ADVERSE REACTIONS

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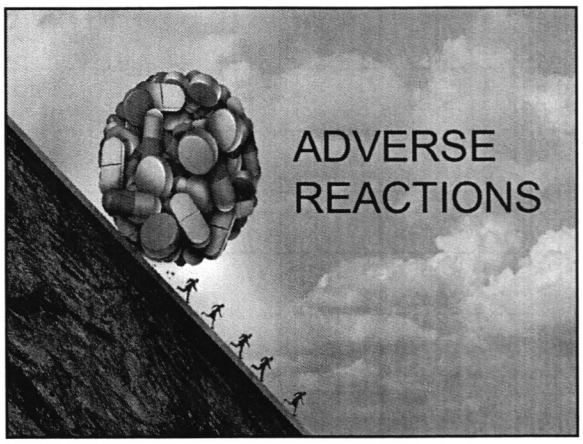
Northeast TB Summit,
November 6, 2019

WISCONSIN DEPARTMENT of HEALTH SERVICES

Division of Public health



Side Effect vs. Adverse Reaction

Side Effect: Unpleasant reaction – can be managed

- A secondary unwanted effect that occurs during drug therapy.
- Usually common and well known and can be managed without interruption of treatment.
- Examples include: stomach upset, orange body fluids, nausea, and rash.

Adverse Reaction: Serious reaction – toxicity

- Unintended pharmacologic effects that occur when a medication is administered correctly but causes harm.
- Examples include: hepatic toxicity, dark urine, hearing loss, fever, and visual changes.

TB Adverse Drug Events

Toxicity
- Serious reactions
- May require treatment or hospital
- Requires change in dose or stopping
- May be life threatening
- Examples:
  - Hepatitis
  - Kidney Failure
  - Serious Allergic reaction
  - Neurological problems
  - Vision changes, eye pain
  - Thrombocytopenia
  - Neutropenia
  - Anemia

Side Effects
- Unpleasant reactions
- Not damaging to health
- Does not require change
- Not life threatening
- Examples:
  - Nausea (mild)
  - Gas
  - Bloating
  - Discolored body fluids
  - Sleeping problems
  - Photosensitivity

Anti-TB Drugs (U.S.)

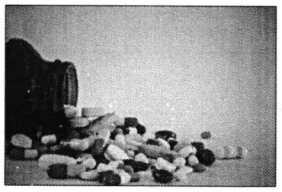
First-Line
Isoniazid (INH or H)
Rifampin (RIF or R)
Rifabutin (RFB)
Rifapentine (RPT)
Pyrazinamide (PZA or Z)
Ethambutol (EMB or E)

Third-Line
Bedaquiline (BDQ or Bdq)
Delamanid (DLM or Dlm)
Clofazimine (CZ)
Pretomanid (Pa)
Imipenem
High-dose INH
High-dose RIF
Amoxicillin

Second-Line
Amikacin (AK)
Streptomycin (SM)
Moxifloxacin (MOX or Mfx)
Levofloxacin (LFX or Lfx)
Ethionamide (ETA or Eto)
Para-aminosalicylic acid (PAS)
Linezolid (LZD or Lzd)
Cycloserine (CS or Cs)

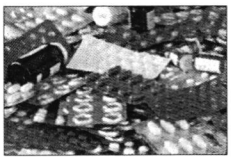
Anti-Tuberculosis Medications

- With TB we have limited curative options in terms of medication and therefore we walk a fine line between side effects and adverse reactions.



- Medications and monitoring must be individualized.
- Some common side effects can be the first sign of an adverse event.
- Medication can also have different effects on people due to: age, other medical conditions, social habits, drug-drug interactions, and foods.

Anti-Tuberculosis Medications



- Almost all TB medications are toxic in some way and second-line TB medications are the most toxic.
- However, treatment of infectious TB is more important than minor side effects or even some adverse events.
- Research is being done to develop more humane, less toxic, and shorter regimens for both TB and drug-resistant TB.

First-Line TB Medications
Isoniazid (INH)

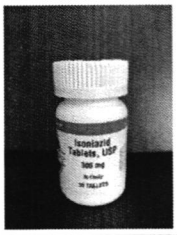
First-Line TB Medications (INH)

Isoniazid (INH) – Isonicotinic acid hydrazide

- Metabolized in the liver (acetylation process under genetic control).
- Excreted in urine.
- Unwanted effects often are dose related.
- Daily dosing: 5mg/kg, max 300mg.
- Intermittent dosing: 15mg/kg, max 900mg.

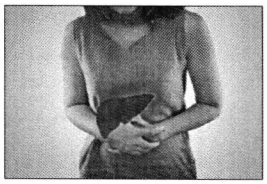
Adverse reactions include:

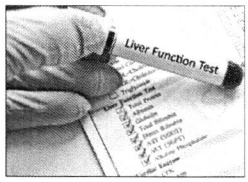
- Hepatotoxicity
- Neurologic syndromes
- Rheumatoid syndrome
- Lupus syndromes
- Monoamine poisoning
- Hematologic hypersensitivity



Hepatotoxicity Caused By INH

10-20% have asymptomatic elevations of aminotransferase (amino or aspartate) up to five times the upper limits of normal which usually returns to normal (hepatic adaptation) without stopping the medication.





Hepatotoxicity Caused By INH

Recommendations:

- Stop treatment if:
  - ALT 3x upper limit of normal (3xULN) with symptoms (+/- 123)
  - ALT 5x upper limit of normal (5xULN) without symptoms (+/- 205)
  - AST 3xULN with symptoms (+/- 114)
  - AST 5x ULN without symptoms (+/- 190)
- Wait until they come down to below 2x ULN before re-starting

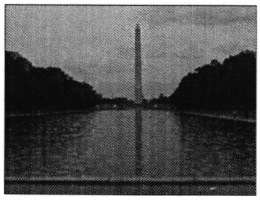

American Thoracic Society Documents

An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy

ALT: alanine aminotransferase; AST: aspartate aminotransferase

Hepatotoxicity Caused By INH

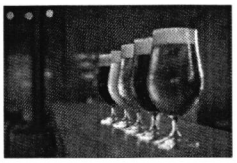
- Given alone estimated rate of hepatitis = 0.6%
- With other agents excluding RIF is 1.6%
- Given with other agents including RIF = 2.7%



- Historically given at higher doses until TB outbreak among government staff in Washington DC in 1970.

Hepatotoxicity Caused By INH

- Risk increases with underlying disease, alcoholism, other hepatotoxic medications, and in postpartum women (due to fast acetylation).




- Fatal hepatitis = 1 and 7/100,000 associated with continued treatment after symptom onset.

Neurologic Syndromes Caused By INH

Peripheral neuropathy is dose-related and increases with activity.

- Occurs less than 0.2% at normal doses.
- Increased risk with nutritional deficiency, diabetes, HIV infection, renal failure, alcoholism and in pregnant or breastfeeding women.

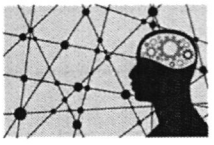
Recommendation:

Supplement with pyridoxine (vitamin B-6): 25-50mg/day.

Neurologic Syndromes Caused By INH

Central nervous system effects.
(autonomic dysfunction)

- Rare.
- Headaches, irritability, dysphoria, depression , psychosis, dysarthria (drunk-like speech), inability to concentrate, insomnia, optic neuritis (blindness), and seizures.



Recommendations:

- Continue treatment if symptoms are minor and tolerable.
- Stop if one of the more serious reactions occurs.

Rheumatoid Syndrome Caused By INH

Joint pain.

- Rare.
- Includes: sudden onset of joint pain, tenderness in hands or other joints like elbows, wrists, shoulders, hip and spine.

Recommendations:

- Continue treatment if symptoms are minor and tolerable.
- Stop if one of the more serious reactions occurs.

Lupus Syndrome Caused By INH

Autoimmune condition (slow acetylation).

- Rare (less than one percent).
- Includes one or more lupus erythematosus clinical symptoms: arthralgia, lymphadenopathy, fever, weight loss, fatigue, and rash.
- Test for antinuclear antibodies (20% will be positive but asymptomatic with no need to discontinue medication).

Recommendations:

Stop medication – symptoms resolve after weeks or months for some.

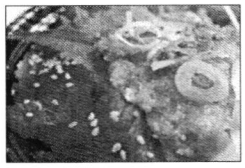
Monoamine Poisoning Caused By INH (Histamine or Tyramine)

Drug-food interaction.

- Rare.
- Symptoms:
  - Cutaneous (rash, hives, edema, local inflammation).
  - Gastrointestinal (nausea, vomiting, diarrhea).
  - Hemodynamic (hypotension).
  - Neurologic (headaches, palpitations, itching, lightheadedness).
  - Occur after consuming foods and drinks with high concentrations of monoamines.

Histamine Poisoning Caused By INH

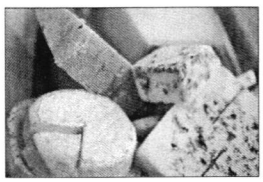
Foods containing histamine: tuna, herring, mackerel, sardines, shellfish, anchovies, mushrooms, tomatoes, spinach, eggplant, and vinegar.

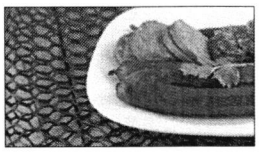


Recommendation:
Stop consuming foods listed above –symptoms should resolve.

Tyramine Poisoning Caused By INH

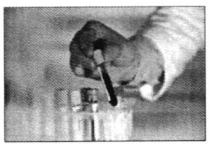
Foods containing tyramine: aged cheese such as Brie, Havarti, Boursin, Gouda, Swiss, Camembert, Stilton, Munster, Provolone, mozzarella, parmesan, feta, cheddar, and blue, and aged wines or fermented meats.





Hematologic Reactions Caused By INH

Hemolytic anemia, thrombocytopenia and neutropenia.



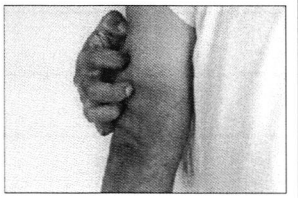
- Rare (less than 1%).
- Symptoms include: paleness, jaundice (thrombocytopenia), dark urine, weakness, dizziness, confusion, enlarged spleen (anemia), low platelets producing easy bruising, prolonged bleeding, rash, enlarged lymph nodes, fever, and increased infections (neutropenia).

Recommendation:
Stop medication –symptoms resolve rapidly (within days).

Hypersensitivity Reactions Caused By INH

Allergic reaction

- Rare < 1 %
- Symptoms:
  - Fever
  - Rash
  - Stevens-Johnson Syndrome (extensive rash that blisters and includes mucus membranes)



Recommendation:

Stop medication – treat symptoms if severe.

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INH DRUG INTERACTIONS	
Hypoglycemics	Monitor glucose, may cause hyperglycemia
Tylenol	↑ hepatotoxicity
Anticoagulants	↑ anticoagulant effect
Valium (& others)	↑ valium toxicity
Carbamazepines	↑ toxicity of both
Disulfiram (Antabuse)	Psychotic episodes
Haldol	↑ haldol toxicity
Ketoconazole	↓ ketoconazole effect
Dilantin	↑ dilantin toxicity
Theophyllin	↑ theophyllin toxicity
Valproate	↑ hepatic and CNS toxicity

First-Line TB Medications Rifampin (RIF)

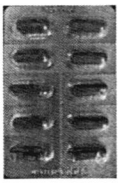
First-Line TB Medications (RIF)

Rifampin (RIF) – Rifamycins also include rifapentine and rifabutin

- Metabolized in the liver by cytochrome P450 3A4 (CYP3A4) enzyme system which can inhibit effectiveness of many other drugs.
- Excreted in urine.
- Unwanted effects often are dose related.
- Dosing is daily or intermittent 10mg/kg, max 600mg.

Adverse reactions include:

- Cutaneous reactions
- Gastrointestinal reactions
- Immunologic reactions
- Hepatotoxicity
- Hypersensitivity
- Discoloration of body fluids



Cutaneous Reactions Caused By RIF

Mild allergic reaction.

- 6% of patients.
- Pruritus (itching), rash, or flushing.

Recommendations:

- Continued treatment may be possible.
- Drug re-challenge over several days, use antihistamine or desensitization process (in hospital or clinic).

Cutaneous Reactions Caused By RIF

Pre-medicate with 25mg diphenhydramine (Benadryl) 30 minutes before dose of drug re-challenge or desensitization.

Suggested Drug Rechallenge Doses Following Non-anaphylactic Allergic Reaction*

Drug	Dose – Day 1	Dose – Day 2	Dose – Day 3
INH	50 mg	300 mg	
RIF	75 mg	300 mg	600 mg
PZA	250 mg	1 gram	full dose
ETA	125 mg	375 mg	500–750 mg
CS	125 mg	250 mg	500–750 mg
EMB	100 mg	500 mg	full dose
PAS	1 gram	4 gram	6–8 grams
SM	125 mg	500 mg	full dose

* Philadelphia TB Program 1995

Cutaneous Reactions Caused By RIF

Oral desensitization for INH, RIF, and EMB

Time from start (hour: minute)	Dose of INH* (mg)	Time from start (hour: minute)	Dose of RIF** (mg)	Dose of EMB** (mg)
0:00	0.1	0:00	0.1	0.1
0:15	0.5	0:45	0.5	0.5
0:30	1	1:30	1	1
0:45	2	2:15	2	2
1:00	4	3:00	4	4
1:30	8	3:45	8	8
2:00	16	4:30	16	16
2:30	32	5:15	32	32
3:30	50	6:00	50	50
5:30	100	6:45	100	100
7:30	150	7:30	150	200
8:30	150	11:00	300	400
17:30	150			
Early next a.m.	150 bid x 3 days		300 bid x 3 days	400 bid x 3 days

* Holland 1990
** Mehr 1994

Gastrointestinal Reactions Caused By RIF

Mild or severe.

- Variable incidence.
- Nausea, anorexia, abdominal pain, vomiting, and diarrhea.

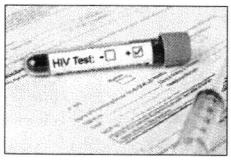
Recommendations:

Watch for underlying hepatotoxicity (check liver enzymes). Most often can continue medication with support:

- Administration of antiemetic or antacid 30 minutes before taking medication.
- Take medication at bedtime.
- Encourage hydration.
- Eat a light (non-fatty) snack before taking medication.

Immunological Reactions Caused By RIF

Severe autoimmune/ hypersensitivity reactions (due to immune system's reaction to anti-rifampin antibodies -ARA).



- Very rare (less than 0.1% of patients).
- More common when HIV-positive.
- Flu-like syndrome (more common with higher and intermittent dosing), thrombocytopenia, hemolytic anemia, or acute renal failure.

Immunological Reactions Caused By RIF

Symptoms:

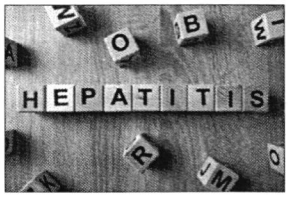
- Persistent high fever
- Exantham (widespread rash)
- Arthralgia
- Malaise
- Low platelet count (bruising, petechiae, or bleeding)
- Paleness
- Jaundice
- Dark urine
- Weakness
- Dizziness
- Confusion
- Enlarged spleen (anemia)
- Low urine output
  Flank pain (kidney failure)

Recommendation:
Stop medication permanently.

Hepatotoxicity Caused By RIF

Transient asymptomatic hyperbilirubinemia or clinical hepatitis.

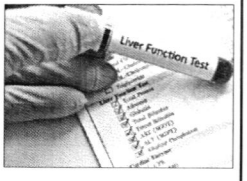
- Low occurrence (under1%, but higher if taken with INH 2.7%).
- Symptoms: nausea, jaundice, anorexia, abdominal pain, vomiting, diarrhea or symptoms of cholestasis.



Recommendation:
Check Liver enzymes including total bilirubin and alkaline phosphatase.

Hepatotoxicity Caused By RIF

- In combination with other TB medications, it is evidenced by disproportionate increase in bilirubin and alkaline phosphatase compared to AST or ALT elevation.
- Total bilirubin > 2.4mg/dl.
- Alkaline phosphatase NL is 20-140 IU/L.

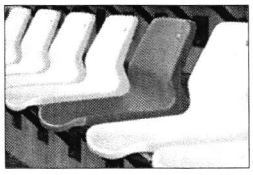


Recommendation:
If liver function tests (LFTs) are slightly elevated but total bilirubin or alkaline phosphatase are significantly elevated, consider re-challenge or alternate treatment without RIF.

Discoloration of Body Fluids Caused By RIF

Common and usually not serious.

- Nearly all patients experience this.
- Orange discoloration of sputum, urine, sweat, saliva, tears.



Recommendation:
Warn patient that soft contact lenses, dentures, and clothing can become permanently stained.

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RIFAMPIN DRUG INTERACTIONS

Anticoagulants	↓ anticoagulants effect antidepressant	Diltiazem	↓ diltiazem effect
Antidepressants	↓ effect	Fluconazole	↓ fluconazole effect
Beta-Blockers	↓ beta blockade	Itraconazole	↓ itraconazole effect
Contraceptives	↓ contraceptive effect	Haloperidol	↓ haloperidal effect
Corticosteroids	Marked ↓ steroid effect	Methadone	↓ methadone effect
Cyclosporine	↓ cyclosporine effect, ↑ Rifampin	Dilantin	↓ dilantin effect
Protease Inhibitors	Marked ↓ activity of PI, ↑ Rifampin	Verapamil	↓ verapamil effect
Delavirdine	Marked ↓ delavirdine effect	Tetracyclines	↓ tetracycline effect
Efavirenz	Slight ↓ efavirenz effect, ↓ Rifampin	Trimethoprim-Sulfa	Possible Rifampin toxicity
Digoxin	↓ digoxin effect	Chloramphenicol	↓ chloramphenicol effect

First-Line TB Medications
Pyrazinamide (PZA)

First-Line TB Medications (PZA)

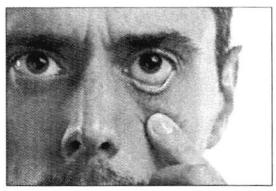
Pyrazinamide (PZA) –synthetic derivative of nicotinamide (B-3)

- Metabolized in the liver.
- Excreted in urine but metabolites can accumulate.
- Major source of hepatotoxicity of TB medications (less in combination with multidrug shorter regimens).
- Daily Dosing: 25mg/kg.
- Intermittent Dosing: 35mg/kg.

Adverse reactions include:

- Hepatotoxicity
- Acute gouty arthritis (hyperuricemia)
- Dermatitis

Hepatotoxicity Caused By PZA



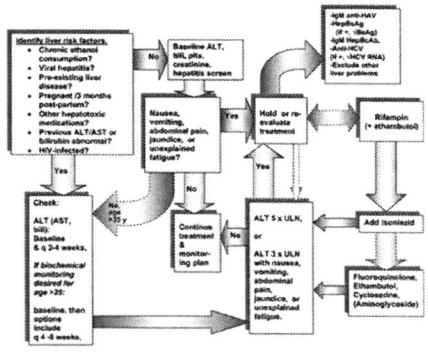
- 10-20% of patients have asymptomatic elevations of aminotransferase (amino or aspartate) up to five times the upper limits of normal.
- This usually returns to normal (hepatic adaptation) without stopping the medication.
- PZA is the most likely cause of hepatotoxicity when liver enzymes are above the recommended levels (7.9% five times the upper limit of normal and 5.3% symptomatic) and usually occurs at the beginning of treatment.
- With long term use of PZA, 2.6% of patients develop elevated LFTs.

Hepatotoxicity Caused By PZA

- Symptoms: nausea, vomiting, abdominal tenderness, discomfort near ribs on right upper abdomen, jaundice, and hepatic enlargement.

Recommendation:

- Stop treatment if ALT or AST is:
  - 3xULN with symptoms OR
  - 5xULN without symptoms.
- If all medication stopped, wait until LFTs decrease to below two times the upper limit of normal (2xULN) and restart a drug challenge according to recommended guidelines.
- **Look for a possible underlying cause.**
- **Monitor LFTs every 2-3 weeks, then every 4-8 weeks if within normal limits.**

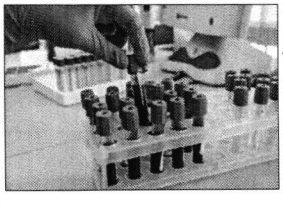


ATS (2006). Hepatotoxicity of Antituberculosis Therapy American Journal of Respiratory and Critical Care Medicine, vol. 174, p. 945.

Acute Gouty Arthritis Caused By PZA (Hyperuricemia)

- 40% of patients have some polyarthralgia.
- Serious acute gouty arthritis is rare unless there is pre-existing gout.
- PZA decreases renal uric acid secretion, metabolites accumulate and increase uric acid.
- Symptoms: pain, tenderness and/or swelling of joints.
- Affects fingers, shoulders, and knees.

Acute Gouty Arthritis Caused By PZA (Hyperuricemia)



- Serum uric acid concentrations elevated (hyperuricemia) to >7.0mg/dl.

Recommendations:

- Use anti-inflammatory medication for symptomatic relief.
- Switch to intermittent dosing (helps prevent accumulation of metabolites).

Dermatitis Caused By PZA

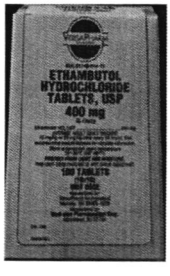
- Photo sensitive dermatitis: inflammation of the skin caused by immunologic reaction to a photosensitizing agent.
- 1 in 100 patients show some kind of photosensitivity, but this is generally rare.
- Symptoms: eczema, itchy red rash, and sunburn after light exposure which can progress and blister.

Recommendation:
Stop the offending drug (most likely PZA).

First-Line TB Medications Ethambutol (EMB)

First-Line TB Medications (EMB)

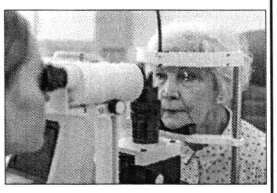
Ethambutol (EMB)
- Metabolized in the liver.
- Daily Dosing: 15-25mg/kg.
- Long-term Dosing: 15mg/kg.



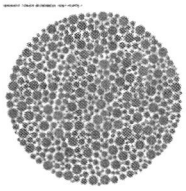
Adverse reactions include:
- Optic neuritis
- Cutaneous reactions

Optic Neuritis Caused By EMB

- Possibly due to decreased copper levels in mitochondria or accumulation of zinc in lysosomes of retinal ganglion cells.
- Dose and duration-related severity.
- Risk is less than1% at doses of 15mg/kg/day.
- Symptoms: blurred vision or red/green color blindness.



Optic Neuritis Caused By EMB



Recommendations:

- Perform baseline vision testing (acuity and colorblindness) and regular (monthly) vision testing while on EMB.
- Stop EMB if visual changes occur.

Cutaneous Reactions Caused By EMB

Allergic reaction.

- Rare (0.2-0.7%).
- Symptoms: fever, rash, and Stevens-Johnson syndrome (extensive rash that blisters and includes mucus membranes).

Recommendations:

- Continued treatment may be possible.
- Drug re-challenge over several days, use antihistamine or desensitization process.
- EMB can be discontinued when drug sensitivities are known and isolate is pan-sensitive (EMB has limited role in treatment).

Second-Line TB Medications

HEPATITIS	NEUROLOGICAL	RENAL	OPTHALMOLOGIC	HEMATOLOGICAL (rare)
Ethionamide	**Peripheral Neurotoxicity:**	Streptomycin	**Vision Changes:**	Linezolid
PAS	Ethionamide	Amikacin	Linezolid	Cycloserine (rare)
Levofloxin (rare)	Linezolid	Capreomycin		Capreomycine (rare)
				Levofloxacin (rare)
	Central Neurotoxicity:			Moxifloxacin (rare)
	Ethionamide			Streptomycin (rare)
	Cycloserine			PAS (rare)
	Fluroquinolones			
	Amikacin			
	Linezolid			

New Medications:

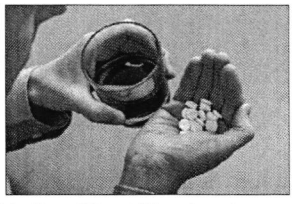
- Bedaquiline (BDQ) – QTc prolongation, nausea, rash
- Pretomanid (Pa) – peripheral neuropathy, anemia, hepatotoxicity, optic neuropathy, QT prolongation (in combined therapy)

Conclusions and What to do

Adverse Drug Reactions (ADRs) –First Line Drugs Depicted in Several Studies

Study, Numbers	Year	Liver %	Rash %	Aches %	Blood %	GI %	Neuro %	Renal %	Optic %	Other %	All %
USPHS -21 no.1451 6 months	1990	2.4	1.1	1.0	0.2	1.5	-	-	-	1.0	-
9months		3.6	0.7	0.0	0.0	0.4	-	-	-	1.1	-
Canada no. 430	2003	3.0	4.0	-	-	2.0	-	-	-	-	9.0
Vancouver Canada no.1061	2007	13.9	7.5	3.2	-	10.0	-	-	0.7	-	-
HR alone		3.2	0.8	-	-	1.2	-	-	-	-	-
China no. 4304	2013	6.3	2.4	2.5	0.7	3.7	2.0	0.7	-	-	-
Not serious		91%	90%	98%	87%	91%	94%	66%	-	-	-

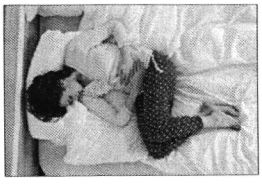
Adverse Drug Reactions: What To Do



Hepatotoxicity

- Ask about alcohol.
- Check LFTs.
- Look for underlying causes (viral hepatitis, nutrition, drug-drug interactions, dehydration).
- Stop medication, counsel patient to limit activities and avoid alcohol, eat small frequent meals to optimize metabolism.
- Drug-challenge (with physician/State advice).

Adverse Drug Reactions: What To Do

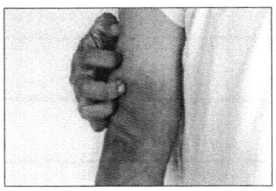


Gastrointestinal

- Assess for hepatitis: fatigue, abdominal pain, jaundice, G.I. bleed (coffee ground emesis), or dehydration.
- Order lab tests as needed (LFTS, CBC, therapeutic drug levels).
- For side effects: anti-emetic 30 min before medication, take medication slowly, change timing, rehydrate, replace electrolytes.

Adverse Drug Reactions: What To Do

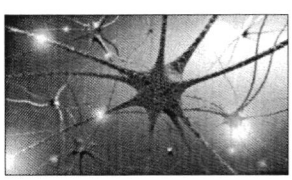
Hypersensitivity (rash)



- Assess for blistering (eyes or lips) and swelling.
- Ask about other medications.
- Labs: CBC, LFTs.
- Hold medications with fever or severe allergy.
- With mild cases consider skin lotion, antihistamine, or hydrocortisone cream.

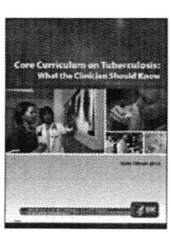
Adverse Drug Reactions: What To Do

Neurological



- Optic neuritis, peripheral neuropathy, depression, headache, psychosis
- Ask about tingling or burning in hands or feet, alcohol consumption, mood changes, insomnia, and/or headache.
- Check vision acuity and color, HgbA1c if diabetic, creatinine, sodium, diet, perform therapeutic drug level testing.

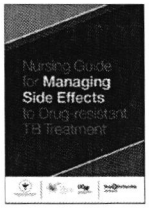
References (CDC Guidelines)

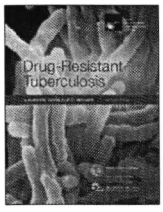


https://www.cdc.gov/tb/publications/guidelines/list_date.htm

https://www.cdc.gov/tb/education/corecurr/index.htm

References (Other)





https://www.dhs.wisconsin.gov/tb/index.htm

http://www.currytbcenter.ucsf.edu/products

Extra slides

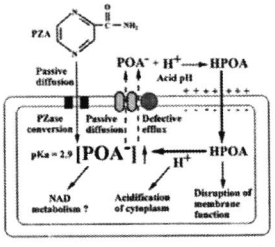


Figure 3 Mode of action of PZA. POA = pyrazinoic acid; HPOA = protonated POA; NAD = nicotinamide adenine dinucleotide.

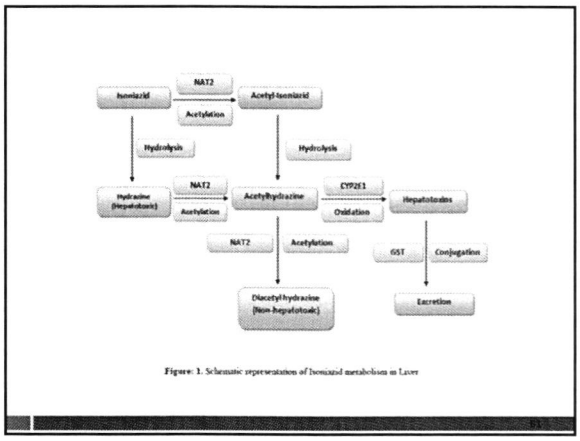


Figure: 1. Schematic representation of Isoniazid metabolism in Liver