TB Meds…Worth the Side Effects??

Tuberculosis Medications: Patient Education
Common and Adverse Side Effects

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Disclosure

No Disclosures

No Relevant Financial Relationships
No Off-Label/Investigation Use of Tuberculosis Meds

Special thank you for information slides from: Dean Tsukayama (compliments of Mayo Clinic).

Also information from Beth Gadkowsk, David Ashkin, Center for Disease Control (CDC), and National Health Institute on public web domain.
Objectives

• Obstacles of Compliance

• First-Line Medications & Side Effects

• Second-Line Meds & Side Effects

• What are Predictors of Success?
Questions/Quiz/Test

1) What greatly affects medication compliance?
   a) Length of Treatment  c) Side Effects
   b) Cost of Meds  d) All (a,b,c)

2) Which TB drug has the most drug interactions?
   a) Isoniazid  c) Rifampin
   b) Pyrazinamide  d) Streptomycin

3) Who is most likely a successful TB patient?
   a) 50-yr old woman  c) Bachelor Rancher
   b) College Student  d) Alcoholic Drifter
Compliance

**Definition:** Degree to which a patient correctly follows medical advice; particularly referring to medication or drug compliance.

--adherence to a drug regimen

Pharmacists/MDs have trouble getting patients to adhere to a 10-day antibiotic regimen….is a 6 month program impossible??
Tips to “Improve” Compliance:

- Daily Dosing
  - Once or twice weekly - NO!

- All Meds Given at One Time
  - Permissible with the 4 first-line TB Meds
  - Give on empty stomach (can give with saltines if gastric problems)
Compliance

Educate the Patient

Do I actually have TB?

(Latent and no symptoms)

How BAD is it (really) to have TB?

How risky to NOT treat TB?

How will patient (and family) benefit from taking the meds?
Compliance

Educate the Patient

Patient needs to understand importance of taking all meds for 6 to 9 to 18 months.

Talk about “resistant” TB….non-compliance has caused “resistance”

If patient gets “resistant” TB, may have to take meds with direct observation OR be quarantined
Compliance

Educate Patient (continued)

Society’s Expectation of NOT spreading the disease

Expense/Cost

Side Effects/How to Take

Positive Attitude/Expectation of Success
# First-Line Medications

<table>
<thead>
<tr>
<th>DRUG</th>
<th>ADVERSE EFFECTS/TOXICITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>Hepatotoxicity, peripheral neuropathy, CNS effects, lupus-like syndrome, monoamine poisoning</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>Flu-like syndrome, hepatotoxicity, anemia, thrombocytopenia, renal failure, drug interactions</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>Hepatotoxicity, polyarthralgia, gout</td>
</tr>
<tr>
<td>Ethambutol (EMB)</td>
<td>Impaired vision, peripheral neuropathy</td>
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# First-Line Medications

<table>
<thead>
<tr>
<th>DRUG</th>
<th>FREQUENT/COMMON SIDE EFFECTS &gt;10% (Some Very Serious)</th>
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<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>Nausea/Vomiting; Diarrhea; Numbness, Tingling or Pain in Hands/Feet; Stomach Cramps</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>Discolored Saliva, Sputum, Sweat, Stool &amp; Urine; Diarrhea; Stomach Cramps Negates Birth Control (oral contraceptives)</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>Joint Pain; Nausea/Vomiting; Loss of Appetite</td>
</tr>
<tr>
<td>Ethambutol (EMB)</td>
<td>Nausea/Vomiting, Headache</td>
</tr>
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# Second-Line Medications

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<thead>
<tr>
<th>DRUG</th>
<th>ADVERSE EFFECTS/TOXICITIES</th>
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<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Ototoxicity, Nephrotoxicity</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Neuropsychiatric toxicity, Peripheral neuropathy</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Hepatotoxicity, Neurotoxicity</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Neurotoxicity, Tendinitis, Hepatotoxicity</td>
</tr>
<tr>
<td>Para-Aminosalicylate (PAS)</td>
<td>Hepatotoxicity, GI Distress, Hypothyroidism, Coagulopathy</td>
</tr>
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# Second-Line Medications

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<tr>
<td>Aminoglycosides</td>
<td>Ototoxicity, Nephrotoxicity, Headache, Fever, Cough</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Dizziness, Drowsiness, fatigue, headache</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Nausea/Vomiting; Diarrhea</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Sun Sensitivity</td>
</tr>
<tr>
<td>Para-Aminosalicylate</td>
<td>Nausea/Vomiting; Diarrhea</td>
</tr>
<tr>
<td>(PAS)</td>
<td></td>
</tr>
</tbody>
</table>
Toxicities vs Adverse Effects vs Side Effects

Side Effects
Adverse Effects
Toxicities

Not Good
Bad
Worse

Toxicities:
May be life-threatening/permanent
May require dose changes/discontinuation
May require hospitalization or additional treatment
Toxicities vs Adverse Effects vs Side Effects

Adverse Events:
- Response is noxious/un-intended
- May be harmful or unpleasant
- May need to change dose/treatment
Toxicities vs Adverse Effects vs Side Effects

Side Effects:
- May be expected or unexpected
- Sometimes go away during treatment

Examples:
- Hair Loss
- Itching
- Constipation
- Insomnia
- Fatigue
- Mouth Sores
- Weight Gain
- Weight Loss
- Bleeding
- Nausea
- Vomiting
- Dry Mouth
- Headache
- Agitation
If possible do baseline testing:

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Liver Function Panel, Creatinine, Complete Blood Count (CBC), Platelets, Visual Acuity, Color Vision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-Up</td>
<td>Eye Exam (if on Ethambutol) ALT (if at risk for hepatotoxicity)</td>
</tr>
</tbody>
</table>
TOP TEN TROUBLES With TB Medications

1. GI Upset
2. Rash and Itching
3. Peripheral Neuropathy
4. Hepatotoxicity
5. Hematologic Toxicity
6. PZA/Gout & EMB/Joints
7. Ethambutol/Vision
8. Hypothyroidism
9. CNS Toxicity
10. Drug Interactions
#1
Gastrointestinal Upset

<table>
<thead>
<tr>
<th>Problem</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia</td>
<td>Give Med with Food</td>
</tr>
<tr>
<td>Gastric Discomfort</td>
<td>Change time of Administration</td>
</tr>
<tr>
<td>(Very Common)</td>
<td>Acid Suppressant</td>
</tr>
<tr>
<td></td>
<td>Check for H pylori</td>
</tr>
<tr>
<td></td>
<td>D/C Med and follow Response</td>
</tr>
<tr>
<td>Nausea</td>
<td>D/C Med and follow Response</td>
</tr>
<tr>
<td></td>
<td>Give anti-emetics</td>
</tr>
<tr>
<td></td>
<td>Check for Hepatitis</td>
</tr>
<tr>
<td>Aversion to Pills</td>
<td>Crush Pills</td>
</tr>
<tr>
<td></td>
<td>Liquid form of Med</td>
</tr>
<tr>
<td></td>
<td>Split the Dose</td>
</tr>
<tr>
<td></td>
<td>Jam, Honey, Applesauce, etc.</td>
</tr>
</tbody>
</table>
#2
Rash/Itching (Pruritis)

- Early onset rash/hives could mean more serious allergic reaction
- Extensive rash? STOP med, check for other affected systems
- Petechiae? Check platelets….suspect rifampin
- Symptomatic treatment with anti-histamines
- Check other drugs or topical preparations
- Re-challenge
  Can start low and work up to therapeutic dose of drug
  Can start with one drug, then add successive drugs every 3 to 4 days. If no reaction, go to preceding drug. Order of which drug to start not established.
#3
Peripheral Neuropathy

- Ask/Check for neuropathy before regimen
- Isoniazid is usual culprit, but quinolones, ethambutol, cycloserine and linezolid have been implicated
- Treat with increasing dose of pyridoxine to a max of 200 mg daily
- If no improvement after treatment, consider discontinuation of isoniazid
- Reminder: TB (itself) can cause neuropathy
Hepatotoxicity

- Risk factors for injury
- Risk in pregnancy
- Liver enzyme elevation
- Other drugs associated with liver injury
- Confirm (if possible) the drug causing injury
- Check for hematologic, renal injury
- Other causes of hepatitis
- Liver-sparing treatment regimen
#4 Hepatotoxicity

Risk Factors for Injury:

- Alcohol Consumption
- Other Liver-Toxic Drugs
- Previous elevation of Liver Damage Markers
  - ALT/AST, PT, PTT, Albumin, Ammonia
- Combo TB drugs
- Elderly
- Asian Male
#4 Hepatotoxicity

Risk in Pregnancy

May have higher rate of INH-induced hepatitis in pregnancy & 3 months post-partum

Defer LTBI treatment in low-risk patients until after pregnancy ??? (ALL???)
Hepatotoxicity

Liver Enzyme Elevation
ALT more specific for liver than AST
Bilirubin – more associated with rifampin
Evaluate for disease severity
- Jaundice
- Coagulopathy
- Hypoglycemia
- High Rise of Enzymes

STOP drug when:
- X5 elevation in asymptomatic patient
- X3 elevation in symptomatic patient
Hepatotoxicity

Drugs Associated with Liver Injury

- Isoniazid
- Rifampin
- Pyrazinamide
- Ethionamide
- Para-Aminosalicylic Acid
- Fluoroquinolones

Symptoms of Liver Injury can include:

- fatigue
- jaundice
- abdominal pain
- vomiting
TB Hepatitis

Isoniazid-associated hepatitis is the most commonly implicated agent leading to drug induced acute liver failure in the United States and the most common reason that adults require emergency liver transplant for drug hepatotoxicity.

Most Common Signs/Symptoms: Fatigue, Nausea, Vomiting, Abdominal Pain, Jaundice
Confirmed the drug-causing injury

Re-challenge with suspected offending agent with more than twofold serum alanine aminotransferase (ALT) elevation, and........

Discontinuation leading to a fall in ALB is the strongest confirmation of the diagnosis
#4
Hepatotoxicity

Check for Hematologic Injury
- Anemia
- Thrombocytopenia
- Leukopenia
- Eosinophilia

Check for Renal Injury
- BUN and Creatinine
- Urine Eosinophils
#4

Hepatotoxicity

Other Causes of Hepatitis

Check for Viral Hepatitis (A, B, C)
Consider Alcoholic Hepatitis
Consider Auto-Immune Hepatitis

May need consult and liver biopsy
Liver-Sparing Treatment Regimen
Excreted Renally, so Easier for Liver

Ethambutol
Quinolone
Aminoglycoside
Cycloserine
Blood and Tissue Issues

Rifampin most frequently implicated; but can occur with all first-line drugs

“Flu-like” syndrome with rifampin..resulting in anemia, leukopenia, thrombocytopenia

G-CSF has been used for neutropenia

Hematology consult may be needed
#6
Gout/Joints

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<thead>
<tr>
<th>Problem</th>
<th>Action</th>
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</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>NSAIDs, if needed</td>
</tr>
<tr>
<td>Uric Acid Elevation</td>
<td>None, if asymptomatic</td>
</tr>
<tr>
<td>Gout Flare</td>
<td>Stop PZA, Use Gout Meds</td>
</tr>
<tr>
<td>Gout-Like Increased Uric Acid</td>
<td>(Possibly EMB) Gout Meds, NSAIDs (Rifampin decreases Uloric levels)</td>
</tr>
<tr>
<td>Persistent Arthritis</td>
<td>Look for Cause—may not be Meds (May be disease-state)</td>
</tr>
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</table>

Note: Isoniazid can lead to joint inflammation as a manifestation of SLE (Lupus) syndrome
Ethambutol and Vision

Check visual acuity & color discrimination at baseline

Higher risk of problems: Renal Dysfunction
Doses >15 mg/kg

Prolonged Treatment: Dose = 15 mg/kg
(longer than 2 months) (no higher)

If visual disturbance – D/C Drug Immediately
Ophthalmology Evaluation Required
Check TSH at base-line and monitor

Seen with ethionamide and PAS (Para-Aminosalicylate)

May need thyroid replacement

How common (really) is hypothyroidism from TB treatment???
#9 CNS Toxicity

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<thead>
<tr>
<th>Problem</th>
<th>Drug</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Quinolone</td>
<td>Observation Consult for Anti-Anxiety Med</td>
</tr>
<tr>
<td></td>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cycloserine</td>
<td></td>
</tr>
<tr>
<td>Seizure</td>
<td>Isoniazid</td>
<td>Monitor Drug Levels of Anti-Seizure Medication</td>
</tr>
<tr>
<td></td>
<td>Cycloserine</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Cycloserine</td>
<td>May Need Anti-Depressant Prevention with high-dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pyridoxine</td>
</tr>
<tr>
<td>Psychosis</td>
<td>Cycloserine</td>
<td>Measure Drug Level &amp; Drop Dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stop Medication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psych Consult</td>
</tr>
</tbody>
</table>
#9
CNS Toxicity

<table>
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<th>Estimated CNS Penetration</th>
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</tr>
<tr>
<td>Ethambutol (EMB)</td>
</tr>
<tr>
<td>Streptomycin (STM)</td>
</tr>
<tr>
<td>Quinolones</td>
</tr>
<tr>
<td>Cycloserine</td>
</tr>
</tbody>
</table>
#10
Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interacts with……</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>Many, many medications…. Most notably HIV medication, coumadin, immunomodulators</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Anti-Seizure Meds Coumadin</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Drugs causing QT prolongation</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Cyclosporine</td>
</tr>
</tbody>
</table>
Summary of Side Effects

For Common significant SE’s, multiple drugs may be responsible

- **Rash** → INH, RIF, PZA, EMB
- **GI** → INH, RIF, PZA
- **Hepatitis** → INH, RIF, PZA

Remember: It also may not be the TB drugs!
(alcohol, other drugs & conditions)
Management Tools

- Consider another drug
- Treat symptoms/continue medication
- Modify drug delivery
- Stop drug
- Re-challenge after abating symptoms
- Measure drug levels
- Hospitalize during med re-challenge
Predictors of Success

1) Advancing Age
   --Older…have seen what disease can do
   --Younger…nothing bad can happen to me
   --Realize Own Mortality

2) Female
   --Just seem to take better care of themselves
3) Having a higher number of symptoms and conditions
   --Can see themselves improving
   --Hard for diseases like latent TB, high blood pressure, high cholesterol

4) Higher cost of prescription drugs
   --Cost dearly, so not going to waste them
   --Perhaps gov’t gift of drugs is obstacle to success
Final Considerations

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

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

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

• For re-challenge, starting drugs one at a time can identify the culprit drug
1) What greatly affects Compliance of Meds?
   a) Length of Treatment  
   b) Cost of Meds  
   c) Side Effects  
   d) All (a, b, c)

2) Which TB drug has the most drug interactions?
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QUESTIONS??