Pharmacology of Anti-TB Medications

Sandra Chai, MD
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Essential Skills for the TB Nurse Case Manager
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*Sandra Chai, MD* has the following disclosures to make:

- No conflict of interests

- No relevant financial relationships with any commercial companies pertaining to this educational activity
Pharmacology of TB Drugs
Purpose of Talk

- We know you don't see TB often
- TB management is complicated!
- We don’t expect you to be TB experts
- You’re on the “front lines” of battle
- So you should be armed with some understanding of our inscrutable orders
- We’re here for you!
- The only dumb question is the one you should have asked, but didn’t!

TB Treatment Objectives

Name 3 for a major award!
Treatment Objectives

1. Kill germs fast to treat the patient and protect the public
2. Kill persistent germs to attain cure and prevent relapse
3. Prevent drug resistance

First-Line Drugs

- A rifamycin, usually rifampin (RIF)
- Isoniazid (INH)
- Pyrazinamide (PZA)
- Ethambutol (EMB)
- And don’t forget Pyridoxine (B6)
Why so many drugs???

- There appear to be at least 2 bacterial subpopulations that differ in their intrinsic drug susceptibility: one divides rapidly and is killed fast and the other is more dormant and dies more slowly (“persistent”)
- Combo of bactericidal (kill rapidly multiplying germs) and bacteriostatic (kill persistent, more dormant germs) drugs is needed
- *It takes a village to kill bacilli!*

Horsburgh C, Barry C. Treatment of Tuberculosis. NEJM 2015;373:2149-60

Bi-phasic kill curve

- Treatment failure with individual drugs due to rapid emergence of resistance (via mutations)
- Likelihood of development of resistance to ≥2 TB drugs is the product of the individual mutation rates
- Protect rifampin susceptibility in populations with a high rate (≥4%) of INH resistance

But that’s not all there is to it.

Name the other key component of TB management for a Major Award!
DOT compared to SAT

- Hastens sputum culture conversion
- Increases successful treatment and cure
- Prevents relapse and resistance

DOT continued

- Face-to-face monitoring for treatment adherence and adverse events
- Reinforce patient education
Phases of Treatment

Intensive/Initial Continuation

Initial/Intensive Phase (RIPE)
2 months/56 doses
Goal: Rapidly reduce the population of actively growing bugs

- RIF 600 mg daily
- INH 300 daily
- PZA 20 mg/kg daily
- EMB 20 mg/kg daily
- [B6 50 mg daily]
Continuation Phase
Course length varies from 2-10 months

Goal: Eradicate persistent bugs

- RIF 600 mg usually 5-7 days/week
- INH 300 mg usually 5-7 days/week
- [B6 50 mg to accompany INH]

Drug Susceptibility Testing

- Rule out drug resistant TB
- Can guide move to continuation phase
- If Plan A is poorly tolerated, susceptibility testing helps craft Plan B (or C...)

Before transitioning from Intensive to Continuation

Must have:

- Susceptibility report
- Sputum culture conversion

A Closer Look at the Drugs:

- Rationale
- Side effects
- Serious adverse events
The Good: Rationale

Rifampin

- Bactericidal
- Active against rapidly dividing and semi-dormant bugs
- Cornerstone of short course therapy
- Well absorbed, good tissue levels
Isoniazid

- Accounts for the majority of early bactericidal activity of multidrug regimens
- Excellent absorption and tissue penetration

Pyrazinamide

- Greatest activity against dormant or semi-dormant (slow-growing) organisms within macrophages or caseous foci
- Allows for short course treatment regimens
- If PZA is lost early, treatment must be extended by 3 months
Ethambutol

- Least potent 1st-line drug
- Primary role is to prevent rifampin resistance when INH resistance may be present
- This is why ETH can be stopped when susceptibility testing confirms INH and RIF sensitivity

Pyridoxine (B6)

- A vitamin, not an antibiotic
- An essential companion of INH
- Decreases likelihood of INH neurotoxicity
The Bad: Side Effects

GI Symptoms
Nausea, abdominal pain, anorexia:
- Rifamycins
- INH
- PZA
- Fluoroquinolones (levo, moxi)
- Other second-line agents
GI Symptoms

If LFTs are normal:

- Symptomatic treatment: antiemetics, antidiarrheals
- No antacids within 2 hrs of fluoroquinolones (levo, moxi)
- Avoid other GI irritants (NSAIDS, etc.)
- Hydrate
- Take meds after a light snack
- Space meds during the day
- Take the culprit at HS

Hepatotoxicity

- INH, RIF, PZA
  - INH and PZA drive up transaminases (ALT, AST)
  - RIF tends to be cholestatic (↑ T. bili, GGT)
- 20% of pts on INH will have asymptomatic elevation of ALT, AST
- Fulminant hepatitis falls under “Ugly”
Hepatotoxicity Risk Factors

- Alcohol
- Other drugs
  - OTC: Acetaminophen, fish oil, herbal meds
  - Antiretroviral agents
- Underlying hepatitis (especially C)

Interventions for Hepatotoxicity

- **STOP meds**
  - If ALT or AST 3x ULN with sx
  - If ALT or AST 5x ULN without sx
  - If T. bili $\geq 3$ mg/dl
- Look for contributing factors
- If meds are held, *step-wise* re-challenge of drugs can begin when ALT is <2x ULN
Interventions for Hepatotoxicity

Tell pts: In case of N+V, abdominal pain or unexplained fatigue, stop meds and call LHU!

Then call us!

Dermatologic Effects

- Maculopapular rash and/or itching: All TB drugs
  - If mild, treat symptomatically and press on
  - If severe, see “Ugly”
- Hives, w/ or w/o fever:
  - #1 INH, then RIF, PZA, others
  - Hold meds
- Flushing w/in 2-3 hrs of meds
  - RIF, PZA
  - Antihistamine if bothersome
Dermatologic Effects

- Photosensitivity: PZA, FQs
- Lichenoid reactions (ETH, INH)
  Purple and pruritic
  ![DermNet New Zealand]
- If not severe, hold and then rechallenge to ID culprit, one med at a time

Aches and Pains

- Flu-like syndrome: RIF, starts 1-2 hrs after dose, lasts several hours
- Myalgias, arthralgias: PZA, FQs INH, rifabutin, more
  May reflect electrolyte disturbance (√ CMP)
  Not an indication to stop drug
- Acute gouty arthritis can occur on PZA in pts with pre-existing gout
- Tendinitis: FQ’s. Symptomatic care if mild; stop drug if moderate or severe. Tendon rupture is rare
Neurotoxicity: Peripheral Neuropathy

- INH. Less commonly linezolid. Rarely ETH, FQs
- Symmetrical "stocking and glove" tingling, prickling, burning
- Increased risk with other conditions associated with neuropathy:
  - DM
  - Alcoholism
  - Malnutrition
  - Renal failure
  - HIV
- Pyridoxine (B6) 50 mg/day reduces risk

Why B6?

- INH causes a functional deficiency of pyridoxine by competing with it in its action as a cofactor in the synthesis of synaptic neurotransmitters
- Extra B6 is needed to overcome this
- Give B6 alongside INH and linezolid
Ophthalmic Toxicity

- ETH, rarely INH
- Red-green color desaturation
- Painless bilateral vision loss
- Insidious onset!
- Reversible if caught early
- Baseline eye exam on ETH
- Monthly sx check: blurred vision, scotoma
- PATIENT EDUCATION
Odds and Ends

- Orange discoloration of body fluids on rifamycins
- Metallic taste: FQ’s. It will go away
- Arrhythmias (QT prolongation): FQ’s, esp. moxi

The Ugly:
Serious Adverse Events
Fulminant INH Hepatitis

- Idiosyncratic
- Rare
- Can be fatal or require transplant
- Typically onset within 2-3 months
- Symptomatic: Fatigue, malaise, anorexia, nausea, “flu-like,” RUQ pain, jaundice (later)
- Risk factors: age, alcohol, concurrent hepatotoxic drugs, underlying liver disease, pregnant and post-partum

- Hold meds; draw CMP; ER? Call us!

Severe Systemic Reactions
Anaphylaxis

- Occurs within minutes of dose
  - Urticaria
  - Angioedema
  - Pruritis
  - Hypotension
  - SOB
- Stop drugs!
- Call 911! Then call us
- Drug desensitization requires expert assistance
Severe Systemic Reactions
Stevens-Johnson Syndrome
Toxic Epidermal Necrolysis

- Severe mucocutaneous reaction
- Extensive necrosis and detachment of dermis

- Hold meds! Go to ER! Call us!

Severe Systemic Reactions
DRESS

- Drug Reaction with Eosinophilia and Systemic Symptoms
- Rare but potentially life-threatening
- RIF, INH, ETH
- 2-8 weeks after start of meds
- Rash, fever, facial edema, lymphadenopathy
- Abnormal LFTs, eosinophilia

- Hold meds! Go to ER? Call us!
When TB goes “off script”
Second-Line Drugs

- Fluoroquinolones: Levo, moxi
- Linezolid
- Cycloserine
- Ethionamide
- PAS

- Streptomycin
- Capreomycin
- Amikacin/kanamycin
- Bedaquiline

“All TB Is Not Treated Equal”
Length of Treatment Courses
### Pulmonary TB

<table>
<thead>
<tr>
<th>Type</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Non-cavitary</td>
<td>6 mo.</td>
</tr>
<tr>
<td>Cavitary</td>
<td>9-12 mo.</td>
</tr>
<tr>
<td>Clinical case (culture negative)</td>
<td>4 mo.</td>
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</tbody>
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### Extra-pulmonary TB

- **Usual 2-month intensive phase**
  - Pleural
  - Lymphadenitis
  - Disseminated (miliary)
  - Pericarditis
  - Peritoneal
  - GU

- **6 months total**
Extra-pulmonary TB

Usual 2-month intensive phase

• CNS
  Meningitis
  Tuberculoma

9-12 months total

• Brain abscess
• Bone

A Few Special Scenarios Need for Steroids

Steroids recommended in addition to antibiotics:

  CNS TB
  Pericarditis
One more Major Award!

Do we treat LTBI in pregnancy?

A Few Special Scenarios
Pregnancy/Postpartum

- Treat TB! But not LTBI unless high risk (recently infected, HIV+)
- U.S. leaves out PZA (but WHO doesn’t)
- Beware hepatotoxicity in the peripartum period
- Breastfeeding is OK
- B6 for both mom (on INH) and breastfed infant
A Few Special Scenarios

TB Drugs in HIV

LTBI

- 30-100x more likely to reactivate than HIV- (5-10%/year as opposed to 5-10% lifetime risk)
- Rifamycins induce hepatic CYP3A4 enzymes, which can accelerate the metabolism of HIV meds (PIs and some NNRTIs)
- Hence, INH is preferred (usual 9 months)
- No need for increased treatment length

Active TB

- TB is an AIDS-defining illness and indicates need for HIV treatment
- Length of TB treatment is as usual
- Rifabutin is a less potent inducer of hepatic CYP3A4 enzymes than rifampin, so is preferred in pts on PIs and NNRTIs. Occasional impact of HIV drugs on rifabutin
- Lots of potential drug interactions. It’s complicated!
A Few Special Scenarios

TB Drugs in HIV

Active TB

- Highly intermittent dosing is avoided
  - ↑ Risk of
    - Relapse
    - Acquired rifampin resistance
- DOT essential
- Watch out for IRIS

A Few Words about

Rifapentine

- PREVENT Tuberculosis study compared 3HP to 9H in over 7500 people
- 12 weeks of 3HP (INH 900 mg + rifapentine 900 mg) is as effective as 9 months of INH 300 mg/day (9H) for LTBI
- But it can be challenging to take
- Systemic drug reactions (SDR) are more common in 3HP than in 9H

Sterling et al. CID 2015;61; 517-34
Data from the PREVENT Tuberculosis study

Systemic drug reactions (SDRs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rate</th>
<th>(Counts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3HP</td>
<td>3.5%</td>
<td>(138/3893)</td>
</tr>
<tr>
<td>9H</td>
<td>0.3%</td>
<td>(15/3659)</td>
</tr>
</tbody>
</table>

Of the 138 3HP SDRs,

- 63% were “flu-like” syndrome: Fever, chills, fatigue, malaise, HA, myalgias, arthralgias
- 17% were rash
- 0.3% were severe: hypotension or syncope

SDRs in 3HP

- Median of 3 doses
- 4 hours after dose
- Resolution by 24 hours
- No permanent sequelae
- “Bad” but not “Ugly”
SDR Demographics

Flu-like
- White
- Female
- ≥35 y/o
- Lower BMI

Severe
- White
- Concommitant meds

Finally, some food for thought

Drugs Best Taken With Food
- Rifapentine: Fatty meal enhances absorption ("You want fries with that?")
- ETH

Drugs Best Taken on an Empty Stomach
- RIF (go figure)
- INH

**FQs:** Avoid antacids within 2 hours
We’re here for you!

Remember:
The only dumb question is the one you should have asked, but didn’t!