Antifungals and Anti-Tuberculosis Agents

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Review of our Fungal "Players"

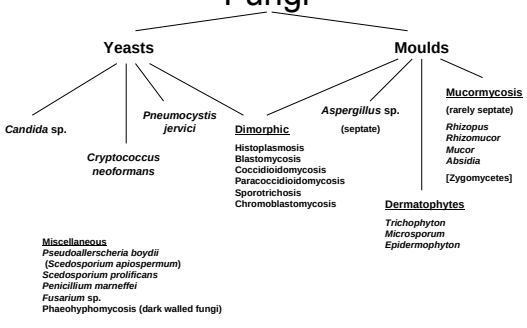
- **Opportunistic fungi**
  - Normal flora
    - *Candida* spp.
  - Ubiquitous in our environment
    - *Aspergillus* spp.
    - *Cryptococcus* spp.
    - *Mucor* spp.
- **Endemic geographically restricted**
  - *Blastomyces* sp.
  - *Coccidioides* sp.
  - *Histoplasma* sp.
- **Newly emerging fungi**
  - *Fusarium*
  - *Scedosporidium*
  - *Trichosporin*

Antifungal Agents

Risk Factors for Fungal Disease

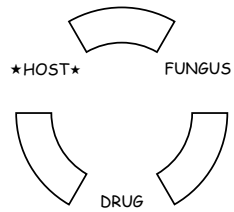
- **Candidiasis**
  - Antibiotics
  - Indwelling catheters
  - Hyperalimentation
  - Multiple abdominal surgeries
  - Prosthetic material
  - Severe burns
  - Neoplastic diseases/chemotherapy
  - Immunosuppressive therapy
  - Diabetes mellitus
  - Extremes of age
- **Aspergillosis**
  - Granulocytopenia (↓ neutrophil numbers or function)
  - T-cell dysfunction
    - hematologic and other malignancies
    - organ allograft recipients
    - immunosuppressive therapy
  - Corticosteroids
  - Chronic granulomatous disease
  - AIDS
  - Burn patients

Fungi

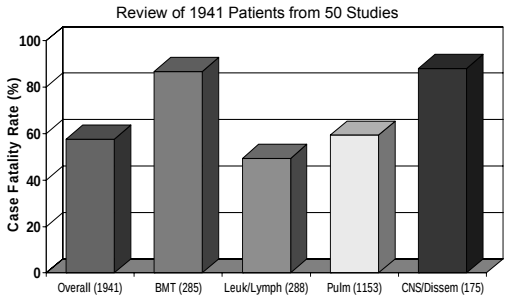


An optimal antifungal drug has...

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

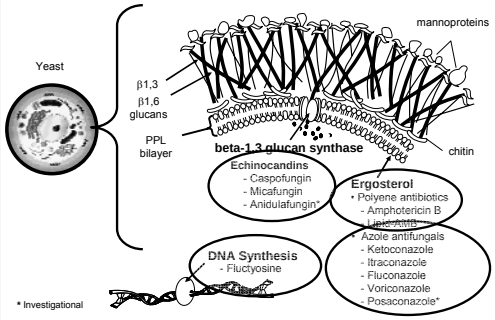


Invasive Aspergillosis Mortality



Lin S-J et al, *Clin Infect Dis* 2001; 32:358-66

Targets of Antifungal Agents

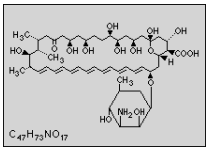


Systemic Antifungal Agents
By Mechanism of Action

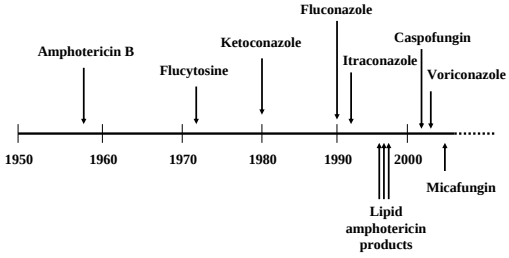
- **Membrane disrupting agents**
  - Amphotericin B
- **Ergosterol synthesis inhibitors**
  - Azoles
- **Nucleic acid inhibitor**
  - Flucytosine
- **Glucan synthesis inhibitors**
  - Echinocandins

Amphotericin B

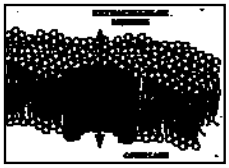
- **A polyene**
- **Clinical use since 1960**
- **Insoluble in water**
  - Solubilized by sodium deoxycholate
- **Most broad spectrum antifungal**
  - "gold standard"
- **Pharmacokinetics**
  - Extensively tissue bound
    - Highest concentrations in liver, spleen, bone marrow with less in kidneys and lung
  - Half-life
    - Tissue ~15 days, Plasma ~5 days

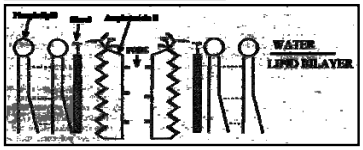


The Promise of a Dynamic Era…



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

Clin Microbiol Rev 1999; 12: 501.

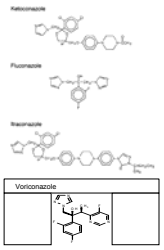
Amphotericin B

Most broad spectrum antifungal – long considered the "gold standard"

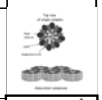
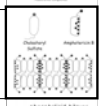
- **Clinical activity**
  - *Candida* sp.
    - *C. lusitaniae* often resistant
  - *Cryptococcus neoformans*
  - Blastomycosis
  - Histoplasmosis
  - *Aspergillus* sp.
  - Zygomycetes
    - *Rhizopus* sp., *Mucor* sp., etc.
- **Little to no activity**
  - *Aspergillus terreus*, *Aspergillus nidulans*, *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

Azole Antifungals

- **Imidazoles**
  - Ketoconazole
- **Triazoles**
  - Itraconazole
  - Fluconazole
  - Voriconazole
- **Mechanism of action**
  - Inhibit ergosterol synthesis through inhibition of CYP450-dependent lanosterol 14-α-demethylase
    - Depletion of ergosterol on fungal cell membrane
- **Resistance**
  - ERG 11 mutations (gene encoding 14-α sterol demethylase) leading to overexpression
  - ↑ azole efflux
  - ↑ production or alteration 14-α-demethylase



Available Lipid-Based Amphotericin B Agents

Product	Chemical Structure	
Lipid Complex ABLC; Abelcet®	**Flattened, ribbon-like complex.** **Molecular ratio (drug:lipid) = 3:7** **Particle size = 1,600 – 11,000 nm.**	
Colloidal Dispersion ABCD; Amphocil® or 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

	Fluconazole	Itraconazole	Voriconazole	Flucytosine	Ampho B	Echinocandins
C. albicans	S	S	S	S	S	S
C. tropicalis	S	S	S	S	S	S
C. parapsilosis	S	S	S	S	S	S to R (?)
C. glabrata	S-DD to R	S-DD to R	S to I	S	S to I	S
C. krusei	R	S-DD to R	S to I	I to R	S to I	S
C. lusitaniae	S	S	S	S	S to R	S

Pappas et al. CID 2004; 38: 161-89.

Lipid Amphotericin B Product Comparison

Factor	Amphotericin B deoxycholate	Amphotericin B colloidal dispersion (ABCD, Amphotec®)	Amphotericin B lipid complex (ABLC, Abelcet®)	Liposomal amphotericin B (Ambisome)
Particle				
Size (nm)				
Infusion related toxicity				
Nephrotoxicity				
Serum concentrations compared to conventional amphotericin				
Tissue concentrations compared to conventional amphotericin				
Dosage				

Azole Antifungals Spectrum of Activity

Organism	Ketoconazole	Fluconazole	Itraconazole	Voriconazole
Yeast				
C. albicans	++	++++	+++	++++
Resistant yeasts	+	++	++	+++
Other yeasts	+	+++	+++	+++
Cryptococcus	++	++++	+++	++++
Moulds				
Aspergillus	0	0	+++	++++
Other moulds	0	0	+	+++
Zygomycetes	0	0	0	0
Endemic fungi	++	+++	++++	+++

Fluconazole

- **Favorable pharmacokinetic and toxicity profile**
  - Low mw and high water solubility → rapid absorption and ↑ bioavailability
    - >90% bioavailability (IV and PO interchangeable)
  - No dependence on low gastric pH
  - Effectively penetrates CSF (50-90% plasma levels)
    - Brain and eye too!
  - >90% renal excretion
- **Adverse effects**
  - Very well tolerated
    - Even up to 1600 mg/day
  - GI, reversible transaminase elevations
- **Dose**
  - 100-800 mg/d (max 1600 mg/d)
    - 6 mg/kg/d for susceptible strains (400 mg/d)
    - 12 mg/kg/d for S-DD strains (800 mg/d)
  - IV and oral interchangeable (>90% bioavailability)

Voriconazole

Precautions (AND LIMITATIONS?)

- **Adverse effects**
  - Transient, dose related visual disturbances (30%)
    - Mechanism unknown – ↓ electrical currents in retina
  - Elevated liver function tests (~13%)
    - May be dose-related
  - Skin reactions (6%)
- **Dosing**
  - Intravenous
    - 6 mg/kg IV q12h x 2 doses, then 4 mg/kg IV q12h
  - Oral (>95% bioavailability on empty stomach)
    - <40 kg – 100 mg PO q12h
    - ≥40 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
  - Hepatic disease
    - Maintenance dose should be halved in patients with mild/moderate liver disease

Itraconazole

LIMITATIONS

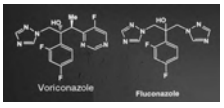
- **Pharmacokinetics**
  - Only ionized at low pH → wide interpatient variability in plasma concentrations
  - Nonlinear serum PK
  - Extensively liver metabolized
- **Adverse effects**
  - Transient GI upset, dizziness, headache
  - Hepatotoxicity (~5%)
  - Negative inotrope
- **Drug Interactions**
  - Propensity and extent greater than fluconazole
  - Substrate of CYP3A4 and inhibitor of CYP3A4
    - Rifampin, phenytoin, phenobarbital
    - CYA
- **IV itraconazole**
  - Formulated in hydroxypropyl-β-cyclodextrin
  - Increases solubility of itraconazole
  - Renal dysfunction
    - A 6-fold ↓ cyclodextrin clearance in pts with CrCL<20 ml/min (therefore not recommended in pts with CrCL<30 ml/min)
- **Spectrum**
  - Paracoccidiodomycosis, blastomycosis, histoplasmosis and sporotrichosis, cutaneous and mucosal candidiasis, Aspergillosis
- **Dosing**
  - 200 mg IV q12h x 4 doses, then 200 mg IV q24h followed by 200 mg PO q12h oral solution
    - Target troughs >0.5 mcg/mL

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* sp. and other molds

Voriconazole

- **Second generation synthetic derivative of fluconazole**
  - Addition of methyl group to the propyl backbone
  - Substitution of triazole moiety with a fluropyrimidine group

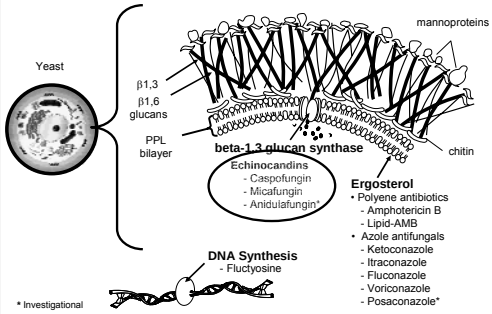


- **Active against yeast and moulds**
  - Fungicidal in vitro against *Aspergillus spp., Scedosporium spp., Fusarium spp.*
  - Fungistatic in vitro against *Candida spp.*
- **Indications**
  - Invasive aspergillosis
  - Esophageal candidiasis
  - Fungal infections caused by *Scedosporium apiospermum* and *Fusarium spp.* in patients intolerant of or refractory to other therapy

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)
  - GI (nausea/vomiting/diarrhea)
- **Clinical uses**
  - Cryptococcal meningitis, hepatosplenic candidiasis, Candida endophthalmitis
  - Used in combination ONLY (usually with amphotericin)
    - Minimizes development of resistance
    - Amphotericin potentiates uptake

Targets of Antifungal Agents



* Investigational

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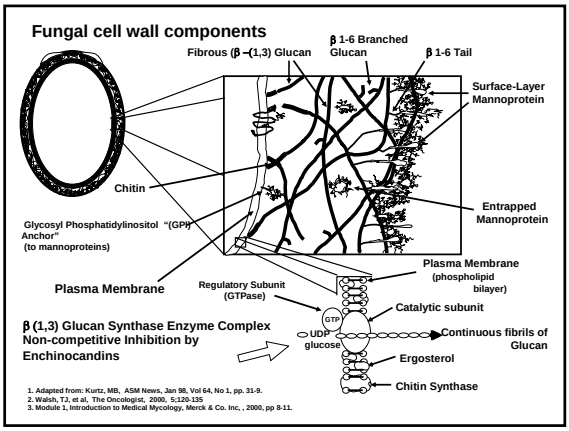
C. parapsilosis	S	S	S	S	S	S to R (?)
C. glabrata	S-DD to R	S-DD to R	S to I	S	S to I	S
C. krusei	R	S-DD to R	S to I	I to R	S to I	S
C. lusitaniae	S	S	S	S	S to R	S

Pappas et al. CID 2004; 38: 161-89.



1. Adapted from: Kurtz, MB, ASM News, Jan 98, Vol 64, No 1, pp. 31-9.
2. Walsh, TJ, et al, The Oncologist, 2000, 5;120-135
3. Module 1, Introduction to Medical Mycology, Merck & Co. Inc, , 2000, pp 8-11.

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%)
    - erythema(1.2-1.5%)
    - rash (0-4.6%)
  - 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	Very Active	Some Activity
C. albicans *C. glabrata* *C. tropicalis* *C. krusei* *C. kefyr* *P. carinii**	***C. parapsilosis*** ***C. gulliermondii*** ***A. fumigatus*** ***A. flavus*** ***A. terreus*** ***C. lusitaniae***	***C. immitis*** ***B. dermatididis*** ***Scedosporium species*** ***P. variotii*** ***H. capsulatum***
Very low MIC, with <u>fungicidal</u> activity and good in-vivo activity. ***only active against cyst forms, and probably only useful for prophylaxis**	Low MIC, but <u>without fungicidal activity</u> in most instances.	Detectable activity, which might have therapeutic potential for man (in some cases in combination with other drugs).

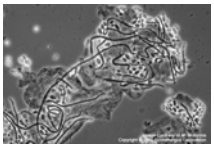
Denning DW, Lancet 2003 (Oct 4);1142-51.

How to Choose?

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

Treament of *Candida* sp. Infections

- **Unknown *Candida* sp.**
  - Fluconazole
    - Normal or high dose
  - Voriconazole
  - Echinocandins
  - Amphotericin B product



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

- **Known *Candida* sp.**
  - Based on species and susceptibility results
  - Comorbid conditions/toxicities

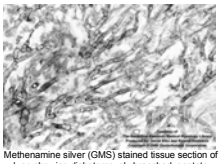
Combination Antifungal Therapy

- **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

Cuenca-Estrella M. JAC 2004; 54: 854-69.
Mukherjee PK et al. Clin Micro Reviews 2005; 18: 163-94.
Marr K. Oncology 2004; 18: S24-29.

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*.

Medical Letter 2002;44:63-65

Drug	Dosage	AWP Cost/Dose
Polyenes		
Amphotericin B deoxycholate	**1-1.5 mg/kg/day IV**	**$17 - $23**
Lipo-AMB (AmBisome)	**3-5 mg/kg/day IV**	**$790 - $1316**
ABLC (Abelcet)	**5 mg/kg/day IV**	**$825**
ABCD (Amphotec)	**3-4 mg/kg/day IV**	**$336 - $448**
Triazoles		
Fluconazole	**400 - 800 mg IV**	**$133 - $266**
	200 - 800 mg PO	**$14 - $56**
Itraconazole	**200 mg IV**	**$194**
	200 mg PO	**$14 - $17**
Voriconazole	**6 mg/kg IV**	**$226**
	4 mg/kg IV	**$148**
	200 mg PO	**$32**
Echinocandins		
Caspofungin	**70 mg IV**	**$460**
	50 mg IV	**$355**
Micafungin	**150 mg IV**	**$310**

Combination Antifungal Therapy

- **Fungi more difficulty 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**

Anti-Tuberculosis Agents

Anti-Tuberculosis Agents

- **First-line Drugs**
  - Rifampin
  - Isoniazid
  - Pyrazinamide
  - Ethambutol
  - Streptomycin
- **Second-line Drugs**
  - Rifabutin
  - Quinolones
  - Capreomycin
  - Amikacin, kanamycin
  - Para-aminosalicylic acid (PAS)
  - Cycloserine
  - Ethionamide

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

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 (cont.)

	Early bactericidal activity	Sterilizing activity	Prevent emergence of resistance
Rifampin	√	√√	√√
Isoniazid	√√	√	√√
Pyrazinamide	x	√√	x
Ethambutol	√	x	√
Streptomycin	x	x	√

- **Toxicities**
  - Hepatoxicity
    - 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. TIW
  - PO vs. IV vs. IM

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 10^8 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^{13} (INH rate of 10^6 + RIF rate of 10^7)

First-Line Agents

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
  - >80% Asian patients are rapid acetylators
  - Drug interactions more likely in slow acetylators
- **Toxicities**
  - ↑ serum transaminases (AST, ALT)
    - Slow acetylators may be at increased risk
  - 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)

Second-Line Agents

First Line Agents (cont.)

- **Pyrazinamide**
  - Mechanism unknown
    - Fatty acid synthetase-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

- **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

- **Capreomycin**
  - Uses
    - MDR-TB
    - IM/IV
    - Cross-resistance with aminoglycosides
  - Toxicities
    - Injection pain
    - Hearing loss, tinnitus
    - Renal dysfunction
- **Amikacin, kanamycin**
  - Aminoglycosides
    - Cross-resistance with streptomycin
  - Uses
    - MDR-TB
    - IV/IM alternative
  - Toxicities
    - Renal toxicity
    - Hearing loss, tinnitus
- **Para-amino salicylic 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)
    - Hepatotoxicity
      - Mortality reported ~21%
    - Hypothyroidism

QUESTIONS?

Second Line Agents

- **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

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)