No Financial Disclosures
Learning Objectives

1. Describe the common adverse reactions to TB medications
2. Explain how to manage adverse reactions to TB medications
Laboratory Monitoring - 1

Baseline liver function tests (e.g., AST, ALT, and bilirubin) are not necessary except for patients with risk factors:

- HIV infection
- History of liver disease
- Regular alcohol use
- Pregnancy or in early postpartum period
Laboratory Monitoring - 2

Repeat laboratory monitoring if patient has:

- Abnormal baseline results
- Current or recent pregnancy
- High risk for adverse reactions
- Symptoms of adverse reaction
- Liver enlargement or tenderness during examination
Gastrointestinal upset

- Epigastric discomfort, nausea
- Management:
  - Antacids
  - Crackers
  - Proton pump inhibitors
- If vomiting as well:
  - Liver test evaluation
Rash

• Itchy - try antihistamine

• Petechial rash – possible sign of thrombocytopenia (suspect rifampin)

• Generalized rash – stop all drugs
  – Fever and mucous membranes involvement:
    • Stevens Johnson syndrome
    • Toxic epidermal necrolysis
    • Drug hypersensitivity syndrome
Management of generalized rash

• Rechallenge of TB drugs
  – Start every 2-3 days,
  – 1\textsuperscript{st} Rifampin
  – 2\textsuperscript{nd} isoniazid
  – 3\textsuperscript{rd} pyrazinamide or ethambutol
Drug Fever

• Stop drugs
• Once fever resolves,
  – Restart medications, one at a time every 2-3 days
Hepatotoxicity

• If bilirubin and alkaline phosphatase elevation
  - rifampin
• If primarily ALT, AST elevation,
• Sequential reintroduction one per week
  – 1st Rifampin
  – 2nd Isoniazid
  – 3rd pyrazinamide

# Specific Drug-Associated Liver Effects

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Effects on Liver</th>
</tr>
</thead>
</table>
| Isoniazid                 | Typically more hepatocellular (ALT/AST); usually fairly rapid reversibility if INH stopped at onset of symptoms  
  • Increased risk with other hepatic metab. Medications (e.g. Rifampin, PZA)                                                                                |
| Rifampin                  | Cholestatic picture more common (↑ Bili); ALT/AST may also be elevated (less common)                                                                                                                                  |
| Pyrazinamide              | Hepatoxicity not uncommon; can be severe are more prolonged / slower resolution                                                                                                                                 |
| Less common:              | Occasionally implicated with hepatotoxicity                                                                                                                                                                           |
|  • Ethionamide            |                                                                                                                                                                                                                   |
|  • Para-aminosalicylic acid |                                                                                                                                                                                                                 |
| Not commonly associated with hepatotoxicity | Consider using these drugs when TB therapy cannot be held in cases of hepatotoxicity (e.g. severe TB)  
  • Especially _early in therapy_ for disseminated, miliary or meningeal TB   |
Other causes of hepatoxicty

• Alcohol
• Biliary tract disease
• Other medications (e.g. acetaminophen)
• supplements
Hepatic disease

• If PZA not used
  – Treatment: 9 months INH, RIF, EMB

• If INH not used
  – Treatment: 6 months RIF, PZA, EMB

• If INH and PZA not used
  – RIF, EMB, FQ, injectable or cycloserine for 12-18 months
Optic neuritis

• Ethambutol
• 22.5 per 1000 persons (2.25%)
• Visual acuity and color discrimination testing
  – Check monthly
# Adverse Effects of First-line Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoniazid</td>
<td>hepatotoxicity, peripheral neuropathy, CNS effects, lupus-like syndrome, monoamine poisoning</td>
</tr>
<tr>
<td>rifampin</td>
<td>flu-like syndrome, hepatotoxicity, anemia, thrombocytopenia, renal failure, drug interactions</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>hepatotoxicity, polyarthritis, gout</td>
</tr>
<tr>
<td>ethambutol</td>
<td>impaired vision, peripheral neuropathy</td>
</tr>
</tbody>
</table>
Isoniazid

• Asymptomatic liver test elevation in 10-20%
• Hepatotoxicity
• Peripheral neuropathy
• Hypersensitivity syndrome
• Central nervous system
  – headaches, dysarthria, irritability, seizures, dysphoria, depression, and inability to concentrate
• Rare: fever, rash, Stevens-Johnson syndrome, hemolytic anemia, vasculitis, and neutropenia
• Diarrhea (due to sorbitol)
Rifamycins

- Orange discoloration of urine
- Hypersensitivity reactions
- Leukopenia, thrombocytopenia
- Liver toxicity – cholestasis: bilirubin and alkaline phosphatase elevation
- Pruritus, rash
- Nausea, abdominal pain, anorexia
- Thrombocytopenia, hemolytic anemia, acute renal failure, and thrombotic thrombocytopenic purpura
Orange urine from rifampin
rifabutin

- Neutropenia, thrombocytopenia
- Hepatoxicity
- Uveitis
- Polyarthralgia
- Pseudojaundice
- GI side effects
- Orange discoloration of urine
- Flu like syndrome
Pyrazinamide

• Hepatotoxicity
• Asymptomatic Hyperuricemia
• Gout
• Polyarthralgia
• Morbiliform rash transient
• Nausea and vomiting
Ethambutol

- Optic neuritis
- Red-green color discrimination
SECOND LINE DRUGS COMMON ADVERSE DRUG REACTIONS
# Adverse Effects of Second-line Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>aminoglycoside</td>
<td>ototoxicity, nephrotoxicity,</td>
</tr>
<tr>
<td>cycloserine</td>
<td>neuropsychiatric toxicity, peripheral neuropathy</td>
</tr>
<tr>
<td>ethionamide</td>
<td>hepatotoxicity, neurotoxicity, hypothyroidism</td>
</tr>
<tr>
<td>fluoroquinolone</td>
<td>neurotoxicity, tendinitis, hepatotoxicity</td>
</tr>
<tr>
<td>PAS</td>
<td>hepatotoxicity, GI distress, hypothyroidism, coagulopathy</td>
</tr>
</tbody>
</table>
Streptomycin

• Vestibular toxicity - monitor for HA, nausea, vomiting, tinnitus, imbalance
• Auditory toxicity (hearing loss) – less than other aminoglycosides
• Nephrotoxic
• Rare: Hemolytic anemia
  Thrombocytopenia
  Agranulocytosis, lupus reactions
Amikacin & Kanamycin

- Audio-toxicity - high frequency hearing loss (irreversible)
- Vestibular dysfunction (irreversible)
- Nephrotoxicity - reversible
- Eosinophilia

Monitoring:
- Renal function / Creatinine
- Weekly serum levels
- Monthly Audiograms / Balance testing
Fluoroquinolones – moxifloxacin, levofloxacin

- Generally *well tolerated* among 2nd line TB drugs
  - Tendonitis; tendon rupture (Achilles tendon most common)
  - QTc prolongation
    - Higher risk when given with other QTc prolonging drugs
    - e.g. bedaquiline, clofazimine, ondansetron, azole-antifungals
    - Insomnia, lightheadedness, dizziness
- Contraindicated in patients with Myasthenia Gravis
Linezolid

• 600 mg once daily dosing for TB
• Myelosuppression
• Peripheral neuropathy
• Ocular toxicity
• Mitochondrial toxicity; hyperlactatemia
• Serotonin toxicity - when administered in combination with a SSRI or a nonselective MAO inhibitor
  – LZD is structurally similar to tolaxotone, a known MAO inhibitor
  – Two of its metabolites are structurally related to moclobemide - a reversible MAO-A inhibitor and has been reported to cause serotonin toxicity

Ethionamide

- Nausea, vomiting, diarrhea
- Dysgeusia - metallic taste
- Arthralgias
- Endocrine disorders:
  - Hypothyroidism
  - Glucose intolerance
  - Sexual dysfunction ▼ Libido, Erectile dysfunction, Menstrual Abnor.
- Peripheral neuropathy - reversible
- Hepatitis (10% cases) - rarely serious
- Caution with co-administration of:
  - PAS (GI distress, hypothyroidism)
  - Isoniazid (peripheral neuropathy, hepatitis)
Cycloserine

• Neurotoxicity
  – Inability to concentrate and lethargy
  – Seizure, depression, psychosis, and suicidal ideation
    • *usually* occurs at peak concentrations > 35 mcg/mL
    • Can also be seen in the normal therapeutic range
    • Need to give Vitamin B6 100 mg per day
  – peripheral neuropathy

• Skin problems include lichenoid eruptions and Stevens-Johnson syndrome
Para-aminosalicylic acid (PAS)
Delayed-release PASER granules (acid-resistant outer coating)

• Bulky, unpleasant taste
• Anorexia, nausea, vomiting, abdominal discomfort

• Hypothyroidism, goiter (PAS has anti-thyroid effect);

• Caution when administering with Ethionamide
  – Hepatic dysfunction
  – Hypersensitivity reaction / skin rash
Bedaquiline

- Increased risk of death (11.4% vs. 2.5% in comparator group)
- Increased QTc (although not felt to be a major risk by CDC group meeting)
  - May be additive with other QTc prolonging drugs
- Hepatotoxicity
- Headache, Nausea, arthralgia, rash
- Drug interactions via Hepatic CYP 3A
  - M2 is major metabolite (4-6x less potent)
  - BDQ does not increase or decrease 3A4 activity
  - Rifampin will decrease BDQ levels (inducer of CYP 3A4)
- Limited data in HIV co-infected patients

https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm

CDC RTMCC meeting January 14-15, 2013

Mayo Clinic Center for Tuberculosis
Clofazimine

- Used for MDR TB, Leprosy

- Side effects include:
  - Bronze skin pigmentation (75-100%)
  - GI / stomach upset; N/V (40-50%)
  - QTc prolongation potential
    - Monitor ECG when given with quinolones and/or BDQ
    - Ocular: Conjunctival and corneal pigmentation due to crystal deposits

- No longer commercially available in the United States
  - Clofazimine can be obtained by submitting an IND through the National Hansen’s Disease (Leprosy) Program (NHDP)
Delamanid

- Nitro-dihydro-imidazooxazole class of compounds that inhibits mycolic acid synthesis
- Major adverse effect:
  - QTc prolongation

M.T. Gler et al. Delamanid for Multidrug-Resistant Pulmonary Tuberculosis
References

3. CDC.gov
THANK YOU.