TB Nurse Case Management
San Antonio, Texas
November 3-5, 2010

TB Medications and Adverse Effects
Debbie Onofre, RN, BSN

November 4, 2010

TB Treatment Basics
Alisha Blair, LVN
Heartland National TB Center
December 9th, 2010
Objectives

• Discuss Medications Available for TB treatment
  – First Line Agents
  – Second Line Agents
• Discuss Various TB regimens
  – Daily
  – TIW
  – BIW
• Identify factors for relapse

Medications Available for TB Treatment

• First Line Agents
  – Isoniazid (INH)
  – Rifampin (RIF)
  – Ethambutol (EMB)
  – Pyrazinamide (PZA)

Commonly Referred to as RIPE
**Isoniazid**

- INH is a first line agent for treatment of all forms of tuberculosis caused by organisms susceptible to the agent
- INH has a early bactericidal activity against rapidly dividing cells

**Preparations and Dosages**

- Isoniazid is available in
  - Tablets 50 mg, 100 mg, 300 mg
  - Syrup 50 mg/5ml
  - Aqueous 100 mg/ml
- **Dose**
  - Adults 5mg/kg (300mg daily)
    15mg/kg (900 mg daily, BIW, or TIW)
  - Children 10-15 mg/kg (300mg daily)
    20-30mg/kg (900mg BIW)
Adverse Effects

- Elevation of Liver Enzymes
- Irritability
- Inability to concentrate
- Peripheral Neuropathy
- Fever
- Rash

- Fatal Hepatitis
- Steven Johnson Syndrome
- Lupus Like Syndrome
- Hemolytic anemia
- Neutropenia
- Tyramine Poisoning
- Jaundice
- Seizures

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
Rifampin

• Rifampin is a first line agent for the treatment of all forms of tuberculosis caused by organisms sensitive to the agent

• Rifampin Activity
  – Effective against rapidly dividing organisms
  – Effective against semi-dormant bacterial populations

Preparations and Dosages

• Rifampin is available in
  – Capsules 150 mg, 300mg
  – Contents of the capsules may be mixed in appropriate diluents to prepare for oral consumption
  – Aqueous solution for parenteral administration

• Dosages
  – Adults 10mg/kg (600 mg once daily, BIW, TIW)
  – Children
Stevens-Johnson Syndrome
Hepatoxicity

Most serious adverse reaction of INH

**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
Most at Risk for Hepatotoxicity

- Underlying liver disease
- Hepatitis B and C
- Alcoholics
- Immediate (4 months) post-partum period
- Those on other hepatotoxic medications

Assessment

- Establish rapport
- Take a good medical history
  - Clarify preexisting conditions that may increase risk of hepatotoxicity:
    - History of Hepatitis B or C
    - History of other liver disease
- Take a good social history
  - ETOH use (both current and history of past heavy use)
- Educate patient of signs and symptoms of hepatotoxicity
Case Study # 1
Hepatotoxicity

38 year old male diagnosed with Pulmonary TB during incarceration. On Mar. 13, he started standard RIPE regimen. Baseline laboratory values were ALT 42,

AST 63. On April 15 he was changed to BIW dosing. EMB was discontinued when susceptibility results showed isolate to be susceptible to INH/RIF. Patient was released from jail and continued medication on DOT by local health department. On June 4, two months after starting anti – TB therapy, follow-up lab results were ALT 304, AST 97 (normal values: AST 10 -42 u/L, ALT 10 - 40 u/L). He was asymptomatic for hepatitis.

Hepatotoxicity Cont.

What is the appropriate response?

Hold TB medications!

ALT > 3 times upper limit of normal and symptomatic
ALT > 5 times upper limit of normal and asymptomatic
Case Study No. 1 – Hepatotoxicity

When re-assessing the patient with hepatitis, what should we evaluate for?

- Consider testing for underlying liver disease (hepatitis A, B, C)
- Do you drink any alcoholic beverages?
- Identify if patient is taking any other Hepatotoxic MEDICATIONS?

Case Study #1- Hepatotoxicity

- Other hepatotoxic drugs
  - Tylenol
  - Alcohol
  - Tetracycline, erythromycin, others
  - Dilantin
  - Valproate
  - Cholesterol lowering medications
  - Antifungal drugs
  - Glucose lowering drugs
  - Valium
**Case Study #1 - Hepatotoxicity**

Anti-TB therapy was re-started by re-introducing one medication at a time when liver enzymes < 2 times upper limit of normal. Liver enzymes were monitored carefully. At a follow up appointment patient admitted to drinking 6 -12 oz. beers almost every day with his neighbor.

**How should we monitor this patient for the remainder of his treatment?**

**Case Study No. 1- Hepatotoxicity**

- Monitor the patient closely
- Re-educate patient to abstain from alcohol while on anti-TB medication
- Review adverse effects
- Encourage compliance
- Instruct patient to self monitor for side effects while on meds
- Consider a liver friendly regimen

*Most importantly:*

Instruct patient to stop taking TB medications immediately and seek medical attention if symptoms of hepatitis occur again.
Managing & Monitoring of INH

- Liver function tests
- Avoid alcohol
- Serum concentrations of phenytoin may be increased
- Avoid foods containing Tyramine, may cause hypertensive crisis, flushing may occur
  - 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
Rifampin

- Pruritis (with or without rash)
- Nausea
- Anorexia
- Abdominal pain
- Flu-like syndrome (usually with intermittent administration)
- Hepatotoxicity
- Elevated liver transaminases
- Fatigue / Drowsiness
- Headache
- Nausea / Vomiting
- Acute renal failure
- Thrombocytopenia
- Orange Discoloration of bodily fluids

Rifabutin

- Asthenia
- Chest pain
- Diarrhea
- Dyspepsia
- Eruption
- Fever
- Flatulence
- Insomnia
- Clostridium difficile associated diarrhea
- Neutropenia (agranulocytosis)
- Uveitis
- Myalgias
- Pain
- Rash
- Taste changes
- Yellow skin
Managing & Monitoring Rifampin

- Monitor CBC monthly
- 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

Ethambutol (EMB)

- Retrobulbar neuritis
  - Decreased visual acuity
  - Decreased red-green color discrimination
- Peripheral Neuritis
- Cutaneous reactions
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

Ophthalmic Toxicity

21 year old male arrested and incarcerated in county jail in February. After being incarcerated for 3 months he began to complain of fever, chills, productive cough, chest pain, night sweats, and weight loss. On October 7, five months after onset of symptoms, he continued to complain of previous symptoms. He was finally evaluated, CXR showed left upper lobe cavitary infiltrate, AFB smear (+) 1-10 per high power field. He was diagnosed with pulmonary TB. On October 12, he was started on the standard 4 drug therapy. The isolate was reported as isoniazid and streptomycin resistant. Pt. was improving, he was afebrile, had 6 lb wt. gain, night sweats had resolved, cough was improving. INH discontinued once susceptibilities were known, and he continued on RIF, PZA, EMB to complete 9 months of adequate therapy.
Case Study #2: Ophthalmic Toxicity

In March, 5 months after start of treatment, he started c/o difficulty driving and reading road signs.

What do we do?

Advised by LHD nurse, by phone, to see “eye doctor”

March 21: seen by optometrist and given corrective lenses (3/30)

EMB continued

Ophthalmic Toxicity

On May 3 (7 months on anti-TB therapy) he complains of worsening vision. Nurse finally assess his vision. Baseline visual acuity in October was 20/20 both eyes, follow up visual acuity was now 20/200 in both eyes.

What would you do?

On May 5 the EMB discontinued; continued on Rif, PZA and Levo added to regimen to complete 9 mo of treatment and referred to a 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

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

Pyrazinamide (PZA)

- Hepatotoxicity
- Nausea
- Vomitting
- Anorexia
- Nonigouty polyarthritis
- Asymptomatic hyperuricemia
- Acute Gouty arthritis
- Dermatitis
- Nausea / Vomiting
Managing & Monitoring of PZA

- Little info about the safety of PZA in pregnancy

- Cleared primarily by the liver, metabolites excreted in the urine and may accumulate with renal insufficiency
  - Reduce dose to three times a week after dialysis

- At risk for hyperuricemia in patients with renal insufficiency

- Liver chemistry monitoring in patients with underlying liver disease

Managing G.I. Intolerance

- Evaluate for other causes of GI symptoms
  - Hepatotoxicity

- Hold Medications

- Repeat LFT’s

- Give light snack before giving meds

- Separate from other drugs by several hours or give at bedtime

- Administer antiemetics
  - Phenergan
  - Zofran
Second-line Drugs

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

Second-Line TB Drugs

<table>
<thead>
<tr>
<th>Amikacin</th>
<th>Levofloxacin, Gatifloxacin, Moxifloxacin</th>
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<tbody>
<tr>
<td>- Rash</td>
<td>- Rash</td>
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<tr>
<td>- Renal toxicity</td>
<td>- GI upset</td>
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<tr>
<td>- Ototoxicity</td>
<td>- Mild CNS toxicity</td>
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<tr>
<td>- Vestibular toxicity</td>
<td>- Arthralgias, rare tendon rupture</td>
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<tr>
<td>- Electrolyte abnormalities (hypokalemia, hypomagnesemia)</td>
<td>- Photosensitivity</td>
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<tr>
<td>- Local pain at IM injection site</td>
<td>- EKG abnormalities</td>
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<table>
<thead>
<tr>
<th>Capreomycin</th>
<th>Ethionamide</th>
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<tbody>
<tr>
<td>- Rash</td>
<td>- Rash</td>
</tr>
<tr>
<td>- Renal toxicity</td>
<td>- GI upset, may be significant</td>
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<tr>
<td>- Ototoxicity</td>
<td>- Hepatotoxicity</td>
</tr>
<tr>
<td>- Vestibular toxicity</td>
<td>- Endocrine effects</td>
</tr>
<tr>
<td>- Electrolyte abnormalities (hypokalemia, hypocalcemia, hypomagnesemia)</td>
<td>(gynecomastia, hair loss, acne, impotence, irregular menses, reversible hypothyroidism)</td>
</tr>
<tr>
<td>- Local pain at IM injection site</td>
<td>- Peripheral neuropathy</td>
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## Second-Line TB Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Rash</th>
<th>CNS toxicity, may include seizure, depression, suicidal ideation, psychosis</th>
<th>Peripheral neuropathy</th>
<th>Skin changes (lichenoid eruptions, Stevens-Johnson Syndrome)</th>
<th>GI upset, may be significant</th>
<th>Hepatotoxicity</th>
<th>Reversible hypothyroidism</th>
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<tbody>
<tr>
<td>Cycloserine</td>
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<tr>
<td>Para-Aminosalicylate (PAS)</td>
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<tr>
<td>Clofazimine</td>
<td>Rash</td>
<td>GI upset</td>
<td>Discoloration and dryness of skin</td>
<td>Photosensitivity</td>
<td>Retinopathy</td>
<td>Myelosuppression</td>
<td>Nausea and diarrhea</td>
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<tr>
<td>Linezolid</td>
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## Auditory Toxicity

- Perform audiometry at baseline and repeat monthly
  - Identify pre-existing hearing loss
  - Refer for evaluation if any decrease from baseline

- Monitor patient’s ability to engage in normal conversation
  - Answering inappropriately
  - Asking speakers to repeat what they have said
  - Increasing volume of radio/TV
  - Withdrawal/isolation

- Hearing loss may be reversible or permanent
Essential Components for Completion of Treatment

- Establish and Maintain a good Nurse – Patient relationship
- Have a Case management plan
- Ongoing patient education
  - toxicity monitoring Indirect
  - Purpose of DOT
  - Possible drug interactions
  - Possible side effects and toxicities

Reporting ADRs

- Form EF12-12274
  - [http://www.dshs.state.tx.us/idcu/investigation/forms/TBEF12-](http://www.dshs.state.tx.us/idcu/investigation/forms/TBEF12-)
  - 12274AdverseDrugReaction.pdf
- Information forwarded to CDC and/or FDA, if necessary
Thank You!