# MANAGING ADVERSE DRUG REACTIONS

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## OBJECTIVES

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 Ototoxicity
- Case Reviews
  - Nursing interventions and medical management

## 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

## CLINICAL MONITORING

- 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

## GENERAL APPROACH

- 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

## ANTIMYOBACTERIAL 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
- Levofloxacin*
- Moxifloxacin*
- Linezolid*

* Not approved FDA for TB Treatment

## ADVERSE DRUG REACTIONS

Place a check mark for the common side effects

| | RIF | INH | PZA | EMB |
|---|---|---|---|---|
| Rash | | | | |
| GI Intolerance | | | | |
| Liver toxicity | | | | |
| Peripheral Neuropathy | | | | |
| Optic Neuritis | | | | |
| Gout | | | | |
| Discoloration of body fluid | | | | |

## ADVERSE DRUG REACTIONS

| | RIF | INH | PZA | EMB |
|---|---|---|---|---|
| Rash | X | X | X | X |
| GI Intolerance | X | X | X | X |
| Liver toxicity | X | X | X | |
| Peripheral Neuropathy | | X | | |
| Optic Neuritis | | X (rare) | | X |
| Gout | | | X | X (rare) |
| Discoloration of body fluid | X | | | |

## 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
- Hepatotoxiciy
- 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)

## HEPATOCELLULAR INJURY: HEPATIC ENZYMES

- 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

## CASE (1)

- 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"

## CASE (1)

- 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)**

## CASE (1)

- 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. Reported severe adverse events (N = 17) associated with isoniazid (INH*) treatment for latent tuberculosis infection (LBTI), by patient characteristics — United States, 2004–2008

| Characteristic | No. |
|---|---|
| Age group (yrs) | |
| ≤15 | 2 |
| 16–35 | 5 |
| >35 | 10 |
| Sex | |
| Male | 6 |
| Female | 11 |
| Race/Ethnicity | |
| Hispanic | 8 |
| Black, non-Hispanic | 1 |
| White, non-Hispanic | 8 |
| Country of birth | |
| United States | 10 |
| Foreign-born | 7 |
| Duration of INH treatment (days) | |
| Median | 104 |
| Range | 28–499† |
| Period from initiation of INH treatment to severe adverse event symptoms (days) | |
| Median | 109 |
| Range | 56–502† |
| Results of testing for viral hepatitis§ | |
| Negative | 16 |
| Abnormal | 1 |
| Outcome | |
| Recovered | 8 |
| Had liver transplant | 5 |
| Died | 5¶ |

Adult median age 39

Dx 2nd and 9th month

HIV, Hep C

MMWR 3/5/10 59(08); 224-229

TABLE 2. Results of onsite case investigations (n = 10) of severe adverse events (SAEs) associated with isoniazid (INH*) treatment for latent tuberculosis infection (LTBI), by case characteristics — United States, 2004–2008

| Characteristics | No. |
|---|---|
| Treated outside of a public health clinic | 2 |
| Had clinical monitoring monthly | 10 |
| Had laboratory monitoring of serum aminotransferase levels monthly | 2 |
| Results of baseline testing of serum aminotransferase† | |
| Within normal limits | 5 |
| Abnormal | 0 |
| Never tested | 5 |
| Period from SAE symptom onset to discontinuation of INH (days) | |
| ≤2 | 1 |
| 3–6 | 1 |
| 7–10 | 4 |
| 11–14 | 0 |
| 15–20 | 2 |
| >20 | 2 |
| SAE diagnosis by different clinician than the one who prescribed INH | 7 |
| Serum aspartate aminotransferase (AST) measurement at SAE diagnosis (international units/liter [IU/L])§ | |
| Median | 2,200 |
| Range | 387–3,000 |
| Serum alanine aminotransferase (ALT) measurement at SAE diagnosis (IU/L)§ | |
| Median | 2,192 |
| Range | 272–3,000 |
| Putative risk factors for INH-induced liver injury¶ | |
| None | 3 |
| Preexisting liver disease | 1 |
| Human immunodeficiency virus (HIV) infection | 1 |
| Concurrent injection-drug use | 0 |
| Concurrent alcohol consumption | 3** |
| Pregnancy or ≤3 months after delivery | 1 |
| Older age | 5 |
| Concurrent use of non-acetaminophen-containing medications with hepatotoxic potential†† | 4 |

AST

ALT

MMWR 3/5/10 59(08); 224-229

## 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

MMWR 3/5/10 59(08); 224-229
http://en.wikipedia.org/wiki/Jaundice

## INH HEPATOTOXICITY

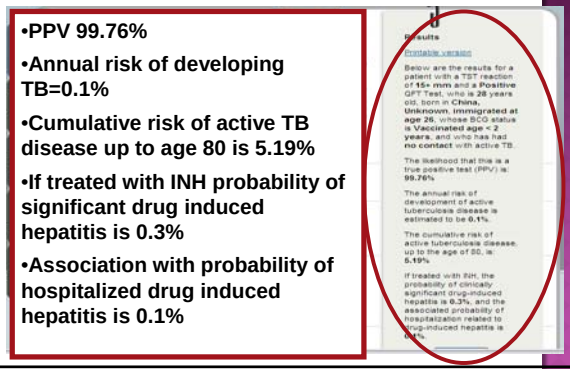
- Asymptomatic ALT increase in
  - ~20% of patient
- Clinical hepatitis 0.1 -0.6%
- Timing: weeks to months of starting drug
- Risk factors:
  - Age
  - Chronic alcohol consumption
  - Active hepatitis B (+HBeAg)
  - Elevated baseline transaminases (AST, ALT)
  - Concomitant use of other hepatotoxic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

AJRCCM, 2006; 174:935-952

## WWW.TSTIN3D.COM


## WWW.TSTIN3D.COM

- **PPV 99.76%**
- **Annual risk of developing TB=0.1%**
- **Cumulative risk of active TB disease up to age 80 is 5.19%**
- **If treated with INH probability of significant drug induced hepatitis is 0.3%**
- **Association with probability of hospitalized drug induced hepatitis is 0.1%**



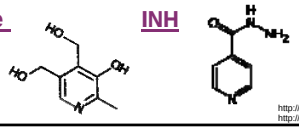
## MANAGEMENT OF HEPATOXICITY

- Hold medication and repeat LFTs
- Continue therapy
  - No symptoms and LFTs (AST/ALT) <= 5X ULN (upper limits of normal)
- Stop therapy
  - Symptomatic and ALT >3X ULN
  - No symptoms and ALT > 5X 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) neurititis
- 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 hepatoxicity than INH or PZA

http://connect.in.com/thrombocytopenia/photo-gallery-more.html

## 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
- Opthalmology evaluaion
- 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

## STREP/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, hypothroidism, impotence
  - Diabetes may be more difficult to manage
  - Acne
  - Irregular menstrual cycles

## LINEZOLID

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

## PARA-AMINOSALICYLATE (PAS)

- **Gatrointestinal 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

## CYCLOSERINE

- 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

http://www.japi.org/june_2011/article_15.html

## 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
- 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

## VISION – 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

## 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

*Peloquin, et al. Aminoglycoside toxicity…Clin Inf Dis 2004;38:1538-44

## COMMON ADVERSE REACTIONS TO DRUG TREATMENT

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

## COMMON ADVERSE REACTIONS TO DRUG TREATMENT

| Caused by | Adverse Reaction | Signs and Symptoms |
|---|---|---|
| Isoniazid | Peripheral neuropathy | Tingling sensation in hands and feet |
| Pyrazinamide | Gastrointestinal intolerance | Upset stomach, vomiting, lack of appetite |
| | Arthralgia | Joint aches |
| | Arthritis | Gout (rare) |
| Streptomycin | Ear damage | Balance problems<br>Hearing loss<br>Ringing in the ears |
| | Kidney damage | Abnormal kidney function test results |

## COMMON ADVERSE REACTIONS TO DRUG TREATMENT

| Caused by | Adverse Reaction | Signs and Symptoms |
|---|---|---|
| Rifamycins<br>Rifabutin | Thrombocytopenia | Easy bruising<br>Slow blood clotting |
| Rifapentine<br>Rifampin | Gastrointestinal intolerance | Upset stomach |
| | Drug interactions | Interferes with certain medications, such as birth control pills, birth control implants, and methadone treatment |

## STUFF HAPPENS; BE PREPARED

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