Mayo Clinic Center for Tuberculosis

Tuberculosis Drug Toxicities & Approaches to Management
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John W. Wilson, MD FIDSA
Associate Professor of Medicine
Division of Infectious Diseases
Mayo Clinic, Rochester MN
Disclosures

• None
Need to acknowledge for patients

TB therapy *can be difficult*

• Prolonged treatment program
• Many pills in treatment program
• Common drug intolerances

• *But treatment is effective!*
### Common Side-effects of TB drugs

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<th>Drug</th>
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Understanding common drug toxicities

• 1<sup>st</sup> step: identify the most likely offending drug by understanding drug profiles:
  → *Brief review* of more common TB drug toxicities:

SECTION I
Isoniazid (INH) – Adverse reactions

- Hepatotoxicity / hepatitis - not related to acetylation status
  - Increased in HIV (4x), HCV (5x) or both HIV-HCV (14x) co-infections
  - Usually in 1st 4-8 weeks of therapy) – typically 0.1-1% risk without underlying liver disease
  - *Rapid improvement* (AST/ALT) after stopping drugs - clue to INH toxicity

- Note transient *asymptomatic elevation* of AST/ALT in 10-15% (usually in 1st 4-8 weeks of therapy) – usually resolves

- **Peripheral neuropathy** – give vitamin B6 (6-50 mg/d) to at risk patients; “stocking glove” process, numbness / tingling

- **Other:**
  - Hypersensitivity – (+) ANA (< 20%); lupus-like reaction (<10%)
  - Arthralgias, pellagra, acidosis
  - **Drowsiness** – therefore favor admin. at night
  - **CNS** - toxic psychosis, behavioral changes, seizure / gen. convulsions
Rifampin – Adverse reactions

- Hepatotoxicity / hepatitis ($\uparrow$ bilirubin is a clue to RFP toxicity; $\uparrow$AST/ALT)
- Cytopenias - $\downarrow$WBC, $\downarrow$Plts (*bleeding problems)
- Orange discoloration of body fluids; stains soft contact lenses
  - Not a toxicity; this is expected
- Light chain proteinuria / nephrotoxicity
  - Coumadin
- Influenza-like syndrome
- Hypersensitivity reactions (lupus-like reactions can occur with rifamycins)
- Drug interactions - induces Cyt. P450 system and will decrease levels of:
  - Steroids
  - OCAs/estrogen
  - Protease inhibitors
  - Coumadin
  - Methadone
  - Theophylline
  - Digoxin
  - Quinidine
  - Dapsone
  - OHAs
  - Azoles
  - Ca2+ channel blockers
Rifampin – Adverse reactions

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  - Dapsone
  - OHAs
  - Azoles
  - Ca2+ channel blockers
Pyrazinamide (PZA) – Adv rxns

• Hepatotoxicity / hepatitis – modest rises in transaminases; *Slow* hepatic/transaminase recovery is clue to PZA toxicity

• Hyperuricemia – can be used as a marker of drug compliancy
  – Development of gout is rare

• *Arthralgias* - particularly of shoulders

• Other: GI upset, Rash, Glucose dysregulation
Ethambutol – adverse reactions

- **Retrobulbar / optic neuritis** - ↓ visual field; ↓ red-green color discrimination
  - Monitoring - Visual acuity & color vision (baseline and monthly)

- **Contraindications:**
  - Pre-existing optic neuritis (from any cause)
  - Inability (i.e. young pt. age) to report visual disturbances

- **Other:**
  - peripheral neuropathy (rare) - occasionally in legs
  - hyperuricemia (rare)
  - hair loss (rare)
Antimicrobial Agents
General Principles - 2nd Line Agents

Less Effective

More Toxic

More Expensive
2nd - line Anti-Tuberculosis Drugs

- Aminoglycosides
  - Streptomycin, Amikacin & Kanamycin
- Capreomycin
- Thioamides
  - Ethionamide
  - Prothionamide
- Fluoroquinolones
  - Moxifloxacin
  - Levofloxacin
  - Ciprofloxacin
- Cycloserine (and Terizidone)
- Para-Aminosalicylic Acid (PAS)
- Other:
  - Linezolid
  - Bedaquiline (TMC 207) – FDA approved 12/2012; a new diarlyquiline
  - New nitroimidazoles (investigational)
Streptomycin

Adverse reactions:

• 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

• “Newer” fluoroquinolones preferred:
  • *Moxifloxacin, Levofloxacin*
    – More active compared to ciprofloxacin, ofloxacin
• Generally *well tolerated* among 2nd line TB drugs
• Notable side effects:
  – Tendonitis; tendon rupture (Achilles tendon most common)
  – QTc prolongation
    • Higher risk when given with other QTc prolonging drugs –
      e.g. bedaquiline, clofazimine, Zofran, azole-antifungals,
      etc.
  – Contraindicated in patients with Myasthenia Gravis
  – Insomnia, lightheadedness, dizziness
Linezolid

- An oxazolidinone
- 600 mg once daily dosing preferred
  - Twice daily dosing recommended for MRSA and other drug-resistant Gram-positive bacteria

- Select Toxicities include:
  - 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

- *GI intolerance – (high likelihood) N/V, diarrhea, dysgeusia; metallic taste
- Arthralgias
- Endocrine disorders: *Hypothyroidism
- *Glucose intolerance
- Sexual dysfunction ↓Libido
- Erectile dysfunction
- Menstrual Abnor.
- Peripheral neuropathy (with prolonged therapy) - reversible
- Hepatitis (10% cases) - rarely serious
- Caution with co-administration of:
  - PAS (GI distress, hypothyroidism)
  - Isoniazid (peripheral neuropathy, hepatitis)
Cycloserine

• CNS toxicity
  – Inability to concentrate and lethargy
  – Seizure, depression, psychosis, and suicidal ideation
    • *usually* occur at peak concentrations > 35 mcg/ml
    • Can also be seen in the normal therapeutic range
    • Need to give Vitamin B6, 100 mg/d

• Other Toxicities:
  – 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
- *GI disturbance - anorexia, nausea, vomiting, abdominal discomfort
- Hypothyroidism, goiter (PAS has anti-thyroid effect); *Caution when administering with Ethionamide
- Hepatic dysfunction
- Hypersensitivity reaction / skin rash
Dose Escalation Strategies:
Ethionamide, Cycloserine, PAS

- Ethionamide & cycloserine
  - Start with 250 mg daily x a few days
  - Increase to 250 mg bid x a few days
  - Increase to 250 mg qAM and 500 mg q/PM
    - Check serum level

- PAS (Paser granules, sachet packets)
  - Start with 2 gm bid x a few days
  - Increase to 2 gm/qAM and 4 gm q/PM x few days
  - Increase to 4 gm bid
    - Check serum level

UCSF/Francis Curry: Drug-Resistant Tuberculosis:
Bedaquiline

- Increased risk of death (11.4% vs. 2.5% in comparator group)
- Elevated QTc (although not felt to be a major risk by CDC group meeting)
  - May be additive with other QTc prolonging drugs - *caution by FDA
- Higher hepatic adverse reactions
- 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 (via accelerated 3A4 metabolism)
- Limited data in HIV co-infected patients

CDC RTMCC meeting January 14-15, 2013
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)
Management strategies for the more common drug toxicities

SECTION II
Approach to Drug-Associated Hepatitis

General Principles:

• Not unusual for patients just starting combination TB therapy to experience upset stomach
  • Pts need counseling that this is *NOT uncommon*
  • INH, Rifampin, PZA all can produce gastritis
    – Symptoms can be similar to hepatitis, but LFTs *remain normal*

• Patients who develop anorexia, nausea, vomiting, abdominal pain, jaundice – more concerning
  • Stop all medications promptly, examine patient and check LFTs
Approach to Drug-Associated Hepatitis
General Principles (cont’d):

• ALT is more specific for hepatocellular injury
  – AST can also be produced from muscle, heart, etc.
• If AST > ALT, assess for excessive alcohol intake
• 10-20% of patients on INH will have asymptomatic rise in transaminases
  – Tends to occur during 1st few months on INH
  – Not a toxicity and does not require cessation of therapy
  – Improves with continuation of therapy
Approach to Drug-Associated Hepatitis

Follow-up assessments:

• Stop meds with any abnormal LFTs and the presence of adverse symptoms
  – Some guidelines state adverse symptoms and transaminases ≥ 3 x upper limits of normal range

• If LFTs abnormal (AST or ALT > 5x upper limit of normal) or if bilirubin is elevated, with or without symptoms, all TB drugs should be **promptly stopped**

• Patient should have LFTs checked 1-2x weekly
  – If symptoms persist > 2 weeks off TB medications or if LFTs continue to worsen, then should suspect progressive hepatitis or an unrelated cause of hepatitis – patient may need hospitalization
    • Underlying HCV, HBV, acute HAV infection
    • other medications (non-TB)
    • Alcoholism (usually AST >ALT)

• As soon as hepatitis is identified, a hepatitis viral profile should be ordered
Approach to Drug-Associated Hepatitis

Important notes:

• If the patient has extensive pulmonary, meningeal or disseminated TB – then may not be able to temporarily observe off therapy:
  – Start a new combination drug regimen that is non-liver metabolized (i.e. EMB, FQ, AMK), while awaiting LFTs to improve:
    • Minimizing risk of further hepatotoxicity
    • May be started even before LFTs return to normal.

• Pattern of LFT abnormalities – clues to offending agent
  – RFP usually produces a **cholestatic pattern** (bilirubin & Alk phos. out of proportions to AST/ALT)
  – INH, RFP, PZA may produce **hepatocellular pattern** (AST/ALT elevated out of proportion to bilirubin or Alk phos)
Approach to Drug-Associated Hepatitis

Restarting Medications after LFTs normalize or significantly improve:

- **Hepatocellular pattern:**
  - Start with Ethambutol and Rifampin x 1 week
    - Recheck LFTs – if stable/improved:
  - Add INH or PZA *(which drug to add is debated; favor adding INH)*
    - Recheck LFTs – if they remain stable:
    - Continue with EMB / Rifampin / INH or EMB / Rifampin / PZA for the duration of therapy
      - At least monthly LFTs (more frequently early on)

- **Notes:**
  - INH and PZA are most commonly associated with hepatotoxicity
    - Some reports implication PZA more frequently
    - Combination using PZA may be more problematic
    - PZA less important in combination TB drug regimen
      AJRCCM 2003 167:1472-77
Approach to Drug-Associated Hepatitis
Restarting Medications after LFTs normalize or significantly improve:

• **Cholestatic pattern:**
  - Start with INH and ethambutol x 1 week
    • Recheck LFTs – if stable/improved:
  - Add PZA
    • Recheck LFTs – if they remain stable:
    • Continue with INH/EMB/PZA – favor adding FQ
      - At least monthly LFTs (more frequently early on)
      - More prolonged duration of therapy without rifamycin used
      - Might consider graded introduction of rifabutin (judgement call)

• If symptoms are not related to TB drugs, then restart entire drug regimen promptly and observe
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<th>Effects on Liver</th>
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| 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:         | Occasionlly 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 meningeval TB |
| Ethambutol           |                                                                                                                                                |
| Levofloxacin         |                                                                                                                                                |
| Amikacin/other aminoglycosides |                                                                                                                                                    |
| Cycloserine          |                                                                                                                                                |
Summary - algorithm

Clinical Policies and Protocols
Bureau of Tuberculosis Control
New York City Department of Health and Mental Hygiene
4th ed. 2008
Other *select* drug reactions:

- CNS changes
  - Behavioral
  - Seizures
- Peripheral neuropathy
- Skin Rash
  - Mild skin rash
  - TEN / SJS
- Hypothyroidism
CNS changes

- Depression
  - Cycloserine
  - Ethionamide
  - INH (in patient with baseline *unstable* or untreated mental health problems)
    - Need to check pt’s mental health history
    - Can cause sleepiness (best to give at night / before bedtime for LTBI therapy)

- Psychosis: Cycloserine, INH

- Seizures: INH, ethionamide

- Remember:
  - **Pyridoxine (Vit B6)** required with Cycloserine and Ethionamide; used with INH in pts with select risk factors
  - Add 50 mg Vit. B6 for each 250 mg of cycloserine (variable) OR 100 mg/d total with CYC
Peripheral Neuropathy

• Symmetric polyneuropathy
  – Early: paresthesias
  – Late: sensory loss, ↓reflexes, ↓proprioception

• Predisposed in patients with:
  – Alcoholism, diabetes, HIV infection, malnutrition

• TB drugs implicated:
  – Isoniazid, ethionamide, cycloserine, linezolid
  – **Note: overly high Vit. B6 doses (> 200 mg/d) can occasionally produce neuropathy

• Treatment
  – Start Vit. B6 if not already done so (typically 100-150 mg/d)
  – Stop/change TB drug therapy (if possible)
  – Low dose TCAs or gabapentin (if refractory)
Skin lesions - I

Hypersensitivity syndrome / TEN / SJS:

- Idiosyncratic reaction
  - Typically during first 1-2 months of therapy
- Progressive skin lesions with fever, and often multi-organ involvement; +/- lymphadenopathy

Management approach:
- Immediate stop all medications
  - Avoid restarted offending agent – if known
- Dermatology consult (may need to be inpatient)
  - Skin biopsies occasionally recommended – depending appearance of skin lesions
- Consider desensitization or cautious restarting of medications (possible inpatient setting)
Skin lesions - II

Maculopapular rash & Itching

• Typically develop early / during first few weeks of therapy
• May resolve with cautious continuation of all medications (if mild skin lesions / symptoms)
• Moderate / severe: need to stop drugs
  – Reported with all 1st line TB drugs
  – Ensure no other non-TB drugs were started
    • E.g. OTC agents, herbal drugs; other prescriptions drugs
  – For non-type I reactions (non-anaphylaxis / non-angioedema):
    • Reintroduce TB medications 1 at a time – observing for recurrence of skin lesions
    • Start with most important TB drugs: Rifampin – then INH – then PZA or EMB
    • Space drug introductions by 3-5 days
Hypothyroidism

• TB drugs implicated:
  – Ethionamide
  – Para-aminosalicylic acid (PAS)

• Risk increased when both drugs used together (at least 40% incidence; possibly higher)
  – A reversible endocrine effect

• Monitoring:
  – Monthly clinical assessments
  – Check sTSH baseline and q 3 months
  – Replace with thyroid hormone (Synthroid) if sTSH rises
    • Do not need to stop TB drugs
The End

Questions?

• TB drug toxicity
• Management of toxicity

• Nevada facts?
  – “Nev-AD-a,” or “Nev-a-duh”
  – NOT “Nev-AH-da”