Disclosures

• None
Objectives

• Describe the common adverse reactions to TB treatment regimens

• Explain how to manage adverse reactions to TB treatment regimens
How should I manage this adverse drug reaction?

Google Search  I'm Feeling Lucky

Chance favors the prepared mind
Louis Pasteur
Anticipating Adverse Effects

- Universal Adverse Effects
- Common AE of first-line drugs
- Important AE of second-line drugs
- Baseline and follow-up monitoring
## 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, polyarthralgia, gout</td>
</tr>
<tr>
<td>ethambutol</td>
<td>impaired vision, peripheral neuropathy</td>
</tr>
</tbody>
</table>
# 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>
## Monitoring for Adverse Effects

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>Liver function panel, creatinine, CBC, platelets, visual acuity and color vision</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>eye exam if on ethambutol, ALT if at risk for hepatotoxicity</td>
</tr>
</tbody>
</table>
Top Ten Troubles

1. Gastrointestinal upset
2. Rash/pruritus
3. Peripheral neuropathy
4. Hepatotoxicity
5. Hematologic toxicity
6. PZA and gout
7. Ethambutol and vision
8. Hypothyroidism
9. CNS toxicity
10. Drug interactions
Tools for management

- Consider a non-TB drug or condition
- Treat symptoms and continue the medication
- Modify drug delivery
- Stop the drug(s) and follow clinically
- Re-challenge after symptoms abate
- Use different drug(s)
- Measure drug levels
- Hospitalize during medication re-challenge
# Gastrointestinal Upset

<table>
<thead>
<tr>
<th>Problem</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric discomfort</td>
<td>Give medication with food</td>
</tr>
<tr>
<td></td>
<td>Change time of administration</td>
</tr>
<tr>
<td></td>
<td>Acid suppression</td>
</tr>
<tr>
<td></td>
<td>Check for H. pylori</td>
</tr>
<tr>
<td></td>
<td>Discontinue drugs and follow response</td>
</tr>
<tr>
<td>Nausea</td>
<td>Discontinue drugs and follow response</td>
</tr>
<tr>
<td></td>
<td>Check for hepatitis</td>
</tr>
<tr>
<td></td>
<td>Anti-emetics</td>
</tr>
<tr>
<td>Aversion to pills</td>
<td>Crush pills</td>
</tr>
<tr>
<td></td>
<td>Liquid form of medication</td>
</tr>
<tr>
<td></td>
<td>Split the dose</td>
</tr>
</tbody>
</table>
Rash/Pruritus

- Check other drugs or topical preparations
- Early onset, urticaria could mean more serious allergic reaction
- Extensive rash - stop medication, check for other affected systems
- Petechiae - check platelets, suspect rifampin
- Symptomatic treatment with antihistamines
- Re-challenge
  - can start low and work up to therapeutic dose of drug
  - can start with one drug, then add successive drugs every 3-4 days if there is no reaction to the preceding drug. Order of drugs not established, I usually start with rifampin.
Peripheral Neuropathy

- Check for neuropathy before starting TB medication
- Isoniazid is the usual culprit, but quinolones, ethambutol and cycloserine have been implicated
- Tuberculosis itself can present with neuropathy
- Treat with increasing dose of pyridoxine to a maximum of 200 mg daily
- If no improvement after treatment, consider discontinuation of isoniazid
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated w/ liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated w/ liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

- alcohol consumption
- other hepatotoxic drugs
- previous elevation of ALT
- combination TB drugs
- elderly
- Asian male
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated with liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

- May have higher rate of INH-induced hepatitis in pregnancy and within 3 months post-partum
- Defer LTBI treatment in low-risk patients until after pregnancy

Hepatotoxicity

• Risk factors for injury
• Risk in pregnancy
• Liver enzyme elevation
• Drugs associated w/ liver injury
• Confirming the drug causing injury
• Check for hematologic, renal injury
• Other causes of hepatitis
• Liver-sparing treatment regimen

• ALT more specific for liver than AST
• Bilirubin more associated with rifampin
• Evaluate for severity of disease (marked enzyme rise, jaundice, coagulopathy, hypoglycemia)
• Stop drug when:
  • x5 elevation in asymptomatic patient
  • x3 elevation in symptomatic patient
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- **Drugs associated w/ liver injury**
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

- isoniazid
- rifampin
- pyrazinamide
- ethionamide
- para-aminosalicylate
- fluoroquinolones*

* but used in liver-sparing regimens
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated w/ liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

Rechallenge with the suspected offending agent with more than twofold serum alanine aminotransferase (ALT) elevation, and discontinuation leading to a fall in ALT, is the strongest confirmation of the diagnosis.

Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated w/ liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

Injury from adverse drug reaction may injure more than one system.
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated w/ liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

- Check for viral hepatitis (A, B, C)
- Consider autoimmune hepatitis
- May need consult and liver biopsy
- Treatment of viral hepatitis may be helpful
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Drugs associated w/ liver injury
- Confirming the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen

Ethambutol
Quinolone
Aminoglycoside
Cycloserine
## CNS Toxicity

<table>
<thead>
<tr>
<th>Problem</th>
<th>Drug</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>anxiety</td>
<td>quinolone, isoniazid, cycloserine</td>
<td>observation</td>
</tr>
<tr>
<td>seizure</td>
<td>isoniazid, cycloserine</td>
<td>monitor drug levels of anti-seizure medication</td>
</tr>
<tr>
<td>depression</td>
<td>cycloserine</td>
<td>prevention with high dose pyridoxine, may need anti-depressant</td>
</tr>
<tr>
<td>psychosis</td>
<td>cycloserine</td>
<td>measure drug level, decrease dose, stop medication, Psychiatry consultation</td>
</tr>
</tbody>
</table>
CNS Toxicity

**ACTION**
- Observe clinically
- Discontinue TB drug
- Measure drug levels
  - anti-seizure med
  - cycloserine
  - isoniazid
- Antidepressant medication
- Psychiatry consult

**Symptoms**
- Quinolone: anxiety, headache, confusion
- Isoniazid: seizure, depression, psychosis
- Cycloserine: depression, psychosis
Hematologic Toxicity

- Rifampin most frequently implicated but toxicity can occur with all first-line drugs
- “flu-like syndrome” with rifampin can result in depression of anemia, leukopenia, and thrombocytopenia
- Hematology consultation can be helpful
- G-CSF has been used for neutropenia
# Pyrazinamide and Gout

<table>
<thead>
<tr>
<th>Problem</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>arthralgia</td>
<td>NSAIDS if needed</td>
</tr>
<tr>
<td>uric acid elevation</td>
<td>nothing if asymptomatic</td>
</tr>
<tr>
<td>flare of gout</td>
<td>stop PZA if possible, try to lower uric acid levels</td>
</tr>
<tr>
<td>persistent arthritis</td>
<td>look for another cause of inflammation</td>
</tr>
</tbody>
</table>

Isoniazid can lead to joint inflammation as a manifestation of SLE syndrome.
Ethambutol and Vision

• Check visual acuity and color discrimination at baseline.

• Higher risk with renal failure or dose greater than 15 mg/kg.

• Dosing should be 15 mg/kg for prolonged course (more than 2 months).

• If visual disturbance suspected, discontinue drug immediately and refer for Opthalmology evaluation

• May lead to severe vision loss if ethambutol not stopped
Hypothyroidism

- Seen with ethionamide and PAS
- Check TSH at baseline and monitor
- May need thyroid replacement
# Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interacting Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoniazid</td>
<td>anti-seizure medication</td>
</tr>
<tr>
<td>rifampin</td>
<td>Multiple drugs, notably HIV medication, coumadin</td>
</tr>
<tr>
<td>quinolone</td>
<td>drugs causing QT prolongation</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>cyclosporine</td>
</tr>
</tbody>
</table>
Other Final Thoughts

- Consider the extent of disease in plan for managing adverse reactions
- How long can a patient be without effective therapy before drug resistance is acquired or worsening of disease is seen?
- Drug resistance may limit available options
- Rifabutin can often substitute for rifampin
Tools for management

- Consider a non-TB drug or condition
- Treat symptoms and continue the medication
- Modify drug delivery
- Stop the drug(s) and follow clinically
- Re-challenge after symptoms abate
- Use different drug(s)
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- Hospitalize during medication re-challenge