Antifungal Drugs

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Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant:** Scynexis, GSK, Astellas, Pulmocide, HealthTrackRx, Basilea, TFF Pharma
- **Research Grant to My Institution:** Karius
- **Clinical Trials (Site PI/Study PI):** Scynexis, F2G
- **Royalties (Chapter Author):** UpToDate

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Agenda

1. Review of Antifungals
2. Questions on antifungals with answers
3. New stuff (not on boards)

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Antifungal Drugs

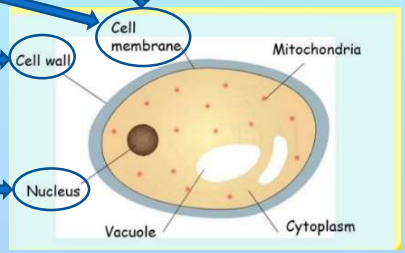
Four Main Drug Classes

Azoles stop ergosterol synthesis for cell membrane

Echinocandins block cell wall synthesis (glucan fibers)

Pyrimidines (Flucytosine) blocks DNA synthesis in nucleus

Polyenes (Amphotericin B) makes cell membrane leak



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Reasons for Treatment Failure

- **"Clinical"**
  - **Host defense inadequate**
    - Underlying disease uncontrolled
    - Persistent neutropenia / Immunosuppressive drug use
  - **Drug exposure inadequate**
    - Toxicity / Non-compliance / Not absorbing
    - Persistent nidus / Protected site
    - Drug interactions
- **"Microbiologic"**
  - **Microbial resistance**
    - Intrinsic - present for all members of the species despite lack of exposure to a drug
    - Acquired - develops *after* exposure to a drug

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Antifungal Resistance
Altered Target Enzymes

AZOLE RESISTANCE IN CANDIDA and ASPERGILLUS

- Fungus modifies the drug target: 14-α-sterol demethylase
  - Changes in ERG11 gene (yeasts), cyp51A gene (molds)
- 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
  - Alterations in FKS1 & FKS2 genes
- Echinocandins no longer block synthesis of beta-D-glucan, which is necessary for cell wall synthesis
- Cross resistance between echinocandins is usual

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Antifungal Resistant Species

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

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

- Induces proinflammatory cytokines: fever, myalgias
- Azotemia (less with saline loading), hypokalemia, renal tubular acidosis, anemia (erythropoietin loss)
  - Amph B deoxycholate (conventional)
  - Liposomal Ampho B (LAMB) - less toxic

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Azoles

ALL AZOLES ARE TERATOGENIC; CYP3A4 DRUG INTERACTIONS

- Fluconazole: *Candida, Cryptococcus, Coccidioides*
  - Good concentration in urine & CSF
- Itraconazole: *Histoplasma, Blastomyces*, ringworm
  - Check blood levels
- Voriconazole: *Aspergillus,* molds other than *Mucorales*, *Candida*
  - Check blood levels; IV formula with cyclodextrin
- Posaconazole: *Aspergillus,* variable *Mucorales*
  - Check blood levels; IV formula with cyclodextrin
- Isavuconazole: *Aspergillus*, variable *Mucorales*
  - Fewer drug interactions, less QTc Prolongation than other azoles
  - Water soluble so no cyclodextrin

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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

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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; 20% Japanese slower (2C19)
- Distribution: Good CSF levels, none in urine
- Formulations: IV contains sulfobutyl ether-B-cyclodextrin which accumulates in azotemia (use oral if CrCl <50 mL/min)
- Drug interactions: increases many other drug levels: cyclosporine, tacrolimus, sirolimus, steroids (budesonide, fluticasone), etc.
- Side effects: visual changes, hallucinations, hepatitis, photosensitivity, peripheral neuropathy
  - After many months of Rx: skin cancer, periostitis

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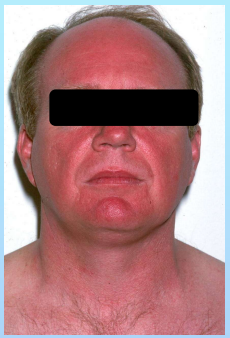
Voriconazole Side Effects
Photosensitivity

…driving in my "Beamer with the ragtop down"….
Jason Aldean



…love you more than that feeling when the bass hits the hook…
Morgan Wallen

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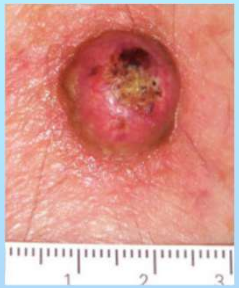
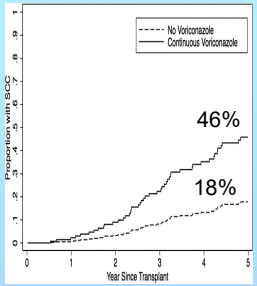
Voriconazole Side Effects
Skin Cancer

N=327 Lung transplant Recipients:
50 with SCC, 277 Controls





Voriconazole Prophylaxis

- 2.6-fold increased risk for SCC
- Impact dose-dependent: risk increased by 5.6% with each 60-day, 200mg BID exposure
- 28% absolute risk increase @ 5 yrs

Singer JP, et al. Journal of Heart and Lung Transplantation. 2012;31:694-69

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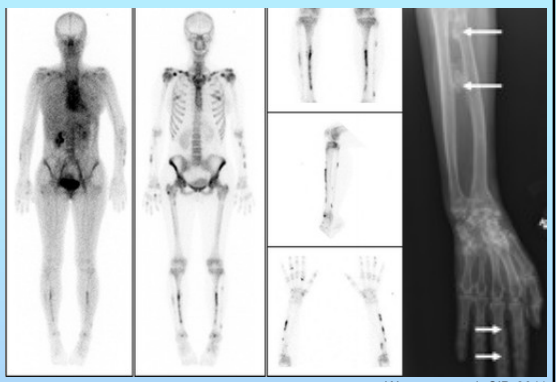
Voriconazole Side Effects

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



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

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Posaconazole THE FUNDAMENTALS

- Approved for: oropharyngeal candidiasis; prophylaxis in GVHD or prolonged neutropenia; 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

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Isavuconazole THE FUNDAMENTALS

- Approved for: Invasive Aspergillosis (noninferior to vori); Mucorales (use is controversial)
- Not approved for Invasive Candidiasis (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
- 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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Echinocandins

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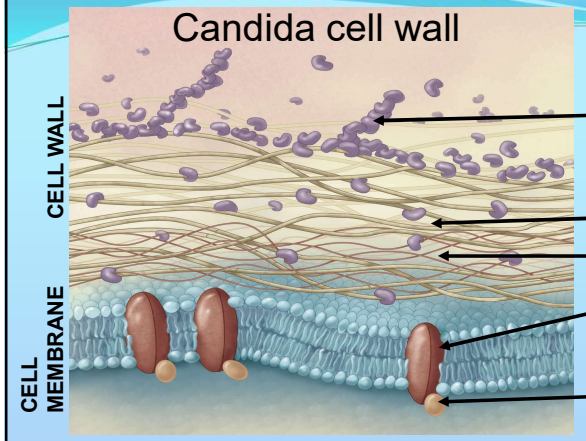

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Caspofungin, Micafungin, Anidulafungin, Rezafungin

- Indications:
  - Invasive Candidiasis (caspo, mica, anidu, reza)
  - Esophageal Candidiasis (caspo, mica, anidu)
  - Febrile Neutropenia and Refractory Aspergillosis (caspo only)
  - Prophylaxis of *Candida* in HSCT (mica 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

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Flucytosine

- Indications: Cryptococcal Meningitis, Invasive Candidiasis
- Distribution: Oral only; Bioavailability 100%; good levels in CSF, eye, urine
- Drug resistance arises during monotherapy; typically used in combination with ampho B
- Side Effects: Accumulates in azotemia: bone marrow suppression, hepatitis, colitis
- Measure blood levels/dose adjust (target ~40-60 mcg/ml)

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Now for a few questions

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

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Question #2

A 72-year-old 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.

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

What is the mechanism of action of the echinocandin class of antifungals?

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-year-old 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.

Which of the following would be most appropriate?

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

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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.

According to the IDSA guidelines and literature, what would you recommend?

A. Itraconazole solution
B. Posaconazole
C. Rezafungin
D. Voriconazole
E. Caspofungin

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Question #6

45-year-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.

What was the most probable cause?

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-year-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.

Which of the following would be preferred?

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

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Question #8

65-year-old 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.

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

A. Flucytosine
B. Phenytoin
C. Glipizide
D. Cyclophosphamide
E. Cytomegalovirus

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Take Home Messages…

- Ampho: NOT *Scedosporium/Lomentosporum, Candida lusitaniae,* or *Asperillus terreus*
- Only amphoB as first line for mucormycosis
- Fluconazole: NOT *Candida krusei, Candida auris;* *+/- Candida glabrata*
- Echinocandins: NOT *Trichosporon, Rhodotorula* or *Crypto*
- Know mechanisms of action:
  - Ergosterol synthesis - azoles
  - Glucan synthesis – echinocandins
  - Ergosterol binding / leaky cell membrane – Amphotericin B
  - DNA synthesis - Flucytosine
- Flucytosine: leuko- and thrombo-cytopenias, diarrhea, hepatitis

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Take Home, continued…

- Voriconazole: phototoxicity, periostitis, skin cancer, visual disturbances and hallucinations
- Azole drug interactions:
  - Increases other drug levels: cyclosporine, tacrolimus, sirolimus, warfarin, midazolam, steroids, etc.
  - Some drugs decrease azole levels: phenytoin, rifampin, etc.

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New Oral Antifungals Approved for Vulvovaginal Candidiasis

Ibrexafungerp – novel ORAL glucan synthase inhibitor (triterpenoid)

- Acute infection: 300mg 12 hours apart on same day
  Cost $ 475
- Recurrent infection: 300mg bid monthly for 6 months
  Cost $2,992

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

- Recurrent infection (in women not breastfeeding/capable of childbearing)
- 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 *C.krusei*), *Aspergillus, Fusarium, Scedosporium*, (not Mucorales). PO, IV.
- **Encochleated amphotericin B**: PO. low absorption.
- **Opelconazole**: aerosol for chronic aspergillosis

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Thank You

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