Antifungals and Anti-Tuberculosis Agents

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Antifungal Agents

Review of our Fungal “Players”

Fungi

Yeast

Moulds

Candida

Cryptococcus

Pneumocystis

Aspergillus

Mucor

Dermatophytes

Opportunistic fungi

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

Newly emerging fungi

- Fusarium
- Scedosporium
- Trichosporin

Endemic geographically restricted

- Blastomycosis sp.
- Coccidioides sp.
- Histoplasma sp.

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

![Graph showing case fatality rates for different types of infections](image)


**Systemic Antifungal Agents**

By Mechanism of Action

- **Membrane disrupting agents**
  - Amphotericin B
- **Ergosterol synthesis inhibitors**
  - Azoles
- **Nucleic acid inhibitor**
  - Fluconosine
- **Glucan synthesis inhibitors**
  - Echinocandins

**The Promise of a Dynamic Era**

The Azoles
- Fluconazole (Diflucan®)
- Itraconazole (Sporanox®)
- Voriconazole (Vfend®)
- Posaconazole (Noxafil®)

Amphotericin B
- Amphotericin B deoxycholate (Fungizone®)
- ABCD (Amphotec®)
- ABLC (Abelcet®)
- Liposomal Amphotericin B (Ambisome®)

Echinocandins
- Caspofungin (Cancidas®)
- Micafungin (Mycamine®)
- Anidulafungin (Eraxis®)

Flucytosine (Ancobon®)

**Targets of Antifungal Agents**

- Polyene antibiotics
  - Amphotericin B
  - Lipid-AMB
- Azole antifungals
  - Ketoconazole
  - Itraconazole
  - Fluconazole
  - Voriconazole
  - Posaconazole
- Echinocandins
  - Caspofungin (Cancidas®)
  - Micafungin (Mycamine®)
  - Anidulafungin (Eraxis®)
- Flucytosine (Ancobon®)

**Amphotericin B**

- A polypeptide
- Clinical use since 1960
- Insoluble in water
- Solubilized by sodium deoxycholate
- Highest concentrations in liver, spleen, bone marrow with less in kidneys and lung
- Half-life
  - Tissue ~15 days, Plasma ~5 days

**Systemic Antifungal Agents**

![Diagram showing targets of antifungal agents](image)

![Diagram showing the promise of a dynamic era](image)
**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

**Amphotericin B**

- Most broad spectrum antifungal – long considered the “gold standard”
  - Clinical activity
    - Candida sp.
    - C. albicans often resistant
    - Cryptococcus neoformans
    - Blastomycosis
    - Histoplasmosis
    - Aspergillus sp.
    - Zymomyces
    - Rhizopus sp., Mucor sp., etc.
  - Little to no activity
    - Aspergillus tamu, Aspergillus nulas, Aspergillus flavus, Fusarium sp., Pseudoallescheria boydii, Scedosporium prolificans, Trichosporon beigelii
  - Toxicities
    - Nephrotoxicity
    - Infusion Related Reactions (IRRs)
    - Electrolyte Abnormalities
    - Thrombophilies
    - Anemia

**Available Lipid-Based Amphotericin B Agents**

<table>
<thead>
<tr>
<th>Product</th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Complex ABLC; Abelcet®</td>
<td>Flattened, ribbon-like complex. Molecular ratio (drug:lipid) = 3.7. Particle size = 1,500 – 11,000 nm.</td>
</tr>
<tr>
<td>Colloidal Dispersion ABLC; Amphotec® or Amphotec®</td>
<td>Elongated disk structure. Molecular ratio (drug:lipid) = 1:1. Particle size = 120 – 140 nm.</td>
</tr>
</tbody>
</table>

**Lipid Amphotericin B Product Comparison**

- Particle
  - Micelle
  - Lipid disks
  - Ribbons, sheets
  - Liposomes, small unilamellar vesicles

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

**Azole Antifungals**

- Imidazoles
  - Ketoconazole
- Triazoles
  - Itraconazole
  - Fluconazole
  - Voriconazole
  - Posaconazole

- Mechanism of action
  - Inhibit ergosterol synthesis through inhibition of CYP51A gene product, lanosterol 14α-demethylase
  - Deposition 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
### Azole Antifungals Spectrum of Activity

<table>
<thead>
<tr>
<th>Organism</th>
<th>Ketoconazole</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
<th>Itraconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeast</td>
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<tr>
<td>C. albicans</td>
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<td>S</td>
<td>S</td>
<td>S</td>
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<tr>
<td>Other moulds</td>
<td>S</td>
<td>S</td>
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<td>S</td>
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<tr>
<td>Zygomycetes</td>
<td>S</td>
<td>S</td>
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<tr>
<td>Aspergillus</td>
<td>S</td>
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<tr>
<td>C. glabrata</td>
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<td>S</td>
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<tr>
<td>C. krusei</td>
<td>S</td>
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<td>S</td>
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<tr>
<td>C. lusitaniae</td>
<td>S</td>
<td>S</td>
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</tbody>
</table>

### Understanding the *Candida* species

<table>
<thead>
<tr>
<th>Organism</th>
<th>Fluconazole</th>
<th>Voriconazole</th>
<th>Itraconazole</th>
<th>Posaconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<tr>
<td>C. lusitaniae</td>
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<td>C. krusei</td>
<td>S</td>
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<tr>
<td>C. parapsilosis</td>
<td>S</td>
<td>S</td>
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<tr>
<td>C. tropicalis</td>
<td>S</td>
<td>S</td>
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</tr>
</tbody>
</table>

### Fluconazole

- **Favorable pharmacokinetic and toxicity profile**
  - Low me and high water solubility → rapid absorption and bioavailability
  - No dependence on low gastric pH
  - Effectively penetrates CSF (50-90% plasma levels)
  - Brain and eye tool
  - >90% renal excretion
- **Adverse effects**
  - Very well tolerated
  - GI upset, headache
- **Dose**
  - 100-800 mg/d (max 1600 mg/d)
  - 60 mg/kg for susceptible strains (400 mg/d)
  - 12 mg/kg for S-D strains (800 mg/d)
  - IV and oral interchangeable (>90% bioavailability)
  - Renal disease
    - Oral (>95% bioavailability on empty stomach)
    - IV: sulfobutyl ether-beta-cyclodextrin, accumulates

### Voriconazole

- Second-generation synthetic derivative of fluconazole
  - Addition of methyl group to the propyl backbone
  - Substitution of triazole moiety with a fluropyrimidine group
- Active against yeast and moulds
  - Fungalidal in vitro against Aspergillus spp., Scedosporium spp., Fusarium spp.
  - Fungalidal in vivo against Candida spp.
- **Adverse effects**
  - Transient, dose-related visual disturbances (30%)
  - Elevated liver function tests (13%)
  - May be dose-related
  - Skin reactions (6%)
- **Drug interactions**
  - Incompatible
  - Reduced bioavailability with cyclosporin, tacrolimus, macrolides, antibiotics, calcium channel blockers
  - May affect the metabolism of CYP3A4 substrates

### Itraconazole

- **Drug Interactions**
  - Propensity and extent greater than fluconazole
  - Substrate of CYP3A4 and inhibitor of CYP2C9
- **IV Efficacy**
  - Formulated in hydroxypropyl-beta-cyclodextrin
  - Increases solubility of itraconazole
- **Renal dysfunction**
  - A 4-fold reduction in clearance in patients with CrCl < 20 mL/min
- **Spectrum**
  - Paracoccidioidomycosis, blastomycosis, histoplasmosis and sporotrichosis, cutaneous and mucosal candidiasis, Aspergillus
- **Dosing**
  - 200 mg IV q12h x 4 doses, then 200 mg IV q48h followed by 200 mg PO q12h oral solution
  - Target trough > 0.5 mcg/mL

### Voriconazole Precautions (AND LIMITATIONS?)

- **Adverse effects**
  - Transient, dose-related visual disturbances (30%)
  - Elevated liver function tests (13%)
- **May be dose-related**
- **Skin reactions (6%)**
- **Drug interactions**
  - **Incompatible**
    - Oral
      - Reduced bioavailability with cyclosporin, tacrolimus, macrolides, antibiotics, calcium channel blockers
      - May affect the metabolism of CYP3A4 substrates
  - **IV**
    - Reduced bioavailability with cyclosporin, tacrolimus, macrolides, antibiotics, calcium channel blockers
      - May affect the metabolism of CYP3A4 substrates
**Flucytosine (5-FC)**

- **Mechanism of action**
  - Flucytosine is deaminated to 5-fluorocytosine (5-FC)
  - Incorporated into RNA and disrupts protein synthesis

- **Resistance**
  - Develops during therapy, especially monotherapy
    - Single point mutation
    - Loss of permease necessary for cytosine transport
    - Activity of UMP pyrophosphorylase or cytosine deaminase

- **Spectrum**
  - Cryptococcus neoformans
  - Candida sp. (except C. krusei)
  - Little to no activity against Aspergillus and other molds

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**Posaconazole (Noxafil®)**

- **Indications**
  - Prophylaxis of invasive Aspergillus and Candida infections in severely immunocompromised hosts, such as HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia (≥ 13 yrs old)

- **Dose** (40 mg/5 mL oral suspension ONLY)
  - Prophylaxis: 200 mg PO 4x/day or 400 mg PO BID

- **Drug interactions**
  - Cimetidine decreases POSA bioavailability

- **Clinical uses**
  - Prophylaxis
  - Treatment: 200 mg PO 4x/day or 400 mg PO BID

- **Adverse effects**
  - N/V, hepatic

- **Prophylaxis**
  - 200 mg (5 mL) PO TID with a high fat meal

- **Indications**
  - Prophylaxis of invasive fungal infections
  - Aspergillus spp. and other molds

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**Flucytosine**

- **Pharmacokinetics**
  - Oral only
  - Distribution
  - CSF levels ~75% of serum levels
  - Elimination
  - 90% excreted via glomerular filtration
  - Half-life ~3-6 hours
  - Renal/hepatic disease
    - Dose adjust in renal dysfunction

- **Adverse effects**
  - Dose-dependent bone marrow suppression (↓ WBC, ↓ platelets)
  - G1 (nausea/vomiting/diarrhea)

- **Clinical uses**
  - Cryptococcal meningitis, hepatosplenic candidiasis, Candida endophthalmitis
  - Used in combination ONLY (usually with amphotericin)

- **Minimizes development of resistance**

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**Aazole Inhibition of CYP P450**

- Ketoconazole
- Fluconazole
- Voriconazole
- Posaconazole
- Amphotericin B
- Voriconazole
- Fluconazole
- Voriconazole
- Posaconazole
Echinocandins - spectrum

Highly Active
- C. albicans
- C. glabrata
- C. tropicalis
- C. krusei
- C. kefyr
- P. carinii

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

Some Activity
- C. immitis
- B. dermatitidis
- Scedosporium species
- P. variotii
- H. capsulatum

Very low MIC, with fungicidal activity and good in-vivo activity, but only active against cyst forms, and probably only useful for prophylaxis in some instances.

Understanding the Candida species

<table>
<thead>
<tr>
<th>Fungi &amp; ( \text{MIC} )</th>
<th>Echinocandins</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>S S S S S S S</td>
</tr>
<tr>
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<td>S S S S S S S</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>S to I (r)</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>I to R</td>
</tr>
<tr>
<td><em>C. lusitaniae</em></td>
<td>S to R (r)</td>
</tr>
</tbody>
</table>

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

Echinocandin Indications

- **Caspofungin**
  - Candidemia and the following Candida infections: intra-abdominal abscesses, peritonitis and pleural space infections
  - Not studied in endocarditis, osteomyelitis or meningitis due to Candida sp.
  - Empirical therapy for presumed fungal infections in febrile neutropenic patients
  - Not studied as initial therapy for IA

- **Micafungin**
  - Esophageal candidiasis
  - Prophylaxis of Candida infections in patients undergoing HSCT

- **Anidulafungin**
  - Esophageal candidiasis
  - Candidemia and other forms of Candida infections (intra-abd abscess, and peritonitis)

Treatment Options for Candida sp.

- **Amphotericin B**
- **Fluconazole**
- **Itraconazole**
- **Voriconazole**
- **Posaconazole (?)**
- **Caspofungin / Micafungin / Anidulafungin**
**Combination Antifungal Therapy**

- **Echinocandins**
  - Pros
  - Cidal against Candida sp.
  - Expanded spectrum to \( \text{Scedosporium} \)
  - Activity against azole-resistant Candida species
  - Lack of common significant drug interactions
  - Well tolerated
  - IV only
  - $$$

- **Fluconazole**
  - Pros
  - Clinical experience and comparable outcomes
  - Activity against the majority of Candida species
  - Well tolerated
  - IV/PO
  - Less costly
  - Cons
  - Potential resistance

- **Benefits**
  - Increased rate and extent of killing (additivity, synergy)
  - 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

- **In vitro studies controversial**
- **Clinical efficacy data rely on case reports/series**
- **Literature probably biased towards reports of success**
- **Many questions remain...**
  - What combination?
  - When?
  - Sequence
  - Initial vs. salvage
  - Multiresistant species

**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
  - Posaconazole (?)

- **Pros**
  - Well tolerated
  - IV/PO

- **Cons**
  - Potential resistance
  - Activity against azole-resistant species
  - Activity against the majority of Aspergillus species
  - Activity against Candida

**Conclusions Related to Combination Antifungal Therapy**

- **Advantages**
  - Decreased rate and extent of killing (antagonism)
  - Increase in drug-related toxicity
  - Increased risk of drug-drug interactions
  - Increased cost compared to monotherapy

- **Disadvantages**
  - Decreased 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

**Anti-Tuberculosis Agents**

- *Methenamine silver (GMS)* stained tissue section of lung showing dichotomously branched, septate hyphae of *Aspergillus fumigatus*.
Anti-Tuberculosis Agents

- **First-line Drugs**
  - Isoniazid
  - Pyrazinamide
  - Ethambutol
  - Streptomycin

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

Anti-Tuberculosis 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

- **Disease burden**
  - Asymptomatic patients have an organism load of ~10^3 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 10^9 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 10^17 (INH rate of 10^6 + RIF rate of 10^7)

Treatment Principles (cont.)

- **3 subpopulations of mycobacteria proposed to exist**
  - Extracellular, rapidly dividing, 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 10^6)
    - 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

Treatment Principles (cont.)

<table>
<thead>
<tr>
<th>Early bactericidal activity</th>
<th>Sterilizing activity</th>
<th>Prevent emergence of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>×</td>
<td>√</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

- **Toxicities**
  - Hepatotoxicity
    - Risk factors = multiple hepatotoxic agents, alcohol abuse

- **Regimen and Dosing**
  - Duration varies
    - Condition 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
Isoniazid (INH)
- Inhibits mycobacterial 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
- PO only
- Mechanism unknown
- PO only
- Metabolized in the liver, but metabolites are renally excreted
- Toxicities
  - ↑↑ Serum transaminases (AST, ALT)
  - ⇓↓↓ Nausea/vomiting
  - Hyperuricemia
  - ↑↑ Converted to pyrazinoic acid (active metabolite)
  - Nephrotoxicity
  - Blood dyscrasias
  - Cross resistance among rifamycins
  - Not good sterilizing drug
  - Poor activity in acidic environment of closed foci
  - Cross resistance among rifamycins
  - Drug interactions still less potent inducer CYP450
  - Rash
  - Red-orange discoloration of body fluids
  - Nephrotoxicity
  - Tend to be mild and reversible

Rifampin
- Inhibits DNA-dependent RNA polymerase
- Bactericidal (very effective)
- PO only
- Toxicities
  - ↑↑ Tend to be mild and reversible
  - Rash
  - Nephrotoxicity
  - Tend to be mild and reversible
  - Dizziness, problems with balance, tinnitus
  - Can be permanent
  - Nephrotoxicity
  - Tend to be mild and reversible

First Line Agents (cont.)
Pyrazinamide
- Mechanism unknown
- PO only
- Metabolized in the liver, but metabolites are renally excreted
- Toxicities
  - ↑↑ ↑↑ Serum transaminases (AST, ALT)
  - Nausea/vomiting
  - Hyperuricemia

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

Streptomycin
- Inhibits protein synthesis (aminoglycoside)
- Bactericidal
- Poor activity in acidic environment of closed foci
- Not good sterilizing drug
- IM/IV
- Renal excretion
- Toxicities
  - Nephrotoxicity
  - Uric acid (active metabolite)
  - Cross resistance among rifamycins
  - Poor activity in acidic environment of closed foci
  - Cross resistance among rifamycins
  - Nephrotoxicity
  - Tend to be mild and reversible
  - Can be permanent

Second Line Agents

Rifabutin
- Often used as an alternative to rifampin
- PO only
- Toxicities
  - Uveitis (ocular pain, blurred vision)

Quinolones
- Levofloxacin, moxifloxacin, gatifloxacin
- Bactericidal against extracellular organisms and achieve good intracellular concentrations
- IV/PO
- Urea
- IV alternative
- Well tolerated option
- Toxicities
  - Headache, insomnia, restlessness

Quinolones
- Levofloxacin, moxifloxacin, gatifloxacin
- Bactericidal against extracellular organisms and achieve good intracellular concentrations
- IV/PO
- Urea
- IV alternative
- Well tolerated option
- Toxicities
  - Headache, insomnia, restlessness
**Second Line Agents**

- **Para-aminosalicylic acid (PAS)**
  - Synthetic structural analog of aminobenzoic acid
  - Bacteriostatic for extracellular organisms only
  - Uses: MDR-TB
  - Toxicities: GI (N/V/D), Hypothyroidism

- **Capreomycin**
  - Uses: MDR-TB, IV
  - Cross-resistance with aminoglycosides
  - Toxicities: Injection pain, Hearing loss, tinnitus, Renal dysfunction

- **Amikacin, kanamycin**
  - Aminoglycosides
  - Cross-resistance with streptomycin
  - Uses: MDR-TB (bacteriostatic), PO only
  - Toxicities: Renal toxicity, Hearing loss, tinnitus

- **Para-aminosalicylic acid (PAS)**
  - Synthetic structural analog of aminobenzoic acid
  - Bacteriostatic for extracellular organisms only
  - Uses: MDR-TB (bacteriostatic), PO only
  - Toxicities (can be severe): GI (N/V/D), Hypothyroidism

**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 regimens
  - 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)

**QUESTIONS?**

- **Cycloserine**
  - Uses: MDR-TB, bacteriostatic for both intracellular and extracellular organisms
  - PO only
  - Toxicities: Central nervous system effects (confusion, irritability, somnolence, headache, vertigo, seizures), Peripheral neuropathy

- **Ethionamide**
  - Uses: MDR-TB (bacteriostatic)
  - Bacteriostatic for extracellular organisms only
  - PO only
  - Toxicities: Nausea/vomiting, Peripheral neuropathy, Psychiatric disturbances, ↑↑ liver enzymes, ↑↑ glucose, Goiter with or without hypothyroidism, Gynecomastia, impotence, menstrual irregularities