



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

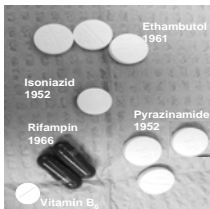
- Address, relieve symptoms
- Reassure patient
- Emphasize importance of treatment completion
- Make every attempt to avoid unnecessary breaks in therapy
- Remind patient that breaks result in prolonged duration of treatment



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

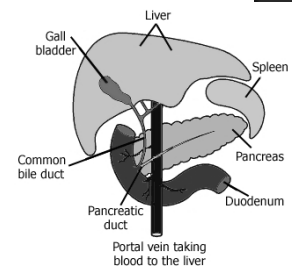
- Mild reactions
- No lasting effect
- Usually do not require change in TB meds
- Discoloration of body fluid
- Gas, bloating, mild nausea
- Itching, mild rash
- Photosensitivity
- Sleep disturbances
- Headache

SERIOUS DRUG COMPLICATIONS

- Serious
- May be life threatening
- Require change in medication
- May require hospitalization
- Significant nausea, vomiting, diarrhea
- 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)



HEPATOCELLULAR INJURY: ^{TOAST} HEPATIC ENZYMES



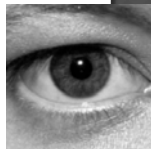
- ALT (SGPT) is more specific for hepatocellular injury than AST (SGOT)
- AST can arise from muscle, heart, or kidney abnormalities
- AST>ALT with alcohol-related disease
- Normal levels defined as within 2 standard deviations of the mean from a healthy population
 - 2.5% of normal, healthy people will 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 (LTBI), 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

The Online TST/IGRA Interpreter
Version 3.0

English Français

The following tool estimates the risk of active tuberculosis for an individual with a tuberculin skin test reaction of 25mm, based on his/her clinical profile. It is intended for adults tested with standard tuberculin (5 TU RT23, or 2 TU RT-23) and/or a commercial Interferon Gamma release assay (IGRA).

L'outil suivant évalue le risque de développer une tuberculose active chez une personne ayant eu une réaction au test cutané à la tuberculine de 25mm selon son profil clinique. L'outil a été conçu pour une utilisation chez une population adulte soumise au test tuberculine standard (5 TU RT23 ou 2 TU RT-23) ainsi qu'aux tests de libération d'interféron-gamma (TLI(IGRA)).

Enter Entrer

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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%

Results

Probable scenario

Below are the results for a patient with a TST reaction of 15+ mm and a Positive QFT Test, who is 28 years old, born in China, Unknown, immigrated at age 26, whose BCG status is Vaccinated age < 2 years, and who has had no contact with active TB.

The likelihood that this is a true positive test (PPV) is 99.76%.

The annual risk of development of active tuberculosis disease is estimated to be 0.1%.

The cumulative risk of active tuberculosis disease, up to the age of 80, is 5.19%.

If treated with INH, the probability of clinically significant drug-induced hepatitis is 0.3%, and the associated probability of hospitalization related to 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) neuritis
- CNS toxicity: Slurred speech, ataxia, seizure, memory

Pyridoxine **INH**

Cc1c(O)c(CO)c(O)c1 NC(=O)c1cccnc1

<http://en.wikipedia.org/wiki/Isoniazid>
<http://en.wikipedia.org/wiki/Pyridoxine>

RIFAMPIN TOXICITY

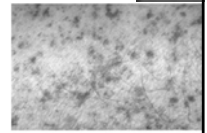


- ◉ Orange discoloration of body fluid
- ◉ Cutaneous reactions:
 - mild
 - generally self-limited
 - Treat symptomatically - antihistamine
- ◉ Gastrointestinal symptoms:
 - nausea, anorexia, abdominal pain
- ◉ Hepatocellular injury less common
 - Insidious cholestasis
 - Anorexia, nausea, vomiting, fever,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

<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

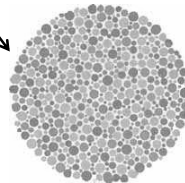
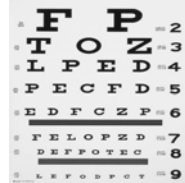


ETHAMBUTOL TOXICITY

- ◉ 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
- ◉ 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

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, 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

PARA-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

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



Fig. 1: Clinical photograph showing extensive papules over the face and neck, with hemorrhagic crusts present over the lips and anterior ears.



Fig. 2: Clinical photographs showing multiple areas of erosions over the hands and feet with thick adherent yellow crusts, some showing whitish scales, hyperpigmentation along with thick dystrophic nails

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

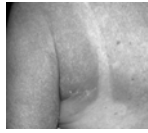
4 W'S OF DRUG RASH WHERE, WHAT, WHEN, WHO?

- 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

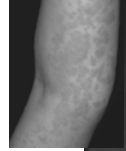
- Itching with or without erythematous rash is common early side effect
 - May resolve after 1st several weeks of therapy without stopping medications
 - For mild or localized reaction, continue treatment & treat the rash and pruritis symptomatically - antihistamines, topical steroids
- Photosensitivity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



<http://medicine.medscape.com/article/1049648-overview>

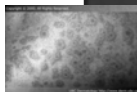
DERMATOLOGIC REACTIONS

- 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 \geq 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 Changed color vision
Isoniazid, Pyrazinamide, or Rifampin	Hepatitis	Abdominal pain Abnormal liver function test results Fatigue Lack of appetite Nausea Vomiting Yellowish skin or eyes 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 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

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

STUFF HAPPENS; BE PREPARED



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