36 – Antifungal Drugs

Speaker: John Bennett, MD

Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Plan of the talk

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

Mechanisms of action of antifungals

- Echinocandins (caspofungin, micafungin, anidulafungin) inhibit glucan synthase, block synthesis of 1-3 beta glucans in the fungal cell wall.
- Azoles inhibit sterol C-14 demethylase, block synthesis of sterol
- Ampho damages fungal cytoplasmic membranes
- Flucytosine converted to 5FU, inhibits DNA synthesis

Mechanisms of antifungal resistance

- Azoles:
  - mutations in CYP51A (codes for C14 demethylase) gene in Candida and Aspergillus
  - mutations in CYP51A promoter region in Aspergillus
  - increased drug efflux in Candida glabrata
- Echinocandins: mutations in FKS1 and FKS2 (code for glucan synthase)

Antifungal resistant species

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

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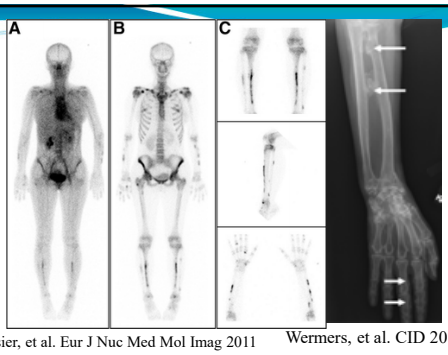
Azole antifungals

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. Best antimold azole for use with ibrutinib.
- Isavuconazonium 372mg=isavuconazole 200 mg
- Load with 200 mg q8h X6 than 200 mg qd, IV or PO
- No dose change for renal or moderate liver failure.
- Cost= $142/d. Fewer side effects than vori. Teratogenic.

Posaconazole

- Approved for prophylaxis in GVHD or prolonged neutropenia.
- 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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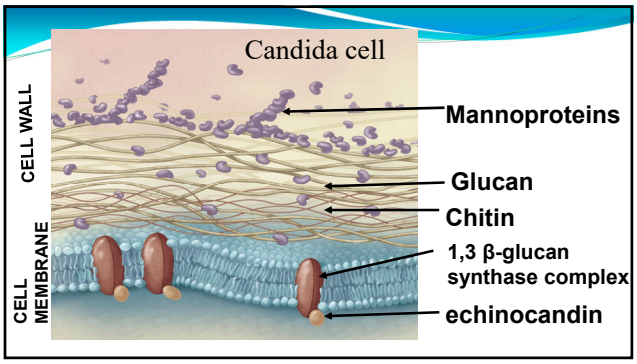
Echinocandins



Caspofungin, Micafungin, Anidulafungin

- All Candida (including C. auris) 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

- Candidiasis guidelines: an echinocandin preferred over fluconazole for initial treatment of candidemia
- Equivalent results in comparison trials of non-neutropenics
  - Micafungin 100 mg/day=Caspofungin 50 mg/day =Liposomal amphotericin B 3 mg/kg per day
  - Fluconazole 400 mg/d=ampho B 0.5-0.6 mg/kg/d
- Comparison trial with unclear result
  Anidulafungin 100 mg/day vs. Fluconazole 400 mg/day
- Isavuconazole 60% response vs caspofungin 71%

Caspofungin and Micafungin in invasive aspergillosis

- No randomized, controlled treatment trials done
- Treatment data are all from data the manufacturer collected in "salvage therapy" "failed" or "intolerant" of prior Rx and number of patients was small
- Anidulafungin: no data.
- IDSA Guidelines: "Primary therapy with an echinocandin is **NOT** recommended. Echinocandins (micafungin or caspofungin) can be used in settings in which azole and polyene antifungals are contraindicated."
- Prophylaxis for aspergillosis: Case series with micafungin

Amphotericin B formulations

- Lipid formulation: AmBisome or Ablecet
- Liposomal formulation: AmBisome
- Deoxycholate formulation: conventional amphotericin B

Pharmacology: penetrate CSF and vitreous humor poorly,

Urine concentrations low

AmBisome can cause acute back or chest pain with first infusion.

Potassium wasting in urine

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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 acute myeloid leukemia and an neutrophil count below 100/mcl for the past three weeks has been febrile for 10 days, first treated with piperacillin-tazobactam Had been on prophylactic micafungin but a blood culture is growing a yeast on Gram stain.

Question #1 Continued

The most likely echinocandin-resistant yeast is which of the following:

A. Candida parapsilosis
B. Candida glabrata
C. Candida auris
D. Trichosporon asahii
E. Candida krusei

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

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Question #3

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

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 acute graft-vs-host disease after allogeneic stem cell transplantation.

Question #5

According to the IDSA guidelines and literature you recommend:

A. itraconazole solution
B. posaconazole
C. micafungin
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.

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

The End

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