Antimycobacterial Agents

Mycobacterial Infections

1.) *Mycobacterium tuberculosis* - tuberculosis (TB)
   a.) leading cause of death worldwide from a single infectious organism
   b.) 1/3 of the world's population harbors *M. tuberculosis*. 15 million Americans infected.
   c.) TB has decreased in U.S. since 1992. 26,283 cases in 1991.
   d.) Multi-drug resistant TB reported in 36 states

2.) Atypical Mycobacterial infections - *M. avium* complex & *M. intracellulare*

3.) *Mycobacterium leprae* - leprosy

**TABLE 42. SUMMARY TABLE OF ANTIYCOBACTERIAL DRUGS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Activity</th>
<th>Route</th>
<th>Pediatric Daily Dose (mg/kg)</th>
<th>Adult Daily Dose (mg/kg)</th>
<th>Usual Adult Daily Dose</th>
<th>Max. Daily Dose</th>
<th>Major Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>bactericidal</td>
<td>oral</td>
<td>10-20</td>
<td>5-10 or 15 mg/kg 2x per wk</td>
<td>300 mg</td>
<td>300 mg or 900 mg 2x per wk</td>
<td>Hepatic Neurologic</td>
</tr>
<tr>
<td>Rifampin</td>
<td>bactericidal</td>
<td>oral</td>
<td>10-20</td>
<td>10 q.d. or 10 mg/kg 2x per wk</td>
<td>600 mg</td>
<td>600 mg</td>
<td>Hepatic Hematologic flu-like symp</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>static</td>
<td>oral</td>
<td>15-25</td>
<td>15-25 or 50 mg/kg 2x per wk</td>
<td>800-1600 mg</td>
<td>2.5 g</td>
<td>Optic neuritis</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>bactericidal</td>
<td>oral</td>
<td>15-30</td>
<td>15-30 or 50-70 2x per wk</td>
<td>1-2 g</td>
<td>2g</td>
<td>Hepatic Hyperuricemia</td>
</tr>
<tr>
<td><strong>Secondary Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>bactericidal</td>
<td>IM</td>
<td>20-40</td>
<td>7-15</td>
<td>0.75-1 g</td>
<td>1 g</td>
<td>Renal, 8th cranial nerve</td>
</tr>
<tr>
<td>p-amino-salicylate</td>
<td>Static</td>
<td>oral</td>
<td>150-200</td>
<td>200 q 6 h</td>
<td>12-16 g</td>
<td>12 g</td>
<td>GI upset</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Static</td>
<td>oral</td>
<td>15-20</td>
<td>7-15</td>
<td>0.75-1 g</td>
<td>1 g</td>
<td>GI upset</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Static</td>
<td>oral</td>
<td>10-20</td>
<td>10-15 q 6 h</td>
<td>0.75-1 g</td>
<td>1 g</td>
<td>Psychoses Seizures</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>bactericidal</td>
<td>IM</td>
<td>15</td>
<td>15 q day</td>
<td>1 g</td>
<td>1 g</td>
<td>Renal, 8th cranial nerve</td>
</tr>
<tr>
<td>Amikacin</td>
<td>bactericidal</td>
<td>IM</td>
<td>7.5-15</td>
<td>15</td>
<td>0.5-1 g</td>
<td>1 g</td>
<td>Renal, 8th cranial nerve</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>bactericidal</td>
<td>oral</td>
<td>not recom.</td>
<td>500-750 mg b.i.d.</td>
<td>1-1.5 g</td>
<td>2 g</td>
<td>Nausea</td>
</tr>
<tr>
<td>Clofazamine</td>
<td>bactericidal</td>
<td>oral</td>
<td>not recom.</td>
<td>100-200 mg per day</td>
<td>100 mg</td>
<td>200 mg</td>
<td>Nausea, Skin pigmentation</td>
</tr>
</tbody>
</table>

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Current Treatment Regimen for Tuberculosis

Isoniazid + Rifampin (+ Ethambutol) + Pyrazinamide for first 2-6 months. Continue with Isoniazid + Rifampin (+ Ethambutol) for additional 6-12 months.

Isoniazid

I. STRUCTURE and MECHANISM OF ACTION

Isoniazid (isonicotinic acid hydrazide, INH) - first synthesized in 1912. Demonstrated effectiveness vs. TB in 1952. Cidal vs. growing organisms, static against "resting" organisms. Several mechanisms postulated. Inhibits synthesis of mycolic acid, a component of mycobacterial cell walls. Appears to require catalase (encoded by \textit{katG} gene) for activity – which converts isoniazid into an active metabolite intracellularly.

II. ANTIMICROBIAL ACTIVITY AND RESISTANCE

a.) MIC 0.025-0.05 µg/ml
b.) If used alone, 71% of cases treated for 3 months will become resistant.
c.) Resistance is by two primary mechanisms:
   i. \textit{inhA} gene is mutated. \textit{InhA} protein is involved in mycolic acid biosynthesis
   ii. \textit{katG} gene is deleted or mutated - encodes for catalase/peroxidase enzyme. Loss of catalase activity is associated with resistance (accounts for 10-25% of strains in NYC)

III. DISPOSITION, METABOLISM, AND EXCRETION

a.) well absorbed and distributed. CSF levels ~20% of serum levels.
b.) Metabolism is primarily through N-acetylation. Polymorphic distribution -genetically controlled. Slow acetylators - 58% of caucasians, 10-15% of orientals, 5% Canadian Aleuts, 83% Egyptians.
c.) 6 hours after dosing - >0.8 µg/ml in slow acetylators, <0.2 µg/ml in rapid acetylators.
d.) excreted as metabolites in urine. No need to adjust dose in renal failure.

IV. ADVERSE EFFECTS

a.) Hepatotoxicity - increases with age, Serious in 2.3% of patients > 50. 10-20% show ↑ in SGOT. More likely to occur in alcoholics.
b.) Neurotoxicity - 17% have peripheral neuropathy receiving doses of 6 mg/kg/day. More frequent in slow acetylators. Pyridoxine is helpful. Also may cause memory loss, Psychosis, or seizures.
c.) Hypersensitivity - lupus, positive ANA test.
V. PRODUCTS and DRUG INTERACTIONS

Isoniazid - 50 mg, 100 mg, and 300 mg tablets; Syrup - 50 mg/ml; Injection 100 mg/ml

Isoniazid (150 mg) + Rifampin (300 mg) - Rifamate® (Marion Merrell Dow)

Isoniazid (50 mg) + Rifampin (120 mg) + Pyrazinamide (300 mg) - Rifater® (MMD)

Take on empty stomach. Minimize alcohol consumption. Avoid tuna, tyramine-containing food. Compliance must be stressed for any antituberculosis drug!

Drug Interactions

Benzodiazepines - ↑ serum levels
Carbamazepine - ↑ isoniazid hepatotoxicity
Cycloserine - ↑ CNS side effect - dizziness
Phenytoin - ↑ serum levels - ataxia, nystagmus -- esp. in slow acetylators
Ketoconazole - Ø serum levels
Rifampin - ↑ hepatotoxicity

Rifampin, Rifabutin, and Rifapentine

![Rifampin molecule]

Rifampin

I. HISTORY and MECHANISM OF ACTION

• Rifampin is a semi-synthetic derivative of a the macrocyclic antibiotic, rifamycin B, that is produced in Streptomyces mediterranei. Introduced in 1967. Rifampin is bactericidal at 0.005-0.2 µg/ml vs. M. tuberculosis.
• Rifabutin is a semisynthetic derivative (ansamycin) of rifamycin S. Rifabutin has improved activity vs. M. avium complex, approved in Dec. 1992.
• Rifapentine, a long-duration, once-weekly agent was approved in June, 1998.
• Rifamycins inhibit bacillary DNA-dependent RNA polymerase.
• Resistance in bacteria is through altered RNA polymerase. In resistant mycobacteria, drug permeability also appears to be affected.
II. USES

a.) tuberculosis (in combination) and leprosy (in combination with dapsone)

b.) alternative agent for *Staph.* in combination with aminoglycosides - including MRSA

c.) treatment of asymptomatic carriers of *Neisseria meningitidis*

d.) alternative agent for *Legionella* not responsive to macrolides

e.) *M. avium* and *M. intracellulare* infections in AIDS - Rifabutin is used for prophylaxis

III. DISPOSITION, METABOLISM, AND EXCRETION

- Well absorbed. Highly lipophilic. Peak serum levels 4-32 µg/ml (mean = 7 µg/ml). Rifabutin bioavailability =20% in AIDS, 53% absorbed.

- CSF concn. is 12-25% of serum concn. (↑ when meninges are inflamed). 80% protein bound.

- Rifampin is rapidly metabolized by deacetylation to active metabolite. 40% excreted in bile - extensive EHC. t1/2 is 3 hrs for 600 mg dose, 5.1 hrs for 900 mg dose. Auto-inducer. After repeated administration half-life is 2-3 hrs. Rifabutin t1/2 = 45 h (16-69 h). Rifapentine is a new rifamycin with an even longer half-life. Dosing is once weekly.

- 6-30% excreted unchanged in urine, 30-60% excreted as desacetyl rifampin. Excreted in breast milk. Milk/plasma ratio is 0.2-0.6. Rifabutin and rifapentine excreted in bile and feces as metabolites.

IV. ADVERSE EFFECTS

a.) Hepatotoxicity. Fatalities due to jaundice have occurred. Monitor liver function q 2-4 wks. Toxicity exacerbated with isoniazid (~35% of patients). Hyperbilirubinemia.


c.) Febrile "flu-like" syndrome, Rash (1-5%).

d.) May turn urine, tears, and other body fluids reddish-orange.

e.) Other rxns. - leukopenia, thrombocytopenia, GI upset, shortness of breath, shock

V. PRODUCTS AND DRUG INTERACTIONS

**Rifampin** - Rifadin® (Aventis)- 150 and 300 mg capsules.
Powder for injection - 600 mg

Take on empty stomach. Food interferes with absorption. Avoid alcohol. **Compliance!**

**Rifabutin** - Mycobutin® (Adria) - 150 mg capsules

If *M. tuberculosis* is also suspected, do not give rifabutin alone. Resistance will rapidly result and there will be cross-resistance to rifampin. Give with isoniazid (+ other drugs) in this case.

**Rifapentine** – Priftin® (Aventis) – 150 mg tablets. Take twice weekly first 2 months, then once weekly after 2 months.
Drug Interactions

Rifampin is a potent inducer of cytochrome P450, esp. CYP3A4, CYP2C9, and CYP2C19. Mechanism by activation of PXR (Pregnane X receptor). Drugs that are metabolized by oxidative metabolism will have an increased clearance and a reduced effect. Some of the drugs where this interaction is most critical are listed below:

- Oral contraceptives
- Cyclosporin
- HIV Protease inhibitors (indinavir, saquinavir, nelfinavir, ritonavir, amprenavir)
- Ketoconazole, Itraconazole
- Phenytoin
- Sulfonylureas
- Statins (e.g. atorvastatin, simvastatin, fluvastatin)
- Tacrolimus
- Theophylline
- Verapamil
- Warfarin

Other drug interactions:

- Enalapril - significant ↑ in blood pressure has been observed.
- Zidovudine - Rifabutin decreased zidovudine AUC by 32%, Cmax by 48%

**Note:** In HIV patients taking protease inhibitors, rifabutin is the preferred agent to replace rifampin because it is a less potent inducer of CYP3A4. Still may need to increase dose of protease inhibitors. Rifapentine appears to be intermediate between rifampin and rifabutin with regard to drug metabolizing enzyme-inducing capability and is not suggested for HIV + patients (not well studied though).

**Ethambutol**

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \text{C}_2\text{H}_5 \\
\text{H} - \text{C} - \text{NH} - \text{CH}_2\text{CH}_2\text{NH} - \text{C} - \text{H} & \quad \text{C}_2\text{H}_5 \\
& \quad \text{CH}_2\text{OH}
\end{align*}
\]

**I. HISTORY and MECHANISM OF ACTION**

- Synthesized at Lederle in 1961.
- It is only active against Mycobacteria.
- Exact mechanism is unknown. Appears to inhibit the transfer of mycolic acids into the cell wall. Also interferes with spermidine synthesis.

**II. USES**

a.) Alternative to INH or Rifampin. Many physicians now include this in primary therapy.

b.) Has activity versus *M. kansasi* and *M. avium-intracellulare*. Used in combinations.
III. ABSORPTION, DISTRIBUTION, AND EXCRETION

Appears to be well absorbed (75-80%). After single oral dose of 15-25 mg/kg, peak concns are 2-5 \( \mu g/ml \). CSF concns. are 10-50% of serum levels. 40% protein bound.

50% excreted unchanged in urine, 8-15% as metabolites in urine, 20-25% in feces.

IV. ADVERSE EFFECTS

a.) Visual effects (retrobulbar neuritis) - blurred vision, colorblindness, blind spots. Check vision regularly. Effects may be reversible if discontinued promptly.

b.) Peripheral neuropathy - rare, some CNS problems

c.) not teratogenic - OK to use in pregnancy.

V. PRODUCTS

Myambutol® (Lederle) 100 and 400 mg tablets

Take with food. Notify physician if changes in vision occur. Have monthly eye tests.

Initial treatment - 15 mg/kg (7 mg/lb.) as single dose q 24 hours with other agents.

Retreatment - 25 mg/kg (11 mg/lb.) q 24 hrs. After 60 days, reduce dose to 15 mg/kg. Give concurrently with at least one other drug that has been shown to be susceptible.

Aluminum antacids may reduce absorption. Compliance!

Pyrazinamide

I. HISTORY and STRUCTURAL CHARACTERISTICS

• Synthesized in 1952. Pyrazinamide (PZA) is the pyrazine analog of nicotinamide.

• Converted to active form, pyrazinoic acid, intracellularly by pyrazinamidase encoded by \( pncA \) gene.

• Highly active, it is useful in short term therapy because pyrazinoic acid kills a population of semidormant tubercle bacilli in an acidic environment (inside macrophages). Accumulation of pyrazinoic acid requires acidic pH.

• May be bacteriostatic or bacteriocidal depending upon concn.

• Resistance occurs due to mutations in \( pncA \).

II. ABSORPTION, DISTRIBUTION, AND EXCRETION

– well absorbed. Peak concns. reached in 2 hrs, typically 30-50 \( \mu g/ml \).

– widely distributed, penetrates CSF in presence of inflammation.

– serum half-life is 10-16 hours. Metabolized by hydrolysis and oxidative metabolism. Major metabolite (5-hydroxyprazinoid acid) eliminated by filtration.
III. ADVERSE EFFECTS

a.) Hepatotoxicity - Determine baseline ALT or AST and at 2-4 week intervals. Usually reversible. Caution in patients with preexistent liver disease (cirrhosis).

b.) Hyperuricemia - may precipitate gouty arthritis. Increase uric acid levels.

c.) Other rxns - fever, loss of appetite, malaise, nausea and vomiting, pain in joints

IV. PRODUCTS and PATIENT INFORMATION

Pyrazinamide (Lederle) - 500 mg tablets
Pyrazinamide (300 mg) + INH (50 mg) + Rifampin (120 mg) - Rifater® (Aventis)

Watch for yellow discoloration of skin or eyes. Fatigue or malaise. Compliance!

Dapsone

I. STRUCTURAL Characteristics

Dapsone (4,4-diaminodiphenylsulphone) is a sulphone that is bactericidal as well as bacteriostatic against M. leprae, the causative agent of leprosy. Dapsone appears to inhibit PABA biosynthesis or the incorporation of PABA into folate.

II. USES

a.) all forms of leprosy (Hansen's disease) & dermatitis herpetiformis

b.) Alternative agent in the treatment of Pneumocystis carinii pneumonia in AIDS in combination with trimethoprim. Especially useful in patients unable to take sulfas.

c.) Prophylaxis of malaria

d.) Treatment of relapsing polychondritis

III. Absorption, DISTRIBUTION, AND EXCRETION

- rapidly and completely absorbed. Steady state concentrations are 0.1-7.3 µg/ml (mean - 2.3 µg/ml)

- plasma half-life is 10-50 hrs (mean = 28 hr). 70-90% bound.

- main metabolite is monoacetyldapsone (polymorphic - slow and fast acetylators). 70-85% of drug is excreted as conjugates. A hydroxylamine metabolite, produced by cyt. P450IIIA has been implicated in toxicity. Significant EHC prolongs elimination.

IV. ADVERSE EFFECTS

a.) Anemia - Deaths have been reported from agranulocytosis, aplastic anemia. Common and severe in patients with G6PD deficiency. Methemoglobinemia is common side effect due to hydroxylamine metabolite.

b.) Hypersensitivity - rash, exfoliative dermatitis. Should discontinue promptly.
V. DRUG INTERACTIONS

- Folic acid antagonists (Pyrimethamine) may increase likelihood of hematologic problems.
- Rifampin lowers dapsone levels 7-10 fold. Induction of CYP3A4.
- Probenicid reduces urinary excretion, increases concentrations in plasma
- Didanosine (DDI) may reduce the absorption of dapsone.

VI. PRODUCTS

Dapsone (Jacobus) - 25 and 100 mg tablets

*Leptospira* 50-100 mg daily in adults. WHO recommends that therapy be continued for at least 10 years after the patient is bacteriologically negative.

*Dermatitis herpetiformis* - individualize dosage. Start with 50 mg daily in adults. If full control is not reached at doses of 50-300 mg daily, higher doses may be tried. Reduce dosage to a minimum maintenance level as soon as possible. In responsive patients there is a prompt reduction in pruritis.

*P. carinii* pneumonia - 100 mg dapsone q.d. for 21 days + 5 mg/kg trimethoprim q 6 h for 21 days. Prophylaxis regimen - 25-50 mg q.d. or 100 mg 2x per week.

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**Clofazamine**

I. STRUCTURE and MECHANISM OF ACTION

- Clofazamine is a phenazine dye. Preferentially distributes into the skin.
- Precise mechanism of action is unknown, but the drug is bactericidal and appears to bind preferentially to mycobacterial DNA. Typical MICs are 0.1-1 µg/ml.
- It also appears to have anti-inflammatory properties which is useful in controlling some symptoms of leprosy.

II. USES

- *Mycobacterium avium* complex (in combination with clarithromycin and ciprofloxacin)
- alternative to dapsone for *Mycobacterium leprae* (leprosy). Useful in dapsone resistance.

III. ABSORPTION, DISTRIBUTION, AND METABOLISM

- fairly well absorbed (45-62%). Typical blood levels of 0.4-1 µg/ml.
- Extensive tissue binding especially in liver, spleen, fat, and in skin. Concentrated in macrophages.
- extremely long half-life (70 days). <1% excreted in urine. Largely unmetabolized with extensive biliary excretion.
IV. ADVERSE EFFECTS

a.) GI effects - usually mild, but in some patients may be severe. Rare reports of bowel obstruction (<1%) due to crystalline deposits of drugs. Lower dosage if patient complains of burning abdominal pain.

b.) Skin pigmentation - crystalline deposits may be formed in any fatty tissue. As drug accumulates, may result in red-brown to black skin discoloration (75-100% after a few weeks of treatment). Dry skin (8-28%).

c.) Crosses placenta, excreted in breast milk

IV. PRODUCTS AND DOSING

Lamprene® (Novartis) - 50 mg and 100 mg capsules.

Dapsone-resistant leprosy - give 100 mg/day with one or more other drugs for 3 years (rifampin, ethionamide), followed by clofazamine alone. Usually observe improvement after 1-3 months.