## Antifungals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Mechanism of Action</th>
<th>Resistance</th>
<th>Spectrum</th>
<th>Pharmacokinetics</th>
<th>Toxocities</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>o Amphotericin B deoxycholate (conventional)</td>
<td>o Bind to ergosterol &amp; alter cell membrane permeability leaky membrane leads to cell death</td>
<td>o Rare</td>
<td>o Most broad spectrum antifungal- “gold standard”</td>
<td>o IV only</td>
<td>“Amphoterrible”</td>
<td>Uses:- Candidiasis, cryptococcal meningitis, invasive aspergillosis,</td>
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<td></td>
<td>o Lipid Amphotericin B (see below)</td>
<td></td>
<td></td>
<td>o Candida sp.</td>
<td>o Well-distributed</td>
<td>Nephrotoxicity Change in renal tubular cell membrane permeability GFR</td>
<td>intraocular injections, bladder irritation, oral suspension for thrush</td>
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<td></td>
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<td></td>
<td></td>
<td>o C. lusitaniae often resistant</td>
<td>o Long tissue t ½</td>
<td>Vasoconstricts afferent arterioles</td>
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<td></td>
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<td></td>
<td>o Cryptococcus neoformans</td>
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<td>Hydration &amp; sodium loading minimizes nephrotoxicity (pre and post hydrate patients with normal saline)</td>
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<td></td>
<td>o Blastomycosis</td>
<td></td>
<td>Infusion Related Reactions (IRRs) Disappear after 3-5 days Cytokine mediated</td>
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<td></td>
<td>o Histoplasmosis</td>
<td></td>
<td>• Chills, fever, tachypnea, rigors, nausea/vomiting</td>
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<td></td>
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<td></td>
<td>o Aspergillus sp.</td>
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<td>Premedications decrease symptoms</td>
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<td></td>
<td>o Zygomycetes</td>
<td></td>
<td>• Diphenhydramine, acetaminophen (standards)</td>
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<td></td>
<td>Rhizopus sp., Mucor sp., etc.</td>
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<td>• Meperidine (rigors- severe shaking chills)</td>
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<td>o NOT active against Aspergillus terreus,</td>
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<td>• Hydrocortisone (rarely for severe reactions)</td>
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<td></td>
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<td>o Electrolyte Abnormalities</td>
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<td>Renal tubular transport defects</td>
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<td>• K+, Mg²⁺, PO⁴</td>
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<td>can still occur after therapy is discontinued (2-3 wks) monitor and supplement patients</td>
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<td></td>
<td>o Thrombophlebitis</td>
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<td></td>
<td>o Anemia</td>
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<td>Amphotericin B Lipid Formulations</td>
<td>• Variations among the formulations o ABCD (Amphotec) Flat lipid discs o ABLC (Abelcet) Ribbons of lipid with amphotericin o AmB (Ambisome) spheres</td>
<td>• Efficacy</td>
<td></td>
<td>• No difference in comparison to conventional Amphotericin B, but do require higher doses (5:1)</td>
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<td>• Advantages</td>
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<td></td>
<td>o Less nephrotoxicity than conventional Amphotericin B</td>
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<td>o AmB has less infusion related reactions (Ambisome – problem is that it’s super expensive)</td>
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<td>• Disadvantages</td>
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<td>o Very high cost</td>
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</table>
### Flucytosine (5-FC)
- Deaminated to 5-fluorocytosine (5-FC)
- Inhibits DNA synthesis
- Single point mutation, must use combination therapy
- Spectrum (limited)
  - Cryptococcus
  - Candida species (except C. krusei)
- Pharmacokinetics
  - Oral only
  - Good levels in CSF, use for cryptococcal meningitis with Amp. B. (problem: greater risk of toxicity & bone marrow suppression)
- Adverse Effects (very toxic)
  - Dose-dependent bone marrow suppression (decreased WBCs and platelets)
  - GI

### Azole Antifungals
- Classified according to structure
  - Imidazoles: Ketoconazole
  - Triazoles: Itraconazole, Fluconazole, Voriconazole
- Inhibit ergosterol synthesis by inhibiting CYP450-dependent 14-α sterol demethylase
- Depletion of ergosterol in fungal cell membrane
- Most are fungistatic against yeast, fungicidal against molds
- Resistance (several ways)
  - Mutation in gene encoding 14-α sterol demethylase
  - Increased azole efflux
  - Increased production of 14-α sterol demethylase overcomes drug effects
- ALL work against candida, cryptococcus, histoplasmosis, blastomycosis
- NONE work against zygomycetes (Rhizopus, Mucor, etc.)
- Itraconazole
  - Aspergillus
- Fluconazole
  - NO activity against Aspergillus
- Voriconazole
  - Resistant yeast
  - More potent against Aspergillus and other molds
  - Some organisms are susceptible-dose dependent. An increased dose can overcome the higher MIC. (see chart for in vitro susceptibility testing of Candida)
- In general, Voriconazole and Caspofungin can be used for all candida species
- Pharmacokinetics of Azole Antifungals
  - All IV and oral
  - Different t½
  - Fluconazole and Itraconazole are QD (once daily)
  - Voriconazole is BID (twice daily)
- pH
  - Itraconazole requires acidic pH for absorption, absorption is poor & erratic (can cause treatment failure)
  - Voriconazole requires acidic pH for absorption, absorption is poor & erratic (can cause treatment failure)
- CNS penetration
  - Itraconazole is poor
  - Fluconazole does penetrate CNS
- Elimination
  - Itraconazole and Voriconazole undergo hepatic elimination (more drug interactions)

### Caspofungin
- Affects the fungal cell wall (Amp. B & azoles work on fungal cell membrane)
- Non-competitively inhibits β (1,3)-D-glucan synthase thereby blocking synthesis of β (1,3)-D-glucan which compromises integrity of the fungal cell wall
- Apergillus-stable, used in combination therapy
- Candida- rapidly cidal, monotherapy
- IV only
- Most benign anti-fungal
- Drug interactions
- Minimal, neither induces nor inhibits CYP450 system

### Toxicity
- Fluconazole (best tolerated, most widely used)
  - Generally well tolerated
- Itraconazole
  - Nausea
  - Vomiting
  - Diarrhea
  - Hepatotoxic
  - Negative ionotropic effect
- Voriconazole
  - Visual disturbances—common, go away after 1st few doses
  - Some hepatotoxicity
  - Rash
  - Hallucinations (patients like them & miss them when they’re gone.)
  - Contraindications/ drug interactions
    - Phenytoin will cause need for greater dose of azoles
- Cyclosporin & Tacrolimus are nephrotoxic. Voriconazole will increase their levels and possibly cause patient to go into renal failure