Managing and Monitoring Side Effects and Toxicities of Anti-TB therapy

Bismarck, North Dakota
June 5, 2019

Catalina Navarro RN BSN
TB Nurse Consultant/Educator
CDC Funded Centers of Excellence
Heartland National TB Center

- Arkansas
- Iowa
- Kansas
- Louisiana
- Missouri
- Nebraska
- North Dakota
- Oklahoma
- South Dakota
- Texas
- City of Houston

- Curry International Tuberculosis Center
- Heartland National Tuberculosis Center
- Southeastern National Tuberculosis Center
- Global Tuberculosis Institute at Rutgers, The State University of New Jersey
Visit us on the Web!

✓ Upcoming and archived trainings
✓ Apply for mini fellowships
✓ Information about consultations
✓ Access and order our products
✓ Contact information

www.heartlandntbc.org
Objectives

• Describe the monitoring process for side effects
  – Discuss the first line medications to treat TB
  – Recognize the most common side effects of the TB meds

• Discuss the nursing interventions and medical management of the most common adverse drug side effect
Purpose of Monitoring Patient

- Recognize adverse side effects
- Assess appropriately
- Intervene rapidly
  - Prevent further morbidity/mortality
  - Minimize treatment interruptions
  - Avoid development of psychological intolerance
  - Support adherence and the therapeutic relationship
Toxicity Monitoring

• “Face-to-face clinical assessments are the cornerstone of clinical monitoring for treatment adherence and adverse events.”

• Patients should be categorically told to immediately stop medications (INH) for nausea, vomiting, abdominal discomfort, or unexplained fatigue and to contact the clinic for further evaluation

• Document, document, document!
Side Effects?

- Careful assessment before treatment may allow some symptoms to be attributed to other causes.

- Most TB patients complete their treatment without any significant adverse drug effects.

- Most of the side effects are manageable and do not require stopping the medication.
Discuss Benefits and Risks

Most patients are willing to continue TB meds if they:

• Understand the benefit of treatment

• Know that symptoms improve after the first several weeks

• Are assure that you are addressing their problems
First-line Drugs

• Isoniazid (INH)

• Rifamycins
  – Rifampin (RIF)
  – Rifabutin (Rfb)
  – Rifapentin

• Ethambutol (EMB)

• Pyrazinamide (PZA)

• Fluoroquinolones
  – Levofloxacin
  – Moxifloxacin
Rifamycins

- **Rifampin** undergoes rapid and complete absorption after oral administration.

- **Rifabutin** is used when there is concomitant medications reactions with rifampin (such as HAART).

- **Rifapentine** has a longer half-life than rifampin.
### AIDSinfo: Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

<table>
<thead>
<tr>
<th>Rifampin</th>
<th>Oral contraceptives less effective Additional non-hormonal contraceptive or alternative recommended.</th>
<th>Significantly decreases PI exposure; co-administration should be avoided</th>
<th>Co-administration of atovaquone and rifampin should be avoided. Consider switching clarithromycin to azithromycin, which has less potential for drug interaction. Dapsone and Doxycycline efficacy may be reduced.</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreases Concomitant Drug Concentrations:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contraceptives: oral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ARV drugs: PIs ± ritonavir, nevirapine, raltegravir, rilpivirine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Antimicrobial: atovaquone, dapsone, clarithromycin, doxycycline</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TB Meds with Food?

INH 1 hr. before or 2 hours after food or may take with small snack if needed

RIF

EMB May be taken with food

PZA
Fluoroquinolones

within **2 hours** of Levofloxacin or Moxifloxacin

- **No** milk based products
- **No** antacids (aluminum-coating)
- **No** vitamins supplements or sucralfate
- **No** iron, magnesium, calcium, zinc
Most Common Side Effects
# Side Effects of First Line Drugs

<table>
<thead>
<tr>
<th>INH</th>
<th>Rifampin</th>
<th>Rifabutin</th>
</tr>
</thead>
<tbody>
<tr>
<td>• G.I. upset</td>
<td>• G.I. upset</td>
<td>• Rash/Skin discoloration</td>
</tr>
<tr>
<td>• Rash</td>
<td>• Rash</td>
<td>• Hepatotoxicity</td>
</tr>
<tr>
<td>• Hepatotoxicity</td>
<td>• Hepatotoxicity</td>
<td>• Leukopenia</td>
</tr>
<tr>
<td>• Peripheral neuropathy</td>
<td>• Thrombocytopenia, hemolytic anemia</td>
<td>• Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>• Renal toxicity</td>
<td>• Uveitis</td>
</tr>
<tr>
<td></td>
<td>• Flu-like syndrome</td>
<td>• Arthralgias</td>
</tr>
<tr>
<td></td>
<td>• Orange staining of body fluids</td>
<td></td>
</tr>
<tr>
<td>PZA</td>
<td>Ethambutol</td>
<td>Fuoroquinolones</td>
</tr>
<tr>
<td>• G.I. upset</td>
<td>• Optic Neuritis</td>
<td>• GI upset</td>
</tr>
<tr>
<td>• Rash</td>
<td>• Rash</td>
<td>• Dizziness,</td>
</tr>
<tr>
<td>• Hepatotoxicity</td>
<td>• Rash</td>
<td>• hypersensitivity photosensitivity</td>
</tr>
<tr>
<td>• Arthralgias</td>
<td>• Gout (rare)</td>
<td>• Headaches, tendonitis</td>
</tr>
<tr>
<td>• Gout (rare)</td>
<td></td>
<td>• tendon rupture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Insomnia.</td>
</tr>
</tbody>
</table>
## Side Effects of HIV and AIDS Drugs

[https://www.webmd.com/hiv-aids/aids-hiv-medication-side-effects#1](https://www.webmd.com/hiv-aids/aids-hiv-medication-side-effects#1)

<table>
<thead>
<tr>
<th>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</th>
<th>Common Side Effects</th>
<th>Special Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziagen (abacavir)</td>
<td>Hypersensitivity reaction</td>
<td>Have genetic testing done prior to therapy.</td>
</tr>
<tr>
<td>Combivir (lamivudine + zidovudine)</td>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>• Videx, or Videx-EC (didanosine or ddl)</td>
<td>Diarrhea, abdominal pain, neuropathy, nausea, vomiting, pancreatitis</td>
<td>Do not combine with stavudine.</td>
</tr>
<tr>
<td>Emtriva (emtricitabine)</td>
<td>Rash and skin darkening of palms or soles, numbness, tingling, or burning sensation</td>
<td></td>
</tr>
<tr>
<td>Epzicom (abacavir + lamivudine)</td>
<td>Nausea, vomiting, upset stomach, diarrhea, fatigue, chills, dizziness, headaches, insomnia</td>
<td>Bactrim or Septra may increase blood levels; do not take with stavudine.</td>
</tr>
<tr>
<td>Epivir (lamivudine)</td>
<td>Nausea, vomiting, upset stomach, diarrhea, fatigue, dizziness, headaches, insomnia</td>
<td></td>
</tr>
</tbody>
</table>
## Side Effects of First Line Drugs

<table>
<thead>
<tr>
<th>INH</th>
<th>Rifampin</th>
<th>Rifabutin</th>
</tr>
</thead>
</table>
| • G.I. upset  
• Rash  
• Hepatotoxicity  
• Peripheral neuropathy | • G.I. upset  
• Rash  
• Hepatotoxicity  
• Thrombocytopenia, hemolytic anemia  
• Renal toxicity  
• Flu-like syndrome  
• Orange staining of body fluids | • Rash/Skin discoloration  
• Hepatotoxicity  
• Leukopenia  
• Thrombocytopenia  
• Uveitis  
• Arthralgias |
| **PZA** | **Ethambutol** | **Fuoroquinololones** |
| • G.I. upset  
• Rash  
• Hepatotoxicity  
• Arthralgias  
• Gout (rare) | • Optic Neuritis  
• Rash | • GI upset  
• Dizziness,  
• hypersensitivity photosensitivity  
• Headaches, tendonitis  
• Tendon rupture  
• Insomnia. |
Peripheral Neuropathy

ARVs: d4T (Stavudine) and ddl (Didanosine)

- Tingling, prickling & burning balls of feet or tips of toes
- Can progress to the fingers and hands
- More likely: Diabetic, alcoholic, HIV infection, pregnancy, poor nutrition, hypothyroidism
- Sensory loss can occur; ankle reflexes lost; unsteady painful gait

Administer Vitamin B6 (pyridoxine) 50mg daily

Note: B6 in doses greater than 200mg can CAUSE neuropathy
Peripheral Neuropathy Evaluation

**Lower Extremities**

- **Patient’s Interview** (Ask your patient the following questions):
  1. Do you have any pain in your feet? 
  2. Does your pain have any of these characteristics? 
     - Sudden
     - Pulsating
     - Electric shock-like sensation
  3. Do you have any of these symptoms in the area? 
     - Rubbing
     - Prickling
     - Nummular
     - Stabbing/Pricking
  4. Is the patient aware with the touch of clothing or bed sheets? 

**Patient’s Assessment** (Questions):
  5. Hypoesthesia to touch
  6. Hypoesthesia to pinprick
  7. Extreme sensitivity to touch
  8. Extreme sensitivity to pinprick

**Upper Extremities**

- **Patient’s Interview** (Ask your patient the following questions):
  1. Do you have any pain in your hands?
  2. Does your pain have any of these characteristics? 
     - Sudden
     - Pulsating
     - Electric shock-like sensation
  3. Do you have any of these symptoms in the area? 
     - Rubbing
     - Prickling
     - Nummular
     - Stabbing/Pricking
  4. Is the patient aware with the touch of clothing or bed sheets? 

**Patient’s Assessment** (Questions):
  5. Hypoesthesia to touch
  6. Hypoesthesia to pinprick
  7. Extreme sensitivity to touch
  8. Extreme sensitivity to pinprick
Monitor all the danger signs.

There...do you feel that?
# Gastro Intestinal Upset

<table>
<thead>
<tr>
<th>INH</th>
<th>Rifampin</th>
<th>Rifabutin</th>
</tr>
</thead>
<tbody>
<tr>
<td>• G.I. upset</td>
<td>• G.I. upset</td>
<td>• Rash/Skin discoloration</td>
</tr>
<tr>
<td>• Rash</td>
<td>• Rash</td>
<td>• Hepatotoxicity</td>
</tr>
<tr>
<td>• Hepatotoxicity</td>
<td>• Hepatotoxicity</td>
<td>• Leukopenia</td>
</tr>
<tr>
<td>• Peripheral neuropathy</td>
<td>• Thrombocytopenia, hemolytic anemia</td>
<td>• Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>• Renal toxicity</td>
<td>• Uveitis</td>
</tr>
<tr>
<td></td>
<td>• Flu-like syndrome</td>
<td>• Arthralgias</td>
</tr>
<tr>
<td></td>
<td>• Orange staining of body fluids</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PZA</th>
<th>Ethambutol</th>
<th>Fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td>• G.I. upset</td>
<td>• Optic Neuritis</td>
<td>• GI upset</td>
</tr>
<tr>
<td>• Rash</td>
<td>• Rash</td>
<td>• Dizziness,</td>
</tr>
<tr>
<td>• Hepatotoxicity</td>
<td></td>
<td>hypersensitivity</td>
</tr>
<tr>
<td>• Arthralgias</td>
<td></td>
<td>photosensitivity</td>
</tr>
<tr>
<td>• Gout (rare)</td>
<td></td>
<td>Headaches, tendonitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>tendon rupture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Insomnia.</td>
</tr>
</tbody>
</table>
Gastrointestinal Upset

RTV (Ritonavir) d4T (Stavudine)  
NVP (Nevirapine)

- Nausea/vomiting/diarrhea (NVD)
- Common in the first few weeks of therapy
- Give a light snack before meds
Responding to GI Upset

• Exclude hepatitis

• If no evidence of liver toxicity
  – Administer antiemetic 30 min prior dose (Zofran)
  – Take with small snack, tea or soda
  – Encourage hydration (Sports drinks – electrolyte replacement)
  – Antacids may be helpful in some patients
Monitoring Gastrointestinal (GI) Upset

• Evaluate the interventions
  – Nausea decreased?
  – Persistent throughout the day?
  – May need to stop the offending medication
  – Is there an adequate replacement?
    • If no, patient may need to tolerate some n/v.
    • If yes, consider switching medication
      – May need expert consultation before switching meds
### Hepatotoxicity with First Line Drugs

<table>
<thead>
<tr>
<th>INH</th>
<th>Rifampin</th>
<th>Rifabutin</th>
</tr>
</thead>
</table>
| • G.I. upset  
• Rash  
• **Hepatotoxicity**  
• Peripheral neuropathy  
• Mild CNS Toxicity | • G.I. upset  
• Rash  
• **Hepatotoxicity**  
• Thrombocytopenia, hemolytic anemia  
• Renal toxicity  
• Flu-like syndrome  
• Orange staining of body fluids | • Rash/Skin discoloration  
• **Hepatotoxicity**  
• Leukopenia  
• Thrombocytopenia  
• Uveitis  
• Arthralgias |
| PZA | Ethambutol | Fuoroquinolones |
| • G.I. upset  
• Rash  
• **Hepatotoxicity**  
• Arthralgias  
• Gout (rare) | • Optic Neuritis  
• Rash | • GI upset  
• Dizziness,  
• hypersensitivity photosensitivity |

**NVP (Nevirapine) EFV (Efavirenz) PIs: TPVr (Tipranavir/Ritanavir)**  
**Most NRTIs (Nucleoside reverse Transcriotase inhibitors)**
Hepatotoxicity

Early Signs

• Fatigue
• Poor appetite
• Taste alteration
• Nausea
• Abdominal discomfort
• Bloating
• Minimal rash

Later Signs

• Vomiting
• Abdominal pain
• Jaundice
• Change in color of urine and stool
• Changes in behavior, memory loss
Risk Factors for Hepatotoxicity

- Underlying liver disease
  - Hepatitis B and C
- Alcoholism
- Immediate (4 months) post-partum period
- Hepatotoxic medications
Monitoring

• **Medical history**
  – Preexisting conditions may increase hepatotoxicity
    • History of Hepatitis B or C
    • History of other liver disease

• **Social history**
  – ETOH use (be specific)

Educate patient of signs and symptoms of hepatotoxicity
Managing Hepatotoxicity

- Check Liver Function Test (LFT) at baseline and monthly

**Stop therapy**

- LFT s> 3 times upper limit of normal and symptomatic

- LFTs> 5 times upper limit of normal and asymptomatic
## Rash

<table>
<thead>
<tr>
<th>INH</th>
<th>Rifampin</th>
<th>Rifabutin</th>
</tr>
</thead>
</table>
| • G.I. upset  
• Rash  
• Hepatotoxicity  
• Peripheral neuropathy  
• Mild CNS Toxicity | • G.I. upset  
• Rash  
• Hepatotoxicity  
• Thrombocytopenia, hemolytic anemia  
• Renal toxicity  
• Flu-like syndrome  
• Orange staining of body fluids | • Rash/Skin discoloration  
• Hepatotoxicity  
• Leukopenia  
• Thrombocytopenia  
• Uveitis  
• Arthralgias |

<table>
<thead>
<tr>
<th>PZA</th>
<th>Ethambutol</th>
<th>Fuoroquinolones</th>
</tr>
</thead>
</table>
| • G.I. upset  
• Rash  
• Hepatotoxicity  
• Arthralgias  
• Gout (rare) | • Optic Neuritis  
• Rash | • GI upset  
• Dizziness,  
• hypersensitivity photosensitivity  
• Headaches, tendonitis  
• Tendon rupture  
• Insomnia. |

**ABC (Abacavir) NVP (Nevirapine) EFV (Efavirenz) d4T (Stavudine) PIs**
Side Effect or Allergic Reaction?

1. Unwanted **side effect** of a certain medicine

2. Caused by an **allergic reaction** to the medicine: Most rashes
Evaluate the Rash

- Where is it?
- What does it look like?
- Does it itch?
- When did it start?
- Has it spread?
- What makes it better or worse?
- Have you had an insect bite?
Other Possible Causes

• Insect bites
• Scabies
• Contact dermatitis
  – Question patient about new soaps, lotions, perfumes, laundry detergents, etc
• Sunburn
• Dry skin
• Other drugs, especially new agents
• Viral or fungal infections
Mild Rash

- Common

- Often resolve after first several weeks of treatment

- Usually do not require stopping medication

- Treated symptomatically with Benadryl, other antihistamines, low-dose prednisone
**Acne**

**Symptoms:**

- Pimples and red areas that appear most often on the face, shoulders, and chest
- Slow onset
- Side effect of INH

From mild to severe
 Fluoroquinolones and Fungal Infection

- Consequences of Long term antibiotic use
- Change the normal flora balances of fungal species
- Itchy rash in fold, warm, and wet areas of the skin
Vision Changes
Ethambutol

- Nausea
- Vomiting
- Loss of appetite
- Fever

- Headaches
- Dizziness
- Rash
  - Changes in visual acuity
  - Changes in red/green color discrimination

ARTs: ddl (Didanosine) Optic Neuritis
Managing & Monitoring Visual Toxicities

- Baseline & monthly visual acuity test (Snellen chart)
- Baseline & monthly color discrimination test (Ishihara tests)
- Question about visual disturbances including blurred vision
- Children to look for eye rubbing, excessive blinking, sitting close TV, difficulty with accurate grasping
  - Hold EMB
  - Refer for Ophthalmologic evaluation
  - Permanent vision impairment if Rx continued
Ishihara Test

You will need:

• Ishihara’s Tests for Colour Deficiency 24 Plate Edition

• Well lit room (natural day light is preferred)

• Comfortable chair for patient

• Quiet room
Ishihara Plate Examples
Toxicity with 3HP

• 4% of all patients using 3HP experience flu-like or other systemic drug reactions

• Fever, headache, dizziness, nausea, muscle and bone pain, rash, itching, red eyes

• Hypotension and syncope have been reported rarely (2/1000 cases treated)
Toxicity with 3HP

• 5% stop 3HP due to adverse events, including systemic drug reactions
  – Reactions typically occur after first 3 – 4 doses
  – Begin approximately 4 hours after ingestion of medication.
  – Symptoms usually resolve without treatment within 24 hours.
  – Neutropenia and elevation of liver enzymes occur uncommonly.
Case Study
Case Study – INH Resistant TB

- 21 year old male diagnosed with PTB
- CXR showed LUL cavitary infiltrate, AFB smear Cx (+)
- On October 2012: RIPE started
- Isolate reported Resistant to INH and Streptomycin
- INH discontinued once susceptibilities were known,
- Pt. continued on RIF, PZA, EMB to complete 9 months of adequate therapy
Case Study - Ophthalmic Toxicity

5 months after treatment initiation patient c/o difficulty driving and reading road signs

As a nurse managing this patient’s anti-TB therapy, what would you do?

– To assess vision screen
– Stop the EMB
– Refer to the Ophthalmologist
Patient contacted nurse by phone, she instructed him to see his “eye doctor”.

He was seen by optometrist and given corrective lenses.

• EMB was continued
Case Study – Visual Monitoring Results

• 7 months on anti-TB therapy he complains of worsening vision.
• Nurse finally assess his vision
• Baseline visual acuity in October: 20/20 both eyes
• Follow up visual acuity: 20/200 in both eyes.
• EMB was discontinued Pt. continued on RIF, PZA
• Levofloxacin was added to complete 9 mo of treatment
• Referral to a retinal specialist.
Case Study – Conclusion

During the last two months of treatment pt evaluated by retinal specialist

– DX: EMB optic neuropathy
– Central scotoma on right and parascotoma on left
– Vision uncorrected: 20/200

Nurse admitted not performing visual acuity screening (Snellen chart) Only color discrimination testing (Ishihara plates) was done
Nursing Guide

The guide is designed to

1) Identify symptoms that may indicate a side effect related to DR-TB treatment or antiretroviral medication

2) Assess for severity as well as other potential contributors

3) Intervene appropriately to minimize patient discomfort, reduce side effect progression, and ultimately support successful treatment completion
Sources:

- CDC Core Curriculum on TB: What the Clinician Should Know; 5th edition

  http://www.tbcontrollers.org/resources/tb-nursing-manual/#.UaVINJxnerg

- TB Drug Information Guide 2nd Edition; Curry International TB Center
  http://www.currytbcenter.ucsf.edu/products/product_details.cfm?productID=WPT-17A

- HIV/AIDS Treatment Guidelines
  https://aidsinfo.nih.gov/guidelines

- HIV/AIDS medication side effects
  https://www.webmd.com/hiv-aids/aids-hiv-medication-side-effects#1
Questions?