrata
- Voriconazole resistant: mucormycosis, uncommon cryptic Aspergillus species higher MIC's: (lentulus, ustus, calidoustus)
- Posaconazole resistance: like vori but more mucormycosis activity
- Echinocandin resistance: Cryptococcus, Trichosporon, Histoplasma, Blastomyces, Coccidioides, moulds other than Aspergillus.

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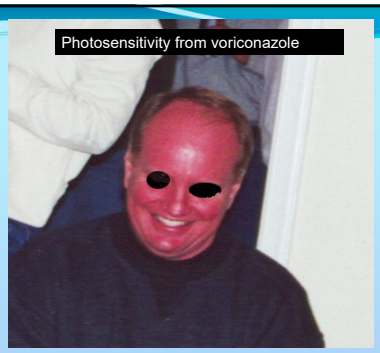
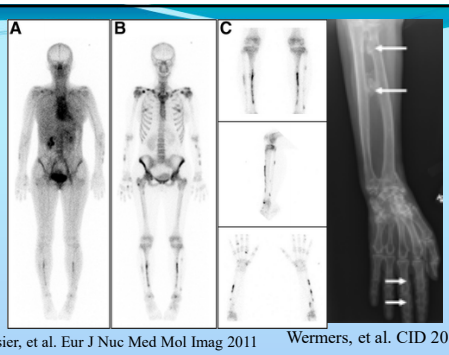
Azole antifungals

Voriconazole: the fundamentals

- Candida, Aspergillus , Scedosporium apiospermum, etc.
- Children are rapid metabolizers. Japanese 20% slow (2C19)
- Good CSF levels, none in urine.
- IV (sulfobutylcyclodextran=16x vori dose) accumulates in azotemia but not obviously toxic. Use oral in azotemia.
- Many drug interactions, Increases other drug levels: cyclosporine, tacrolimus, serolimus, steroids (budesonide, fluticasone), etc
- Side effects: hallucinations, hepatitis, photosensitivity, visual changes, peripheral neuropathy
- Many months of Rx: skin cancer, periostitis



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



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

Wermers, et al. CID 2011

Isavuconazonium/Isavuconazole

- Noninferior to vori in invasive aspergillosis.
- Use for mucor controversial
- Inferior to caspofungin for candidemia
- No good data on prophylaxis
- Pharma: like vori but long half life (5.4 days), no drug in CSF or urine. Fewer drug interactions than vori or posa. Teratogenic.
- Isavuconazonium 372mg=isavuconazole 200 mg
- Load with 200 mg q8h X6 then 200 mg qd, IV or PO
- No dose change for renal or moderate liver failure.

Posaconazole

- Approved for prophylaxis in GVHD or prolonged neutropenia. Aspergillosis good data, not approved.
- Extended release three 100 mg tablets twice first day then daily. IV same dose, has cyclodextran. 7-10 days for steady state. Check trough levels (usually 1-5 mcg/ml)
- Has been used in mucormycosis once patient has responded to amphotericin B
- Interactions with CYP3A4 increase some drug levels
- Well tolerated. Hypertension, hypokalemia

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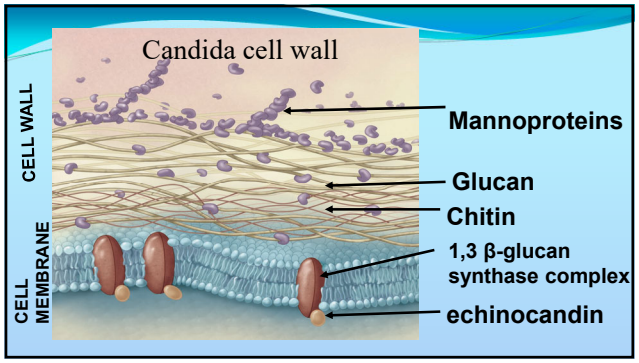
FLUCONAZOLE

- FEW SIDE EFFECTS ,WIDE DOSAGE RANGE. DRY SKIN, ALOPECIA
- FOUND IN URINE, CSF. ACCUMULATES IN AZOTEMIA.
- DRUG-DRUG INTERACTIONS. TERATOGENIC
- CANDIDIASIS, COCCIDIOIDAL MENINGITIS, PROPHYLAXIS IN HSCT,
- VERY LOW BIRTHWEIGHT INFANTS, RINGWORM, OTHERS
- NO MOLD ACTIVITY

Echinocandins



Caspofungin, Micafungin, Anidulafungin

- All Candida (including C. auris and C. parapsilosis) susceptible but resistance can arise during long therapy. Mold activity: Aspergillus
- Cryptococcus, Trichosporon, endemic mycoses resistant
- IV once daily. Plasma half life: 10-15 hr.
- No drug in urine. Azotemia: same dose
- Protein binding high: poor penetration into CSF and vitreous humor of eye
- Drug interactions: none important

Clinical trials in deeply invasive candidiasis

- Treatment candidemia)
  Caspofungin, micafungin, anidulafungin effective
- Isavuconazole "not noninferior" to caspofungin in candidemia (don't use)
- Prophylaxis for candidiasis: trials in micafungin (neutropenia), fluconazole (HSCT), posaconazole (HSCT)

Caspofungin and Micafungin in invasive aspergillosis

- IDSA Guidelines: "Primary therapy with an echinocandin is **NOT** recommended.
- Prophylaxis for aspergillosis: micafungin best studied, most often used, not FDA approved

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Flucytosine

- Bioavailability 100%, good levels in CSF, eye, urine
- Accumulates in azotemia: bone marrow depression, hepatitis, colitis. Measure blood levels/dose adjust.
- Drug resistance arises during monotherapy.
- Used with ampho in cryptococcal meningitis

Now for a few questions

Question #1

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. A. Candida parapsilosis
b. B. Cryptococcus gattii
c. C. Candida auris
d. D. Candida krusei
e. 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 #3

PREVIEW QUESTION

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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Question #4

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 Continued

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. micafungin
D. voriconazole
E. caspofungin

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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.

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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

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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 #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 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 (Pseudallescheria boydii), Candida lusitaniae, Asperillus terreus*
- Only ampho for mucormycosis
- Fluconazole: not *Candida krusei , Candida auris,*
- +/- *Candida glabrata*
- Echinocandins: not Trichosporon or crypto
- Know mechanisms of action: glucan, sterol, cell membrane, DNA synthesis
- Flucytosine WBC & plt fall, diarrhea, hepatitis

Take home, continued

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

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New approved antifungals

Otesaconazole (Vivjoa, CT-1161) Oral drug for recurrent vulvovaginal candidiasis in *women not of reproductive potential or breast feeding.* Teratogenic. Take weekly 3 months persists ca. 2 years . Trials for onychomycosis

Ibrexafungerp (Brexafemme) Oral drug for refractory vulvovaginal candidiasis. 2 tabs. $572. Echinocandin-like

Investigational antifungals in clinical trials

- **Olorofim**. Novel drug for Aspergillus, cocci, rare molds (not Mucorales or yeast). PO
- **Rezafungin**. IV once weekly echinocandin.
- **Fosmanogepix**. Novel drug for Candida, Aspergillus, rare molds (not Mucorales). PO, IV
- **Encochleated amphotericin B**: PO. low absorption.

The End

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