MANAGING ADVERSE DRUG REACTIONS

For anti-tuberculosis medications:
- Describe clinical monitoring for adverse drug reactions
- Review specific drug side effects
- Review adverse drug reactions
  - Hepatitis, GI disturbances
  - Dermatologic reactions
  - CNS toxicity and peripheral neuropathy
  - Ocular and Otototoxicity
- Case Reviews
  - Nursing interventions and medical management

OBJECTIVES

CLINICAL MONITORING
- Ongoing Process
- Initial assessment - nurse/physician
  - Identify high risk individuals
  - Check baseline labs
- Staff and Patient education
  - Aware of adverse drug reactions
  - Instruct patient to report signs or symptoms
    - Rash
    - Decrease appetite, nausea, vomiting, abdominal pain
    - Fatigue or weakness
    - Dark urine
    - Persistent numbness in hands or feet
- Document, document, document!
- Encounters
  - Monthly refill visits
    - Rationale for treatment
    - Adherence with therapy
  - Symptoms of adverse drug reaction
  - Commitment to continue therapy
  - Limited # doses of medication dispensed
- DOT visits
- Case management
  - Assessment/PLAN in place
  - Good communication with team: MD, RN, MA, DIS
GENERAL APPROACH
- Recognize that diagnosis and treatment are difficult
  - Symptoms
    - Drug-related
    - Due to other causes - including TB itself
    - Fear of drugs
  - Serious adverse reactions
    - Need to be anticipated
    - Require monitoring for
    - May prompt discontinuation / changing medication

ADDRESS, RELIEVE SYMPTOMS
- Reassure patient
- Emphasize importance of treatment completion
- Make every attempt to avoid unnecessary breaks in therapy
- Remind patient that breaks result in prolonged duration of treatment

ANTIMYCOBACTERIAL DRUGS
First-Line Drugs
- Isoniazid (INH)
- Rifampin (RIF)
- Pyrazinamide (PZA)
- Ethambutol (EMB)

Second-Line Drugs
- Streptomycin
- Cycloserine
- p-Aminosalicylic acid
- Ethionamide
- Amikacin or kanamycin*
- Capreomycin
- Levofoxacin*
- Moxifloxacin
- Linezolid*

* Not approved FDA for TB Treatment

ADVERSE DRUG REACTIONS
Place a check mark for the common side effects

<table>
<thead>
<tr>
<th></th>
<th>RIF</th>
<th>INH</th>
<th>PZA</th>
<th>EMB</th>
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<tbody>
<tr>
<td>Rash</td>
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<td>Gl Intolerance</td>
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<td>Gout</td>
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<tr>
<td>Discoloration of body fluid</td>
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### Adverse Drug Reactions

<table>
<thead>
<tr>
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<th>RIF</th>
<th>INH</th>
<th>PZA</th>
<th>EMB</th>
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<tr>
<td>Rash</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>GI Intolerance</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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</tr>
<tr>
<td>Discoloration of body fluid</td>
<td>X</td>
<td></td>
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</tr>
</tbody>
</table>

### Minor Side Effects
- Mild reactions
- No lasting effect
- Usually do not require change in TB meds
- Discoloration of body fluid
- Gas, bloating, mild nausea
- Itching, mild rash
- Photosensitivity
- Sleep disturbances
- Headache

### Serious Drug Complications
- Serious
- May be life threatening
- Require change in medication
- May require hospitalization
- Significant nausea, vomiting, diarrhea
- Hepatotoxicity
- Toxic skin / systemic reactions
- Hearing loss
- Kidney failure
- Vision loss
- Hematologic reactions
- Electrolyte abnormalities
- Neurologic damage
- Death

### Hepatic Drug Metabolism
Drug is swallowed
- Absorbed from the GI tract into blood vessels
- Enters liver via portal vein
- Metabolized in liver
- One process involves cytochrome P450 class of enzymes
- Enters circulation or stored in bile
- Bile enters duodenum
- Drug is excreted in stool or reabsorbed (Enterohepatic circulation)
ALT (SGPT) is more specific for hepatocellular injury than AST (SGOT)
AST can arise from muscle, heart, or kidney abnormalities
AST>ALT with alcohol-related disease
Normal levels defined as within 2 standard deviations of the mean from a healthy population
- 2.5% of normal, healthy people will have ALT “above upper limit of normal” (ULN)
- It is customary to compare multiples of ULN
  - Interlaboratory variation
  - Variation within an individual up to 45% in a day

44 year old female diagnosed with latent TB infection
8/3 seen by physician and nurse
- Started INH
Baseline labs:
- AST-19, ALT-19, T. bili-0.3, Alk phos-68
9/1 - Nurse Refill Visit #2
- Repeat AST on 09/01 was 27
10/6 - Nurse Refill Visit #3
11/10 - Nurse Refill Visit #4
11/30 admitted for “jaundice”

- No signs or symptoms of any hepatic problems reported at any health dept visits
- 2 weeks prior to admission - ER visit - cough
  - CXR negative
  - Tessalon® perles and hydrocodone cough syrup
- Increasing fatigue, weakness, diarrhea, yellowing of eyes
- Return to hospital
  - AST-3627→1410
  - ALT 2159→1621
  - Alk phos 190→179
  - Total Bili 25→27.5 (Direct 13→16.6)

RUQ ultrasound: no intrahepatic ductal dilation, + cholelithiasis, no cholecystitis, no liver abnormalities
Abdominal MRI: no biliary ductal dilation, no gallstones, no liver lesions
Liver biopsy: patchy hepatocellular necrosis with acute and chronic inflammation, mild portal fibrosis, no granuloma/viral inclusions
Diagnosis: Acute Hepatitis- secondary to INH toxicity
TABLE 1. Descriptive adverse events (N = 17) associated with isoniazid (INH) treatment for latent tuberculosis infection (LTBI), by patient characteristics — United States, 2004–2008

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
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<tbody>
<tr>
<td>Age group (yr)</td>
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<tr>
<td>≤15</td>
<td>2</td>
</tr>
<tr>
<td>16–35</td>
<td>12</td>
</tr>
<tr>
<td>&gt;35</td>
<td>3</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
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<tr>
<td>Hispanic</td>
<td>8</td>
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<tr>
<td>Black, non-Hispanic</td>
<td>1</td>
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<tr>
<td>White, non-Hispanic</td>
<td>8</td>
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<tr>
<td>Country of birth</td>
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</tr>
<tr>
<td>United States</td>
<td>10</td>
</tr>
<tr>
<td>Foreign born</td>
<td>7</td>
</tr>
<tr>
<td>Duration of INH treatment (days)</td>
<td>104</td>
</tr>
<tr>
<td>Median</td>
<td>28–105</td>
</tr>
<tr>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Period from initiation of INH treatment to severe adverse event symptoms (days)</td>
<td>109</td>
</tr>
<tr>
<td>Median</td>
<td>56–107</td>
</tr>
<tr>
<td>Minimum</td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td></td>
</tr>
<tr>
<td>Results of testing for viral hepatitis</td>
<td>16</td>
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<tr>
<td>Negative</td>
<td>10</td>
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<td>Abnormal</td>
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<td>Outcome</td>
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<tr>
<td>Recovered</td>
<td>9</td>
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<tr>
<td>Died</td>
<td>8</td>
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<tr>
<td>Adult median age</td>
<td>39</td>
</tr>
</tbody>
</table>

Dx 2nd and 9th month

HIV, Hep C

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TABLE 2. Results of case investigations (N = 11) of severe adverse events (SAEs) associated with isoniazid (INH) treatment for latent tuberculosis infection (LTBI), by case characteristics — United States, 2004–2008

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated outside a public health clinic</td>
<td>2</td>
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<tr>
<td>Had clinical monitoring monthly</td>
<td>10</td>
</tr>
<tr>
<td>Had laboratory monitoring of serum aminotransferase levels monthly</td>
<td>9</td>
</tr>
<tr>
<td>Results of laboratory testing of serum aminotransferases</td>
<td>10</td>
</tr>
<tr>
<td>Within normal limits</td>
<td>5</td>
</tr>
<tr>
<td>Nonnormal</td>
<td>5</td>
</tr>
<tr>
<td>Period from SAE symptom onset to discontinuation of INH (days)</td>
<td>7</td>
</tr>
<tr>
<td>≤2</td>
<td>1</td>
</tr>
<tr>
<td>3–6</td>
<td>4</td>
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<tr>
<td>7–11</td>
<td>3</td>
</tr>
<tr>
<td>12–15</td>
<td>1</td>
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<tr>
<td>≥16</td>
<td>1</td>
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<tr>
<td>ALT diagnosis by different clinician than the one who prescribed INH</td>
<td>7</td>
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<tr>
<td>Serum aminotransferase concentrations measured at SAE diagnosis</td>
<td>10</td>
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<tr>
<td>Median</td>
<td>272–250</td>
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<tr>
<td>Range</td>
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<tr>
<td>Retrospective analysis for INH-induced liver injury</td>
<td>10</td>
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<tr>
<td>None</td>
<td>3</td>
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<tr>
<td>Preexisting liver disease</td>
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<tr>
<td>Human immunodeficiency virus (HIV) infection</td>
<td>1</td>
</tr>
<tr>
<td>Concurrent alcohol use</td>
<td>1</td>
</tr>
<tr>
<td>Pregnancy or ≤6 months after delivery</td>
<td>1</td>
</tr>
<tr>
<td>CHF</td>
<td>1</td>
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<tr>
<td>Use of non-isoniazid-containing medications with hepatotoxic potential</td>
<td>5</td>
</tr>
</tbody>
</table>

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Severe INH liver injuries among persons being treated for LTBI in US 2004-2008

- Idiosyncratic reaction, independent of dosing
- Can occur anytime in treatment
  - 9/17 beyond the 3rd month
- Can occur in children
  - 2/17 in children
- Diagnosed not by prescribing physician
  - 10/17
- Did NOT STOP the medication when symptoms developed
  - 8/17 continue to take the medication

INH Hepatotoxicity

- Asymptomatic ALT increase in
  - ≤20% of patient
- Clinical hepatitis 0.1 -0.6%
- Timing: weeks to months of starting drug
- Risk factors:
  - Age
  - Chronic alcohol consumption
  - Active hepatitis B (+HBeAg)
  - Elevated baseline transaminases (ALT, AST)
  - Concomitant use of other hepatotoxic drugs
  - 3rd trimester pregnancy to 3 months post-partum
  - Pre-existing liver disease
Management of Hepatotoxicity

- Hold medication and repeat LFTs
- Continue therapy
  - No symptoms and LFTs (AST/ALT) ≤ 5 X ULN (upper limits of normal)
- Stop therapy
  - Symptomatic and ALT > 3 X ULN
  - No symptoms and ALT > 5 X ULN
- Restarting therapy
  - LFTs < 2 X ULN
  - Rechallenge medications - One drug at a time
  - Monitor Labs
  - May need “Liver friendly regimen”
    - EMB, FQ, strep/amikacin, (capreomycin, cycloserine)

INH Neurotoxicity

- Dose related, uncommon
- Risk factors
  - Other conditions with neuropathy:
    - Malnutrition, diabetes, HIV, renal failure, alcohol, pregnant female
- Mild peripheral neuritis - Stocking glove syndrome - 2%
- Retrobulbar (optic) neuritis
- CNS toxicity: Slurred speech, ataxia, seizure, memory

Pyridoxine

INH

http://en.wikipedia.org/wiki/Isoniazid
http://en.wikipedia.org/wiki/Pyridoxine
Rifampin Toxicity

- Orange discoloration of body fluid
- Cutaneous reactions:
  - mild
  - generally self-limited
  - Treat symptomatically - antihistamine
- Gastrointestinal symptoms:
  - nausea, anorexia, abdominal pain
- Hepatocellular injury less common
  - Insidious cholestasis
    - Anorexia, nausea, vomiting, fever, jaundice
    - Rif is much less likely to cause hepatotoxicity than INH or PZA

Rifampin: Hypersensitivity Reactions

- Flu-like syndrome with fever, chills, headache, & bone pain
  - Can begin 1-2 hrs after medication dose and resolve spontaneously after 6-8 hrs
  - More common in intermittent dosing, higher dose
  - Can try daily therapy if mild
- Severe immunologic reactions - rare, each < 0.1% patients
  - Low platelet count / petechiae
  - Kidney dysfunction
  - Hemolytic anemia
  - Thrombotic thrombocytopenic purpura

Rifampin Drug Interactions

- Rifampin induces cytochrome P450 class of enzymes
- Involved in drug metabolism
- Rifampin interacts with
  - Narcotics (methadone) - ↓
  - Corticosteroids - ↓
  - Warfarin (coumadin) - ↓
  - Phenytoin (dilantin) - ↓
  - Contraceptives (estrogens) - ↓
  - HIV protease inhibitors & non-nucleoside reverse transcriptase inhibitors - complex interactions

Pyrazinamide

- Hepatotoxicity: Both dose-dependent & idiosyncratic
- Causes hepatotoxicity less often than INH but can be more prolonged
- Can continue after drug discontinued
- Can be most severe
- Can cause granulomatous hepatitis
  - Fever, rash, lymphadenopathy, elevated ALT
**Pyrazinamide Toxicity**
- Gastrointestinal symptoms: nausea, vomiting
- Arthralgias common - Rx symptomatically
- Elevated uric acid
  - PZA is a pro-drug → active compound Pyrazinoic acid
  - blocks renal tubular excretion of uric acid
  - increase uric acid
  - Allopurinol does not reverse this
  - Routine measurement of uric acid is not recommended
  - Gout is rare
  - Hyperuricemia without gout is not a reason for discontinuing drug

**Ethambutol Toxicity**
- Retrobulbar neuritis: decrease visual acuity or red-green color discrimination
- Increase risk with renal insufficiency
- Peripheral neuritis
- Cutaneous reactions: <1%
- Joint pain

**Ethambutol Toxicity**
- Baseline and monthly
  - Visual acuity test (Snellen chart)
  - Color discrimination test (Ishihara tests)
- Patient Education
- Monthly symptom check
  - blurred vision etc
- Ophthalmology evaluation
- Hold medication - for any symptoms

**Quinolones**
- Arthralgias, tendonitis, tendon rupture - very rare
  - All ages
  - Greater risk age >60
  - Patients taking corticosteroids
  - Transplant patients
- EKG abnormalities: QT prolongation
- Nausea & diarrhea: 0.5-2%
- Rash/Pruritis/Photosensitivity: 0.2-0.4%
- Avoid in pregnancy
**STREPS/AMIKACIN/CAPREOMYCIN**
- Ototoxicity
- Vestibular toxicity
- Nephrotoxicity
- Electrolyte disturbances
  - Potassium, calcium, and magnesium depletion
  - Cardiac dysrhythmias
- Local pain at IM injection site
- Avoid in pregnancy

**ETHIONAMIDE**
- Gastrointestinal Effects - severe
  - May improve with food or at bedtime
- Hepatotoxicity: 2%
- Neurotoxicity: peripheral neuropathy, optic neuritis, depression, psychosis
- Endocrine disturbances
  - Gynecomastia, hair loss, hypothyroidism, impotence
  - Diabetes may be more difficult to manage
  - Acne
  - Irregular menstrual cycles

**LINEZOLID**
- Nausea & diarrhea
- Myelosuppression
  - Dose dependent
  - Reversible
- Peripheral neuropathy
  - Not dose dependent
  - May not be reversible
- Optic neuritis
- Serotonin syndrome
- Rash

**PAPA-AMINOSALICYLATE (PAS)**
- Gastrointestinal distress: 11%↓ dose/stop med
- Hypothyroidism is common
  - Reversible, ↑with ethionamide
  - Goiter can develop
- Hepatitis: 0.3%
- Malabsorption - fat malabsorption
  - Doubling of prothrombin time
  - Vitamin K is a fat soluble vitamin
  - Levels of fat soluble vitamins (A, D, E) can be measured & monitored
- Rash, lymphadenopathy, leukocytosis, arthralgia
**CYCLOSPORINE**

- Central Nervous System Effects: headaches, restlessness, suicidal ideation, psychosis, seizures (3% 500mg/day)
- Caution in patients with underlying seizure disorders or mental illness
- Pyridoxine 100-200mg/day may decrease neurotoxic side effect
- Peripheral neuropathy
- Rash - skin changes (lichenoid eruptions, Stevens-Johnson Syndrome)

**CASE (2)**

- 25 year old female
- diagnosed with lymph node TB
- started on four drug: RIF, INH, EMB, PZA
- On day 8: developed generalized papulosquamous rashes involving both thighs, legs, trunk, face and oral cavity
- She was admitted outside and was put on antibiotics along with steroids
- Patient improved slightly, was discharged after 5 days. TB meds were continued

**CASE (2)**

- 4-5 days later patient again developed increase generalized body rashes
- Febrile, vitals -stable
- Treated with steroids and TB medication discontinued

**4 W'S OF DRUG RASH**

WHERE, WHAT, WHEN, WHO?

- Where is it? Where did it start? Where has it spread to?
- What does it look like? What makes it better or worse
- When did it start?
- Who has it?

- Insect bites, scabies
- Contact dermatitis
- New soap, detergent, lotions, perfumes
- Sunburn
- Dry skin
- Other drugs -new
- Other infections
**DERMATOLOGIC REACTIONS**

- Itching with or without erythematous rash is common early side effect
  - May resolve after 1st several weeks of therapy without stopping medications
  - For mild or localized reaction, continue treatment & treat the rash and pruritis symptomatically - antihistamines, topical steroids

- Photosensitivity
  - PZA, fluoroquinolones

**DERMATOLOGIC REACTIONS**

- Hives, urticaria, erythematous rash
  - Any drug
  - Stop all drugs immediately, rechallenge 1 at a time
    - Wait for rash to resolve
    - Start RIF 1st (least likely to be cause)
    - If no recurrence after 2-3 days start INH
    - Continue with EMB or PZA
    - Discontinue any drug which causes recurrence

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  - PZA, fluoroquinolones

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  - Any drug
  - Stop all drugs immediately, rechallenge 1 at a time
    - Wait for rash to resolve
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    - If no recurrence after 2-3 days start INH
    - Continue with EMB or PZA
    - Discontinue any drug which causes recurrence

- Angioedema, anaphylaxis, or airway compromise
  - Stop drug - consider desensitization in ICU

**OTHER SERIOUS DERMATOLOGIC REACTIONS**

- Spectrum of diseases - generalized, involve mucus membranes, cause fever - epidermis separates from dermis
  - Stevens-Johnson Syndrome
  - Toxic Epidermal Necrolysis (severe form SJS)

- Mortality high

- Quinalones

- Emergency, hospitalization

- Stop offending drug, do not use again

**GI UPSET**

- Improves if drugs are administered with food or closer to bedtime

- Ethionamide
  - Causes profound GI symptoms
  - Metallic taste, nausea, vomiting that can be severe, loss of appetite, abdominal pain
  - Dose-related
  - May give as split dose

- P-Aminosalicylic Acid (PAS)
  - Significant GI intolerance, less with granular formulation
  - Dose-related

- INH
  - Commercial liquid preparations contain sorbitol which can cause diarrhea
Neurotoxicity: Peripheral Neuropathy

- Numbness, tingling hands & feet in stocking-glove pattern
- Risk factors: diabetes, alcoholism, HIV, hypothyroidism, pregnancy, poor nutrition, inadequate dietary intake of pyridoxine
- Pyridoxine supplements
  - 10-50 mg daily (should this be routine?) for INH
  - 100-200 for cycloserine &/or ethionamide

Peripheral Neuropathy

- INH
  - Dose-related
  - Interferes with biologic function of vitamin B6
- Ethionamide
  - Increased incidence with prolonged use
- Linezolid
  - Increased incidence with prolonged use
  - 600 mg daily instead of twice daily is used to prevent this
- Ethambutol, cycloserine
  - Rare

CNS Effects

- INH
  - Inability to concentrate, irritability, dysarthria, seizures, dysphoria
- Cycloserine (Dr K’s mnemonic - cyclo, pshycho)
  - Headache, restlessness, psychosis, seizures (dose-related)
  - Pyridoxine 100-200 mg daily to prevent / treat
- Ethionamide
  - Anxiety, depression, psychosis
  - Increased incidence with prolonged treatment
- Fluroquinolones
  - Dizziness, insomnia, tremulousness, headache

visión - e - e eye

- Ethambutol
  - Retrobulbar neuritis
  - Dose related - very rare (if at all) with currently recommended doses
  - Decreased red-green color discrimination (1 or both eyes), decreased visual acuity
  - ↑With renal disease
- Ethionamide
  - Optic neuritis
  - Dose related
**Ototoxicity: 8th Cranial Nerve Damage**

- Streptomycin
  - Vestibular (balance) and hearing disturbance
  - Related to single dose size and cumulative dose (>100-200 g)
  - Increased with incidence if diuretics are used
  - Monitor with audiogram, Romberg
  - Hearing loss can be permanent - consider stopping
- Amikacin & Kanamycin
  - Less vestibular toxicity than SM
- Capreomycin

These drugs also cause nephrotoxicity & require monitoring

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**Ototoxicity: Aminoglycosides**

- Injectable agents - 15mg/kg daily or 25 mg/kg TIW
- Ototoxicity often permanent
  - Hearing loss > 20 db occurred in 32/87 (37%) patients, 88% had persistent loss at end of follow-up
  - Associated with older age, duration of treatment, & total dose, not to vestibular or renal toxicity
- Amikacin > Kanamycin > Streptomycin
- TIW = daily Rx


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**Common Adverse Reactions to Drug Treatment**

<table>
<thead>
<tr>
<th>Caused by</th>
<th>Adverse Reaction</th>
<th>Signs and Symptoms</th>
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<tbody>
<tr>
<td>Any drug</td>
<td>Allergy</td>
<td>Skin rash</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Eye damage</td>
<td>Blurred or changed vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Changed color vision</td>
</tr>
<tr>
<td>Isoniazid, Pyrazinamide, or Rifampin</td>
<td>Hepatitis</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abnormal liver function test results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lack of appetite</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yellowish skin or eyes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dark urine</td>
</tr>
</tbody>
</table>

- Isoniazid Peripheral neuropathy
  - Tingling sensation in hands and feet
- Pyrazinamide Gastrointestinal intolerance
  - Arthralgia
  - Arthritis
  - Upset stomach, vomiting, lack of appetite
  - Joint aches
  - Gout (rare)
- Streptomycin Ear damage
  - Kidney damage
  - Balance problems
  - Hearing loss
  - Ringing in the ears
  - Abnormal kidney function test results
### Common Adverse Reactions to Drug Treatment

<table>
<thead>
<tr>
<th>Caused by</th>
<th>Adverse Reaction</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifamycins</td>
<td>Thrombocytopenia, Gastrointestinal intolerance, Drug interactions</td>
<td>Easy bruising, Slow blood clotting, Upset stomach, Interferes with certain medications, such as birth control pills, birth control implants, and methadone treatment</td>
</tr>
<tr>
<td>Rifabutin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifapentine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
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</tr>
</tbody>
</table>

Acknowledgement:
Special thanks to Dr. Dana Kissner, Wayne State University