TB
Managing Adverse Drug Effects

Dana Kissner, M.D.
Detroit TB Program / Wayne State University School of Medicine
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Disclosures

- Financial – none
- 10 medications are approved by the FDA for TB
  - INH, RIF (1971), Rifapentine (2000), PZA, EMB, Streptomycin, Cycloserine, Ethionamide, PAS, Bedaquiline (2012)

  - All other drugs discussed here are NOT FDA approved for TB

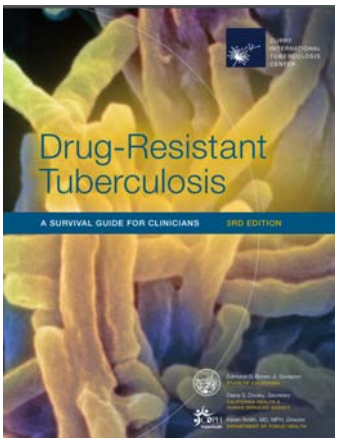
Objectives

- You will be aware of & recognize drug-drug and drug-food interactions
- You will know how to manage symptoms due to TB drugs that do not require stopping the offending drug
- You will recognize & correctly manage important adverse effects that require change in TB regimen

Topics

- Introduction – resources, approach to TB treatment
- Drug-Drug and Drug-Food Interactions
- Symptom management of side effects
- Serious drug reactions
  - Recognizing them
  - Managing them
  - Monitoring for them
- Specific drugs

Introduction

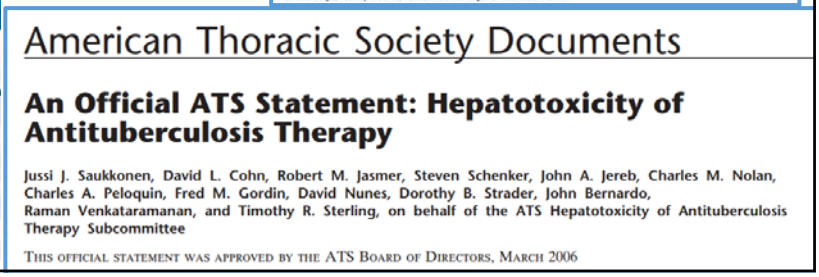


Resources. Educate / partner with your patient. Anticipate problems. Balance risks and benefits.

Good sources for TB drug information

- Drug-Resistant TB Survival Guide Chapters 8 & 9, 2016
- ATS/CDC/IDSA Guidelines on Treatment of TB, 2016
- ATS Statement on Hepatotoxicity, 2006


Clinical Infectious Diseases
IDSA GUIDELINE
IDSA hivma
Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis


American Thoracic Society Documents

An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy

Jussi J. Saukkonen, David L. Cohn, Robert M. Jasmer, Steven Schenker, John A. Jereb, Charles M. Nolan, Charles A. Peloquin, Fred M. Gordin, David Nunes, Dorothy B. Strader, John Bernardo, Raman Venkataramanan, and Timothy R. Sterling, on behalf of the ATS Hepatotoxicity of Antituberculosis Therapy Subcommittee

THIS OFFICIAL STATEMENT WAS APPROVED BY THE ATS BOARD OF DIRECTORS, MARCH 2006

Treatment of TB is difficult

- Symptoms will likely occur and may be
  - Drug-related
  - Due to other causes – including TB itself
  - Related to fear of drugs / anxiety
- Serious adverse reactions
  - Need to be anticipated
  - Should be monitored for
  - May prompt discontinuation / changing medication

Make your patient your partner

- Discuss risks and benefits of treatment
- Educate patient about side effects and when to stop medicine
- Encourage patient to report side effects
- Reassure patient that you know how to safely handle adverse effects
- Provide contact information for patient
- Regularly monitor patient
  - Clinic visits / **symptom review, identify concomitant medicines**
  - Tests where indicated
- MDR & XDR-TB can be likened to cancer to help patients understand and deal with side effects

Recognize when drug can be continued
Recognize when drug needs to be stopped

Continue drug

- Address, relieve symptoms
- Symptoms may abate after initial weeks
- Emphasize importance of Rx completion
- Make it a common goal to complete Rx on time

Do Good, Cure TB

Stop drug

- Recognize signs & symptoms of drug toxicity
- Know when to stop / not administer drug
- Promptly report symptoms
- Communicate - physician, nurse, DOT worker, patient

Do No Harm

Drug-Drug & Drug-Food Interactions

Obtain accurate medication list. Recognize when adverse events are caused by drug interactions.

Case 1

- 36 year old man from Yemen
- Very anxious
- On INH 900 mg. and RIF 600 mg. 3 days a week (continuation phase)
- Sees different doctors and did not report change in medication to us during a routine clinic visit
- Complained of new severe symptoms after taking each dose of INH / RIF. Said he could not go on this way

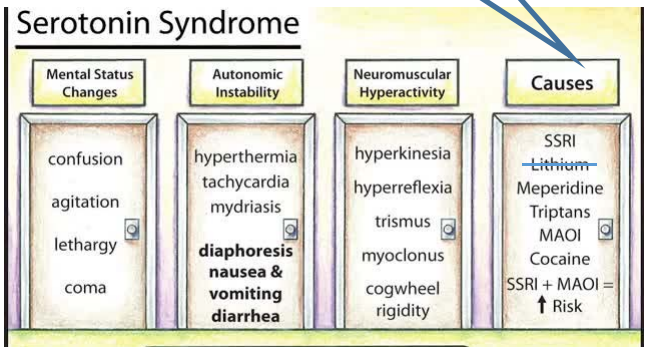
Case 1 Symptoms

- Chills
- Profuse sweating
- Stiffening of limbs, unable to get out of bed for many hours
- Twitching of muscles
- Agitation
- Blood tests done
  - CPK (muscle enzyme), Creatinine (test of kidney function) elevated
- What is this?

Serotonin Syndrome

- 3 different doctors had prescribed medicine
  - Trazodone (serotonin modulator) for insomnia
  - Escitalopram & Fluoxetine for depression (SSRIs)
  - Taken with 900 mg. INH =>
- Serotonin Syndrome
- Treatment
  - Fluids, benzodiazepams
  - Cyproheptadine, an antihistamine, blocks serotonin production

Additive with Isoniazid
Linezolid can also cause SS



Other INH drug drug interactions

- Anticonvulsants
- Decreases seizure threshold

Foods that interact with INH

- Tyramine-containing food, worse if also taking MAO-inhibitors
  - Hypertension, flushing, palpitations, headache, diaphoresis, nausea, 2-3 hours post dose
  - Fermented, cured, aged, spoiled food
    - Aged cheese
    - Cured or smoked meat
    - Fava beans, broad beans
    - Red Wine, beer on tap or home-brewed
    - Soy products (Miso soup, tofu)
    - Sauerkraut
    - Overripe fruits

- Histamine-containing food
  - Hypotension, headache, sweating, palpitations, flushing diarrhea, itching, wheezing, shortness of breath
    - Tuna, Skipjack, Saury

Rifamycins: Do interaction checks with <u>all</u> concomitant medicines

- Rifampin induces cytochrome P450 class of enzymes
  - Involved in drug metabolism
- Drugs.com claims this:
  - 762 medications are known to **interact** with **rifampin**
- Rifampin decreases levels of
  - Narcotics (methadone)
  - Azole antifungal agents (can be complex interactions, e.g. ketoconazole)
  - Corticosteroids
  - Warfarin (coumadin), Factor Xa inhibitors
  - Phenytoin, lamotrigine
  - Hormonal Contraceptives
  - Tadalafil, Sildenafil (ED & pulmonary artery hypertension)
- HIV protease inhibitors & nonnucleoside reverse transcriptase inhibitors – **complex interactions**

Rifamycins

- Interfere with beta blockers and calcium channel blockers

Symptoms that do not necessitate stopping drug

Symptomatic treatment. Patient reassurance.

Case 2

- 80 year old Syrian Kurdish man with B1 TB status, cough, dementia, and abnormal chest x-ray
- Given first dose of INH, RIF, Ethambutol, and PZA in clinic and observed for a while
- Sudden and dramatic agitation, itching, flushing, and watery eyes. Vital signs remained normal
- He was given hydroxyzine and observed
- Symptoms resolved
- Eventually he tolerated all medications
- What happened?

Side effects that do not necessitate stopping drug

- Flushing, itching, involving face / scalp; watering & reddening eyes
  - Rifampin or PZA, self-limited
- Nausea, vomiting, anorexia that don't persist; diarrhea, metallic taste
  - Multiple drugs
- Skin rash (maculopapular), itching
  - Multiple drugs
- Photosensitivity, skin discoloration that reverses when drug is stopped
  - PZA, Clofazimine, or fluoroquinolones
  - Clofazimine causes skin color changes pink->red/blue->brown
- Reversible CNS symptoms
- Bone & joint symptoms
  - PZA. Less so EMB, INH
- Endocrine effects (less common)

GI symptoms Management

- Seek other possible causes
- Trial of medications
  - Promethazine 12.5 – 25 mg. 30 minutes before dose, every 6 hours prn nausea
  - Ondansetron 8 mg. 30 minutes before dose, every 8 hours prn nausea
  - Metoclopramide 10 mg. every 6 hours prn nausea
  - Lorazepam 0.5 mg sublingual 30 minutes before dose for anticipatory nausea
- Give TB medicine with light snack
- INH
  - Commercial liquid preparations contain sorbitol which can cause diarrhea
- Reassure patient

Particular drugs

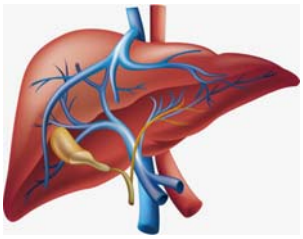
- PAS – very poorly tolerated
  - GI symptoms dose related
  - Malabsorption
    - Steatorrhea (fat malabsorption)
    - Doubling of prothrombin time
    - Vitamin K is a fat soluble vitamin
    - Levels of fat soluble vitamins (A, D, E) can be measured & monitored
    - Granular formulation better tolerated
- 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

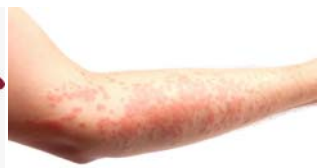
Maculopapular rash, itching
Treatment

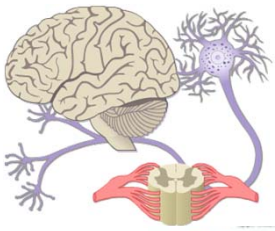
- Benadryl 25-50 mg before dose, every 4-6 hours as needed
  - Other antihistamines: chlorpheniramine 4 mg. before dose and every 6 hours as needed, hydroxyzine 25 – 50 mg., and Loratadine 10 mg. before dose
- Hydrocortisone cream
- Low dose prednisone
- Reassure patient
- Very localized rashes are unlikely to be due to drug
- Consider other causes
- **Take good history of skin problems prior to starting TB medicines**

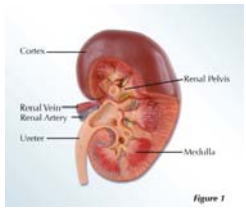
Arthralgias
Gout unlikely

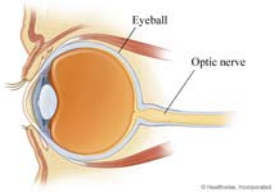
- PZA causes elevated uric acid
  - PZA is a pro-drug, converted to the active compound Pyrazinoic acid
  - Pyrazinoic acid blocks renal tubular excretion of uric acid => elevated uric acid
- Allopurinol does not reverse this
- Routine measurement of uric acid is not recommended
- Gout is rare
- Hyperuricemia without gout is not a reason for discontinuing drug
- Treat with nonsteroidal anti-inflammatory drugs
- Reassure patient
- Look for other etiologies

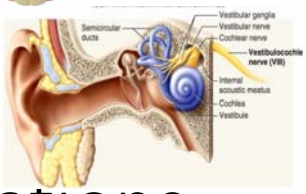






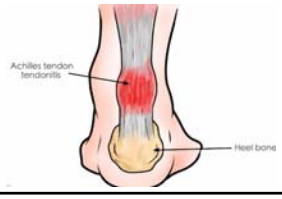






Serious Drug Complications

Drug induced liver injury (DILI) and hepatitis. Serious skin problems. Others. Monitoring



Serious Drug Complications

- Hepatotoxicity
- Serious skin / systemic reactions
- Neurologic, CNS, psychiatric
- Vision loss
- Hearing loss / vestibular dysfunction
- Kidney failure, Electrolyte abnormalities
- Hypersensitivity, hematologic (blood) reactions
- Tendonitis / rupture
- Death

Drug Effects on Liver: A Spectrum

- Fulminant liver disease / death
- Drug induced liver injury (DILI)
  - 700 drugs approved in US can cause liver toxicity
  - **Important to detect early**
- Hepatic adaptation
  - Protective response
- Cholestasis
  - Bile does not flow freely from liver to bowel
- Asymptomatic elevations in bilirubin

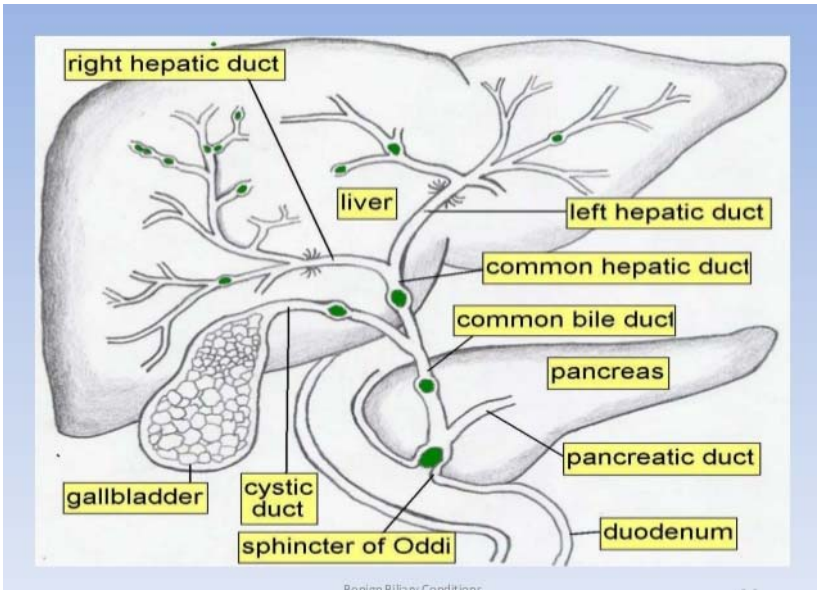
Laboratory tests for liver disease

- Liver cells & bile duct cells contain enzymes
  - Released into blood if liver is damaged
- **ALT (SGPT)**
  - Released from damaged liver cells into blood
  - Most specific test for **DILI**
  - Can be elevated in **hepatic adaptation**
- AST (SGOT)
  - Released from damaged liver cells into blood
  - Not specific to liver (found in heart, muscle, Red Blood Cells)

Laboratory tests for liver disease or bile flow problems

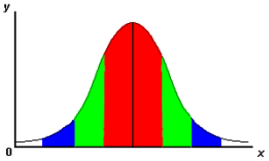
- Alkaline phosphatase
  - Enzyme found in liver cells & cells lining bile ducts
  - Elevated in **bile duct obstruction, cholestasis, infiltrative diseases of liver**
    - Elevated in children & pregnant women
- Bilirubin
  - Results from the breakdown of red blood cells (elevated in hemolysis)
  - Normally, it passes through the liver, is conjugated (made water soluble), & excreted in stool
  - When the liver cannot handle bilirubin normally **or bile flow** is impaired, bilirubin leaks into the blood stream

Biliary system



ALT and AST

- 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
  - Inter-laboratory variation – each lab determines its ULN
  - Variation within an individual up to 45% in a day

INH

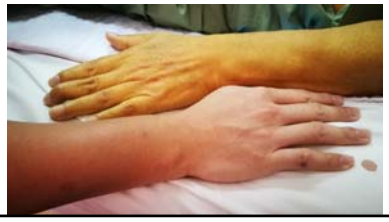
- Cleared in liver by acetylation
- Genetic variation => fast, slow, & intermediate acetylators
  - Significance unclear
  - Genotyping suggests slow acetylators develop higher peak ALT & more frequent elevations >3 X ULN than fast acetylators
- **Up to 20% people treated with INH alone have low-grade, transient, asymptomatic ALT increase – "hepatic adaptation"**

INH

- Rate of hepatotoxicity when used alone: 0.1-0.6%
- Idiosyncratic (not dose-related)
- Incidence & severity increases with age
- Risk increases with:
  - Chronic alcohol consumption
  - Active hepatitis B (+HBeAg)
    - Can be treated concurrently with TB
    - Tenofovir disoproxil (Viread) is OK
    - Tenofovir alafenamide (Vemlidy) is contraindicated with Rifampin
  - Elevated baseline transaminases (AST, ALT)
  - Concomitant use of other hepatotoxic drugs (PZA)
  - 3rd trimester pregnancy to 3 months post-partum
  - Pre-existing liver disease

Rifampin

- Dose-dependent interference with bilirubin uptake => subclinical, elevated **unconjugated** bilirubin & jaundice
  - May be transient
  - May occur early in treatment
- Can also cause asymptomatic elevation **conjugated** bilirubin (several mechanisms)
- Icterus / jaundice, elevated bilirubin & alkaline phosphatase



Rifampin hepatotoxicity

- Hepatocellular injury less common
  - Insidious **cholestasis**
    - Decrease in bile flow due to impaired secretion by hepatocytes or to obstruction of bile flow through intra-or extrahepatic bile ducts
  - Anorexia, nausea, vomiting, fever, jaundice
  - Mildly elevated ALT, elevated bilirubin
  - Usually occurs in first month of treatment
  - RIF is much less likely to cause hepatoxicity than INH or PZA

Drug induced liver injury (DILI) - INH Cholestatic liver disorder - RIF

- ALT > 3 times upper limit of normal or
- Alkaline phosphatase > 2 times upper limit of normal or
- Total bilirubin > 2 times upper limit of normal AND increased ALT or increased alkaline phosphatase

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- Categories hepatocellular versus cholestatic based on ratio of ALT to alkaline phosphatase (R).
- R=(ALT/ULN) divided by (Alk Phos/ULN)
  - Hepatocellular if $R \leq 5$
  - Cholestatic if $R \leq 2$
  - Mixed if $2 \leq R \leq 5$

Pyrazinamide

- Both dose-dependent & idiosyncratic hepatotoxicity
- 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

Monitoring for hepatotoxicity

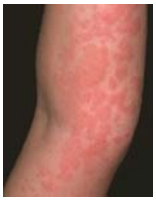
- Assess risk before treatment
- Baseline blood tests NOT generally recommended for healthy patients treated with INH or RIF used alone
- Face-to-face clinical assessments are cornerstone of monitoring
- For low risk individuals follow-up monitoring with LFTs is not indicated
- For high risk individuals obtain ALT & bilirubin at baseline & q 2-4 weeks
- ALT is preferred marker for hepatotoxicity in those with symptoms

Management of hepatotoxicity

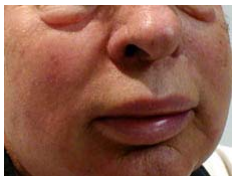
- Stop all hepatotoxic drugs if
  - ALT is ≥ 3 times ULN with symptoms OR
  - ≥ 5 times ULN without symptoms
- Consider substituting non-hepatotoxic drugs (ethambutol, fluoroquinolone*)
- When ALT < 2 times ULN, reintroduce rifampin
- After 3-7 days, reintroduce INH
- Consider reintroducing PZA only if hepatotoxicity was not severe

***There are reports of acute liver disease associated with moxifloxacin & levofloxacin. Liver disease is very rare and may be part of a hypersensitivity reaction.**

Serious dermatologic reactions



- Hives, urticaria, erythematous rash
  - Any drug
  - Stop all drugs immediately, re-challenge 1 at a time starting at low doses
    - 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
    - Can pre-medicate with Benadryl and/or prednisone

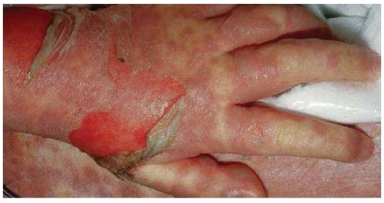


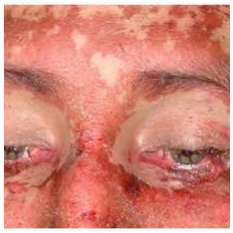
- Angioedema, anaphylaxis, or airway compromise
  - Stop drug – consider desensitization in ICU

***Page 255-256 of Survival Guide gives tables for drug reintroduction and oral desensitization derived from the Philadelphia TB program guidelines; includes some secondary drugs.**

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
- Quinolones
- Emergency, requires hospitalization
- Stop offending drug, do not use again





Neurotoxicity
Peripheral Neuropathy

- Numbness, tingling hands & feet in stocking-glove pattern
- Can cause permanent impairment
- 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

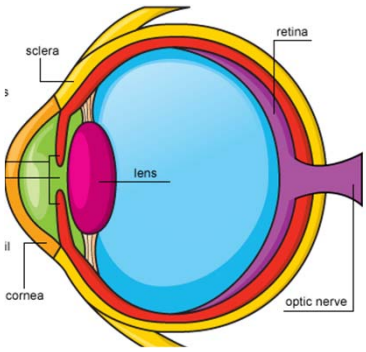
- INH
  - Dose-related
  - Interferes with biologic function of vitamin B6
- Ethionamide
  - Increased incidence with prolonged use
- Linezolid
  - Increased incidence with prolonged use
  - 600 mg daily or 300 mg twice daily instead of 600 mg twice daily is used to prevent this in TB
- Ethambutol, cycloserine
  - Rare

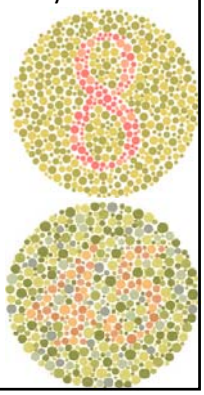
Central nervous system (CNS) reactions

- INH
  - Inability to concentrate, irritability, dysarthria, seizures, dysphoria
- Cycloserine (my mnemonic – cyclo, psycho)
  - Headache, restlessness, psychosis, seizures (dose-related)
  - Pyridoxine 100-200 mg daily to prevent / treat
  - Therapeutic drug monitoring is recommended
- Ethionamide
  - Anxiety, depression, psychosis
  - Increased incidence with prolonged treatment
- Fluoroquinolones
  - Dizziness, insomnia, tremulousness, headache

Vision
Discontinue drug, use lowest effective doses

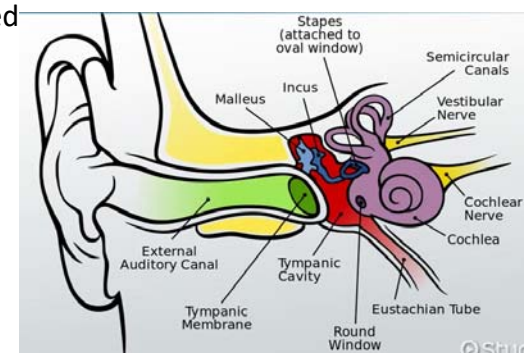
- Ethambutol
  - Retrobulbar neuritis
  - Dose & duration related – rare with currently recommended doses & no risk factors
  - Decreased red-green color discrimination (1 or both eyes), decreased visual acuity
  - Increased risk with renal disease
- Ethionamide
  - Optic neuritis
  - Dose related
- Linezolid
  - Optic neuropathy
  - Duration-related
  - Check serum B 12 and RBC folate levels





Ototoxicity
8th Cranial Nerve Damage

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

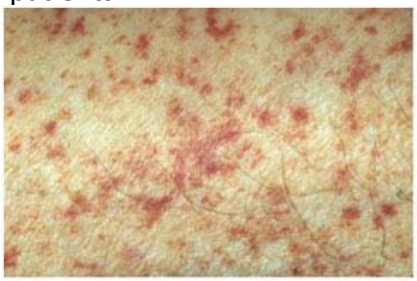


Renal failure
Electrolyte abnormalities

- All injectables cause renal failure
- Capreomycin causes profound electrolyte disturbances
  - Potassium, calcium, and magnesium depletion
  - Proteinuria is common

Hypersensitivity reactions

- Rifampin
  - 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
- Fluoroquinolones
  - May involve acute liver failure



Myelosuppression

- Linezolid
  - Requires monitoring

Endocrine disorders

- Ethionamide
  - Gynecomastia, alopecia, hypothyroidism, impotence
  - Diabetes may be more difficult to manage
  - Acne
  - Irregular menstrual cycles
- PAS
  - Hypothyroidism is common
    - Increased incidence when used with ethionamide
    - Reversible when drug stopped
    - Goiter can develop

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FDA News Release

FDA updates warnings for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions

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For Immediate Release July 10, 2018

Release The U.S. Food and Drug Administration today is requiring safety labeling changes for a class of antibiotics called fluoroquinolones to strengthen the warnings about the risks of mental health side effects and serious blood sugar disturbances, and make these warnings more consistent across the labeling for all fluoroquinolones taken by mouth or given by injection.

Inquiries

Media

Theresa Eisenman
301-796-2969

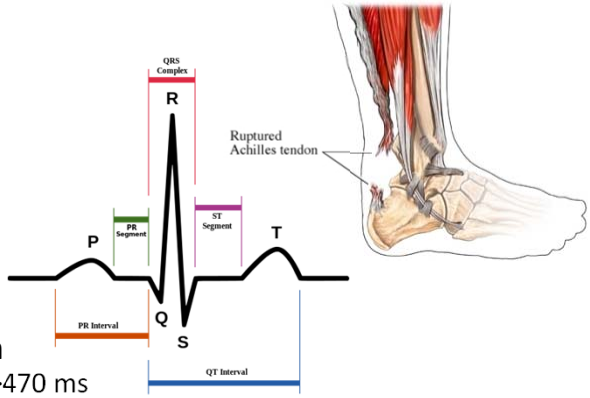
Consumers

888-INFO-FDA

Related Information

- Fluoroquinolone Antimicrobial Drugs Information

Fluoroquinolones



- Tendonitis, tendon rupture – very rare
  - All ages
  - Greater risk age >60
  - Patients taking corticosteroids
  - Transplant patients
- QTc prolongation => arrhythmias, death
  - Abnormal QTc in males >450 ms, females >470 ms
- Nausea & diarrhea
- Hypoglycemia that can => coma
- Disturbances in attention, disorientation, agitation, nervousness, memory impairment, and delirium
- Acute liver failure / hypersensitivity

Monitoring
Symptoms, concomitant medicines

- PZA, Ethionamide, PAS
  - Liver function tests (ALT, AST, Bilirubin, Alkaline Phosphatase) monthly
- Linezolid
  - CBC and differential monthly
  - Causes myelosuppression
- Injectables
  - BUN, Creatinine, electrolytes, magnesium, calcium monthly or more often
  - Audiometry and vestibular function monthly
  - Therapeutic drug monitoring
- Ethionamide, PAS
  - Thyroid function tests (TSH) every 3 months
- Ethambutol, Linezolid, Clofazimine
  - Screen for visual acuity and color discrimination monthly

Baseline & Follow-up Evaluations for Drug Susceptible Disease (from 2016 treatment guidelines)

Activity	Baseline	Month of Treatment Completed 1	2	3	4	5	6	7	8	End of Treatment Visit
MICROBIOLOGY										
Sputum smears and culture[1]	☐	☐	☐	☐	☐					☐
Drug susceptibility testing[2]	☐			☐						
IMAGING										
Chest radiograph or other imaging[3]	☐		☐							☐
CLINICAL ASSESSMENT										
Weight[4]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Symptom and adherence review[5]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Vision assessment[6]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
LABORATORY TESTING										
AST, ALT, bilirubin, alkaline phosphate[7]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Platelet count[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Creatinine[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
HIV[9]	☐									
Hepatitis B and C screen[10]	☐									
Diabetes Screen[11]	☐									

Shaded boxes optional, or contingent on other information

Case 3

- 36 year old from Yemen, in U.S. for 10 years
- Worked in dental clinics in Yemen and U.S.
- Fevers, back pain, fatigue, anorexia, very ill appearing
- Imaging – cirrhotic appearing liver, massive ascites, large spleen
- LFTs normal, Albumin 2.8 (low), Prothrombin time 13 (elevated)
- Grew MTB, **QFT TB antigen minus nil 8.53**
- HepBe antigen positive
- Hepatitis B virus DNA Quantitative PCR 7,00l,000 IU

Case 3

- Tenofovir disoproxil (Viread) 300 mg. daily by pill
  - Nucleoside/Nucleotide Reverse Transcriptase inhibitor (NRTI)
- Standard TB medications
- Weekly clinic visits and LFTs
- Slow recovery, did well, completed treatment with no complications