Antifungal Agents

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Antifungal Agents- Objectives

• Be familiar with dosing, administration, and toxicities of amphotericin B and flucytosine.
• Be familiar with dosing and monitoring of flucytosine.
• Understand the pharmacokinetic, spectrum, and drug interactions differences between the various azole agents.
• Be familiar with the appropriate treatment of candidal infections.
Introduction

• T-cell Opportunistic Fungi
  – Histoplasmosis, Cryptococcus, Coccidiodomycosis, Blastomycosis

• Phagocyte Opportunistic Fungi
  – Aspergillosis, Mucor, Fusarium

• New azoles, liposomal amphotericin
• New antifungals and formulations
• Altered fungal pathogenicity
• Changes in antifungal susceptibility testing
Amphotericin B (Fungizone®)

- **Mechanism of Action**
  - Polyene macrolide, fungicidal or fungistatic (lower dose) activity
  - Binds fungal cell membrane ergosterol altering permeability → leakage of cytoplasm
  - Toxicity due to binding of mammalian cell cholesterol
  - Colloidal dispersion with desoxycholate or formulated as a liposomal preparations

- **Resistance**
  - Rare- complexity of interaction with fungal cell membrane, rare cases in immunocompromised patients
  - *C. glabrata and krusei* MAY require higher doses esp in immunocompromised hosts
Amphotericin B (Fungizone®)

- **Pharmacokinetics**
  - Protein bound: 91-95%
  - Vd: 4L/kg, high tissue binding (lung, liver, spleen > kidneys, adrenals), limited into peritoneal cavity
  - Liposomal prep most concentrated in liver and spleen
  - Low CSF conc (2-4% serum)
  - t1/2 24-48 hr, terminal t1/2 15 days
  - Elimination: Not fully known, 3% in urine after 24 hr, 40% eliminated over 1 wk
Amphotericin B (Fungizone®)

- Acute Infusion Related Adverse Effects
  - Fever, chills (18-90%)
    - TNF, IL, PGE2 mediated
    - Premedication
      - Meperidine 25-50 mg IV/IM
      - APAP, ASA, IBU, diphenhydramine
      - Hydrocortisone 25 mg IV
  - Nausea, vomiting
Amphotericin B (Fungizone®)

- Acute Infusion Related Adverse Effects
  - Headache, myalgias
  - Thrombophlebitis
  - Acidic pH of reconstituted solution
  - Dilute to < 0.1 mg/mL (peripheral)
  - Central venous administration if possible
Amphotericin B (Fungizone®)

• Chronic Adverse Effects- Nephrotoxicity
  – 15-90%, generally reversible after discontinuation
  – Incr. electrolyte transport $\rightarrow$ incr O2 demand $\rightarrow$ direct anoxic tubular injury
  – Tubular epithelium damage $\rightarrow$ inc Cl uptake in distal tubule $\rightarrow$ incr tubuloglomerular feedback $\rightarrow$ afferent arteriole vasoconstriction $\rightarrow$ decr GFR and solute delivery $\rightarrow$ renal cortical ischemia
Amphotericin B (Fungizone®)

- Chronic Adverse Effects - Nephrotoxicity
  - ? Related to total dose (>5 g) vs daily dose (> 1 mg/kg)
  - Sodium loading (500 mL NS before and/or after dose) may suppress tubuloglomerular feedback
  - Avoid nephrotoxic drugs
  - QOD dosing - controversial
Amphotericin B (Fungizone®)

- **Other Chronic Adverse Effects**
  - Potassium, magnesium wasting
    - incidence of 80%
    - due to increased renal cell permeability or increased excretion
    - onset within 2 weeks
  - Normochromic/normocytic anemia
    - direct inhibition of erythropoietin production or renal toxicity
    - generally after 10 weeks of therapy
    - reversible
Amphotericin B (Fungizone®)

• Drug Interactions
  – Nephrotoxic drugs: cyclosporine, aminoglycosides, foscarnet, pentamidine
  – Cisplatin, nitrogen mustards-increases renal toxicity of amphotericin
  – Flucytosine-additive toxicity
    • ampho decreased flucytosine’s renal excretion → increased flucytosine’s bone marrow suppression potential
Amphotericin B (Fungizone®)

- Clinical Uses
  - Choice for deep invasive or systemic mycoses including candidiasis
  - Choice for cryptococcal meningitis
  - Effective against most fungi except
    Pseudoallescheria boydii and Cryptococcus lusitaniae
  - Variable activity against
    Trichosporin, Fusarium, C. lusitaniae, and Mucormycosis
Amphotericin B (Fungizone®)

- **Bladder Irrigation**
  - Continuous: 50 mg/L in sterile H2O at 40 mL/hr via triple lumen catheter for 48-72 hrs
  - Intermittent: 50 mg/L, instill 200-300 mL and cross clamp for 60-90 min, drain, repeat q 6 hrs for 48 hrs
Amphotericin B IV Therapy

- Not H2O soluble, complexed with desoxycholate - reconstitute with D5W or sterile H2O only
- Test Dose 1.0 mg test in 25-100 mL over 10-60 min
  - Controversial whether needed
  - Do not premedicate
- Initiate at full dose or titration of dose over 3-4 days
- Full dose 0.25 to 0.5-1.5 mg/kg/day
- Infuse over 45-60 min, 1-2 hr vs 4-6 hr
  - Renal dysfunction- infuse over 4-6 hrs to prevent hyperkalemia
Amphotericin B (Fungizone®)

- QD vs QOD dosing of 2X daily dose
  - Controversial effect on adverse effects
- Duration of IV therapy
  - total mg dose vs mg/kg
  - 500-1000mg for nondisseminated candida; blasto 1 gm; histo/crypto 2-4 gm
- Newer Methods of Delivery
  - Liposomal
  - Intranasal
  - Aerosolized
Liposomal Amphotericin B

- Liposomal prep will be taken up by phagocytic cells into the RES → close proximity to pathogen (spleen, liver, lung). Less toxic to mammalian cells and higher doses can be given
  - Abelecet® (Ampho B Lipid Complex)
    - 5 mg/kg/day IV
  - Amphotec® (cholesteryl sulfate complex)
    - 3-6 mg/kg/day IV
  - AmBisome® (unilamellar liposomal product)
    - 3-5 mg/kg/day IV
Liposomal Amphotericin B

• True efficacy controversial
• Lower incidence nephrotoxicity
• Infusion related reactions may still occur
  – Amphotec >> Ambisome
• Second-line therapy for patients intolerant of or refractory to ampho B
  – Therapeutic failure
  – Initial renal insufficiency (SCr > 2.5, ClCr < 25 ml/min)
  – Significant rise in SCr during ampho B
Flucytosine (5-FC) (Ancobon®)

- **Mechanism of Action**
  - Transported by cytosine permease into cell → transformed by fungal cell cytosine deaminase to 5-FU and floxuridine which inhibit DNA synthesis.
  - Cytosine deaminase present in fungal but not human cells; intestinal flora contributes to conversion to 5FU

- **Resistance**
  - High incidence- not used as monotherapy
  - Loss or mutation of enzymes
Flucytosine (5-FC) (Ancobon®)

- Pharmacokinetics
  - Rapid GI absorption; bioavailability >80%
  - Protein binding <10%
  - Vd: TB H2O (0.6-0.8 L/kg), CSF concentrations 63-88% of serum
  - t1/2: 3-5 hr
  - Elimination: > 90% renal
Flucytosine (5-FC) (Ancobon®)

- **Adverse Effects**
  - Concentration-dep. bone marrow suppression
    - Maintain peak concentration 60-80 mg/L (2hr post dose)
    - Neutropenia, leukopenia, pancytopenia
    - Allopurinol may minimize myelosuppression
    - Caution in renal impairment
  - Nausea, vomiting, diarrhea (10%)
    - Dose dependent, use smaller divided doses
  - Increased hepatic transaminases (1-10%)
Flucytosine (5-FC) (Ancobon®)

- Used as combination therapy for Cryptococcus, Candida, Aspergillus

- **Dosage**
  - 50-150 mg/kg/day po (q6h)
  - ClCr 11-50ml/min- q 12-24 hr vs 50% q6h
  - ClCr <10ml/min - q24-48 hr vs 25% q6h

- **Monitor**
  - Peak concentration, LFTs, SCr, WBC
Azole Antifungal Agents

• Mechanism of Action
  – Inhibition of fungal CYP450 enzyme lanosterol 14-demethylase → decre conversion of lanosterol to ergosterol in fungal cell membrane. Fungistatic
  – Lower affinity for mammalian CYP450 enzymes

• Imidazoles: Miconazole, clotrimazole, ketoconazole

• Triazoles: Fluconazole, itraconazole
  – Lower toxicity profiles
<table>
<thead>
<tr>
<th>Indice Route</th>
<th>Keto</th>
<th>Fluc po/IV</th>
<th>Itra po/IV</th>
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<tbody>
<tr>
<td>Bound (%)</td>
<td>&gt;99</td>
<td>12</td>
<td>&gt;99</td>
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<tr>
<td>t1/2 (h)</td>
<td>7-10</td>
<td>20-30</td>
<td>24-42</td>
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<tr>
<td>Metabolism/excretion</td>
<td>hep/bile&amp; urine</td>
<td>renal (90%)</td>
<td>hep/ bile&amp; urine</td>
</tr>
<tr>
<td>CSF:serum</td>
<td>&lt;10</td>
<td>60-80</td>
<td>&lt;10</td>
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Ketoconazole (Nizoral®)

• Pharmacokinetics
  – Weak Base- pH (i.e. acid) dependent absorption
    • Achlorhydria decreases bioavailability
  – Carbohydrates may decr, lipids incr absorption

• Resistance
  – High MICs in Candida sp reported during prolonged use in patients with AIDS
Ketoconazole- ADRs

- Nausea, vomiting common - dose related (800 mg/day)
- Hepatoxocity (2-8%)
  - Increased transaminases, rare hepatitis/fatal
- Rash
- Dose related inhibition of CYP450 enzymes for testosterone and adrenal corticosteroid synthesis - gynecomastia, oligospermia, decreased libido
**Ketoconazole - Drug Interactions**

- Inhibition of CYP450 3A4 (*invitro*: keto > itra or fluc)
  - Rifampin, phenytoin - decri ketoconazole
  - Incr cyclosporine, phenytoin, warfarin, terfenadine, astemizole, cisapride, methylprednisolone, theophylline
- H2-antagonists, antacids, omeprazole - decreases absorption of ketoconazole
Ketoconazole (Nizoral®)

• Uses:
  – Mucosal candidiasis, histoplasmosis, blastomycoses, coccidioidomycosis, dermatophytes
  – Not for cryptococcus, CNS infections, or disseminated/deep candidiasis

• Dosing:
  – Serious infections   800 mg/day
  – Other               200-400 mg/day
  – ?Adjust in hepatic dysfunction
Fluconazole (Diflucan®)

- Pharmacokinetics:
  - Absorption not dependent on pH or food; High F

- Resistance:
  - *C. krusei* & *T/C- glabrata* (dose-dep R) are inherently less susceptible to azoles but are occasionally virulent & have been selected out with fluconazole use
  - *C. albicans* & *C tropicalis* are virulent and occasionally resistant
  - Overexpression of target enzyme, point mutations in enzymes, efflux pumps
Fluconazole (Diflucan®)

- Adverse Effects- Low incidence
  - Nausea, vomiting, rash
  - Increased in AIDs population
  - Asymptomatic incr transaminases (7%)

- Drug Interactions (CYP450 3A4)
  - Increased phenytoin, cyclosporine, rifabutin, warfarin, AZT
  - Rifampin may decrease fluconazole concentrations
Fluconazole- Uses

• Mucosal or vulvovaginal candidiasis
• Alternative to amphot B: systemic, deep, hepatosplenic candidiasis
• Cryptococcal meningitis- choice for maintenance, ? 800 mg/d for treatment
• Effective for coccidioidal meningitis
• Less active (vs itraconazole) against Histoplasmosis, Blastomycosis, & not active against Aspergillosis
Fluconazole - Dosage

- **Oropharyngeal** 200 LD, MD 100 mg/d
- **Vaginal infections** 150 mg X 1
- **Serious infections** 400-800 mg/day
- **Adjustment in renal dysfunction**
  - ClCr 21-50 mL/min 50% dose
  - ClCr <20 mL/min 25% dose
  - Removed by hemodialysis
- **Cost:**
  - $94/200 mg IV, $377/800 mg IV, $9/200 mg PO
Itraconazole (Sporanox®)

• Pharmacokinetics
  – Oral absorption dependent on acidic pH and improved with food for tablet not suspension (check blood concentration if poor response)
  – Non-linear- increased t1/2 with prolonged dosing

• Adverse Effects
  – Nausea, vomiting, incr transaminases
  – Hypertension, hypokalemia- higher doses
Itraconazole (Sporanox®)

• Drug Interactions
  – H2-antagonists, antacids, omeprazole- decreased oral tablet itraconazole absorption
  – Rifampin, carbamazepine, phenobarbital, phenytoin- decrease itraconazole concentration
  – Itraconazole increases cyclosporine, terfenadine, astemizole, ?cisapride, ?digoxin, ?warfarin, lovastatin, simvastatin, triazolam
Itraconazole (Sporanox®)

• Uses:
  – Blastomycosis, Histoplasmosis, Aspergillosis, Coccidioidomycosis, Sporotrichosis, non-albicans candida

• Dose:
  – PO: Serious 200 mg TID X3 days then 200 mg QD-BID
  – IV: 200 mg BID for 4 doses then 200 mg QD
    • Not if ClCr < 30 mL/min- accumulation of vehicle -> pancreatic cancer in animals
  – ? Adjustment in hepatic impairment
Echinocandins Class

- Inhibit fungal β (1,3)-glucan synthetase
  - Depletes cell wall glucan and leads to lysis of cell (likely cidal)
  - Active against aspergillus and candida (albicans and non-albicans) sp
  - Not active ag cryptococcus

- FK463 (Fujisawa)
- VER- 002 (Vesicor)
Echinocandin Class: Caspofungin

• Cancidas®-Merck & Co
  – Inhibits fungal cell wall glucan synthesis ($\beta$ (1,3)-D-glucan synthase not in mammalian cells)
  – Spectrum of activity
    • 2nd line therapy for invasive aspergillus refractory or intolerant (SCr) of AMB, lipid AMB, or itraconazole
      – Improvement in 1/3 of refractory cases
    • Very active also against *Candida* (incl non-albicans)sp and *histoplasma* sp
    • Not active against *cryptococcus*, less activity vs ampho B against *rhizopus* and *fusarium* sp
Echinocandin Class: Caspofungin

– Pharmacokinetics
  • Liver metabolized (not P450)-minimal renal clearance
  • $t_{1/2}$ 9-10 hr
  • Poor CSF penetration

– Dosing & Administration
  • 70 mg IV load then 50 mg QD IV over 1 hr
  • Duration based upon severity of disease/response
    – Av duration 30 days for aspergillosis, 2 wks for candidal esophagitis
  • Do not mix with dextrose containing solutions
  • No adjustment for renal insufficiency, not HD off, reduce in moderate hepatic insufficiency
Echinocandin Class: Caspofungin

- Not studied < 18 yrs age

- Drug interactions
  - Cyclosporine- not recommended, incr LFTs
  - Incr clearance of tacrolimus
  - Dexamethasone, carbamazepine, nelfinavir, phenytoin, rifampin may incr clearance of caspofungin (70 mg IV QD in non-responders)

- ADRS
  - Generally well tolerated- fever, phlebitis/thrombophlebitis, headache, nausea, vomiting, rash, mild LFT elevations

- Cost
  - $282/50 mg, $363/70 mg
New Azoles in Development

• Voriconazole- Pfizer (2nd gen fluconazole)
  • Good absorption, tissue penetration, urinary excretion
  • Active against variety of albican and non-albicans Candida species (more potent vs fluconazole against C krusei) and Aspergillus sp. resistant to Ampho B or itraconazole
  • BID dosing via IV or PO routes
  • Side effects- retinal visual disturbances (self-limited)

• Ravuconazole- BMS
  • Fluconazole based with Candida activity

• Posaconazole- Schering Plough
Terbinafine (Lamisil®)

• Mechanism of Action
  – Allylamine- prevents fungal ergosterol biosynthesis via inhibition of fungal squalene epoxidase.

• Spectrum
  – Cidal- dermatophytes, *Aspergillus*, *Blastomyces*, *Histoplasma*
  – Static- *C. albicans*
  – Antiprotozoal activity- *in vitro*
Terbinafine- Pharmacokinetics

- Oral F 70-80%, not affected by food
- 90-100 hr terminal t1/2, SS in 10-14 days
- Large Vd - lipophilic distribution
  rapid diffusion into infected nail plate
- Highly protein bound
- Elimination- Hepatic metabolism, renal elimination (80%) of metabolites
- Impaired hepatic or renal function- incr AUC
Terbinafine - Therapeutic Uses

- Onchomycosis - Dermatophyte
  - 250 mg/day PO for 6 weeks (fingernail)
  - 250 mg/day PO for 12 weeks (toenail)
  - Pulse dosing 250 mg BID 1 week/month X 3-4 months

- Cutaneous Dermatophyte, Candida or Pityriasis (tinea) infections - topical therapy
Terbinafine

• Adverse Reactions
  – 10% GI disturbances, skin rxns, flu Sx
  – No interference with testosterone or cortisol production.

• Drug Interactions
  – Rifampin - increased Cl 100%
  – Cimetidine- decreased Cl 33%
  – Terfenadine- decreased Cl 16%
Candida Prophylaxis in Neutropenia

- **Mucosal:** Clotrimazole, fluconazole, nystatin
- **Systemic:** Nystatin, po/IV ampho B, po/IV fluconazole

- **1997 IDSA Neutropenic Fever guidelines**
  - Fever despite 4-6 days appropriate antibiotics
  - Ampho B or liposomal ampho B until resolution of neutropenia
Fungal Prophylaxis in AIDS

- 1999 USPHS/IDSA Guidelines
- Dependent on episode of infection, CD4+, residence in endemic areas, patient tolerance
- Need comparative trials assessing cost effectiveness of various regimens
Treatment of Candidal Infections

- *Candida* sp 4th leading pathogen in nosocomial bloodstream infections.
- Colonization precedes invasion
- **Risks:**
  - Neutropenia
  - Bowel trauma/surgery
  - Immunosuppression
  - BS Ab tx
  - Diabetes
  - Time in ICU
  - Ventilation
  - Colonization > 2 sites
  - Cancer
  - TPN
  - Burns
  - CV cath
Treatment of Candidemia

- Remove existing central venous catheters
- IV amphotericin B (traditionally preferred) or IV/PO fluconazole
- Combination with fluucytosine for very severe cases
- Continue therapy for 2 weeks after the last positive blood culture and resolution of symptoms and signs of infection
Treatment of Disseminated Candidiasis

- Mortality 50%
- Vast dissemination
- Hard to diagnose
- Risks - colonization, prolonged antibiotics, cv catheters, TPN, gut surgery, prolonged ICU stay
- Ampho B or fluconazole (IV/PO) with flucytosine if refractory infection
Treatment of Candiduria

- Risk factors - indwelling catheter, broad-spectrum Ab tx, elderly age
- Treatment
  - Change catheter (<20% cure) or remove catheter (40% cure)
  - If symptomatic, neutropenic, low birth weight infant, urologic manipulation, or those with renal allografts
    - Fluconazole 200 mg/day for 7-14 days or ampho B for 1-7 days
    - Ampho B bladder irrigations (only if localized to the bladder) - transient effect