TB Nurse Case Management
Salina, Kansas
March 31-April 1, 2010

TB Medications and Adverse Reactions

Pat Infield, RN, BSN

March 31, 2010

TB Medications and Adverse Effects

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Objectives

- Describe the monitoring process for adverse drug events associated with anti-TB drugs.
  - Side effects versus drug toxicities
  - Recognizing the most common adverse effects of TB therapy

- Discuss the nursing interventions and medical management of the most common adverse drug events seen in patients on first- and second-line antituberculosis therapy.
  - Case studies
  - Management and monitoring adverse reactions in special patients

Side effects

Usually *predictable* or dose dependent effect of drug (that is not the principle effect) for which the drug was chosen

- Maybe Desirable
- Undesirable, unpleasant but mild reactions
- No long lasting health effects
- No change in therapy
Common Anti – TB Drug Side Effects

- Gas
- Bloating
- Mild nausea
- Discoloration of body fluids
- Irritability
- Difficulty sleeping
- Photosensitivity

Adverse Drug Reaction Definitions

“An undesirable response associated with use of a drug that either compromises therapeutic efficacy, enhances toxicity, or both.”

“An unintended harmful reaction to a drug administered at normal dosage”

- May be life threatening
- Require modifying dose or discontinuing drug
- May require additional therapy or hospitalization
Serious Adverse Reactions
Anti-TB Drugs

- Hepatotoxicity
- Ophthalmic toxicity
- CNS toxicity
- Neurotoxicity
- Ototoxicity
- Renal toxicity

Drug Management Goals

- Recognize adverse drug events
- Assess appropriately
- Intervene rapidly
  - Prevent further morbidity/mortality
  - Minimize treatment interruptions
  - Reduce opportunities for “medical mismanagement”
  - Avoid development of psychological intolerance
  - Support adherence and the therapeutic relationship
The Monitoring Process

- Development of core “understanding”
  - Side effects are common
    - “You may feel worse before you feel better”
  - Symptoms usually improve with time
  - Steps can and will be taken to minimize side effects and toxicities
  - Treatment will lead to cure and prevent transmission to family and friends

The Monitoring Process

- Case management plan-use standardized form
  - Outlines important toxicity monitoring events that must occur during the course of treatment
    - Direct
      - Laboratory studies
      - Vision screening (visual acuity and color discrimination)
      - Audiometry
      - Vestibular screening
    - Indirect
      - Patient interview
      - Observation
The Monitoring Process

- Asses the patient prior to each DOT dose and monthly, at a minimum, in a face-to-face encounter with the health care provider
  - Use a standardized toxicity assessment form
    - Ask each question carefully
    - Thoroughly document all positive responses
    - Report all positive responses, particularly any changes
      - Field staff should have a clear understanding of the reporting process

- Both open-ended and specific, pointed questions should be utilized, as appropriate
  - How is your appetite?
    - Have you lost weight? How much?
    - Do your clothes fit differently?
    - Do you still eat dessert?
  - How is your energy?
    - How able are you to engage in your usual activities?
    - How far/long can you walk now compared to . . .?
First-line Drug Reactions

- Isoniazid (INH)
- Rifampin (RIF)
  - Rifabutin
- Ethambutol (EMB)
- Pyrazinamide (PZA)

Isoniazid (INH)

Common Reactions
- Epigastric discomfort
- Elevated liver transaminases, mild
- Hypersensitivity rxn, mild
- Nausea / vomiting
- Paresthesias, mild
  - Peripheral neuropathy
- Pyridoxine deficiency

Serious Reactions
- Agranulocytosis
- Aplastic anemia
- Hepatotoxicity, incl. fatal
- Hypersensitivity rxn
- Optic neuritis
- Peripheral neuropathy
- Seizures
- Thrombocytopenia
- Toxic psychosis
Managing & Monitoring of INH

- Avoid alcohol
- Monitor seizure disorders, especially if taking Phenytoin
- Avoid foods containing Tyramine, may cause hypertensive crisis
  - If flushing occurs instruct patients to decrease intake monoamines
  - 10 to 25 mg of tyramine required for a severe reaction

Tyramine Containing Foods

- Aged cheese
- Aged or cured meats (e.g., air-dried sausage)
- Any potentially spoiled meat, poultry, or fish
- Broad (fava) bean pods
- Marmite concentrated yeast extract
- Sauerkraut
- Soy sauce and soy bean condiments
- Tap beer, Chianti wine and vermouth
- Liquid and powdered PROTEIN DIETARY SUPPLEMENTS
Baseline Laboratory Monitoring

LTBI-INH

- Baseline LFT’s (ALT, bilirubin) are not necessary except for patients with the following risk factors:
  - HIV infection treated with HAART
  - History of chronic liver disease (hepatitis B/C, alcohol hepatitis, cirrhosis)
  - Previous abnormal ALT and/or bilirubin
  - Regular use of alcohol
  - Pregnancy or early postpartum (within 3 mos of delivery)
  - Other: consider individually, e.g., “health individuals” > 35 yrs., other hepatotoxic drugs

Laboratory Monitoring - Active TB

- Initiation of Therapy
  - All
    - AST, ALT, bilirubin, alkaline phosphatase, serum creatinine, CBC with platelet count
  - If at risk of hepatitis B/C (IDU, birth in Asia/Africa, HIV infected); hepatitis B/C serology
Laboratory Monitoring

- **Periodic**
  - Unnecessary if treated with first-line drugs unless
    - Baseline lab abnormalities
    - Clinical reason to obtain lab measurements
  - **Other**
    - Rifabutin: monthly CBC with platelet count if
      - Treatment with higher doses (>300mg daily)
      - Clinical reasons, e.g., advanced AIDS, decreased WBC, decreased platelet count
    - Amikacin: Serum creatinine weekly for first several weeks, then monthly

Rifampin

<table>
<thead>
<tr>
<th>Common Reactions</th>
<th>Serious Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>Agranulocytosis / Leukopenia</td>
</tr>
<tr>
<td>Anorexia</td>
<td><strong>Anaphylaxis</strong></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Hemolytic anemia</td>
</tr>
<tr>
<td>Dizziness / Ataxia</td>
<td>Hemorrhage / DIC</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Elevated liver transaminases</td>
<td>Interstitial nephritis / Renal failure</td>
</tr>
<tr>
<td><strong>Fatigue</strong> / Drowsiness</td>
<td>Porphyria exacerbation</td>
</tr>
<tr>
<td>Headache</td>
<td>Pseudomembranous colitis</td>
</tr>
<tr>
<td>Hypersensitivity rxn, mild</td>
<td>Psychosis</td>
</tr>
<tr>
<td><strong>Nausea</strong> / <strong>Vomiting</strong></td>
<td>Shock</td>
</tr>
<tr>
<td><strong>Visual changes</strong></td>
<td><strong>Thrombocytopenia</strong></td>
</tr>
</tbody>
</table>
Managing & Monitoring Rifampin

- Advise women using hormonal contraceptive to use another form of control
- Reduction of methadone almost to an ineffective level
- Cannot use with some Antiretroviral drugs

<table>
<thead>
<tr>
<th>Rifabutin</th>
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<tbody>
<tr>
<td><strong>Same as Rifampin +</strong></td>
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</table>

**Common Reactions**
- Asthenia
- Chest pain
- Diarrhea
- Dyspepsia
- Eructation
- Fever
- Flatulence
- Insomnia
- Myalgias
- Pain
- Rash
- Taste changes
- Yellow skin

**Serious Reactions**
- Clostridium difficile associated diarrhea
- Neutropenia (agranulocytosis)
- Uveitis
### Ethambutol (EMB)

#### Common Reactions
- Abdominal pain / Dyspepsia
- Anorexia
- **Blurred vision** / Dizziness
- Disorientation / Hallucinations
- Elevated LFTs
- Fever
- Headache
- Hyperuricemia
- Joint pain
- Malaise
- Nausea / Vomiting
- Rash / Pruritus

#### Serious Reactions
- Anaphylaxis
- **Blindness**, irreversible
- Erythema multiforme
- Hepatotoxicity, incl. fatal
- Hypersensitivity syndrome
- Leukopenia
- Neutropenia
- Optic neuritis
- Peripheral neuropathy
- Pulmonary infiltrates
- Thrombocytopenia

### Managing & Monitoring EMB

- Baseline & monthly visual acuity test (Snellen chart)

- Baseline & monthly color discrimination test (Ishihara tests)

- Question pt regarding possible visual disturbances including blurred vision & scotomata
  - Observe children for eye rubbing, excessive blinking, sitting close TV, difficulty with accurate grasping
    - Hold Rx
    - Refer for Ophthalmologic evaluation
    - Permanent vision impairment if Rx continued
## Pyrazinamide (PZA)

<table>
<thead>
<tr>
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<th>Serious Reactions</th>
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<tbody>
<tr>
<td>□ Anorexia</td>
<td>□ Anemia</td>
</tr>
<tr>
<td>□ Arthralgia</td>
<td>□ Hepatotoxicity</td>
</tr>
<tr>
<td>□ Elevated LFTs</td>
<td>□ Interstitial nephritis</td>
</tr>
<tr>
<td>□ Gout</td>
<td>□ Porphyria</td>
</tr>
<tr>
<td>□ Hyperuricemia</td>
<td>□ Thrombocytopenia</td>
</tr>
<tr>
<td>□ Malaise</td>
<td></td>
</tr>
<tr>
<td>□ Nausea / Vomiting</td>
<td></td>
</tr>
<tr>
<td>□ Photosensitivity</td>
<td></td>
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<tr>
<td>□ Rash / Urticaria</td>
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## Managing & Monitoring of PZA

- Little info about the safety of PZA in pregnancy
- Serum uric acid measurements are not recommended as a routine but may serve as a surrogate marker for compliance.
“Incidence of Serious Side Effects from First-Line Antituberculosis Drugs Among Patients Treated for Active TB”

- PZA: 1.48/100 person months of exposure
- INH: 0.49/100 person months of exposure
- RIF: 0.43/100 person months of exposure
- EMB: 0.07/100 person months of exposure

“The drug most likely responsible for the occurrence of hepatitis and rash during therapy for active TB is PZA”

Special Considerations in Pregnancy

- Treatment of TB disease: INH, RIF, EMB
- Treatment of LTBI
- Increased risk of hepatotoxicity
- Increased risk of INH-associated peripheral neuropathy
- S/S pregnancy similar to those of adverse drug events
Special Considerations in Children/Adolescents

- LTBI: baseline LFT’s not indicated unless
  - History or physical findings of liver disease
  - Alcohol or drug abuse
  - Symptomatic HIV/AIDS
  - Other hepatotoxic drugs
- LTBI: periodic LFT’s
  - If signs/symptoms of hepatotoxicity develop
  - After 1st and 3rd month of treatment if at risk of hepatotoxicity
- Routine laboratory monitoring for other first-line drugs generally not indicated

Special Considerations
Children/Adolescents

- Monthly face-to-face clinical assessments
- EMB
  - Considered safe to use in children too young for routine eye testing (15-20 mg/kg/day)
    - If EMB given for greater than 2 months, refer to Ophthalmologist for baseline and F/U exams
  - Older children: baseline and monthly assessment of visual acuity and color discrimination
### Second-line Drugs

- Cycloserine
- Ethionamide
- Levofloxacin
- Moxifloxacin
- PAS
- Streptomycin
- Amikacin
- Kanamycin
- Capreomycin
- Linezolid

### Levofloxacin

**Common Reactions**

- Abdominal pain
- Headache
- Constipation / Diarrhea
- Insomnia
- Dizziness
- Nausea / Vomiting
- Dyspepsia
- Tendonitis
Levofoxacin Continued Serious Reactions

- Anaphylaxis
- **Arthralgia / Myalgia**
- Arthropathy (animal studies)
- Blood dyscrasias
- C. diff associated diarrhea
- Depression / Suicidal ideation
- **Hepatotoxicity, incl. fatal**
- Hypersensitivity rxn
- ICP increase / Seizures
- Myelosuppression
- Nephrotoxicity
- **Peripheral neuropathy**
- Phototoxicity / Photosensitivity
- Pneumonitis, allergic
- QT prolongation / Torsades de pointes
- Serum sickness
- Skin rxns, severe
- **Tendon rupture**
- Superinfection
- Toxic psychosis
- Vasculitis

Monitoring & Managing Levo.

**Tendonitis/Tendon Rupture**

- Tendon rupture (usually Achilles) is rare

- If tendon inflammation mild:
  - Rest the joint/NSAID’s
  - Evaluate dose and reduce if possible
  - If symptoms progress, stop the fluoroquinolone
  - Evaluate risks and benefits of continuing drug in regimen
### Moxifloxacin

#### Common Reactions
- Diarrhea
- Dizziness
- Nausea

#### Serious Reactions
- Anaphylaxis
- Arthropathy (animal studies)
- Blood dyscrasias
- Depression / Suicidal ideation
- Hepatotoxicity, incl. fatal
- Hypersensitivity rxn
- ICP increase / Seizures
- Myelosuppression
- Nephrotoxicity
- Peripheral neuropathy
- Phototoxicity
- Pneumonitis, allergic
- Pseudomembranous colitis
- QT prolongation / Torsades de pointes
- Serum sickness
- Skin rxns, severe
- Superinfection
- Tendon rupture
- Toxic psychosis
- Vasculitis
**Streptomycin Common Reactions**
- Amblyopia
- Anaphylaxis
- Angioneurotic edema
- Azotemia
- Deafness
- Eosinophilia
- Exfoliative dermatitis
- Fever
- Hemolytic anemia
- Injection site rxn
- Leukopenia
- Muscle weakness
- Nausea / Vomiting
- Pancytopenia
- Paresthesias, facial
- Rash / Urticaria
- Thrombocytopenia
- Vertigo

**Streptomycin Serious Reactions**
- Anaphylaxis
- Angioneurotic edema
- Auditory ototoxicity
- Exfoliative dermatitis
- Hemolytic anemia
- Hypersensitivity rxn
- Nephrotoxicity
- Neuromuscular blockade
- Neurotoxicity
- Pancytopenia
- Superinfection
- Thrombocytopenia
- Vestibular ototoxicity
Linezolid

- Side Effects
  - Rash
  - Myelosuppresion
  - Nausea and diarrhea
  - Optic neuropathy
  - Peripheral neuropathy

Other Second Line Drugs

<table>
<thead>
<tr>
<th>Amikacin</th>
<th>Capreomycin</th>
<th>Ethionamide</th>
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<tbody>
<tr>
<td>- Rash</td>
<td>- Rash</td>
<td>- Rash</td>
</tr>
<tr>
<td>- Renal toxicity</td>
<td>- Renal toxicity</td>
<td>- GI upset, may be significant</td>
</tr>
<tr>
<td>- Ototoxicity</td>
<td>- Ototoxicity</td>
<td>- Hepatotoxicity</td>
</tr>
<tr>
<td>- Vestibular toxicity</td>
<td>- Vestibular toxicity</td>
<td>- Endocrine effects</td>
</tr>
<tr>
<td>- Electrolyte abnormalities (hypokalemia, hypermagnesemia)</td>
<td>- Electrolyte abnormalities (hypokalemia, hypercalcemia, hypomagnesemia)</td>
<td>(gynecomastia, hair loss, acne, impotence, menstrual irregularity, reversible hypothyroidism)</td>
</tr>
<tr>
<td>- Local pain at IM injection site</td>
<td>- Local pain at IM injection site</td>
<td>- Peripheral neuropathy</td>
</tr>
</tbody>
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<thead>
<tr>
<th>Cycloserine</th>
<th>Para-Aminosalicylate (PAS)</th>
<th>Clofazimine</th>
</tr>
</thead>
<tbody>
<tr>
<td>- CNS toxicity, may include seizure, depression, suicidal ideation, psychosis</td>
<td>- Rash</td>
<td>- Rash</td>
</tr>
<tr>
<td>- Peripheral neuropathy</td>
<td>- GI upset, may be significant</td>
<td>- GI Upset</td>
</tr>
<tr>
<td>- Skin changes (lichenoid eruptions, Stevens Johnson Syndrome)</td>
<td>- Hepatotoxicity</td>
<td>- Discoloration and dryness of skin</td>
</tr>
<tr>
<td></td>
<td>- Reversible hypothyroidism</td>
<td>- Photosensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Retinopathy</td>
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Case Studies

Hepatotoxicity

38 y.o. male diagnosed with PTB during incarceration

- Mar. 13: started standard RIPE regimen
  - Baseline laboratory values: ALT 42, AST 63

- April 15: changed to BIW dosing; EMB d/c[d when susceptibility results showed isolate to be susceptible to INH/RIF

- June 4: F/U laboratory values: ALT 304, AST 97
  - Asymptomatic for hepatitis
Hepatotoxicity Cont.

What is the appropriate response?

- **Hold TB medications!**
  ALT ≥ 5x ULN in asymptomatic patient, or ≥ 3X ULN in patient with signs/symptoms consistent with hepatitis

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Hepatotoxicity

When can therapy be safely restarted?

Once ALT is < 2X ULN
Hepatotoxicity Cont.

Should other TB therapy be started?

If it is likely there will be a delay of > 2-3 wks
consideration can be given to starting a “liver friendly”
regimen (EMB, fluoroquinolone, aminoglycoside) while
waiting for LFT’s to normalize

Hepatotoxicity Cont.

What treatment should be considered when ALT returns
to < 2X normal?

- RIF/EMB X 3-7 day
  Monitor LFT’s twice weekly

- If LFT’s stable after 3-7 days, add INH
  Continue to monitor LFT’s twice weekly

- If LFT’s stable, EMB can be discontinued and pt. returned
to BIW dosing and tx. completed with INH/RIF
Immune Reactions

77 y.o. contact to daughter, PTB suspect

- **Jan. 31**: initial clinic visit
  - TST + (15 mm)
  - C/O several weeks of productive cough, now asymptomatic
  - CXR: blunting of CPA
  - Sputum AFB smear + (<1/HPF); culture pending
  - PMH: arthritis, 71 yr tobacco hx, hospitalized 1 mo prior for pneumonia/bronchitis

- **Feb. 4**: started RIPE standard regimen
  - Baseline LFT’s WNL

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Immune Reactions

**Feb. 13**: ER visit; c/o generalized rash, swelling of lower lip

- RX: injection (?) plus prednisone 20 mg. BID

- TB medications held

- Local TB physician consulted

- Reinitiate one drug at a time to identify offending agent

- Request consult from State TB expert physician consultant
Immune Reactions Cont.

**Feb. 17:** Received dose of INH 300mg in TB clinic

- Prior to dose, c/o itching of scalp, no visible rash or swelling
- Clinic RN requested consult from State TB physician consultant that day

What concerns might you have in rechallenging this patient with TB medications?

**Follow up:**

- Provider given rechallenge protocol, but elected to hold TB medications pending further evaluation
- All sputum cultures eventually reported negative for AFB
- CXR: minimal abnormality, not suggestive of TB
- Patient remained asymptomatic
- + TST may be from recent exposure to daughter or may represent old infection in a 77 y/o ♀ living along the US/Mexico border

Consider risks vs. benefits of treatment
Immune Reactions

Other possible causes
- Scabies
- Insect bites
- Contact dermatitis
  - Question patient about new soaps, lotions, perfumes, laundry detergents, etc.
- Sunburn
- Dry skin
- Other drugs, especially new agents
- Viral or fungal infections
- Etc.

Evaluate The Rash
- When did it start?
- Where is it?
- What does it look like now? Is that different?
- Has it spread?
- What makes it better or worse?
- Does it itch?
- Have you had an insect bite?
Severe Drug Reactions

- Anaphylaxis

- Widespread urticaria associated with fever, other systemic symptoms, mucous membrane involvement are characteristic of Stevens-Johnson Syndrome

- Do not attempt to rechallenge or desensitize patient to the drugs
Drug rash

- Usually begins on chest and later spreads to upper arms and thighs
- Itches
- Maculopapular
- Urticaria/hives that are new
- May be associated with more severe symptoms of airway compromise, angioedema, etc.
- Occurs and worsens after medications
Maculopapular Drug Eruption
Petechial rash

Petechial Rash
**Urticaria/Hives**

- **21 yo male diagnosed with PTB in October**

  - **February-March**: Incarcerated in county jail
    - May: onset of illness (fever, chills, productive cough, chest pain, night sweats, wt. loss)

  - **May**: Onset of illness
  - **October 7**: Initial Clinic Visit
    - CXR: LUL cavitary infiltrate
    - AFB smear + (1-10/HPF), sent for culture

  - **October 12**: Started RIPE standard regimen

  - **November 9**: Isolate reported INH/SM resistant
Ophthalmic Toxicity

What do we do next?

- Pt. improving: afebrile, 6 lb wt. gain, night sweats resolved, cough improving

- INH discontinued; continued on RIF, PZA, **EMB** to complete 9 mo. treatment

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Ophthalmic Toxicity

- **March**: pt. c/o difficulty driving, reading road signs

  **What do we do?**

  - Advised by LHD nurse to see “eye doctor”
    **March 21**: seen by optometrist and given RX for corrective lenses (3/30)

  - EMB continued
Ophthalmic Toxicity

May 3: Pt. c/o worsening vision
- Visual acuity: 20/200 both eyes
  - Baseline visual acuity (October): 20/20 both eyes

What would you do?

May 5: EMB discontinued; continued on RIF regimen to complete 9 mo of tx.

Referred to retinal specialist

Ophthalmic Toxicity

Follow-up
- Seen by retinal specialist in May and June
  - DX: EMB optic neuropathy
  - Central scotoma on right and parascotoma on left
  - Vision uncorrected: 20/200
  - Vision best corrected: 20/60

- Nurse admitted not performing visual acuity screening (Snellen chart), only color discrimination testing (Ishihara plates)
Optic Neuritis

Uveitis
Central Nervous System

48 y.o. female with drug susceptible PTB

- PMH significant for treatment for depression 1992-1996
- Jan. 15: started RIPE standard regimen
- Jan. 24: reported to ER with c/o insomnia, loss of energy, fatigue, anorexia, difficulty concentrating, unable to work, uncontrollable crying spells, suicidal ideation

Central Nervous System

What do we do?

- Prescribed Effexor-XR
- Discharged to her home under husband’s supervision with f/u appointment for psychiatric evaluation
Central Nervous System

- **Jan. 26**: initial evaluation by psychiatrist
  - Dx’ed with substance induced mood disorder
  - INH held; continued on RIF, PZA, EMB

- **Feb. 1**: CV for DOT

**What do we assess for?**

- Described as “like a different person”; reported feeling better, mood and affect brighter, make-up applied, neatly dressed, denied suicidal ideation

Central Nervous System

- **Feb. 10**: F/U with psychiatrist

  - No evidence of depressive signs/symptoms
  - Effexor-XR continued
Reporting ADRs

- Form EF12-12274
  - [http://www.dshs.state.tx.us/idcu/investigation/forms/TBEF12-12274AdverseDrugReaction.pdf](http://www.dshs.state.tx.us/idcu/investigation/forms/TBEF12-12274AdverseDrugReaction.pdf)

- Information forwarded to CDC and/or FDA, if necessary