Mayo Clinic Center for Tuberculosis
Tuberculosis Treatment
Managing Adverse Drug Reactions

Dean Tsukayama, M.D.
Hennepin County Public Health Clinic
Hennepin County Medical Center
Disclosures

I have no relevant financial relationships
Objectives

• Recognize the common side effects of first line tuberculosis medication

• Know the risk factors, associated drugs, and management of hepatotoxicity.

• Be familiar with the side effects of second-line tuberculosis medication
A Current Case

30 year old student, born abroad, came to US in 2014, good general health, had positive QFT, abnormal CXR/CT, on screening. Asymptomatic, exam unremarkable. Sputum and bronchoscopy-smear-negative, cultures pending.

<table>
<thead>
<tr>
<th>DAY</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>presumptive 4 drug treatment started</td>
</tr>
<tr>
<td>12</td>
<td>rash/pruritus, no swelling/dyspnea, neutropenia, abnormal LFTs, medication stopped</td>
</tr>
<tr>
<td>13</td>
<td>bronchoscopy cultures growing MTB</td>
</tr>
<tr>
<td>20</td>
<td>labs better, rash persists</td>
</tr>
<tr>
<td>27</td>
<td>restarted rifampin</td>
</tr>
<tr>
<td>28</td>
<td>rash returns, rifampin stopped</td>
</tr>
<tr>
<td>29</td>
<td>rash better, isoniazid started</td>
</tr>
<tr>
<td>DAY</td>
<td>Description</td>
</tr>
<tr>
<td>-----</td>
<td>-------------</td>
</tr>
<tr>
<td>31</td>
<td>ethambutol started</td>
</tr>
<tr>
<td>32</td>
<td>recurrence of rash/fever, ethambutol stopped, isoniazid continued</td>
</tr>
<tr>
<td>33</td>
<td>worsening rash on isoniazid, medications stopped</td>
</tr>
<tr>
<td>34</td>
<td>patient travels out of town</td>
</tr>
<tr>
<td>41</td>
<td>pyrazinamide started</td>
</tr>
<tr>
<td>42</td>
<td>new rash appears</td>
</tr>
</tbody>
</table>
Anticipating Adverse Reactions

- Universal Adverse Reactions
- Common AR of first-line drugs
- Important AR 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 Problems

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
- Desensitization for difficult cases
- 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

- Pregnancy
- Liver enzyme elevation
- Drug-associated
- Confirming the culprit drug
- Hematologic or renal injury
- Other causes of hepatitis
- Liver-sparing regimens

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

Risk factors for injury

- Pregnancy
- Liver enzyme elevation
- Drug-associated
- Confirming the culprit drug
- Hematologic or renal injury
- Other causes of hepatitis
- Liver-sparing regimens

• may have higher rate of IHN-induced hepatitis in pregnancy and within 3 months postpartum

Defer LTBI treatment in low-risk patients until after pregnancy

Hepatotoxicity

- ALT more specific for liver than AST

  Bilirubin rise more associated with rifampin

  Severe disease- marked enzyme rise, jaundice, coagulopathy, hypoglycemia

Stop drug when:
  5x elevation in asymptomatic patient
  3x elevation in symptomatic patient
Hepatotoxicity

Risk factors for injury
- Pregnancy
- Liver enzyme elevation

Drugs associated with injury
- Confirming the culprit drug
- Hematologic or renal injury
- Other causes of hepatitis
- Liver-sparing regimens

Drugs associated with injury:
- isoniazid
- rifampin
- pyrazinamide
- ethionamide
- para-aminosalicylate
- fluoroquinolones*

* but used in liver-sparing regimens
Hepatotoxicity

Risk factors for injury
  Pregnancy
  Liver enzyme elevation
  Drug-associated

Confirming the culprit drug

Hematologic or renal injury

Other causes of hepatitis

Liver-sparing regimens

Rechallenge with the suspected offending agent resulting in 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

Pregnancy
Liver enzyme elevation
Drug-associated

Confirming the culprit drug

Hematologic or renal injury

Other causes of hepatitis

Liver-sparing regimens

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

Risk factors for injury

- Pregnancy
- Liver enzyme elevation
- Drug-associated

Confirming the culprit drug

Hematologic or renal injury

Other causes of hepatitis

Liver-sparing regimens

- 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

- Pregnancy
- Liver enzyme elevation
- Drug-associated
- Confirming the culprit drug
- Hematologic or renal injury
- Other causes of hepatitis

Liver-sparing regimens

Low risk for hepatotoxicity

- 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>
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 Ophthalmology evaluation

- Severe and permanent vision loss possible 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, rifampin</td>
</tr>
<tr>
<td>rifampin</td>
<td>Multiple drugs, notably HIV medication, coumadin, isoniazid, quinolones</td>
</tr>
<tr>
<td>quinolone</td>
<td>drugs causing QT prolongation</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>cyclosporine</td>
</tr>
</tbody>
</table>
Quinolones

- tendinitis/tendon rupture*
- prolonged QT interval
- dysglycemia
- hepatitis
- peripheral neuropathy/seizure
- drug interactions

Linezolid

- hematologic suppression
- peripheral neuropathy
- optic neuropathy
- serotonin syndrome
- hepatotoxicity
- drug interactions

* Black Box Warning
Serotonin Syndrome

Serotonin syndrome symptoms typically occur within several hours of taking a new drug or increasing the dose of a drug you're already taking. Signs and symptoms include:

- Agitation or restlessness
- Confusion
- Rapid heart rate and high blood pressure
- Dilated pupils
- Loss of muscle coordination or twitching muscles
- Heavy sweating
- Diarrhea
- Headache
- Shivering
- Goose bumps

Severe serotonin syndrome can be life-threatening. Signs and symptoms include:

- High fever
- Seizures
- Irregular heartbeat
- Unconsciousness

http://www.mayoclinic.com
QT interval prolongation

- can lead to life-threatening arrhythmias
- TB drugs- fluoroquinolones, bedaquiline, delamanid
- Additive effect with other QTIP drugs
- Common drugs with effect- antidepressant, antifungals, macrolides, methadone
QT interval prolongation

• concerning if QT interval > 480
• action required if QT > 500
• If adding quinolone to regimen already containing QT prolonging drug, do baseline ECG and repeat one week after adding second drug
Back to our case

<table>
<thead>
<tr>
<th>DAY</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>43</td>
<td>referral to allergist</td>
</tr>
<tr>
<td>48</td>
<td>begins desensitization to isoniazid in allergist’s office, beginning with 0.1 mg</td>
</tr>
<tr>
<td>51</td>
<td>up to 150 mg in the morning, reports rash on right thigh that has been present before desensitization started, second dose of 150 mg given in the afternoon</td>
</tr>
<tr>
<td>58</td>
<td>tolerating full dose of isoniazid, compounded rifabutin started at initial dose of 20 mg.</td>
</tr>
<tr>
<td>67</td>
<td>tolerating full doses of isoniazid and rifabutin</td>
</tr>
<tr>
<td>106</td>
<td>doing well at last follow-up</td>
</tr>
</tbody>
</table>
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
- Desensitization for difficult cases
- Hospitalize during medication re-challenge
- Call your friends
Other Considerations

• The extent of disease must factor into 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
Considerations

• For non-serious adverse effects, can continue to treat, adding measures to treat symptoms

• For serious adverse effects, stopping all the TB drugs is a reasonable step

• Consider the seriousness of the reaction in deciding whether re-challenge is possible

• For re-challenge, starting drugs one at a time can identify the culprit drug

• Rifabutin can sometimes be substituted for rifampin
How should I manage this adverse drug reaction?

Chance favors the prepared mind
Louis Pasteur
Question 1

Name 4 major adverse effects associated with the four first line anti-tuberculous drugs?

a. hepatotoxicity
b. peripheral neuropathy
c. polyarthragia
d. impaired vision
Question 2

Name the 5 baseline tests that should be done for patients starting anti tuberculous treatment?

a. liver function panel
b. Creatinine
c. CBC:platelets
d. visual acuity
e. color vision