

TB Medications: Recognizing and Responding to Adverse Drug Events

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First-Line TB Drugs

| | | |
|---|--|---|
| INH <ul style="list-style-type: none"> - GI upset - Rash - Hepatotoxicity - Peripheral neuropathy - Mild CNS toxicity | Rifampin <ul style="list-style-type: none"> - GI upset - Rash - Hepatotoxicity -Thrombocytopenia, hemolytic anemia - Renal toxicity - Flu-like syndrome - Orange staining of body fluids | PZA <ul style="list-style-type: none"> - GI upset - Rash - Hepatotoxicity - Arthralgias - Gout (rare) |
| Ethambutol <ul style="list-style-type: none"> - Optic neuritis - Rash | Rifabutin <ul style="list-style-type: none"> - Rash/skin discoloration - Hepatotoxicity - Leukopenia, thrombocytopenia - Uveitis - Arthralgias | Streptomycin: no longer considered a first line drug |



Second-Line TB Drugs

| | |
|---|---|
| Amikacin <ul style="list-style-type: none"> - Rash - Renal toxicity - Ototoxicity - Vestibular toxicity - Electrolyte abnormalities (hypokalemia, hypomagnesemia) - Local pain at IM injection site | Levofloxacin, Gatifloxacin, Moxifloxacin <ul style="list-style-type: none"> - Rash - GI upset - Hepatotoxicity (rare) - Mild CNS toxicity - Arthralgias, rare tendon rupture - Photosensitivity - EKG abnormalities |
| Capreomycin <ul style="list-style-type: none"> - Rash - Renal toxicity - Ototoxicity - Vestibular toxicity - Electrolyte abnormalities (hypokalemia, hypocalcemia, hypomagnesemia) - Local pain at IM injection site | Ethionamide <ul style="list-style-type: none"> - Rash - GI upset, may be significant - Hepatotoxicity - Endocrine effects (gynecomastia, hair loss, acne, impotence, menstrual irregularity, reversible hypothyroidism) - Peripheral neuropathy |

Second-Line TB Drugs

| | |
|---|---|
| Cycloserine <ul style="list-style-type: none"> - Rash - CNS toxicity, may include seizure, depression, suicidal ideation, psychosis - Peripheral neuropathy - Skin changes (lichenoid eruptions, Stevens-Johnson Syndrome) | Para-Aminosalicylate (PAS) <ul style="list-style-type: none"> - Rash - GI upset, may be significant - Hepatotoxicity - Reversible hypothyroidism |
| Clofazimine <ul style="list-style-type: none"> - Rash - GI upset - Discoloration and dryness of skin - Photosensitivity - Retinopathy | Linezolid <ul style="list-style-type: none"> - Rash - Myelosuppression - Nausea and diarrhea - Optic neuropathy - Peripheral neuropathy |

Adverse Drug Events Defined

- **Side effects**
 - Unpleasant, but mild reactions
 - No long lasting health effects
 - Do not usually require changes in therapy
- **Side effects**
 - Gas
 - Bloating
 - Mild nausea
 - Discoloration of body fluids
 - Irritability
 - Difficulty sleeping
 - Photosensitivity

Adverse Drug Events Defined

- **Drug toxicity**
 - More serious
 - May be life threatening
 - Require changes in dose or discontinuation of drug
 - May require additional therapy and/or hospitalization
- **Drug toxicity**
 - Significant GI upset
 - Hepatotoxicity
 - Dermatologic and hypersensitivity reactions
 - Neurotoxicity
 - CNS toxicity
 - Ophthalmic toxicity
 - Ototoxicity
 - Renal toxicity
 - Musculoskeletal adverse effects

The “Agenda”

| DRUG | TOXICITY | INFORMATION |
|---|--|--|
| INH Rifampin/Rifabutin PZA EMB (Amikacin) (Levofloxacin) | GI Upset Hepatotoxicity Immune Reactions Ophthalmic Toxicity Neurotoxicity CNS Toxicity Ototoxicity Musculoskeletal Nephrotoxicity | Drugs Involved Monitoring Assessment Response |

Goals

- **Recognize adverse drug events**
- **Assess appropriately**
- **Intervene rapidly**
 - Prevent further morbidity/mortality
 - Minimize treatment interruptions
 - Reduce opportunities for “medical mismanagement”
 - Avoid development of psychological intolerance
 - Support adherence and the therapeutic relationship

| Tuberculosis Health Assessment History | | | |
|--|----|---|---|
| SIGN & SYMPTOMS OF TB | MC | DATE OF ONSET | COMMENTS |
| Cough (Persistent >3 Weeks) | | | |
| Weight Loss | | | Totally/semi Det. wt. 2 mos ago |
| Fever /Chills | | | Totally/intermittent |
| Exhaustion of Breath | | | |
| Chest Pain | | | |
| Fatigue | | | |
| Loss of Appetite | | | |
| Night Sweats | | | |
| Hemoptysis | | | |
| Hoarseness | | | |
| Eye pain or Blurry Vision | | | |
| Swelling of Lymph Nodes | | | |
| Profound Irritation, Bloody Urine or Urinary Pain | | | |
| Swelling of Joints / Vascles | | | |
| Headache, Decreased Level of Consciousness or Neck Stiffness | | | |
| Pain / Swelling in Other Locations | | | |
| SOCIAL HISTORY | MC | COMMENTS | |
| Tobacco use | | _____ pkts / day _____ years of use | Education: [] High Sch. [] A. H. [] JH. Sch. [] College |
| Alcohol | | Current (alcoholic drinks per week) | Work: [] Own [] Home [] Unemployed [] Hourly/retail [] Unemployed (3-5 months) [] Low Income [] Unemployed [] Homeless/Other |
| REVALENT | | | Long-Term Care: [] Hosp. Home [] Hosp./Nursing [] Residential [] Mental Health Care [] Alcohol/Drug Treatment [] Other |
| Drug Abuse | | Non-injecting _____ Injecting _____ Drugs? | Arrests: [] Jail/Prison [] Jail/Prison [] Local Jail [] ICE [] Juvenile Correctional [] Other Cor. [] Unknown. Incarceration date: _____ |
| Migration (not low in source of TB) | | | Occupation: [] Health Care [] Correctional [] Agricultural [] Other Occupation [] Not employed in past 24 mo [] Student [] Child [] Unemployed [] Retiree [] Institutionalized [] Unk. |
| Foreign Birth | | If Foreign-Born, Country: _____ Mo/Yr Entry US: _____ | If Probable TB Case Suspect (≥ 15 years old) Country of birth for primary grandchild: _____ Patient lived outside US for > 3 months [] Yes [] No If yes, country: _____ |
| Foreign Travel or Residence | | | Living in: _____ |
| Barriers to Compliance | | | |
| ADDITIONAL COMMENTS | | | |
| | | | |
| Signature of person taking history | | Signature of therapist (if used) | |

* - If History is Positive * - If History is Negative
 TB-202 Tuberculosis Health Assessment History - 2-05

The Monitoring Process

- **Discuss with patient**
 - Disease process
 - Importance of adherence to treatment regimen
 - Anticipated duration of therapy
 - Role of DOT
 - Possible drug interactions
 - Possible side effects and toxicities
 - Monitoring
 - Patient and health care staff actions should adverse drug events occur

The Monitoring Process

- **Development of core “understandings”**
 - Side effects are common
 - “You may feel worse before you feel better”
 - Symptoms usually improve with time
 - Steps can and will be taken to minimize side effects and toxicities
 - Treatment will lead to cure and prevent transmission to family and friends



Texas Department of State Health Services
Tuberculosis Education/Counseling Record

NAME: _____ D.O.B.: ____/____/____ SSN: ____/____/____

| Instructions: | Comments: | | | | | | | | | |
|---|---------------|------|------|------|------|------|------|------|------|------|
| | Initial Visit | 1 Mo | 2 Mo | 3 Mo | 4 Mo | 5 Mo | 6 Mo | 7 Mo | 8 Mo | 9 Mo |
| TRANSMISSION/PATHOGENESIS: • Significance of TB • Airborne disease • Infectiousness of case • Shared sputum • PPD(-) > 10 weeks after initial infection • 10% of infected will develop disease • TB infection vs. disease | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| INFECTION CONTROL MEASURES: [] • Proper use of masks • Infection transmission • Respiratory measures, coughing/sneezing, DOT/3C visits • Use of tissues for coughing/sneezing • Sputum collection | Y | Y | Y | Y | | | | | | |
| EVALUATION: • PPD testing significance • CTR results • No further PPD testing if = (always -) | Y | | | | | | Y | | | |
| HIGH RISK GROUP/FACTORS: • Diabetes • Alcohol/drug abuse (VUDE) • Silicosis • Corticosteroids • Gastric resection • HIV • Foreign born • Resident of correctional or long term care facility | Y | Y | Y | | | | | | | |
| MEDICATION: • Possible side effects, actions to take if side effects occur • Increased risk of side effects if post-partum, alcohol abuse, history of liver disease • Therapy = cure of disease or prevention of infection/disease • Adherence = dosage/frequency, length of treatment, DOT/DOPT | Y | Y | Y | | | | | | | |
| DRUG INTERACTIONS: • INH • Rifampin • Proton pump inhibitors, statins, quinolones, Contraceptives, methotrexate, azithromycin, and immunosuppressives, protease inhibitors, Nucleosides | Y | | | | | | | | | |
| ADHERENCE: • Case = control order, quarantine, MDR-TB, drug • LTH = disease later, DOT | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| RATIONALE FOR DOT/DOPT: • Aware compliance and adherence • DOT = prevents drug resistance and is standard of care • DOT = children < 5, HIV+, contacts to MDR-TB, other high risk | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |



Allergic reactions including rashes and hives may be caused by any of the drugs. If severe immune reactions occur (including swelling of lips, breathing difficulty or wheezing), stop taking the drug and contact the nurse or physician immediately; or, to seek emergency medical help, dial 911 or visit the ER (Emergency Room) at a hospital.

The risks are small and the health problems that may arise usually clear up completely. Sometimes the side effects may be bad, and very rarely they may cause lasting damage or death. The Texas Department of State Health Services will check me regularly for side effects. I will be responsible for telling my healthcare provider about any unusual symptoms and following treatment recommendations and instructions. The Texas Department of State Health Services believes that the benefits of drug treatment for tuberculosis disease is always much greater than the risks.

I have answered all of the questions about my medical history and my present health condition fully and truthfully. I have told the doctor or other clinic staff about any conditions that might suggest I should not take the medication(s). I have had the chance to ask questions about this health condition, the benefits and risks of specific tuberculosis drugs, including how long side effects may last and how bad the side effects may be. I understand the risks of not taking treatment. I understand that no promises can be made about cure or side effects. Any blank spaces on this form have been filled in. **By signing below, I consent to treatment for tuberculosis disease.**

SECTION I:

Patient's name: _____

Patient's Signature: _____ Date: _____

Person authorized to consent (if not patient): _____

Relationship: _____

Signature: _____ Date: _____

SECTION II:

I certify that the person who has the power to consent cannot be contacted and has not previously objected to the service being requested:

Patient's name: _____

Name of person giving consent: _____

Signature: _____ Date: _____

Relationship to patient: _____ Phone: _____

Address: _____

SECTION III:

Counselor's Signature: _____ Date: _____


Interpreter's Signature (if used): _____ Date: _____

78 - 411 (Revised 8/04)




The Monitoring Process

- **Case management plan**
 - Outlines important toxicity monitoring events that must occur during the course of treatment
 - Direct
 - Laboratory studies
 - Vision screening (visual acuity and color discrimination)
 - Audiometry
 - Vestibular screening
 - Indirect
 - Patient interview
 - Observation



**Texas Department of State Health Services
TB Case and Suspect Management Plan**

Patient's Name: _____ Initial Report Date: _____
 Name Case Manager: _____ Case Management Team: _____

Directions: Blank boxes indicate required TB services to be provided. Document date and initials of the provider in the appropriate box when the task is completed. Document comments in progress notes.

| Activity/Interval | 0 Begin | 2 Wks | 4 Wks | 8 Wks | 12 Wks | 16 Wks | 20 Wks | 24 Wks |
|---|------------|----------|----------|----------|-----------|-----------|-----------|-----------|
| Timeline Date | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Responsibility Assign case manager; establish case; document in client's record | | | | | | | | |
| Medical Evaluation Obtain medical history; document on TB-202 Obtain release (L-202); request previous medical records MD evaluation RN evaluation Mantoux skin test (if not previously done) Chest X-ray Supervised option for AFB1 or isoniazid according to protocol HIV screening for risk factors; counseling and testing Nutritional assessment | | | | | | | | |
| Treatment Drug regimen according to protocol or specific order Initiate DOT on all case-managers. Daily 3X weeks, 2X/week (Mon/Thurs or Tues/Fri) or 2X/week (Tues/Wed) if completion of adequate therapy. Document DOT on TB-205. Parenteral 3X months and ethambutol 3X months (or until susceptibilities are reported and client's opinion is known to the case manager) Vitamin B6 (if pregnant, diabetic, at risk for peripheral neuropathy) Obtain Informed Consent form TB-011 (TB-010A, if Spanish speaking, only) initially and for any drugs added @196days | | | | | | | | |
| Consultation Obtain expert consult for drug resistant cases, complicated/adjudicated cases or client who remains symptomatic or sputum positive after 2 months therapy, unless consult is client request | | | | | | | | |
| Finality/Clinical Assessment Clinical assessment according to protocol; document (TB-205 and progress notes as appropriate) Visual acuity (Snellen) and color discrimination (Ishihara Plates) visually and monthly if on EMB or ethambutol; document (TB-205) Weight; weight check monthly and monthly if on isoniazid, rifampin, kanamycin, streptomycin; document (TB-205) | | | | | | | | |

TB-201 TB Case and Suspect Management Plan for Outpatient Care - 05/01 (Continued on Reverse)

TB Case and Suspect Management Plan for Outpatient Care

| Activity/Interval | 0 Begin | 2 Wks | 4 Wks | 8 Wks | 12 Wks | 16 Wks | 20 Wks | 24 Wks |
|--|------------|----------|----------|----------|-----------|-----------|-----------|-----------|
| Adherence Issue Order to Implement Measures for a Client With Tuberculosis form TB-010 (TB-010A, if Spanish speaking, only) on TB-205 request Follow-up normal appointments within 1 working day; initiate case-related management according to TB01 policy (see TB Policy Manual, Section 5) and notify Regional office Evaluate barriers to treatment | | | | | | | | |
| Isolation Conduct risk stratification to assess living situation, notify home caregiver living situation and exclude from work or school if indicated When to return to work/school following a risk stratification therapy, 2 consecutive negative sputum on different days and an improvement of symptoms | | | | | | | | |
| Education Appropriate client education provided initially and monthly per protocol; review importance and timing of medication side effects, toxicity and document on TB-205 | | | | | | | | |
| Public Health Contact Investigation Interview case/contact and contacts; plan contact investigation using the "Concentric Circle" approach Initiate contact investigation within 3 working days; interview and evaluate risk; conducting CCR, medical evaluation within 7 days; document on TB-205 Targeted contact investigation if >50% of close high-risk contacts have positive Mantoux skin tests Provide second skin test (TST) 2 weeks after first is conducted with the specific of contacts who were skin test negative on the initial test; document on TB-205 Provide education and counseling for contacts | | | | | | | | |
| Reporting Report suspected case to state designated case registry within 1 working day of notification Submit TB-005 with TB-004I and also final report within 7 days of diagnostic culture TB-004I at least quarterly, and at the time of culture Submit TB-300 within 14 working days of initiating contact investigation and after second test of negative contacts is complete | | | | | | | | |
| Quality Assurance Review Clinical supervisor or TB Program Manager reviews and evaluates contact investigation Team review of client record | | | | | | | | |
| Social Services Enroll in Medicaid, if eligible; make appropriate referrals to designated treatment programs and refer for HIV services, if necessary | | | | | | | | |

PRINTED NAME: _____ SIGNATURE: _____ INITIALS: _____
 PRINTED NAME: _____ SIGNATURE: _____ INITIALS: _____
 PRINTED NAME: _____ SIGNATURE: _____ INITIALS: _____
 PRINTED NAME: _____ SIGNATURE: _____ INITIALS: _____

TB-201 TB Case and Suspect Management Plan for Outpatient Care - 05/01

The Monitoring Process

- **Assess the patient prior to each DOT dose and monthly, at a minimum, in a face-to-face encounter with the health care provider**
 - Use a standardized toxicity assessment form
 - Ask each question carefully
 - Thoroughly document all positive responses
 - Report all positive responses, particularly any changes
 - Field staff should have a clear understanding of the reporting process

The Monitoring Process

- Both open-ended and specific, pointed questions should be utilized, as appropriate
 - How is your appetite?
 - Have you lost weight? How much?
 - Do your clothes fit differently?
 - Do you still eat dessert?
 - How is your energy?
 - How able are you to engage in your usual activities now as compared to ... ?
 - How far/long can you walk now compared to ... ?

Texas DSHS TB Clinical Forms

<http://www.dshs.state.tx.us/idcu/disease/tb/forms/default.asp>

Laboratory Monitoring

- **Initiation of therapy**
 - All
 - AST, ALT, bilirubin, alkaline phosphatase, serum creatinine, CBC with platelet count
 - HIV
 - If at risk of hepatitis B/C (IDU, birth in Asia/Africa, HIV-infected): hepatitis B/C serology

Laboratory Monitoring

- **Periodic**
 - Unnecessary if treated with first-line drugs unless
 - Baseline lab abnormalities
 - Clinical reasons to obtain lab measurements
 - Other
 - Rifabutin: monthly CBC with platelet count if
 - Treatment with higher doses (> 300 mg. daily)
 - Clinical reasons, e.g., advanced AIDS, decreased WBC, decreased platelet count
 - Amikacin: serum creatinine weekly for first several weeks, then monthly

Adverse Drug Events Gastrointestinal Upset

- **Drugs: PZA, rifabutin, fluoroquinolones, (ethionamide, PAS, clofazamine)**
- **Common in first few weeks of therapy**
 - Nausea and vomiting are most common
 - Abdominal cramps
 - Gas
 - Diarrhea
 - Anorexia

Adverse Drug Events Gastrointestinal Upset

- **Intervention**
 - Evaluate for other causes of GI symptoms, particularly hepatotoxicity
 - Hold medications
 - Repeat LFT's
 - Give a light snack before medications
 - Ask patient which medication is causing the GI upset
 - Separate from other drugs by several hours or give at bedtime
 - Space medications out during the day to lessen pill burden

Adverse Drug Events Gastrointestinal Upset

- Administer antiemetics or antacids
 - Phenergan, Reglan, Zofran
 - Antacids cannot be given within 2 hours of fluoroquinolones
- Eliminate or minimize alcohol consumption
- Minimize use of NSAID's
- Diagnose and treat gastritis, acid reflux, *H. pylori* infections
 - Sucralfate (Carafate) cannot be given within 2 hours of fluoroquinolones
- Encourage hydration
- If outpatient interventions fail, hospitalization should be pursued

Adverse Drug Events Hepatotoxicity

- **Drugs:**
 - INH
 - Most likely to cause hepatitis
 - Hepatotoxicity appears to be increased when used with rifampin
 - Rifampin/Rifabutin
 - PZA
 - Fewer episodes of hepatitis, but more severe and prolonged
 - Fluoroquinolones
 - (Ethionamide)
 - (PAS)

Adverse Drug Events Hepatotoxicity

- **Risk factors**
 - Chronic alcohol consumption
 - Viral hepatitis
 - Pre-existing liver disease
 - Pregnant/3 months post-partum
 - Other hepatotoxic medications
 - Previous ALT/AST or bilirubin abnormal
 - HIV-infected

Adverse Drug Events Hepatotoxicity

- **Other hepatotoxic drugs**
 - Tylenol
 - Alcohol
 - Tetracycline, erythromycin, others
 - Dilantin
 - Valproate
 - Cholesterol lowering medications
 - Antifungal drugs
 - Glucose lowering drugs
 - Valium

Adverse Drug Events Hepatotoxicity

- **Laboratory monitoring**
 - Baseline: all
 - Periodic
 - Liver risk factors: ALT (AST, bilirubin) q 2-4 weeks
 - Severe, preexisting liver disease: PT/INR
 - Women?
 - Age over 35?
 - If significantly elevated transaminases: screen for viral hepatitis and exclude other liver problems

Adverse Drug Events Hepatotoxicity

- **Clinical monitoring**
 - Face-to-face monthly assessments
 - EARLY signs and symptoms are non-specific
 - Fatigue
 - Poor appetite
 - Taste alteration
 - Nausea
 - Abdominal discomfort
 - Bloating
 - Minimal rash

Adverse Drug Events Hepatotoxicity

- LATER signs and symptoms
 - Vomiting
 - Abdominal pain
 - Jaundice
 - Change in color of urine and stool
 - Changes in behavior, memory loss

Adverse Drug Events Hepatotoxicity

- **If hepatitis suspected, hold medications and repeat LFT's immediately**
 - Continue therapy
 - ALT < 5 times upper limit of normal and asymptomatic
 - 20% of patients on standard therapy have asymptomatic elevation of transaminases
 - Stop therapy
 - ALT > 3 times upper limit of normal and symptomatic
 - ALT > 5 times upper limit of normal and asymptomatic
 - Disproportionate increases in bilirubin and/or alk. phos.
 - Evaluate for viral hepatitis, biliary disease and exposure to other hepatotoxins (alcohol, hepatotoxic drugs)

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Adverse Drug Events Hepatotoxicity

- **Consider a “liver friendly regimen”**
 - Likely to be a delay of greater than 2-3 weeks in restarting therapy while waiting for LFT's to normalize
 - Patient would not tolerate well an interruption in therapy
 - Early in treatment course
 - Clinically ill
 - AFB smear positive
 - Amikacin, levofloxacin, EMB

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Adverse Drug Events Hepatotoxicity

- **Restarting therapy**
 - When ALT < 2 times upper limit of normal
 - One hepatotoxic drug plus EMB
 - Usually rifampin
 - » Least hepatotoxic
 - » Most active drug
 - Monitor ALT for 3-7 days
 - Stop therapy if symptoms recur or ALT increases
 - If initial drugs are tolerated, add second hepatotoxic drug (INH) and monitor carefully, as above
 - If symptoms recur or ALT increases, stop last drug added

Adverse Drug Events Hepatotoxicity

- If INH, RIF and EMB tolerated, evaluate need for PZA ... usually not needed
 - May supplement with fluoroquinolone if extensive disease
 - Extend therapy (9 months total) if PZA not given for full 8 weeks
- Some patients may tolerate only one hepatotoxic drug
 - Adjust duration of regimen and include second-line drugs, as needed
 - RIF, EMB, levofloxacin X 12 months
 - INH, EMB and levofloxacin X 12-18 months plus possible streptomycin or amikacin for first 2 months
- Rarely, patients tolerate none of the first-line hepatotoxic drugs
 - Treat as an MDR-TB for 18-24 months

Adverse Drug Events Immune Reactions

- **Maculopapular rash and pruritis**
 - Evaluating the rash
 - When did it start?
 - Where is it?
 - What does it look like now? Is that different?
 - Has it spread?
 - What makes it better or worse?
 - Does it itch?
 - Have you had an insect bite?

Adverse Drug Events Immune Reactions

- Other possible causes
 - Scabies
 - Insect bites
 - Contact dermatitis
 - Question patient about new soaps, lotions, perfumes, laundry detergents, etc.
 - Sunburn
 - Dry skin
 - Other drugs, especially new agents
 - Viral or fungal infections
 - Etc.

Adverse Drug Events

Immune Reactions

- Drug rash
 - Usually begins on chest and later spreads to upper arms and thighs
 - Itches
 - Maculopapular
 - Urticaria/hives that are new
 - May be associated with more severe symptoms of airway compromise, angioedema, etc.
 - Occurs and worsens after medications



Adverse Drug Events

Immune Reactions

- Mild, limited maculopapular rashes and/or itching
 - Common
 - Often resolve after first several weeks of treatment
 - Usually do not require stopping medication
 - Treated symptomatically with Benadryl, other antihistamines, low-dose prednisone
- **Petechial rash**
 - May be a sign of a rifampin hypersensitivity reaction and thrombocytopenia
 - Hold medications and check platelet count
 - If low, stop rifampin and monitor platelet count until it returns to baseline
 - Do not restart rifampin

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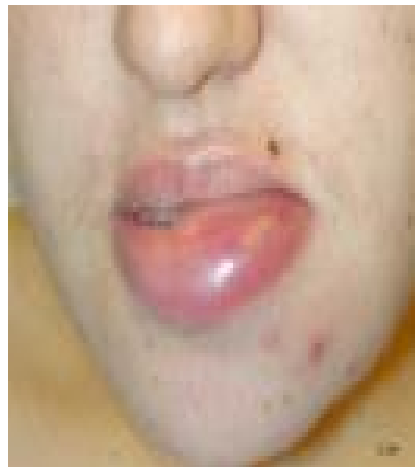
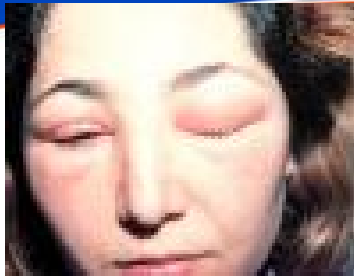
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Adverse Drug Events

Immune Reactions

- **Urticaria/Hives**
 - Hold medications until reaction resolves
 - If no evidence of anaphylaxis, angioedema, airway compromise, may elect to attempt a drug rechallenge or desensitization under controlled conditions
- **Severe Drug Reactions**
 - Generalized rashes associated with fever, other systemic symptoms, mucous membrane involvement are characteristic of Stevens-Johnson Syndrome
 - Do not attempt to rechallenge or desensitize patient to the drugs

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Adverse Drug Events

Ophthalmic Toxicity

- **Drugs:** EMB, rifabutin
- **Baseline and monthly assessment**
 - Question patient regarding visual disturbances
 - Observe children for eye rubbing, excessive blinking, sitting closer to TV, difficulty with accurate grasping
 - Baseline acuity testing with Snellen, Illiterate or Kindergarten charts and color discrimination testing with Ishihara plates
 - Monthly screening if EMB doses > 15-25 mg/kg, receiving EMB for > 2 mo., or renal insufficiency
 - Educate patient to report any changes in vision, erythema or eye pain



Visual Acuity Screening

| Initial Snellen Reading | Reading Indicating Significant Decrease | Significant Number of Lines | Decrease in Number of Points |
|-------------------------|---|-----------------------------|------------------------------|
| 20/13 | 20/25 | 3 | 12 |
| 20/15 | 20/25 | 2 | 10 |
| 20/20 | 20/30 | 2 | 10 |
| 20/25 | 20/40 | 2 | 15 |
| 20/30 | 20/50 | 2 | 20 |
| 20/40 | 20/70 | 2 | 30 |
| 20/50 | 20/70 | 1 | 20 |



Adverse Drug Events Ophthalmic Toxicity

- **Optic neuropathy**
 - EMB is most common drug causing toxicity to optic nerve
 - Although a small number of patients have developed sudden, irreversible vision loss, most experts feel that doses of 15 mg. per kg. given for 2 months or less are rarely associated with toxicity to the optic nerve
 - Decreased visual acuity, color blindness, scotoma (“blind spots”)
 - Stop EMB
 - Refer to ophthalmologist
 - Do not restart EMB unless another cause is identified

Adverse Drug Events Ophthalmic Toxicity

- **Uveitis**
 - Rifabutin given in higher doses or with drugs that decrease renal clearance, e.g., protease inhibitors can cause generalized inflammation of the eye
 - Painful, erythematous eyes and blurred vision
 - Hold rifabutin until symptoms resolve
 - Rifabutin can be reinstated at a lower dose
 - Consider referral to ophthalmologist to rule-out other causes
 - If infection ruled-out, steroid eye drops may be used
 - If recurring uveitis, stop rifabutin

Adverse Drug Events Neurotoxicity

- **Peripheral neuropathy**
 - Drugs: INH, EMB, (ethionamide, cycloserine)
 - More common in patients with
 - Diabetes
 - Alcoholism
 - HIV infection
 - Hypothyroidism
 - Pregnancy
 - Inadequate dietary intake of pyridoxine (Vitamin B6)
 - Usually symmetrical
 - Initial symptoms: tingling, prickling, burning in balls of feet/tips of toes
 - May progress to sensory loss, loss of reflexes, unsteady gait
 - May also involve hands and fingers

Adverse Drug Events Neurotoxicity

- Pyridoxine prophylaxis
 - 50 mg. daily usually adequate for standard treatment regimen
 - My be increased to 100-150 mgs. daily
 - At higher doses, toxicity may develop in patients with ESRD

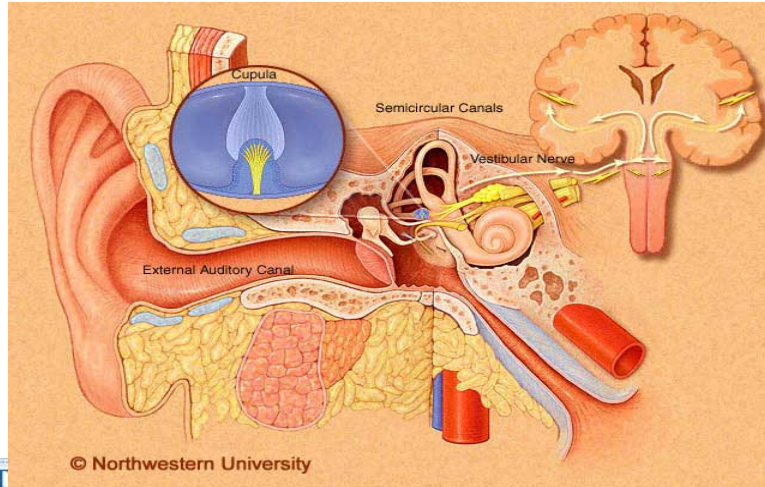
Adverse Drug Events Central Nervous System

- **Drugs:** INH, fluoroquinolones, amikacin, (ethionamide, cycloserine)
- **Mild effects**
 - Drowsiness, headaches, loss of concentration, irritability, agitation, mild mood changes, insomnia
 - Usually occur early in therapy and tend to lessen with time
 - Usually not necessary to discontinue medication
 - Intervention
 - Give medication at time of day to minimize effects
 - Analgesics/NSAID's may relieve headache
 - Limit caffeine intake
 - Exercise

Adverse Drug Events Central Nervous System

- **Depression**
 - Situational vs. drug induced
 - Intervention
 - Assess/address underlying psychosocial issues
 - Assess for co-existing substance abuse and refer for counseling
 - Assess for suicidal ideation
 - If significant, refer for psychiatric evaluation/consideration for trial of antidepressant therapy
- **Psychosis**

Adverse Drug Events Ototoxicity



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Adverse Drug Events Ototoxicity

- **Drugs**
 - Aminoglycosides: AK, KM, SM
 - SM most commonly associated with ototoxicity
 - Capreomycin
- **8th cranial nerve**
- **Auditory and/or vestibular toxicity**

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Adverse Drug Events Ototoxicity

- **Risk factors**
 - Advanced age
 - Total dose: cumulative effect
 - Duration of therapy (>10 days)
 - Renal impairment
 - Dehydration
 - Co-administration of “loop” diuretics (Lasix, Bumex, Demadex)
 - Increased trough and/or peak serum drug levels
 - Prior aminoglycoside/capreomycin exposure

Adverse Drug Events Auditory Toxicity

- **Signs and symptoms**
 - Early
 - Fullness, ringing, roaring, hissing, or “buzzing” in ears
 - High frequency hearing loss (not conversational frequencies)
 - “s”, “th”, and “fff” sounds may be missed or confused
 - Speech of women and children may be more difficult to understand
 - Generally reversible

Adverse Drug Events Auditory Toxicity

- Later
 - Impairment at lower frequencies (conversational frequencies)
 - Problem hearing on the telephone?
 - Trouble hearing when noisy background or when two or more people are talking at once?
 - Times when people seem to mumble or not speak clearly?
 - Often asking people to repeat themselves?
 - People complain that you turn the TV volume up too high?
 - Permanent or only partially reversible

Adverse Drug Events Auditory Toxicity

- **Perform audiometry at baseline and repeat monthly**
 - Identify pre-existing hearing loss
 - Refer for evaluation if any decrease from baseline

Adverse Drug Events Vestibular Toxicity

- **Signs and symptoms**
 - Parallel cochlear damage
 - Early
 - Fullness and intermittent ringing in ears
 - 2-3 times per week dosing may allow continued use of injectable agent for another month or more
 - » Close observation for progression of S/S: tinnitus and unsteadiness
 - » Careful monitoring of TDL's

Adverse Drug Events Vestibular Toxicity

- Later
 - If tinnitus or unsteadiness develop, hold all drugs for several days to see if symptoms improve
 - If due to vestibular toxicity, symptoms generally do not improve
 - If injectable agent continued/substituted, permanent S/S of toxicity will develop
 - Vertigo
 - Dizziness
 - Nausea
 - Ataxia
 - Nystagmus

Adverse Drug Events Vestibular Toxicity

- **General prevention and monitoring**
 - If >59 yrs., decrease dose to 10 mg./kg., 5-7 days/week
 - Baseline and periodic assessment of renal function
 - BUN, Cr/GFR
 - CrCl, if any concerns and monitor Cr/GFR weekly for 1st several weeks, then monthly
 - If baseline CrCl <70 ml./min., adjust dose to 12-15 mg./kg., 2-3 days/week

Adverse Drug Events Vestibular Toxicity

- Initial and periodic monitoring of TDL's with appropriate dose adjustments
- Reduce dosing interval to 3 times/week after 4-6 months, if culture (-)
- Avoid "loop" diuretics
- Maintain adequate hydration
- **Vestibular toxicity monitoring**
 - Baseline and monthly vestibular screen
 - Assess
 - Hearing: fullness, stuffiness, unusual noises, hearing loss
 - Dizziness, unsteadiness, giddiness, lightheadedness, floating sensation

Adverse Drug Events Vestibular Toxicity

- Weakness
- Nausea
- General gait and balance: weaving, swaying, staggering
- Heel-to-Toe walk: jerkiness, excess swaying, falling
- Romberg: excess swaying, falling
- Past-Pointing: consistent deviation to one side

Adverse Drug Events Musculoskeletal

- **Myalgias/Arthralgias**
 - Drugs: PZA, levofloxacin, rifabutin (at higher doses)
 - Usually not necessary to discontinue medications
 - NSAID's usually helpful in relieving discomfort
 - If acute swelling, erythema, warmth present, evaluate for infection, autoimmune disease, gout
 - PZA causes asymptomatic increase in uric acid, but rarely causes gout except in patients with preexisting gout or decreased renal function
 - If receiving injectable therapy, consider possible electrolyte imbalance; draw serum electrolytes and correct deficiencies

Adverse Drug Events Musculoskeletal

- **Tendonitis/Tendon Rupture**
 - Drugs: levofloxacin/other fluoroquinolones
 - Tendon rupture (usually Achilles) is rare
 - If tendon inflammation mild:
 - Rest the joint/NSAID's
 - Evaluate dose and reduce if possible
 - If symptoms progress, stop the fluoroquinolone
 - If tendon inflammation is significant
 - Stop the fluoroquinolone
 - Rest the joint/NSAID's
 - Evaluate risks and benefits of continuing drug in regimen

Adverse Drug Events Nephrotoxicity

- **Drugs: amikacin/other aminoglycosides, (capreomycin)**
- **Baseline serum creatinine**
 - 24-hour creatinine clearance if baseline serum creatinine abnormal
- **Lower initial dose in patients over age 59 yrs. (10 mg. per kg.; max. dose 750 mg.)**
- **If baseline creatinine clearance less than 70ml./min., consider use of intermittent dosing initially**
- **Monitor peak and trough serum drug levels and adjust dose accordingly**
- **Encourage hydration**

Adverse Drug Events

Nephrotoxicity

- **Monthly serum creatinine; repeat 24-hour creatinine clearance if necessary**
- **Observe for decreased urine output and/or edema**
- **If renal function decreases during treatment**
 - Hold injectable agent 1-2 weeks until renal function stabilizes
 - Ensure adequate hydration
 - Check serum electrolytes and correct, if needed
 - Evaluate/Adjust dosing of other drugs, as needed
 - Consider intermittent dosing with appropriate dosing adjustment
 - Monitor peak/trough serum drug levels
 - Monitor renal function carefully