Treatment of TB: Managing Adverse Drug Effects

Dana G. Kissner, MD
Detroit Department of Health & Wellness Promotion
Wayne State State University
Poisons and medicine are oftentimes the same substance given with different intents

*Peter Mere Latham 1789–1875 English physician & educator*
Topics

- General considerations
- List of adverse effects of TB drugs
- Drug effects on liver
  - Drug metabolism by liver
  - Spectrum of drug effects on liver
  - Commonly used lab tests
  - Effects of individual drugs on liver
  - Monitoring for toxicity
  - Management of drug effects on liver
  - Management of GI intolerance
- Dermatologic complications
- Neurologic complications
  - Includes optic (eye) and otic (ear) ones
- Individual drugs – other side effects
General Considerations
Treatment of TB / LTBI is Difficult

- **Symptoms**
  - Drug-related
  - Due to other causes – including TB itself
  - Fear of drugs

- **Adverse reactions**
  - Need to be anticipated
  - Require monitoring for
  - May prompt discontinuation / changing medication
TB Program Must-Haves

- Ready access to care for adverse events
- Adequate education of staff
- Good communication among staff, health care providers, patients
- Standardized approaches
  - Patient education
  - Medical history form
  - Patient instructions
  - # of doses of medications dispensed at a time for self-medication
General Approach

- Address, relieve symptoms
- Reassure patient
- Emphasize importance of Rx completion
- Be firm: treatment must be completed
- Make it a common goal to complete Rx on time

- Recognize signs & symptoms of drug toxicity
- Know when to stop / not administer drug
- Promptly report symptoms
- Communicate – physician, DOT worker, patient

Do Good
Do no harm
General Approach

- Make every attempt to avoid unnecessary breaks in therapy
- Remind patient that breaks result in prolonged duration of treatment
- Counting doses helps

Do No Harm

Cure TB
Types of Adverse Effects of TB Drugs
Serious Drug Complications

- Hepatotoxicity
- Hearing loss
- Kidney failure
- Vision loss
- Toxic skin / systemic reactions
- Hematologic (blood) reactions
- Electrolyte abnormalities
- Neurologic damage
- Death
Less Serious Complications

- Skin rash, itching
- Nausea, vomiting, diarrhea
- Reversible CNS symptoms
- Bone & joint symptoms
- Endocrine effects (less common)
Effects of Drugs on the Liver
Drug is swallowed

Absorbed from the GI tract into blood vessels

Enters liver via portal vein

Metabolized in liver

One process involves cytochrome P450 class of enzymes

Enters circulation or stored in bile

Bile enters duodenum

Drug is excreted in stool or reabsorbed (Enterohepatic Circulation)

Rifampin Activates

Bile Duct

Portal Vein

Mouth

Esophagus

Stomach

Intestines

Digestive tract

from www.hepfoundation.org.nz
Drug Effects on Liver: A Spectrum

- Fulminant liver disease / death
  - 30% cases in US are caused by drugs
- Drug induced liver injury (DILI)
  - 700 drugs approved in US can cause liver toxicity
  - Important to detect early / stop drug
- Hepatic adaptation
  - Protective response
- Cholestasis
  - Bile does not flow freely from liver to bowel
- Asymptomatic elevations in bilirubin
Liver cells & bile duct cells contain enzymes
  ◦ Released into blood if liver is damaged

ALT (SGPT)
  ◦ Most specific test for DILI
  ◦ Can be elevated in hepatic adaptation

AST (SGOT)
  ◦ Not specific to liver (found in heart, muscle, RBCs)
Lab Tests to Detect Bile / Bile Duct Problems

- **Alkaline phosphatase**
  - Enzyme found in liver cells & cells lining bile ducts
  - Elevated in bile duct obstruction, cholestasis, infiltrative diseases of liver
    - Elevated in children & pregnant women

- **Bilirubin**
  - Results from the breakdown of red blood cells.
  - Normally, it passes through the liver, is conjugated (made water soluble), & excreted in stool
  - When the liver cannot handle bilirubin normally or bile flow is impaired, bilirubin leaks into the blood stream
    - Causes jaundice or icterus
ALT (SGPT) is more specific for hepatocellular injury than AST (SGOT)

AST > ALT with alcohol-related disease
  ◦ AST/ALT > 2
Normal levels defined as within 2 standard deviations of the mean from a healthy population
- 2.5% of normal, healthy people will have ALT “above upper limit of normal” (ULN)

It is customary to compare multiples of ULN
- Inter-laboratory variation
- Variation within an individual up to 45% in a day
ALT: *DANGER!* *STOP*

- ALT $\geq 3$ times ULN if symptoms are present
- $\geq 5$ times ULN without symptoms
INH

- Cleared in liver by acetylation

- Up to 20% people treated with INH alone have low-grade, transient, asymptomatic ALT increase – “hepatic adaptation”

INH

- Rate of hepatotoxicity when used alone: 0.1–0.6%
- Timing: weeks to months of starting drug
- Incidence & severity increases with age
- Risk increases with:
  - Chronic alcohol consumption
  - Active hepatitis B (+HBeAg)
  - Elevated baseline transaminases (AST, ALT)
  - Concomitant use of other hepatotoxic drugs
  - 3rd trimester pregnancy to 3 months post-partum
  - Pre-existing liver disease
Rifampin

- Dose-dependent interference with bilirubin uptake => subclinical, elevated **unconjugated** bilirubin & jaundice
  - May be transient
  - May occur early in treatment

- Can also cause asymptomatic elevation **conjugated** bilirubin (several mechanisms)

- Jaundice, elevated bilirubin & alkaline phosphatase
Rifampin Hepatotoxicity

- Hepatocellular injury less common
  - Insidious cholestasis
  - Anorexia, nausea, vomiting, fever, jaundice
  - Mildly elevated ALT, elevated bilirubin
  - Usually occurs in first month of treatment
  - RIF is much less likely to cause hepatotoxicity than INH or PZA
Both dose-dependent & idiosyncratic hepatotoxicity

Causes hepatotoxicity less often than INH *but*
  ◦ *Can be more prolonged*
  ◦ *Can continue after drug discontinued*
  ◦ *Can be most severe*

Can cause granulomatous hepatitis
  ◦ Fever, rash, lymphadenopathy, elevated ALT
Monitoring for Hepatotoxicity

LTBI

- Assess risk before treatment
- Baseline blood tests NOT generally recommended for healthy patients treated with INH or RIF alone
- Face-to-face clinical assessments are cornerstone of monitoring
- Obtain ALT & bilirubin at baseline & q 2–4 weeks for those with risk factors.
  - Use ULN for ALT
- ALT is preferred marker for hepatotoxicity in those with symptoms
Hepatotoxicity: Special Considerations

- If baseline ALT > 3 times ULN screen for cause, assess risk for LTBI vs. risk for liver disease
- Test for HBeAg if ALT is elevated in those who are Hepatitis B surface antigen–seropositive
  - If HBeAg is +
    - Rifampin may be preferred
    - Consider referral for possible pre-treatment of Hepatitis B if ALT ≥ 2 times ULN
    - Monitor every 2–4 weeks clinically & with ALT
Management of Hepatotoxicity: LTBI

- Stop hepatotoxic drugs immediately for persistent nausea, vomiting, abdominal pain, unexplained fatigue.
- Measure ALT, bilirubin ASAP
  - For intermittent, transient symptoms administer drugs with food, reassure patient
  - **Withhold INH if ALT ≥3 times ULN if symptoms are present OR >5 times ULN without symptoms**
- Rechallenge
  - If it is unclear that INH was the cause
  - INH was withheld before threshold was reached
Monitoring for & Managing Hepatotoxicity: Tuberculosis

- Obtain baseline ALT, AST, bilirubin, alkaline phosphatase, creatinine, platelet count on all adults
- Periodic monitoring for those with risk factors
- Drugs should not be discontinued for mild GI complaints
Stop all hepatotoxic drugs if ALT is $\geq 3$ times ULN with symptoms OR $\geq 5$ times ULN without symptoms

Substitute non-hepatotoxic drugs
- EMB, injectables, quinolones

When ALT $< 2$ times ULN, reintroduce rifampin
After 3–7 days, reintroduce INH
Consider reintroducing PZA only if hepatotoxicity was not severe
GI Upset

- Improves if drugs are administered with food or closer to bedtime
- Ethionamide
  - Causes profound GI symptoms
  - Metallic taste, nausea, vomiting that can be severe, loss of appetite, abdominal pain
  - Dose-related
  - May give as split dose
- P-Aminosalicylic Acid (PAS)
  - Significant GI intolerance, less with granular formulation
  - Dose-related
- INH
  - Commercial liquid preparations contain sorbitol which can cause diarrhea
Skin Toxicity
Dermatologic Reactions

- Itching with or without erythematous rash is common early side effect
  - May resolve after 1st several weeks of therapy without stopping medications
  - For mild or localized reaction, continue treatment & treat the rash and pruritis symptomatically – antihistamines, topical steroids

- Photosensitivity
  - PZA, fluoroquinolones
Hydroxyzine (Atarax, Vistaril)

- **Indications**
  - Itching: 25–100 mg every 6–8 hours
  - Nausea, vomiting: 25–100 mg every 4–6 hours (IM or PO)
  - Anxiety: 50–100 mg every 6 hours
  - Insomnia: 50–100 mg

- **Maximum daily dose:** 600 mg
Dermatologic Reactions

- Hives, urticaria, erythematous rash
  - Any drug
  - Stop all drugs immediately, re-challenge 1 at a time
    - Wait for rash to resolve
    - Start RIF 1st (least likely to be cause)
    - If no recurrence after 2–3 days start INH
    - Continue with EMB or PZA
    - Discontinue any drug which causes recurrence

- Angioedema, anaphylaxis, or airway compromise
  - Stop drug – consider desensitization in ICU
Other Serious Dermatologic Reactions

- Spectrum of diseases – generalized, involve mucus membranes, cause fever – epidermis separates from dermis
  - Stevens–Johnson Syndrome
  - Toxic Epidermal Necrolysis (severe form SJS)
- Mortality high
- Quinolones
- Emergency, hospitalization
- Stop offending drug, do not use again
Neurotoxicity
Neurotoxicity: Peripheral Neuropathy

- Numbness, tingling hands & feet in stocking-glove pattern

- Risk factors: diabetes, alcoholism, HIV, hypothyroidism, pregnancy, poor nutrition, inadequate dietary intake of pyridoxine

- Pyridoxine supplements
  - 10–50 mg daily (should this be routine?) for INH
  - 100–200 for cycloserine &/or ethionamide
Peripheral Neuropathy

- **INH**
  - Dose-related
  - Interferes with biologic function of vitamin B6
- **Ethionamide**
  - Increased incidence with prolonged use
- **Linezolid**
  - Increased incidence with prolonged use
  - 600 mg daily or 300 mg twice daily instead of 600 mg twice daily is used to prevent this
- **Ethambutol, cycloserine**
  - Rare
CNS Effects

- **INH**
  - Inability to concentrate, irritability, dysarthria, seizures, dysphoria

- **Cycloserine (my mnemonic – cyclo, psycho)**
  - Headache, restlessness, psychosis, seizures (dose-related)
  - Pyridoxine 100–200 mg daily to prevent / treat

- **Ethionamide**
  - Anxiety, depression, psychosis
  - Increased incidence with prolonged treatment

- **Fluroquinolones**
  - Dizziness, insomnia, tremulousness, headache
Ethambutol
- Retrobulbar neuritis
- Dose related – very rare with currently recommended doses
- Decreased red–green color discrimination (1 or both eyes), decreased visual acuity
- \[\uparrow\] With renal disease
- Stop drugs if occurs

Ethionamide
- Optic neuritis
- Dose related
Ototoxicity: 8th Cranial Nerve Damage

- Streptomycin
  - Vestibular (balance) and hearing disturbance
  - Related to single dose size and cumulative dose (>100–200 g)
  - Increased incidence if diuretics are used
  - Monitor with audiogram, Romberg
  - Hearing loss can be permanent / stop drug

- Amikacin & Kanamycin
  - Less vestibular toxicity than SM

- Capreomycin

These drugs also cause nephrotoxicity & require monitoring
Injectable agents – 15mg/kg daily or 25 mg/kg TIW

- Ototoxicity often permanent
  - *Hearing loss ≥ 20 db occurred in 32/87 (37%) patients, 88% had persistent loss at end of follow-up
  - Associated with older age, duration of treatment, & total dose, not to vestibular or renal toxicity
  - Amikacin > Kanamycin > Streptomycin
  - TIW = daily Rx

Side Effects of Individual TB Drugs
Rifampin: Drug Interactions

- Rifampin induces cytochrome P450 class of enzymes
  - Involved in drug metabolism
- Rifampin interacts with
  - Narcotics (methadone) – ↓
  - Corticosteroids – ↓
  - Warfarin (coumadin) – ↓
  - Phenytoin (dilantin) – ↓
  - Contraceptives (estrogens) – ↓
  - HIV protease inhibitors & nonnucleoside reverse transcriptase inhibitors – complex interactions
Rifampin: Hypersensitivity Reactions

- Flu-like syndrome with fever, chills, headache, & bone pain
  - Can begin 1–2 hrs after medication dose and resolve spontaneously after 6–8 hrs
  - More common in intermittent dosing, higher dose
  - Can try daily therapy if mild

- Severe immunologic reactions – rare, each < 0.1% patients
  - Low platelet count / petechiae
  - Kidney dysfunction
  - Hemolytic anemia
  - Thrombotic thrombocytopenic purpura
Rifampin

- Red–orange discoloration urine, tears, perspiration, feces
  - Can permanently discolor soft contact lenses
Pyrazinamide (PZA)

- Arthralgias common – Rx symptomatically
- Elevated uric acid
  - PZA is a pro-drug, converted to the active compound Pyrazinoic acid
  - Pyrazinoic acid blocks renal tubular excretion of uric acid => elevated uric acid
  - Allopurinol does not reverse this
  - Routine measurement of uric acid is not recommended
- Gout is rare
- Hyperuricemia without gout is not a reason for discontinuing drug
Ethionamide

- Endocrine disturbances
  - Gynecomastia, alopecia, hypothyroidism, impotence
  - Diabetes may be more difficult to manage
  - Acne
  - Irregular menstrual cycles
Capreomycin

- Electrolyte disturbances
  - Potassium, calcium, and magnesium depletion

- Proteinuria is common
Quinolones

- Tendonitis, tendon rupture – very rare
  - All ages
  - Greater risk age >60
  - Patients taking corticosteroids
  - Transplant patients
- QTc prolongation
- Nausea & diarrhea
Hypothyroidism is common
- Increased incidence when used with ethionamide
- Reversible when drug stopped
- Goiter can develop

Malabsorption
- Steatorrhea (fat malabsorption)
- Doubling of prothrombin time
  - Vitamin K is a fat soluble vitamin
- Levels of fat soluble vitamins (A, D, E) can be measured & monitored
Linezolid

- Myelosuppression
- Serotonin syndrome
- Nausea & diarrhea
## Adverse Drug Reactions

<table>
<thead>
<tr>
<th></th>
<th>RIF</th>
<th>INH</th>
<th>PZA</th>
<th>EMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>GI Intolerance</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Optic Neuritis</td>
<td>X</td>
<td>(rare)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Gout</td>
<td></td>
<td>X</td>
<td>X</td>
<td>(rare)</td>
</tr>
<tr>
<td>Discoloration of body fluid</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Courtesy of Shu-Hua Wang, MD, MPH & TM
Stuff Happens; Be Prepared
August 5, 2009

- 53 year old African American woman
- HIV negative; former crack user
- Sickle cell trait
- In 2005 treated for miliary / CNS TB
  - Completed Rx 5/31/06
- Hospital admission 8/5/09
  - 2 weeks fever, chills, anorexia, abdominal swelling
  - TB peritonitis suspected – 1700 mil ascitic fluid drained
Subsequent course 8/2009

- Discharged to DDHWP 8/14/2009
  - Continued on RIPE by DOT daily
- August 22 -26, 2009 re-admitted with abdominal girth, shortness of breath

<table>
<thead>
<tr>
<th></th>
<th>8/22</th>
<th>8/23</th>
<th>8/26</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alk Phos</td>
<td>105*</td>
<td>112*</td>
<td>122*</td>
</tr>
<tr>
<td>ALT</td>
<td>199</td>
<td>521</td>
<td>463</td>
</tr>
<tr>
<td>AST</td>
<td>1067</td>
<td>2212</td>
<td>286</td>
</tr>
<tr>
<td>Bili direct</td>
<td>1.9</td>
<td>2.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Bili total</td>
<td>3</td>
<td>4.3</td>
<td>2.7</td>
</tr>
</tbody>
</table>

* normal, others

Urine bilirubin + urobilinogen 4
INR 2, albumin 2.1 (low)
Subsequent course 8/2009

- Ascitic fluid aspirated. Lab values unchanged.
- All TB medications were discontinued.
- Discharged to DDHWP on 8/14.
What should be done now

- Look for cause. What happened?
  - Tylenol level <10
  - Review of hospital records: Hepatitis A, B, C serologies all negative
  - BP was normal on admission
  - At most she drank 1 frozen daiquiri
What should you do now with respect to TB meds?

- Should you take into consideration the fact that she looks ill & remains symptomatic?
- Are you worried about drug resistance?

8/27 started on

- Moxifloxacin 400 mg daily
- Capreomycin 1 g IM daily
- EMB 1200 mg daily (weight 155 lb)
What do you want to do & watch out for?

- Capreomycin
  - Electrolyte abnormalities!
  - Kidney disease, hearing loss, vestibular dysfunction are dose and cumulative dose-dependent
- This is a complicated case and needs close observation and support
September – October, 2009

- C/O light-headedness with standing, continued poor appetite
- Ascites resolved
- Weight stable 153–155#
- Frequent visits & blood tests planned
## September – October, 2009

<table>
<thead>
<tr>
<th></th>
<th>9/2/09</th>
<th>9/14/09</th>
<th>9/29/09</th>
<th>10/5/09</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>4.3</td>
<td>3.0*</td>
<td>2.5*</td>
<td>2.6*</td>
</tr>
<tr>
<td>Magnesium</td>
<td></td>
<td></td>
<td>1.1*</td>
<td>1.6</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>125**</td>
<td>131**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST</td>
<td>68**</td>
<td>56**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>126**</td>
<td>46**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bili</td>
<td>1.2</td>
<td>.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* *Low
** *High
Aggressively replace potassium & magnesium
  ◦ Potassium pills large & hard to swallow

Do you think this is TB?
  ◦ Mid Sept culture +, no resistance

Rifampin reintroduced 9/29

Capreomycin changed to M, W, F on 9/29
  ◦ Continued in case RIF not tolerated

Capreomycin discontinued 10/6

Would you reintroduce another first line drug? When?
INH: Acetylators

- Genetic variation => fast, slow, & intermediate acetylators
  - Significance unclear
  - Genotyping suggests slow acetylators develop higher peak ALT & more frequent elevations >3 X ULN than fast acetylators
    - Unknown significance