Antifungal Agents

Fungi

Yeasts
- Candida sp.
  - C. albicans
  - C. tropicalis
  - C. parapsilosis
  - C. krusei

Moulds
- Aspergillus sp.
  - A. fumigatus
  - A. flavus
  - A. niger

Opportunistic fungi
- Normal flora
  - Candida spp.
- Ubiquitous in our environment
  - Aspergillus spp.
  - Cryptococcus spp.
  - Mucor spp.

Endemic geographically restricted
- Blastomyces sp.
  - Coccidioides sp.
  - Histoplasma sp.

Newly emerging fungi
- Fusarium
- Scedosporium
- Trichosporon

Risk Factors for Fungal Disease

Candidiasis
- Antibiotics
- Indwelling catheters
- Hyperalimentation
- Multiple abdominal surgeries
- Prosthetic material
- Severe burns
- Neoplastic diseases/chemotherapy
- Immunosuppressive therapy
- Diabetes mellitus
- Extremes of age

Aspergillosis
- Granulocytopenia (↓ neutrophil numbers or function)
- T-cell dysfunction
- Hematologic and other malignancies
- Organ allograft recipients
- Immunosuppressive therapy
- Corticosteroids
- Chronic granulomatous disease
- AIDS
- Burn patients

An optimal antifungal drug has...

- Wide spectrum of activity
- Favorable pharmacokinetic profile
- Adequate in vivo efficacy
- Low rate of toxicity
- Low cost
Invasive Aspergillosis Mortality

Review of 1941 Patients from 50 Studies


Targets of Antifungal Agents

Systemic Antifungal Agents
By Mechanism of Action

- Membrane disrupting agents
  - Amphotericin B

- Nucleic acid inhibitor
  - Fluconosine

- Ergosterol synthesis inhibitors
  - Azoles

- Glucan synthesis inhibitors
  - Echinocandins

Amphotericin B

- Polyene
- Clinical use since 1960
- Insoluble in water
  - Solubilized by sodium deoxycholate
- Most broad spectrum antifungal
  - "gold standard"

Pharmacokinetics
- Extensively tissue bound
  - Highest concentrations in liver, spleen, bone marrow with less in kidneys and lung
- Half-life
  - Tissue ~15 days, Plasma ~5 days

The Promise of a Dynamic Era...

Amphotericin B Binds to Ergosterol and Generates Pores

- Mechanism of action
  - Binds to ergosterol and alter cell membrane permeability → cell death
  - Also binds to cholesterol → adverse effects

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Amphotericin B
Most broad spectrum antifungal – long considered the “gold standard”

- Clinical activity
  - Candida sp.
  - C. lusitaniae often resistant
  - Cryptococcus neoformans
  - Blastomycosis
  - Histoplasmosis
  - Aspergillus sp.
  - Zygomycetes
    - Rhizopus sp., Mucor sp., etc.
  - Little to no activity
    - Aspergillus terreus
    - Aspergillus nidulans
    - Aspergillus flavus
    - Fusarium sp.
    - Pseudoallescheria boydii
    - Scedosporium prolificans
    - Trichosporon beigelii

- Pharmacokinetics
  - Intravenous formulation only
  - Distribution
  - Extensively tissue bound
  - Half-life
  - Tissue ~15 days
  - Plasma ~5 days

- Toxicities
  - Nephrotoxicity
  - Infusion Related Reactions (IRRs)
  - Electrolyte Abnormalities
  - Thrombophlebitis
  - Anemia

Available Lipid-Based Amphotericin B Agents

- Lipid Complex ABLC, Abelcet®
  - Flattened, ribbon-like complex
  - Molecular ratio (drug:lipid) = 3:7
  - Particle size = 1,600 – 11,000 nm.

- Colloidal Dispersion ABCD, Amphotec®
  - Elongated disk structure
  - Molecular ratio (drug:lipid) = 1:1
  - Particle size = 120 – 140 nm.

- Liposomal L-AmB, Ambisome®
  - Closed, fluid-filled liposome
  - Molecular ratio (drug:lipid) = 1:9
  - Particle size = 45 - 80 nm.

Understanding the Candida species

- Fusicoccin
  - Itraconazole
  - Fluconazole
  - Voriconazole

Azole Antifungals

- Imidazoles
  - Ketoconazole

- Triazoles
  - Itraconazole
  - Fluconazole
  - Voriconazole

- Mechanism of action
  - Inhibit ergosterol synthesis through inhibition of CYP51-dependent lanosterol 14α-demethylase
  - Depletion of ergosterol on fungal cell membrane

- Resistance
  - ERG 11 mutations (gene encoding 14α-sterol demethylase) leading to overexpression
  - ↑ azole efflux
  - ↑ production or alteration 14α-demethylase

Lipid Amphotericin B Product Comparison

- Yeast:
  - C. albicans
  - Yeast: ketoconazole: fluconazole: itraconazole: voriconazole

- Other yeasts
  - ketoconazole: fluconazole: itraconazole: voriconazole

- Resistance yeasts
  - ketoconazole: fluconazole: itraconazole: voriconazole

- Moulds
  - Aspergillus
  - Other moulds
  - Zygomycetes
  - Other fungi

- Echinocandins
  - Amphotericin B
  - Fusidic acid

- Azole Antifungals Spectrum of Activity
Fluconazole

- Favorable pharmacokinetic and toxicity profile
  - Low and high water solubility → rapid absorption and ↑ bioavailability
  - >90% bioavailability (IV and PO interchangeable)
  - No dependence on low gastric pH
  - Effectively penetrates CSF (50-60% plasma levels)
- Brain and eye too!
- >90% renal excretion

- Adverse effects
  - Very well tolerated
  - Even up to 1600 mg/day
  - O/L, reversible transaminase elevations

- Dose
  - 100-800 mg/d (max 1600 mg/d)
  - GI, reversible transaminase elevations
  - Elevated liver function tests (~13%)
  - May be dose-related
  - Skin reactions (6%)

Itraconazole

- Spectrum
  - Paracoccidioidomycosis, blastomycosis, histoplasmosis and sporotrichosis, cutaneous and mucosal candidiasis, Aspergillosis

- Adverse effects
  - Transient GI upset, dizziness, headache

- Pharmacokinetics
  - Extensively liver metabolized
  - Nonlinear serum PK

- clinical uses
  - Fungal infections caused by Aspergillus spp., Scedosporium spp., Fusarium spp.
  - Candida spp.
  - Cryptococcal meningitis, hepatosplenic candidiasis, Candida endophthalmitis

- Drug Interactions
  - Propensity and extent greater than fluconazole
  - Metabolized by CYP3A4

- IV itraconazole
  - Formulated in hydroxypropyl-β-cyclodextrin

- IV voriconazole
  - Increases solubility of itraconazole

- Mechanism of action
  - Flucytosine is deaminated to 5-fluorocytosine (5-FC)

- Resistance
  - Loss of permease necessary for cytosine transport

- Spectrum
  - Cryptococcus neoformans
  - Candida sp. (except C. krusei)

- Clinical uses
  - Cryptococcal meningitis, hepatosplenic candidiasis, Candida endophthalmitis

- Flucytosine (5-FC)

- Pharmacokinetics
  - Oral only
  - >95% bioavailability on empty stomach

- Dosing
  - 200 mg IV q12h x 4 doses, then 200 mg IV q24h followed by 200 mg PO q12h oral solution

- Adverse effects
  - Transient, dose related visual disturbances (30%)

- Resistance
  - Loss of permease necessary for cytosine transport

- Spectrum
  - Cryptococcus neoformans
  - Candida sp. (except C. krusei)

- Clinical uses
  - Cryptococcal meningitis, hepatosplenic candidiasis, Candida endophthalmitis

- Voriconazole

- Precautions (AND LIMITATIONS?)
  - Transient, dose related visual disturbances (30%)
  - Elevaded liver function tests (~13%)
  - May be dose-related
  - Skin reactions (6%)

- Dosing
  - Intravenous
    - 8 mg/kg IV q12h x 2 doses, then 4 mg/kg IV q12h
    - 40 kg – 100 mg PO q12h
    - 20 kg – 200 mg PO q12h

- Organ dysfunction
  - Renal disease
    - Oral dosing recommended in patients with CrCL<50 ml/min
    - IV vehicle, sulfobutyl ether-beta-cyclodextrin, accumulates

- Clinical uses
  - Cryptococcal meningitis, hepatosplenic candidiasis, Candida endophthalmitis

- Flucytosine

- Pharmacokinetics
  - Oral only
  - >95% bioavailability on empty stomach

- Dosing
  - Dose-dependent bone marrow suppression (↓ WBC, ↓ platelets)
  - GI (nausea/vomiting/diarrhea)
  - Renal/hepatic disease
  - Maintenance dose should be halved in patients with mild/moderate liver disease
**Echinocandins**

**Adverse effects**
- Clinical experience to date suggests that these drugs are extremely well-tolerated
- Most common AEs are infusion related:
  - Phlebitis/Thrombophlebitis (11.3-15.5%)
  - Mild to moderate infusion-related AE including:
    - Fever (3.6-26.2%)
    - Headache (6.11.3%)
    - Rash (0.4-0.9%)
    - Symptoms consistent with histamine release (2%)
- Most AEs were mild and did not require treatment discontinuation
- Most common laboratory AE
  - Asymptomatic elevation of serum transaminases (10.6-13%)

**Echinocandins - spectrum**

**Highly Active**
- C. albicans
- C. glabrata
- C. tropicalis
- C. krusei
- C. kefyr
- P. canii

**Very Active**
- C. parapsilosis
- C. guilliermondii
- A. fumigatus
- A. flavus
- A. terreus
- C. lusitaniae

**Some Activity**
- C. kimmitis
- B. dermatitidis
- Scrobicillium species
- P. variotii
- H. capsulatum

**Very low MIC, with fungicidal activity and good in-vivo activity.**

**Only active against cyst forms, and probably only useful for prophylaxis.**

**How to Choose?**

- **Spectrum**
  - Likely pathogens
  - Documented pathogens
  - Site of infection
  - Concomitant diseases
  - Hepatic/renal function
  - Toxicities
  - Drug Interactions
  - IV/PO
  - Cost

**Understanding the Candida species**

<table>
<thead>
<tr>
<th></th>
<th>Fluconazol e</th>
<th>Voriconazol e</th>
<th>Posaconazole*</th>
<th>Amphot B</th>
<th>Echinocandins</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>$</td>
<td>$</td>
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<tr>
<td>C. tropicalis</td>
<td>$</td>
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<td>S</td>
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<tr>
<td>C. parapsilosis</td>
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<td>$</td>
<td>$</td>
<td>$</td>
<td>S to R (7)</td>
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<tr>
<td>C. glabrata</td>
<td>$ to D to R</td>
<td>$ to I</td>
<td>$ to I</td>
<td>$ to I</td>
<td>S</td>
</tr>
<tr>
<td>C. krusei</td>
<td>R to D to R</td>
<td>$ to I</td>
<td>$ to I</td>
<td>$ to I</td>
<td>S</td>
</tr>
<tr>
<td>C. lusitaniae</td>
<td>$</td>
<td>$</td>
<td>$</td>
<td>$</td>
<td>$ to R (5)</td>
</tr>
</tbody>
</table>

Enzymatic activity, which might have therapeutic potential for man (in some cases in combination with other drugs).
Treatment of Candida sp. Infections

- **Unknown Candida sp.**
  - Fluconazole
  - Voriconazole
  - Echinocandins
  - Amphotericin B product
- **Known Candida sp.**
  - Based on species and susceptibility results
  - Comorbid conditions/Toxicities

Yeast cells and pseudohyphae in material from the oral cavity, KOH preparation, phase-contrast microscopy.

Aspergillosis Treatment

- **Risk factors**
  - granulocytopenia (↓ neutrophil numbers or function)
  - T-cell dysfunction
  - Hematologic and other malignancies
  - Organ allograft recipients
  - Immunosuppressive therapy
  - Corticosteroids
  - Chronic granulomatous disease
  - AIDS
  - Burn patients
- **Drug therapy options**
  - Amphotericin B product
  - Itraconazole
  - Echinocandins
  - Voriconazole

Methenamine silver (GMS) stained tissue section of lung showing dichotomously branched, septate hyphae of Aspergillus fumigatus.

Combination Antifungal Therapy

- **Advantages**
  - Enhanced rate and extent of killing (additivity, synergy)
  - Decrease in antifungal drug resistance
  - Increase in the spectrum of activity
  - Enhancement in the tissue distribution of the two drugs
  - Reduction in drug-related toxicity, particularly if the dosage of a toxic drug can be reduced
- **Disadvantages**
  - Decreased rate and extent of killing (antagonism)
  - Increase in drug-related toxicity
  - Increased risk of drug-drug interactions
  - Increased cost compared to monotherapy

Combination Antifungal Therapy: Benefits

- Improved clinical and microbiologic outcome
- Decreased toxicity
- Decreased likelihood of resistance
- Broader spectrum in empiric therapy
- Little objective clinical data

Medical Letter 2002;44:63-65

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>AWP Cost/Dose</th>
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<tbody>
<tr>
<td><strong>Polyenes</strong></td>
<td></td>
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<tr>
<td>Amphotericin B deoxycholate</td>
<td>1-1.5 mg/kg/day IV</td>
<td>$17 - $33</td>
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<td>3-6 mg/kg/day IV</td>
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<td><strong>Triazoles</strong></td>
<td></td>
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</tr>
<tr>
<td>Fluconazole</td>
<td>400 - 900 mg IV</td>
<td>$133 - $266</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>200 - 600 mg PO</td>
<td>$14 - $106</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>200 mg PO</td>
<td>$94 - $177</td>
</tr>
<tr>
<td><strong>Echinocandins</strong></td>
<td></td>
<td></td>
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<tr>
<td>Caspofungin</td>
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Anti-Tuberculosis Agents

- **Combination Antifungal Therapy**
  - Fungi more difficult to diagnose, less amenable to treatment, and associated with highest attributable mortality compared to bacterial pathogens
  - Often consider combination therapy in refractory mycoses

- **Benefits**
  - Improved clinical and microbiologic outcome
  - Decreased toxicity
  - Decreased likelihood of resistance
  - Broader spectrum in empiric therapy

- **Little objective clinical data**
Antituberculosis Therapy

Drug therapy is the cornerstone of TB management.

Goals:
- Kill TB rapidly
- Prevent emergence of resistance
- Eliminate persistent bacilli from the host to prevent relapse

Drug therapy:
- First-line agents: greatest efficacy with acceptable toxicity
- Second-line agents: less efficacy, greater toxicity, or both
- If properly used, can achieve cure rate ~98%
- Increasing prevalence of multidrug-resistant TB (MDRTB)

Treatment Principles (cont.):

3 subpopulations of mycobacteria proposed to exist:
- Extracellular, rapidly dividing mycobacteria, often within cavities (10^7 to 10^9)
  - Killed most readily by INH > RIF > streptomycin > other drugs
  - Organisms residing within caseating granulomas (semi-dormant metabolic state; 10^5 to 10^7)
  - Activity of PZA > INH and RIF
- Intracellular mycobacteria present within macrophages (10^4 to 10^6)
  - RIF, INH, PZA and quinolones believed to be most active

Disease burden:
- Asymptomatic patients have an organism load of ~10^5 organisms
- Cavitary pulmonary TB has a load of 10^11 organisms
- As the number of organisms increases, likelihood of drug-resistant mutants increases
- Mutants found at rates of 1 in 10^6 to 1 in 10^8 organisms

Drug therapy regimens:
- Latent TB
  - Monotherapy, usually with isoniazid (INH)
  - Risk of selecting out resistant organisms is low
- Active TB
  - Combination therapy of at least 2 drugs, generally three or more
  - Rates for multiple drug mutations occur as an additive function
  - 1 in 10^10 (INH rate of 10^6 × RIF rate of 10^4)

Toxicities:
- Hepatotoxicity
  - Risk factors = multiple hepatotoxic agents, alcohol abuse
- Regimen and Dosing:
  - Duration varies
  - Combination of patient, extent of disease, presence of drug resistance, and tolerance of medications
  - Adherence is important (DOT)
  - Daily vs. TW
  - PO vs. IV vs. IM

First-Line Agents

- Rifampin
- Isoniazid
- Pyrazinamide
- Ethambutol
- Streptomycin

Second-line Drugs
- Rifabutin
- Quinolones
- Capreomycin
- Amikacin, kanamycin
- Para-aminosalicylic acid (PAS)
- Cycloserine
- Ethionamide

Early bactericidal activity: √
Sterilizing activity: □
Prevent emergence of resistance: △

- Rifampin
- Isoniazid
- Pyrazinamide
- Ethambutol
- Streptomycin
Isoniazid (INH)

- Inhibits mycolic acid synthesis
  - Long-chain fatty acids of the mycobacterial cell wall
  - Bactericidal against growing MTB
  - Bacteriostatic against nonreplicating MTB
- PO only
  - Well absorbed
- Metabolized in liver by N-acetyltransferase
  - Slow vs. fast acetylators
  - Half life 2-4 hrs vs. 0.5-1.5 hrs
  - ~68% Asian patients are rapid acetylators
  - Drug interactions more likely in slow acetylators
- Toxicities
  - ↑ serum transaminases (AST, ALT)
  - Neurotoxicity
    - Usually manifests as peripheral neuropathy → administer pyridoxine (vitamin B6) daily
  - ↑ risk alcoholics, children, diabetics, malnourished, dialysis patients, HIV+

Streptomycin

- Inhibits protein synthesis (aminoglycoside)
  - Bactericidal
  - Poor activity in acidic environment of closed foci
  - Not good sterilizing drug
- IM/IV
  - Renal excretion
  - Toxicities
    - Vestibular toxicity
      - Dizziness, problems with balance, tinnitus
    - Can be permanent
    - Nephrotoxicity
      - Tends to be mild and reversible

Rifampin

- Inhibits DNA-dependent RNA polymerase
  - Bactericidal (very effective)
  - Allows short course therapy (6-9 mos vs. ≥18 mos)
  - IV/PO
- Toxicities
  - ↑ hepatic enzymes (AST, ALT, bilirubin, alkaline phosphatase)
  - GI distress
  - Red-orange discoloration of body fluids
  - Rash
  - DRUG INTERACTIONS, DRUG INTERACTIONS, DRUG INTERACTIONS
    - Potent inducer of CYP450 metabolism (↓ concentrations of other drugs)

First Line Agents (cont.)

- Pyrazinamide
  - Mechanism unknown
  - Fatty acid synthase-1
  - Converted to pyrazinoic acid (active metabolite)
  - Bactericidal
  - PO only
  - Metabolized in the liver, but metabolites are renally excreted
- Toxicities
  - ↑ liver enzymes
  - Hyperuricemia
  - Nausea/vomiting

- Ethambutol
  - Inhibits cell wall components
  - Generally bacteriostatic
  - PO only
  - Renal excretion
  - Toxicities
    - Optic neuritis (dose-related)
    - Hyperuricemia

Second-Line Agents

Second Line Agents

- Rifabutin
  - Often used as an alternative to rifampin
  - Less potent inducer CYP450
  - Drug interactions still important
  - Cross resistance among rifamycins
  - PO only
  - Toxicities
    - Uveitis (ocular pain, blurred vision)

- Quinolones
  - Levofloxacin, moxifloxacin, gatifloxacin
  - Bactericidal against extracellular organisms and achieve good intracellular concentrations
  - IV/PO
  - Uses
    - MDR-TB
    - IV alternative
    - Well tolerated option
  - Toxicities
    - Nausea, abdominal pain
    - Headache, insomnia, restlessness
### Second Line Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Uses</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capreomycin</strong></td>
<td>MDR-TB</td>
<td>Injection pain, hearing loss, tinnitus, renal dysfunction</td>
</tr>
<tr>
<td><strong>Para-amino salicylic acid (PAS)</strong></td>
<td>Synthetic structural analog of aminobenzoic acid</td>
<td>Cross-resistance with aminoglycosides</td>
</tr>
<tr>
<td><strong>Amikacin, kanamycin</strong></td>
<td>MDR-TB</td>
<td>Cross-resistance with aminoglycosides</td>
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<tr>
<td><strong>Amikacin, kanamycin</strong></td>
<td>MDR-TB</td>
<td>Cross-resistance with aminoglycosides</td>
</tr>
<tr>
<td><strong>Cycloserine</strong></td>
<td>MDR-TB</td>
<td>Central nervous system effects, confusion, irritability, somnolence, headache, vertigo, seizures, Peripheral neuropathy</td>
</tr>
<tr>
<td><strong>Ethionamide</strong></td>
<td>MDR-TB</td>
<td>Nausea/vomiting, Peripheral neuropathy, Psychiatric disturbances, ↑ liver enzymes, ↑ glucose, Goiter with or without hypothyroidism, Gynecomastia, impotence, menstrual irregularities</td>
</tr>
</tbody>
</table>

### Drug-Resistant TB

- **Acquired resistance**
  - Suboptimal therapy that encourages selective growth of mutants resistant to one or more drugs

- **Primary resistance**
  - Infection from a source case who has drug-resistant disease

- **Factors leading to suboptimal therapy**
  - Intermittent drug supplies
  - Use of expired drugs
  - Unavailability of combination preparations
  - Use of poorly formulated combination preparations
  - Inappropriate drug regimen
  - Addition of single drugs to failing regimens in the absence of bacteriologic control
  - Poor supervision of therapy
  - Unacceptably high cost to patient (drugs, travel to clinic, time off work)