## Antifungal Agents

Suzanne Tschida, Pharm.D., BCPS  
Clinical Specialist/Pharmacy Manager  
Regions Hospital and  
College of Pharmacy, University of Minnesota

### Antifungal Agents- Objectives

- Be familiar with dosing, administration, and toxicities of amphotericin B and fluconazole.
- Be familiar with dosing and monitoring of fluconazole.
- Understand the pharmacokinetic, spectrum, and drug interactions differences between the variousazole agents.
- Be familiar with the appropriate treatment of candidal infections.

### Introduction

- **T-cell Opportunistic Fungi**  
  - Histoplasmosis, Cryptococcus, Coccioidomycosis, Blastomycosis
- **Phagocyte Opportunistic Fungi**  
  - Aspergillosis, Mucor, Paracoccidioidomycosis
- New azoles, liposomal amphotericin
- New antifungal classes 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 deoxycholate 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

**Chronic Adverse Effects - Nephrotoxicity**
- 15-90%, generally reversible after discontinuation
- Increased electrolyte transport → increased O2 demand → direct anoxic tubular injury
- Tubular epithelium damage → increased Cl uptake in distal tubule → increased tubuloglomerular feedback → afferent arteriole vasoconstriction → decreased GFR and solute delivery → renal cortical ischemia

**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

**Other Chronic Adverse Effects**
- Potassium, magnesium wasting
  - Incidence of 80%
  - Due to increased renal cell permeability or increased excretion
  - Nephrotoxic drugs: cyclosporine, aminoglycosides, foscarnet, pentamidine
- Cisplatin, nitrogen mustards - increases renal toxicity of amphotericin
- Flucytosine-additive toxicity
  - Decreased flucytosine's renal excretion → increased flucytosine's bone marrow suppression potential

**Clinical Uses**
- Choice for deep invasive or systemic mycoses including candidiasis
- Choice for cryptococcal meningitis
- Effective against most fungi except *Pseudallescheria 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 non-disseminated 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)
    - 3 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 fluorouridine 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

- **Adverse Effects**
  - Concentration-dep. bone marrow suppression
  - Maintain peak concentration 60-80 mg/L (2hr post dose)
  - Neutopenia, leukopenia, pancytopenia
  - Allopurinol may minimize myelosuppression
  - Caution in renal impairment
  - Nausea, vomiting, diarrhea (10%)

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

- **Monitor**
  - Peak concentration, LFTs, SCR, WBC

**Azole Antifungal Agents**

- **Mechanism of Action**
  - Inhibition of fungal CYP450 enzyme lanosterol 14-demethylase → decrease conversion of lanosterol to ergosterol in fungal cell membrane. Fungistatic
  - Lower affinity for mammalian CYP450 enzymes
  - Imidazoles: Miconazole, clotrimazole, ketoconazole
  - Triazoles: Fluconazole, itraconazole, voriconazole
    - Lower toxicity profiles

<table>
<thead>
<tr>
<th>Indice</th>
<th>Keto</th>
<th>Fluc</th>
<th>Itra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>po</td>
<td>po/IV</td>
<td>po/IV</td>
</tr>
<tr>
<td>Bound (%)</td>
<td>&gt;99</td>
<td>12</td>
<td>&gt;99</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>7-10</td>
<td>20-30</td>
<td>24-42</td>
</tr>
<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>
</tr>
</tbody>
</table>

**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)
- Hepatotoxicity (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 (in vitro: keto > itra or fluc)
  - Rifampin, phenytoin - decrease ketoconazole
  - Increase cyclosporine, phenytoin, warfarin, terfenadine, astemizole, cisapride, methylprednisolone, theophylline
- H2-antagonists, antacids, proton pump inhibitors - decrease absorption of ketoconazole

Ketoconazole (Nizoral®)
- Uses:
  - Mucosal candidiasis, histoplasmosis, blastomycoses, coccidioidomycosis, dermatophytes
  - Not for cryptococci, 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 ampho B: systemic, deep, hepatosplenic candidiasis
- Cryptococcal meningitis- choice for maintenance, ? 800 mg/day for treatment
- Effective for coccidioidal meningitis
- Less active (vs itraconazole) against Histoplasmosis, Blastomycosis, & not active against Aspergillosis
<table>
<thead>
<tr>
<th>Fluconazole -Dosage</th>
<th>Itraconazole (Sporanox®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Oropharyngeal 200 LD,MD100mg/d</td>
<td>• Pharmacokinetics</td>
</tr>
<tr>
<td>• Vaginal infections 150 mg X 1</td>
<td>- Oral absorption (tablet not susp) dependent on acidic pH and improved with food for tablet not suspension (check blood concentration if poor response)</td>
</tr>
<tr>
<td>• Serious infections 600-800 mg/day</td>
<td>- Non-linear- increased t1/2 with prolonged dosing</td>
</tr>
<tr>
<td>• Adjustment in renal dysfunction</td>
<td>• Adverse Effects</td>
</tr>
<tr>
<td>ClCr 21-50 mL/min 50% dose</td>
<td>- Nausea, vomiting, increased transaminases</td>
</tr>
<tr>
<td>ClCr &lt;20 mL/min 25% dose Removed by hemodialysis</td>
<td>- Hypertension, hypokalemia- higher doses</td>
</tr>
<tr>
<td>• Cost: $94/200 mg IV, $377/800 mgIV, $9/200 mg PO</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Itraconazole (Sporanox®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drug Interactions</td>
</tr>
<tr>
<td>- H2-antagonists, antacids, omeprazole- decreased oral tablet itraconazole absorption</td>
</tr>
<tr>
<td>- Rifampin, carbamazepine, phenobarbital, phenytoin- decrease itraconazole concentration</td>
</tr>
<tr>
<td>- Itraconazole increases cyclosporine, terfenadine, astemizole, cisapride, digoxin, warfarin, lovastatin, simvastatin, triazolam</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Itraconazole (Sporanox®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Uses:</td>
</tr>
<tr>
<td>- Blastomycosis, Histoplasmosis, Aspergillosis, Coccidiodomycosis, Sporotrichosis, non-albicans candida</td>
</tr>
<tr>
<td>• Dose:</td>
</tr>
<tr>
<td>- PO: Serious 200 mg TID X3days then 200 mg QD-BID</td>
</tr>
<tr>
<td>- IV: 200 mg BID for 4 doses then 200 mg QD</td>
</tr>
<tr>
<td>- Not if ClCr &lt; 30 mL/min- accumulation of vehicle -&gt; pancreatic cancer in animals</td>
</tr>
<tr>
<td>- ? Adjustment in hepatic impairment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Voriconazole (VFEND®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Newer Triazole</td>
</tr>
<tr>
<td>- Inhibits essential step in ergosterol biosynthesis (CYP450-mediated 14a-lanosterol demethylation)</td>
</tr>
<tr>
<td>- More specific to fungal vs mammalian CYP450 enzymes</td>
</tr>
<tr>
<td>• FDA Indications</td>
</tr>
<tr>
<td>- Invasive aspergillosis, serious refractory infections due to <em>Fusarium</em> or <em>Scedosporium</em> sp</td>
</tr>
<tr>
<td>- Non- FDA Approved Uses</td>
</tr>
<tr>
<td>• Oropharyngeal/esophageal candidiasis in HIV patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Voriconazole (VFEND®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pharmacokinetics</td>
</tr>
<tr>
<td>- Hepatic metabolism by CYP2C19, CYP2C9, CYP3A4</td>
</tr>
<tr>
<td>- CYP2C19 exhibit genetic polymorphisms</td>
</tr>
<tr>
<td>- 15-20% active, 5-6% inactivates blocks are poor metabolizers and have higher AUC</td>
</tr>
<tr>
<td>- &gt;2% excreted unchanged in urine</td>
</tr>
<tr>
<td>- No adjustment of dose for oral drug for renal failure</td>
</tr>
<tr>
<td>- Avoid IV drug in moderate/severe renal impairment (ClCr &lt; 50 mL/min) due to accumulation of cyclosporin in urine</td>
</tr>
<tr>
<td>- Not hemodialyzed off</td>
</tr>
<tr>
<td>• t1/2 6 hr (dose-dependent)</td>
</tr>
</tbody>
</table>
Voriconazole (VFEND®)

- **Loading Dose**
  - IV: 6mg/kg q12h x2
  - PO: 200mg

- **Maintenance Dose**
  - IV: 6mg/kg q12h
  - PO: 4mg/kg q12h

- **Dosing Adjustments**
  - Increase oral dose to 300mg q12h if response is inadequate.
  - Decrease IV maintenance dose to 3mg/kg q12h if patient is intolerant to drug.
  - If coadministered with phenytoin, increase IV maintenance dose to 5mg/kg q12h or oral dose to 400mg q12h.

- **Half Maintenance Dose** in patients with mild/moderated hepatic cirrhosis.

- **Cost**
  - approx $250 for 4 mg/kg IV q12h or $50 for 200 mg q12h PO.

**Voriconazole Drug Interactions**

- **Inducers**
  - Rifampin, rifabutin, carbamazepine, and barbiturates are contraindicated as will decrease exposure to voriconazole.
  - Phenytion is cautioned - will decrease exposure to voriconazole but also voriconazole will increase exposure to phenytion.

- **Inhibitors**
  - Simvastatin, terfenadine, astemizole, cisapride, pimozide, quinidine, rifabutin, and ergot alkaloids are contraindicated as will increase exposure to voriconazole.

**New Azoles in Development**

- **Ravuconazole- BMS**
  - Fluconazole based with Candida activity.

- **Posaconazole- Schering Plough**

**Echinocandins Class**

- Inhibit fungal β(1,3)-glucan synthetase
  - Depletes filamentous fungal 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**

- Inhibits fungal cell wall glucan synthesis (β(1,3)-D-glucan synthase not in mammalian cells)
- Spectrum of activity
  - 2nd line therapy for invasive aspergillus - refractory or intolerant (SCG) of AMB, lipid AMB, or itraconazole
  - Improvement in 1/3 of refractory cases.
  - Indicated for candidal esophagitis (50-70 mg/day IV for 2 wks) incl those with HIV/low CD4 counts.
  - Not active against cryptococcus, less activity vs amphi B against echinococcus and fusarium sp.
- **Cancidas[®] - Merck & Co**
- Inhibits fungal cell wall glucan synthesis (β(1,3)-D-glucan synthase not in mammalian cells)
- Spectrum of activity
  - 2nd line therapy for invasive aspergillus - refractory or intolerant (SCG) of AMB, lipid AMB, or itraconazole
  - Improvement in 1/3 of refractory cases.
  - Indicated for candidal esophagitis (50-70 mg/day IV for 2 wks) incl those with HIV/low CD4 counts.
  - Not active against cryptococcus, less activity vs amphi B against echinococcus and fusarium sp.
Echinocandin Class: Caspofungin

- Pharmacokinetics
  - Liver metabolized (not P450)-minimal renal clearance
  - t1/2 9-10 hr
  - Poor CSF penetration (protein bound 80-96%)
- 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
  - Crizotinib, cyclosporine, rifabutin, ritonavir, rifampin may incr clearance of caspofungin (50 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

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

- Onychomycosis -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 rxs, 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/surg
  - Immunosup
  - BS Ab tx
  - Coloniz > 2 sites
  - CV cath

Treatment of Candidemia
- Remove existing central venous catheters
- IV amphotericin B (traditionally preferred) or IV/PO fluconazole
- Combination with fluconazole for very severe cases
- Continue therapy for 2 weeks after the last + 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 fluconazole 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