Management of TB Drug Adverse Reactions

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Director, HIV program
Conflicts/Disclosure

• None.
In 2015, there were an estimated 10.4 million new (incident) TB cases
- 5.9 million (56%) among men
- 3.5 million (34%) among women
- 1.0 million (10%) among children
- People living with HIV accounted for 1.2 million (11%) of all new TB cases.
## Anti-Tuberculous Drugs

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Group 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Amikacin</td>
<td>Levofloxacin</td>
<td>Ethionamide</td>
<td>Linezolid</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Capreomycin</td>
<td>Moxifloxacin</td>
<td>Prothionamide</td>
<td>Clofazimine</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Kanamycin</td>
<td>Gatifloxacin</td>
<td>Cycloserine</td>
<td>High-dose</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Streptomycin</td>
<td>Ofloxacin</td>
<td>Terizidone</td>
<td>Isoniazid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PAS</td>
<td>Amoxicillin/</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clavulanate</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Imipenem</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Clarithromycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thiacetazone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bedaquiline</td>
</tr>
</tbody>
</table>

### Drug Groups
- **First line**:
  - Isoniazid
  - Rifampin
  - Pyrazinamide
  - Ethambutol
- **Second-line**:
  - Amikacin
  - Capreomycin
  - Kanamycin
  - Streptomycin
- **Third-line**:
  - Levofloxacin
  - Moxifloxacin
  - Gatifloxacin
  - Ofloxacin
  - Ethionamide
  - Prothionamide
  - Cycloserine
  - Terizidone
  - PAS
  - Linezolid
  - Clofazimine
  - High-dose Isoniazid
  - Amoxicillin/Clavulanate
  - Imipenem
  - Clarithromycin
  - Thiacetazone
  - Bedaquiline
Duration of Tuberculosis Treatment

Drug-Susceptible
- First-line drugs
- INH/RIF/EMB/PZA X 2 months
- INH/RIF X 4 months

MDR
- 2nd and 3rd Line drugs
- A minimum of 4 (preferably 5 or 6) active drugs
- More toxicity
- 18+ months

XDR
- 2nd and 3rd Line drugs
- A minimum of 4 (preferably 5 or 6) active drugs
- More toxicity
- 24+ months
- Consider surgery
Potency and Tolerability of TB Drugs

Increasing potency, reliability, reproducibility of susceptibility testing

First-line Drugs
- Rifampin
- Isoniazid
- Pyrazinamide
- Ethambutol

Fluoroquinolones
(moxifloxacin, gatifloxacin, levofloxacin)

Injectable agents
Aminoglycosides (streptomycin, amikacin, kanamycin)
Polypeptides (capreomycin)

Oral bacteriostatic agents
(ethionamide, prothionamide, cycloserine/terizidone, p-aminosalicylic acid, thiacetazone)

Agents with unclear efficacy
(clofazimine, amoxicillin-clavulanate, clarithromycin, linezolid)

Second-line Drugs

Decreasing tolerability

DR-TB: Drug-related Adverse Effects

- Depression/psychosis: 19%
- Hearing impairment: 13%
- Hepatitis: 13%
- Kidney impairment: 11%
- Loss of mobility: 8%
- Vision impairment: 7%
- Seizures: 1%
Adverse Events during Treatment of TB

• Very common
  – More than 80% of patients on treatment for DR-TB will have adverse events
• Even mild and common events can affect treatment outcomes
• Some adverse events life-threatening
• Some adverse events cause permanent disability
• Critical drugs may be discarded if not properly addressed
• Timely recognition and management of adverse events important for adherence and completion of treatment
Topics

• Drug-based approach
• Symptoms-based approach

BUT MORE IMPORTANTLY:

• General approach to managing drug reactions during treatment of tuberculosis
Learning Objectives

At the end of this talk, participants should be able to:

– Describe the General approach to managing drug adverse reactions
– Describe the drug-based approach to managing drug adverse reactions
– Describe the symptoms-based approach to managing drug adverse reactions
General Approach

- Resuming Treatment
- Educating patients
- Prevention
- Early Identification
- Systematic Evaluation
- Isolation Cause
- Managing Reaction
Education

- Importance of treating TB
- Importance of adherence
- Importance of Completion of treatment
- Potential side effects of prescribed treatment
- Simple ways of self managing common side effects
- Communication channel
Prevention

- Education
- Proper dosing
- Drug interactions
- Comorbidities
  - Liver
  - Kidney
  - CNS
Early Identification

- DOT
- Clinical visits
- Routine monitoring
- Communication channel for patient complaints/concerns
Systematic Evaluation

- Drug-based approach
- Symptoms-based approach
- Coordinated
- Thoughtful
- Comprehensive
Non-TB Drugs

Non-TB Disease-Related

Disease-Related

TB Drugs

TB

Non-TB

Comorbid Conditions

Progression Extra-pulmonary IRIS

7 I’s
Isolation of cause

- May enable single-drug substitution
- Retain key regimen components
- Minimize impact on pill burden and treatment duration
Managing AE

- Depends on severity
- Simple measures and reassurance may suffice
- Life-threatening will require discontinuation of entire regimen
- May need to check drug levels
- Monitor AE until resolution
## Severity Scales

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurosensory Alteration (includes paresthesia and painful neuropathy)</td>
<td>Minimal paresthesia causing no or minimal interference with usual social &amp; functional activities OR No symptoms with sensory alteration on examination</td>
<td>Sensory alteration or paresthesia causing greater than minimal interference with usual social &amp; functional activities</td>
<td>Sensory alteration or paresthesia causing inability to perform usual social &amp; functional activities</td>
<td>Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions</td>
</tr>
<tr>
<td>Specify type, if applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>NA</td>
<td>NA</td>
<td>1 to 3 seizures</td>
<td>Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)</td>
</tr>
<tr>
<td>New Onset Seizure ≥ 18 years of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ACTG Brief Peripheral Neuropathy Screen (BPNS)

1. Elicit Subjective Symptoms

Ask the subject to rate the severity of each symptom on a scale of 01 (mild) to 10 (most severe) for right and left feet and legs. Enter the score for each symptom in the columns marked R (right lower limb) and L (left lower limb).

<table>
<thead>
<tr>
<th>Normal</th>
<th>Mild</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>00</td>
<td>01</td>
<td>02</td>
</tr>
<tr>
<td>03</td>
<td>04</td>
<td>05</td>
</tr>
<tr>
<td>06</td>
<td>07</td>
<td>08</td>
</tr>
<tr>
<td>09</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>R</th>
<th>L</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Pain, aching, or burning in feet, legs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. &quot;Pins and needles&quot; in feet, legs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Numbness (lack of feeling) in feet, legs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Grade Subjective Symptoms

Use the single highest severity score above to obtain a subjective sensory neuropathy score.

<table>
<thead>
<tr>
<th>Subjective Sensory Neuropathy Score</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>01 – 03</td>
<td>1</td>
</tr>
<tr>
<td>04 – 06</td>
<td>2</td>
</tr>
<tr>
<td>07 – 10</td>
<td>3</td>
</tr>
</tbody>
</table>

3. Evaluate Perception of Vibration

Compress the ends of a 128-Hz tuning fork just hard enough that the sides touch. Place the vibrating tuning fork on a bony prominence on the subject’s wrist or hand to be sure that he/she can recognize the vibration or "buzzing" quality of the tuning fork. Again, compress the ends of the tuning fork just hard enough that the sides touch. Immediately place the vibrating tuning fork gently but firmly on the top of the distal interphalangeal (DIP) joint of one great toe and begin counting the seconds. Instruct the subject to tell you when the "buzzing" stops. Repeat for the other great toe.

<table>
<thead>
<tr>
<th>Vibration perception</th>
<th>Result</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felt &gt; 10 seconds</td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Felt 6-10 seconds</td>
<td>Mild loss</td>
<td>1</td>
</tr>
<tr>
<td>Felt &lt;5 seconds</td>
<td>Moderate loss</td>
<td>2</td>
</tr>
<tr>
<td>Not felt</td>
<td>Severe loss</td>
<td>3</td>
</tr>
<tr>
<td>Unable to or did not assess</td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>

4. Evaluate Deep Tendon Reflexes
# LFT Monitoring AND CUT-OFFS FOR STOPPING DRUGS

<table>
<thead>
<tr>
<th>Authority</th>
<th>Monitoring in presence of risk factors (especially liver diseases)</th>
<th>Cut-off levels for DILI and stopping drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATS</td>
<td>Yes</td>
<td>ALT &gt;200 IU/l or, ALT 120 IU/l with symptoms</td>
</tr>
<tr>
<td>BTS</td>
<td>Yes</td>
<td>ALT or AST &gt;200 IU/l, rise in bilirubin</td>
</tr>
<tr>
<td>ERS, WHO, IUATLD</td>
<td>-</td>
<td>AST &gt;200 IU/l</td>
</tr>
<tr>
<td>HKTBS</td>
<td>Yes</td>
<td>ALT &gt;200 IU/l, bilirubin &gt; 40μmol/l</td>
</tr>
</tbody>
</table>

LFT, liver function test; ALT, alanine transaminase; ALP, alkaline phosphatase; ATS, American Thoracic Society; BTS, British Thoracic Society; ERS, European Respiratory Society; WHO, World Health Organisation; IUATLD, International Union Against Tuberculosis and Lung Disease; HKTBS, Hong Kong Tuberculosis Service
Resumptions of Treatment

- The ultimate aim of drug reintroduction is to establish an effective regimen in a safe and speedy fashion.
- Sequential reintroduction may help identify the cause.
- Different algorithms exist.
- Symptomatic pre/peri treatment may be necessary.
## GUIDELINES ON THE MANAGEMENT OF TB-ASSOCIATED DILI

<table>
<thead>
<tr>
<th>Authority</th>
<th>Stopping TB drugs if clinical or symptomatic hepatitis</th>
<th>When to restart TB drugs</th>
<th>What TB drugs to start</th>
<th>Recommended LFT monitoring on rechallenge</th>
<th>What if DILI recurs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATS</td>
<td>Yes</td>
<td>ALT &lt; 80</td>
<td>R +/- E full dose</td>
<td>Check ALT 3-7 days after H rechallenge</td>
<td>Stop last drug added</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ALT within normal limits</td>
<td>After 3-7 days H (full dose) Z only if mild DILI</td>
<td>Daily monitoring of LFT</td>
<td>Stop offending drug, alternative regimen advised by fully trained physician</td>
</tr>
<tr>
<td>BTS</td>
<td>Yes</td>
<td>ALT within normal limits</td>
<td>S + E (if unwell or sputum smear positive within two weeks of commencing treatment) H (dose titration, every 2-3 days) R (dose titration, every 2-3 days) Z (dose titration, every 2-3 days)</td>
<td>LFT monitoring (no recommendation on frequency)</td>
<td>Stop all drugs, start S + E and start other drugs one at a time</td>
</tr>
<tr>
<td>ERS, WHO, IUATLD</td>
<td>Yes</td>
<td>LFT within normal limits</td>
<td>Start all drugs at full dosage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HKTBS</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
WHICH RECHALLENGE PROGRAM IS BEST

175 HIV-negative patients randomized to receive one of three rechallenge regimens

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm I</td>
<td>H, R, and Z at maximum dosages from day 1</td>
</tr>
<tr>
<td>Arm II</td>
<td>R at maximum dosage from day 1, H at maximum dosage from day 8, and Z at maximum dosage from day 15</td>
</tr>
<tr>
<td>Arm III</td>
<td>H at dosage of 100 mg/day from day 1, maximum dosage from day 4; R at dosage of 150 mg/day from day 8, maximum dosage from day 11; and Z at dosage of 500 mg/day from day 15, maximum dosage from day 18</td>
</tr>
</tbody>
</table>

*NOTE.* Maximum dosage was determined according to body weight, as follows: H, 5 mg/kg; R, 10 mg/kg; and Z, 25 mg/kg. H, isoniazid; R, rifampicin; Z, pyrazinamide.

No significant difference in recurrence rate (p=0.69)

# Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interacting Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>isoniazid</td>
<td>anti-seizure medication, coumadin</td>
</tr>
<tr>
<td>rifampin</td>
<td>Multiple drugs, notably HIV medication, immunomudulators, coumadin</td>
</tr>
<tr>
<td>quinolone</td>
<td>drugs causing QT prolongation</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>cyclosporine</td>
</tr>
</tbody>
</table>
## 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,</td>
</tr>
<tr>
<td></td>
<td>monoamine poisoning</td>
</tr>
<tr>
<td>rifampin</td>
<td>flu-like syndrome, hepatotoxicity, anemia,</td>
</tr>
<tr>
<td></td>
<td>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>
Signature Toxicities of Tenofovir

- Nephrotoxicity
- Osteopoenia
- Nephrotoxicity
Signature Toxicities of Emtricitabine

skin discoloration

skin discoloration
Signature Toxicities of Zidovudine

Bone marrow suppression with anemia and/or neutropenia
Signature Toxicities of Abacavir

Hypersensitivity reaction
Signature Toxicities of Efavirenz

- Rash
- CNS symptoms
- Teratogenic
Signature Toxicities of Nevirapine
Signature Toxicities of PIs

Hyperlipidemia
Signature Toxicities of Atazanavir

- Increased indirect bilirubin
- Prolonged PR interval/heart block
Signature Toxicities of Dolutegravir

Hypersensitivity
Symptoms-Based Approach

- Nausea/vomiting
- Liver Toxicity
- Rash
- Peripheral neuropathy
- Renal Failure
- Hypothyroid
- Hypokalemia
- Arthralgia
Nausea/vomiting

- Up to 90% early in treatment
- Causes: Ethionamide, PAS, INH, PZA, FQ, BDQ, preg
- Ensure hydration, fractionate doses, fractionate meals, anti-emetics
- Additional testing: K+, LFTs, pancreatic function
- May need to re-dose medications if vomiting happens within 30 minutes of taking tablets
Liver Toxicity

- More concerning for drug-induced injury when bilirubin and transaminases elevated (Hy’s law)
- Viral hepatitis, alcohol, PZA, INH, Rif, any of the TB medications
- Baseline: screen for HBV, HCV
- Screening: symptoms
- Laboratory monitoring if baseline abnormal or with certain conditions
• Up to 10% of patients
• Mild hives to SJS
• Screening: symptoms
• Cause: any drug; consider timing of onset, past episodes
• Mgmt. depends on severity
  • if severe, discontinue therapy and serially reintroduce
• Additional testing: consider infectious causes
Peripheral neuropathy

• Up to 30% of patients
• LZD, INH, CS, Ethionamide
• HIV, DM, alcohol use
• Screening: symptoms, subjective neuropathy scale
• Mgmt.:
  • Decrease LZD; if CS or INH, d/c;
  • Physical therapy; sturdy shoes; SSRIs;
• Management of comorbidity
• B6 for INH, LZD, CS
<table>
<thead>
<tr>
<th>Renal Failure</th>
</tr>
</thead>
</table>
| 1
| 2
| 3
| 4
| 6
| 7
| 8

- Up to 10% during DR-TB Rx
- More common in persons with HIV, DM
- Common causes: injectable, other nephrotoxic drugs (e.g. TDF)
- Screening: monthly on injectables
- Management:
  - Hydration
  - Manage comorbidity
  - d/c injectable,
- Up to 10% of patients
- More common in HIV infected
- Causes: Ethionamide, PAS
- Screening: symptoms
  - Fatigue, sensitivity to cold, constipation, dry skin, depression
- TSH if on ethionamide, PAS
- Management: Thyroid replacement therapy
- Additional testing: QTc
• Up to 15% during DR-TB Rx
• Cause: injectables
• More common with vomiting, diarrhea, alcohol
• Weakness, fatigue, muscle cramps, constipation

Screening: monthly while on injectable, if QTc prolonged
• Mgmt.:
  • Replete K, Mg
  • Ensure hydration
  • Calcium if QTc prolongation

Hypokalemia
• TB itself can cause arthritis
• Arthralgias are common, usually transient
• Physical exercise may help
• Treatment with nonsteroidal anti-inflammatory drugs may be useful
• If acute swelling, redness, and warmth, aspirate for diagnosis
• PZA may increase uric acid levels
  • Often asymptomatic
  • UA levels don’t match severity
• If arthritis, usually non-deforming and non-erosive
• Usually do not warrant stopping PZA or other anti-TB drugs
Laboratory Adverse Events

- Anemia
- Thrombocytopenia
- Leukopenia
- Hearing Loss
- Vision Loss
- Depression
- Psychosis
- Seizures
Anemia

- Can occur in as many as 25% of patients
- More common in patients with HIV, alcohol use
- Screening: symptoms, HgB monthly if on LZD
- Poor prognostic sign if persists with treatment
- Common causes: TB, LZD, HIV, ART
- Management strategies: iron supplementation, decrease dose of LZD, transfusion if indicated, discontinue other medications
Thrombocytopenia

- Relatively uncommon (<5%)
- More common in patients with co-morbidities such as HIV, alcohol use
- Screening: symptoms – easy bruising, bleeding
- Common cause: LZD, alcohol
- Mgmt.: lower dose or d/c LZD, monitor for bleeding
- Additional testing: Check WBC, other co-morbidities, alcohol screening
Leukopenia

- Relatively uncommon (<5%)
- More common in patients with co-morbidities such as HIV, alcohol use
- Screening: Monthly CBC
- Common cause: LZD, alcohol, HIV
- Mgmt.: lower dose or d/c LZD, monitor for infections
- Additional testing: HIV, alcohol screening
Hearing Loss

- Can occur in as many as 30% of patients
- Major cause of permanent disability
- Screening: symptoms, monthly audiometry while on injectable
- Common cause: injectable agents
- Management strategies: EARLY IDENTIFICATION KEY; discontinue injectable
Vision Loss

- Screening: symptoms, visual acuity, color testing
- Common causes: age, cataract, EMB, LZD, Rifabutin
- Management: r/o other causes, d/c or lower dose of EMB and or LZD
- Additional testing: examination of optic nerve
Depression

• Common, may occur in more than 50% of patients
• Often based on life circumstances; can wax and wane during treatment
• Screening: symptoms
• Common causes: life, CS, INH
• ASSESS FOR HARM TO SELF
• Management: counseling, psychosocial support, group therapy, antidepressants (avoid TCAs on BDQ; avoid SSRIs on LZD); hospitalize if suicidal
• Additional testing: TSH, drug and alcohol screen
Psychosis

- Can occur in as many as 5% of patients
- Can be severe and life-threatening
- Screening: symptoms
- Common causes: CS, INH, EFV, alcohol withdrawal
- ASSESS FOR HARM TO SELF OR OTHERS
- Management: discontinue CS; antipsychotics; hospitalize for safety
- Additional testing: fever, TSH, drug and alcohol screen
Seizures

- May occur in up to 10% of patients
- Not felt to be more common if pre-existing condition
- Important to differentiate from syncope
- Screening: symptoms
- Common causes: CS, INH, alcohol withdrawal, imipenem
- Management: lower dose or discontinue CS or INH, anticonvulsants
- Additional testing: neurologic exam, head CT or MRI
Summary

• Adverse events are very common
• Even mild and common events can affect treatment outcomes
• Some adverse events can be life-threatening
• Some adverse events cause permanent disability
• Timely recognition and management of adverse events important for adherence and completion of treatment
• Critical drugs may be discarded if AEs not properly managed
Call for Papers

Journal of Clinical Tuberculosis and Other Mycobacterial Diseases

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