Guidelines for the Management of Adverse Drug Effects of Antimycobacterial Agents

Lawrence Flick Memorial Tuberculosis Clinic
Philadelphia Tuberculosis Control Program
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# Drug Used in the Treatment of Tuberculosis

## First Line Drugs

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<th>Generic Name</th>
<th>Trade Name</th>
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<tr>
<td>isoniazid (INH)</td>
<td>Laniazid®, Nydrazid®</td>
</tr>
<tr>
<td>rifampin</td>
<td>Rifadin®, Rimactane®</td>
</tr>
<tr>
<td>rifapentine</td>
<td>Priftin®</td>
</tr>
<tr>
<td>pyrazinamide (PZA)</td>
<td>various generic products available</td>
</tr>
<tr>
<td>ethambutol</td>
<td>Myambutol®</td>
</tr>
<tr>
<td>streptomycin</td>
<td>streptomycin</td>
</tr>
<tr>
<td>INH/rifampin combination</td>
<td>Rifamate®</td>
</tr>
<tr>
<td>INH/rifampin/PZA combination</td>
<td>Rifater®</td>
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## Second Line Drugs

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
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<tbody>
<tr>
<td>amikacin</td>
<td>Amikin®</td>
</tr>
<tr>
<td>capreomycin</td>
<td>Capastat Sulfate®</td>
</tr>
<tr>
<td>clofazimine</td>
<td>Lamprene®</td>
</tr>
<tr>
<td>cycloserine</td>
<td>Seromycin®</td>
</tr>
<tr>
<td>ethionamide</td>
<td>Trecator-SC®</td>
</tr>
<tr>
<td>kanamycin</td>
<td>kanamycin</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>Levaquin®</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>Floxin®</td>
</tr>
<tr>
<td>para-aminosalicylic acid</td>
<td>Paser®</td>
</tr>
<tr>
<td>rifabutin</td>
<td>Mycobutin®</td>
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Section I

Most Common Adverse Drug Effects Listed
by the Type of Adverse Effect
Dermatologic (Skin) Adverse Effects

Mild “flushing” reactions (two different types of reactions)

Clinical presentations

Reaction 1
- flushing and/or itching of the skin with or without a rash
- usually involves the face and scalp; may cause redness/watering of the eyes
- usually occurs 2-3 hours after drug ingestion

Reaction 2
- flushing and/or itching of the skin with or without a rash PLUS hot flashes, palpitations, headache and/or increased blood pressure
- occurs immediately after ingestion of certain foods (see below)
- usually resolves within 2 hours

Causative agents

Reaction 1: rifampin, pyrazinamide

Reaction 2: isoniazid + tyramine containing foods (cheese, red wine) or certain fish (tuna, skipjack)

Management

Reaction 1
- flushing is usually mild and resolves without therapy
- if flushing is bothersome to the patient, an antihistamine may be administered to treat or prevent the reaction (refer to Appendix 1, page 49)

Reaction 2
- advise patient not to ingest foods listed above while receiving INH

Refer also to individual drug monographs:
- isoniazid pages 32-34
- pyrazinamide pages 38-39
- rifampin pages 42-45
Dermatologic (Skin) Adverse Effects

Moderate/severe hypersensitivity (immune) reactions

Clinical Presentation
hives (raised, itchy rash) with or without fever

Causative Agents
INH < rifampin < PZA < ethionamide < cycloserine < ethambutol < para-aminosalicylic acid < streptomycin

Note: in children, viral infections (e.g. Epstein-Barr and Herpes Simplex) commonly result in hives that may be confused with a drug reaction.

Management

Children
1. Discontinue all drugs
2. Rule out a viral infection
   a. full physical exam
   b. complete blood count (examine for lymphocytosis)
3. If a viral infection is present, restart all of the TB medications (no rechallenge is required)
4. If a viral infection is ruled out, follow drug rechallenge guidelines outlined in the adult management guidelines (below); doses must be adjusted for age and weight.

Adults
1. Discontinue all drugs until the reaction resolves
2. Identify the causative drug by rechallenging (restarting) each drug every 4 days according to Table 1 (example follows on next page).

Table 1

<table>
<thead>
<tr>
<th>Drug</th>
<th>Challenge Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
</tr>
<tr>
<td>isoniazid</td>
<td>50mg</td>
</tr>
<tr>
<td>rifampin</td>
<td>75mg</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>250mg</td>
</tr>
<tr>
<td>ethionamide</td>
<td>125mg</td>
</tr>
<tr>
<td>cycloserine</td>
<td>125mg</td>
</tr>
<tr>
<td>ethambutol</td>
<td>100mg</td>
</tr>
<tr>
<td>para-aminosalicylic acid (PAS)</td>
<td>1.0gm</td>
</tr>
<tr>
<td>streptomycin</td>
<td>125mg</td>
</tr>
</tbody>
</table>
a. begin the rechallenge with INH 50mg on day 1
   1) if the original reaction was severe, begin the rechallenge with 1/10 the day 1 dose listed in Table 1 (e.g. INH 5mg)

b. if a reaction does not occur after the day 1 dose, increase the INH to 300mg on day 2
c. if a reaction does not occur after the day 2 dose, continue INH 300mg q day
d. continue to add drugs in the order and doses specified on Table 1 every 4 days
   1) if the original reaction was severe, begin the rechallenge with 1/10 the day 1 dose listed in Table 1
   2) if the day 2 dose is less than the normal recommended dose based on the patient’s weight, increase to the appropriate dose on day 3
      (a) example for ethambutol dosing in a 70kg person: day 1=100mg, day 2=500mg, and day 3=1000mg

3. If a reaction occurs during drug rechallenge and the causative drug can not be discontinued, drug desensitization will be necessary¹,³

   **Drug desensitization should not be attempted with severe skin reactions or those involving the mouth or mucous membranes (e.g. exfoliative dermatitis and Stevens-Johnson Syndrome)¹.**

a. consideration should be given to desensitizing patients under **monitored conditions for severe reactions**
b. the patient should be receiving ≥ 2 other TB medications before undergoing drug desensitization³
c. three desensitization protocols have been utilized
   (i) general protocol¹
      (a) initiate the day 1 dose as indicated in Table 1
      (b) if a reaction occurred after day 1 of drug rechallenge, begin desensitization with 1/10 of the day 1 dose
      (c) double each dose and administer twice daily until the recommended daily dose has been achieved
      (d) administer the recommended daily dose for 3 days, then switch to once daily dosing (e.g. INH 150mg bid x 3 days, then 300mg q day)
      (e) if a reaction develops during desensitization, decrease the dose to the highest dose (the previous dose) that did not cause a reaction and begin increasing the doses in smaller increments
   (ii) rapid desensitization for isoniazid⁴ (refer to Appendix 2, page 50)
   (iii) rapid desensitization for rifampin and ethambutol⁵ (refer to Appendix 3, page 51)
d. steroids may be utilized if drug desensitization is urgent¹:
   (i) severe TB
   (ii) severe drug reaction
   (iii) hypersensitivity to > 1 drug
e. patients should receive daily dosing after drug desensitization is completed (no twice weekly or thrice weekly regimens)
Gastrointestinal Adverse Effects
Nausea/vomiting

Causative Agents

Ranked by frequency: + ++ +++ ++++ ++++
uncommon common very common

+++++ clofazimine, ethionamide, para-aminosalicylic acid (PAS)
++++ rifampin
+++ rifabutin, isoniazid (twice and thrice weekly dosing)
++ ethambutol, pyrazinamide, ofloxacin, levofloxacin
+ isoniazid (qD), rifapentine, cycloserine, aminoglycosides∗, capreomycin∗

Management

Children

1. Examine how the medication is being administered
   a. Is the medication being administered as a liquid?
      1) administration of large volumes may cause vomiting because of the limited stomach capacity in infants and children
      2) if this is the cause, the child usually vomits immediately after medication administration
      3) refer to Appendix 4, page 52
   b. Is the child gagging when medicine is administered?
      1) children frequently “gag” to avoid taking medicine
      2) administration of medication through a syringe is the best method to avoid “gagging”
      3) refer to Appendixes 4-5, pages 52-53
   c. Does the child take the medicine on an empty stomach?
      1) if so, give medications after meals (e.g. ask school nurse to administer medications after lunch)

2. Rule out other causes of nausea and vomiting
   a. How often does nausea and vomiting occur?
   b. When does it start in relation to taking the medications?
   c. Could the child have a viral infection?

3. If the TB medications are the likely cause of gagging, nausea or vomiting, follow the nausea and vomiting management algorithm on page 9.

∗Although nausea and vomiting are uncommon adverse effects of the aminoglycosides (streptomycin, amikacin, kanamycin) and capreomycin, it may be an indication of vestibular toxicity (inner-ear toxicity). If this occurs, contact a TB Control physician.
Adults

1. Rule out other causes of nausea and vomiting
   a. Ask questions:
      “Have you had stomach problems in the past?”
      “If so, did it feel like this?”
      “What made your stomach problems better in the past?”
      “Did you eat/drink or do anything differently than usual the day you had nausea/vomiting?”
      “How often do you have nausea and vomiting?”
      “When does it start in relation to taking your TB medications?”
      “How long does it last?”
      “Does it happen every time you take your medicine?”
      “Is it difficult for you to swallow your pills?”
      “How much water or juice do you drink when taking your pills?”
   b. Consider measuring liver function tests to rule out drug induced hepatic dysfunction (refer to “Hepatotoxicity” section, pages 12-13).

2. If the TB medications are the likely cause of the patient’s nausea/vomiting, follow the management algorithm on the following page.

Refer also to individual drug monographs, pages 19-48
Gastrointestinal Adverse Effects

Diarrhea

Clinical Presentation

≥ 3 loose bowel movements per day

Causative Agents

Ranked by frequency: + ++ +++ ++++ ++++
uncommon common very common

+++++ clofazimine, ethionamide, para-aminosalicylic acid (PAS)
+++ rifampin
++ rifabutin, ofloxacin, levofloxacin
+ isoniazid, ethambutol, pyrazinamide, rifapentine, cycloserine,
aminoglycosides, capreomycin

Management

1. Rule out other causes of diarrhea

   a. Children

      1) Are liquid preparations being administered?
         a) diarrhea can be caused by the lactose and sucrose contained in liquid preparations
         b) usually, the first episode of diarrhea occurs when therapy is initiated
         c) crush medications (refer to Appendix 4, page 52) instead of using liquid preparations

      2) Is the diarrhea caused by a viral infection?
         a) rotavirus season is between February to May and is a common cause of diarrhea in children
         b) send viral stool cultures
         c) an example of diarrhea that is more likely caused by a virus than the medications is if the child develops diarrhea after previously tolerating the medicine for a prolonged time period

   b. Adults

      1) Ask questions
         “Have you had problems with diarrhea in the past?”
         “Did you eat/drink anything unusual within 1-2 days of the onset of diarrhea?”
         “When does the diarrhea occur in relation to taking your TB medications?”
         “How long does it last?”
         “Does it happen every time you take your TB medications?”

      2) If suspected, rule out C. difficle
2. Withhold drugs until diarrhea resolves

3. Restart drugs one at a time every 4 days
   a. begin with drugs that are least likely to cause diarrhea
   b. consider crushing pills/capsules and administering as outlined in Appendix 4, page 52
   c. if the patient was receiving a twice or thrice weekly regimen when the diarrhea began, consider switching to a 5x/week regimen

4. If diarrhea recurs when one particular drug is added to the regimen, consider discontinuing the causative agent and adding other TB drugs and/or extending the duration of treatment

5. If diarrhea occurs with multiple drugs, consider separating medication administration times
   a. different drugs in the regimen should be administered several hours apart
   b. do not split doses for individual drugs (possible exceptions: ethionamide, ofloxacin)
   c. example: administer INH 300mg in the morning and rifampin 600mg in the evening

6. If diarrhea continues and an alternate regimen can not be utilized consider the addition of an antimotility agent
   a. loperamide (Imodium®)
      1) adult dose: 4mg x 1, then 2mg after each loose stool (maximum dose=16mg/d)
      2) child dose:
         day 1
         2-6 years (13-20kg) 1mg three times daily
         6-8 years (20-30kg) 2mg twice daily
         8-12 years (>30kg) 2mg three times daily
         day 2 and subsequent days: 0.1mg/kg/dose after each loose stool (dose should not exceed the day 1 dose for each age/weight group)
   b. adsorbents (kaolin-pectin, polycarbophil) should not be prescribed because decreased absorption of the TB drugs may occur

Refer also to individual drug monographs, pages 19-48.
Gastrointestinal Adverse Effects
Hepatotoxicity (Hepatitis)

Clinical Presentation

- symptoms: nausea, vomiting, abdominal tenderness, discomfort near the ribs on the right upper abdomen, jaundice (yellowing of skin and whites of the eyes)
- signs: hepatic enlargement, increased LFTs

Causative Agents

INH + rifampin > INH alone >> pyrazinamide alone > rifampin alone > ethionamide

Hepatotoxicity in Children

Note: hepatotoxicity is very uncommon in children. If suspected, the child should be referred to the Flick Memorial Tuberculosis Clinic for evaluation.

Routine Monitoring for Hepatotoxicity in Adults

1. Obtain baseline liver function tests (LFTs)
   a. serum transaminase enzymes
      1) aspartate aminotransferase (AST) [normal 0-40 u/l]
      2) alanine aminotransferase (ALT) [normal 0-40 u/l]
   b. alkaline phosphatase [normal 25-115 u/l]
   c. gamma glutamyl transpeptidase (GGTP) [normal 10-50 u/l]
   d. total bilirubin [normal 0.2-1.5 mg/dl]

2. Obtain follow-up LFTs:
   a. patients < 35 years old with normal baseline LFTs and without a history of hepatic disease: follow-up labs are not required unless the patient becomes symptomatic
   b. patient > 35 years old, daily alcohol consumption, abnormal baseline LFTs or a history of hepatic disease: obtain LFTs every 4-6 weeks

Management in Adults

1. **Asymptomatic patients** with an increase in LFTs from baseline:
   a. if the increase in LFTs is < 3-5x normal: continue the current regimen and monitor for symptoms of liver dysfunction (see “Clinical Presentation” section)
   b. for **asymptomatic patients**, if the serum transaminases increases > 3-5x normal: hold INH until levels return to baseline

* Early reports of pyrazinamide hepatotoxicity occurred in patients who received 40-50mg/kg/d for prolonged periods. Hepatotoxicity has not been reported with extensive use of lower doses (15-30mg/kg/d) in short course regimens.
1) if the patient is receiving a two drug regimen, substitute at least one other drug (e.g. ethambutol) until the INH is restarted
2) if the transaminases increase with rechallenge of INH, discontinue INH, substitute another drug (e.g. ethambutol) and adjust the treatment duration as required\textsuperscript{3,8}
c. if the serum total bilirubin increases: therapy usually does not require modification (rifampin competes with bilirubin for elimination resulting in increased serum bilirubin initially; bilirubin levels usually return to normal with continued therapy)\textsuperscript{2}

2. **Symptomatic patients** (see “Clinical Presentation”)
   a. Hold all drugs and obtain LFTs
   b. If LFTs are within the normal ranges, refer to the Management of Nausea/Vomiting section (pages 7-9)
   c. If LFTs are elevated, hold drugs until symptoms resolve and the transaminases decreases to < 2x normal\textsuperscript{3,6}
      1) ethambutol and pyrazinamide should be started if drug therapy can not be held secondary to the patient’s clinical condition
         a) use streptomycin if pyrazinamide is suspected to be the cause of hepatotoxicity
      2) rechallenge the patient after resolution of signs and symptoms by adding drugs to the regimen every 4 days\textsuperscript{6}:
         a) rifampin for 3 days, if patients remains asymptomatic then add
         b) INH for 3 days, if patients remains asymptomatic then add
         c) pyrazinamide (15-20mg/kg/d) for 3 days
      3) if signs and symptoms recur with rechallenge, discontinue the responsible drug and modify the regimen and/or duration of therapy as required

Refer also to drug monographs:
   ethionamide pages 30-31
   isoniazid pages 32-34
   pyrazinamide pages 38-39
   rifampin pages 42-45
Miscellaneous Adverse Effects
Arthalgias (joint pain)

**Arthalgias Type 1**

Causative Agents\(^1,2\)
pyrazinamide &gt; ethambutol &gt; isoniazid

Clinical Presentation
pain and tenderness of joints: fingers, shoulders, knees, etc. (usually mild)

Management
• TB medications do not require discontinuation
• low dose nonsteroidal antiinflammatory agents (NSAIDS) can be used for pain relief as needed
• if symptoms persist, consider referral for rheumatologic evaluation

**Arthalgias Type 2 (Gouty Arthritis)**

Causative Agents\(^1,2\)
pyrazinamide &gt; ethambutol

Clinical Presentation
• symptoms: pain, tenderness and swelling of joints: fingers, shoulders, knees, etc.
• symptoms are usually severe
• signs: elevated serum uric acid concentrations

Management
1. TB medications usually do not require discontinuation
2. If acute swelling is present, the affected joint should be aspirated and examined for urate crystals to confirm the diagnosis of acute gouty arthritis.
3. Therapy
   a. nonsteroidal antiinflammatory agents include:
      - indomethacin (Indocin®) 50mg tid-qid until pain relief, then 25mg tid-qid
      - ibuprofen (Motrin®, Advil®) 800mg tid
      - naproxen (Naprosyn®) 750mg x1, then 250mg q 8 hour
   b. colchicine is an alternative to NSAIDS
      1) dose: 0.5-1.2 mg x1, then 0.5-0.6 mg q 1-2 hours until joint pain is relieved or nausea, vomiting or diarrhea occurs
      2) pain usually resolves after 4-8 mg cumulative dose
      3) maximum dose: 8mg
   d. a steroid taper may be required for severe attacks
4. Recurrent episodes may occur while the patient remains on pyrazinamide or ethambutol.
   a. consider using prophylactic colchicine
      1) 0.6mg one to two times daily
      2) continue until causative agent is discontinued
5. Consider referral for rheumatologic evaluation for acute gouty arthritis attacks

Refer also to drug monographs:
   ethambutol pages 28-29
   isoniazid pages 32-34
   pyrazinamide pages 38-39
Miscellaneous Adverse Effects
“Influenza Syndrome”

Causative Agents
rifampin > rifabutin (intermittent regimens > daily regimens)

Clinical Presentation
• fever, headache, bone pain
• usually occurs 1-2 hours after drug administration
• usually resolves within 12 hours of drug administration

Management
• switch from intermittent therapy to daily dosing (7 days/week)
• symptomatic therapy may be required when switching from intermittent to daily therapy to prevent the reaction with initial doses

Refer also to the rifampin monograph pages 42-45
Miscellaneous Adverse Effects
Neurotoxicity (Nervous System)

Peripheral Neuropathy

Causative Agents\textsuperscript{1,2}
INH >>> ethambutol

Clinical Presentation
- prickling, tingling or burning sensation of the fingers and/or toes
- usually occurs in a stocking glove distribution

Management
- peripheral neuropathy rarely occurs in children unless severe malnutrition is present\textsuperscript{8,9}
- peripheral neuropathy is uncommon if the patient is receiving pyridoxine (vitamin B\textsubscript{6})
- if peripheral neuropathy occurs, it can be treated with pyridoxine 100-200mg po q day while the patient is receiving INH\textsuperscript{1}

Nervous System Effects in Children

Causative Agents
INH

Clinical Presentation
- drowsiness or hyperactivity
- dizziness
- tonic/clonic seizures (rare)\textsuperscript{7}

Management

1. Drowsiness
   a. make sure the dose does not exceed 10mg/kg/d
   b. add pyridoxine 50mg to the regimen
   c. administer medications around afternoon naps or at bedtime (e.g. administer school DOT at the end of the day so the child can take a nap after school)

2. Hyperactivity
   a. make sure the dose does not exceed 10mg/kg/d
   b. switch to twice weekly dosing as soon as possible
      1) if the child becomes hyperactive only on the days of medication administration, then the medication is the cause
      2) add pyridoxine 50mg daily for 6 weeks, then twice weekly for the remainder of therapy

3. Dizziness
   a. make sure the dose does not exceed 10mg/kg/d

4. Tonic/clonic seizures
   a. hospitalize the child and administer isoniazid to document the reaction
   b. if a seizure occurs, discontinue isoniazid and add an alternative agent to the regimen

Refer also to drug monographs: ethambutol (pages 28-29), isoniazid 32-34
Miscellaneous Adverse Effects
Optic Neuritis (vision)

Causative Agents
ethambutol\textsuperscript{1,2} >> INH\textsuperscript{3}

Clinical Presentation
- blurred vision (decrease in the “sharpness” of objects)
- “spots” present in patient’s field of vision
- red/green color blindness
- optic neuritis has not been documented in children\textsuperscript{7}

Management
- children with complaints of vision changes should be referred to the Flick Memorial Tuberculosis Clinic for evaluation
- discontinue drug

Refer also to drug monographs:
- ethambutol pages 28-29
- isoniazid pages 32-34
Section II

Adverse Drug Effects (ADE) and Drug Interactions*
Listed Alphabetically by Drug

* This list is not all inclusive. Common and/or clinically important adverse drug effects and drug interactions are included.
Aminoglycosides (amikacin, kanamycin, streptomycin)

Adverse Drug Effects (ADEs)

Nephrotoxicity (kidneys)

Clinical Presentation
- nonoliguric acute renal failure (patient continues to have 1-2 liters/day urine output)\(^{10}\)
- serum creatinine increases 7-10 days after initiation of therapy
- magnesium and potassium wasting may occur

Frequency/Characteristics\(^{2,11}\)
- the frequency of agents causing nephrotoxicity is kanamycin = amikacin > streptomycin
- the mechanism of toxicity is acute tubular necrosis

Risk Factors\(^{12}\)
- high aminoglycoside serum concentrations
- prolonged aminoglycoside use
- concurrent use of other nephrotoxic drugs
- hepatic disease
- increasing age
- hypotension
- volume depletion
- pre-existing renal impairment

Management
- discontinue aminoglycoside therapy

Ototoxicity (ears)

Clinical Presentation
- cochlear toxicity: loss of hearing (usually high frequency hearing loss occurs first)\(^{12}\)
- vestibular toxicity: vertigo, incoordination, dizziness, nausea

Frequency\(^{9,12}\)
- cochlear: kanamycin ≥ amikacin > streptomycin
- vestibular: streptomycin > kanamycin ≥ amikacin

Risk Factors\(^2\)
- high aminoglycoside serum concentrations
- total dose (amikacin > 15gm\(^2\), kanamycin > 14gm\(^2\), streptomycin 120gm\(^9\))
- concomitant ototoxins (e.g. loop diuretics)
- prior aminoglycoside use
- increasing age (>60)\(^9\)
- pre-existing hearing loss

Management
- discontinue aminoglycoside therapy
Hypersensitivity (immune mediated reaction)

Clinical Presentation
- hives (raised, itchy rash)
- fever may occur

Frequency/Characteristics\(^2\)
- most common adverse effect of streptomycin (rash, hives, fever)
- occurs rarely with amikacin and kanamycin

Management
refer to the Hypersensitivity Management Guidelines, pages 5-6

Monitoring for ADEs

Table 2\(^{8,9}\)

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*ATS=American Thoracic Society; CDC=Center for Disease Control
Capreomycin

Adverse Drug Effects (ADEs)

Nephrotoxicity (kidneys)

Clinical Presentation
- increased blood urea nitrogen and serum creatinine
- alkalosis and potassium, magnesium and calcium wasting may occur

Frequency/Characteristics
- 36% of 722 patients who received capreomycin had ↑ in BUN to > 20mg/dl
- the mechanism of toxicity is usually acute tubular necrosis

Risk Factors
- increasing age
- pre-existing renal dysfunction
- concomitant nephrotoxic drugs

Management
- limit the dose of capreomycin to 750mg/day in elderly patients
- discontinue capreomycin if nephrotoxicity occurs

Ototoxicity (ears)

Clinical Presentation
- cochlear toxicity: loss of hearing (usually high frequency hearing loss occurs first)
- vestibular toxicity: vertigo, incoordination, dizziness, nausea

Frequency/Characteristics
- uncommon
- clinically apparent hearing loss occurred in 3% of 722 patients who received capreomycin
- hearing loss usually occurs before vestibular toxicity (dizziness, incoordination)

Risk Factors
- pre-existing hearing loss
- impaired renal function
- increased age

Management
- discontinue capreomycin therapy
Monitoring for Adverse Effects

ATS Recommendations
• audiometry at baseline and then at least every other month
• vestibular function should be assessed periodically

CDC Recommendations
• assess hearing and vestibular function
• monitor Scr and BUN
Clofazimine

Adverse Drug Effects (ADEs)

Gastrointestinal (stomach)

Clinical presentation\textsuperscript{14,15}
- nausea, vomiting, abdominal pain, loss of appetite and/or diarrhea
- severe cramping, abdominal pain and diarrhea may occur in patients receiving $> 100$mg/day for prolonged time periods (may progress to a partial or complete bowel obstruction if drug is not discontinued)

Frequency/Characteristics\textsuperscript{14,15}
- up to 60\% of patients will experience gastrointestinal adverse effects
- gastrointestinal effects are the major dose limiting effect of clofazimine
- dose related ($\uparrow$ dose $= \uparrow$ adverse gastrointestinal effect)

Management
- clofazimine should be administered with food
- refer to Nausea/Vomiting and Diarrhea Management Guidelines, pages 7-11
- if severe abdominal pain and diarrhea occur, discontinue therapy

Dermatologic (skin)

Clinical Presentation
pigmentation (pink to brownish-black discoloration) of the skin, hair, urine and feces\textsuperscript{15}

Frequency/Characteristics\textsuperscript{3,14,15}
- occurs in 75-100\% of patients
- develops within the first few weeks after initiation of therapy
- resolution usually occurs 6-12 months after drug discontinuation but may take up to 4 years

Management
- counsel patients that discoloration of skin, urine, etc. is likely to occur
- the benefits of clofazimine should be weighed against cosmetic changes that may occur

Ocular (eyes)

Clinical Presentation\textsuperscript{15}
- red-brown discoloration of conjunctiva, cornea and lacrimal fluid (tears)
- vision is usually not affected
Frequency/Characteristics\textsuperscript{14}
- 38-57% of patients may develop conjunctival discoloration
- dose related (↑ dose = ↑ discoloration)
- resolution usually occurs when clofazimine is discontinued

Management
- counsel patients that discoloration may occur
- the benefits of clofazimine should be weighed against cosmetic changes that may occur

Monitoring for Adverse Effects

ATS Recommendations\textsuperscript{9}
- symptom assessment
Cycloserine

Adverse Drug Effects (ADEs)

Neurotoxicity (nervous system)

Clinical Presentation\(^2,14\)
- emotional/behavioral effects include excitement, anxiety, aggression, confusion, depression, suicidal ideation and psychosis
- other effects include headache, drowsiness, peripheral neuropathy, convulsions and seizures

Frequency/Characteristics\(^2,14\)
- most frequently reported adverse effect of cycloserine
- 30% of patients receiving 500mg daily experience these effects within 2 weeks of therapy
- 8% of patients receiving 500mg twice daily will develop convulsions
- dose related: occurs more frequently with peak serum concentrations > 30 mcg/ml
- alcohol ingestion increases the risk of seizures
- adverse nervous system effects resolve when the drug is discontinued

Management
- avoid cycloserine use in patients with a history of seizures or psychologic problems\(^2,14\)
- counsel patients not to ingest alcohol during therapy
- administer pyridoxine 150mg/day while the patient is receiving cycloserine\(^9\)
- decrease the dose or discontinue the drug if adverse nervous system effects occur\(^2,14\)

Hypersensitivity (immune mediated reaction)

Clinical Presentation
- hives (raised, itchy rash)
- fever may occur

Frequency/Characteristics\(^2\)
- rare

Management
- refer to the Hypersensitivity Management Guidelines, pages 5-6

Drug Interactions\(^{14,16}\)

Phenytoin
- phenytoin metabolism is inhibited
- toxic serum concentrations may result

Isoniazid
- nervous system adverse effects may increase with concomitant use
Monitoring for Adverse Effects

ATS Recommendations
- assess mental status

CDC Recommendations
- assess mental status
- monitor cycloserine levels
Ethambutol

Adverse Drug Effects (ADEs)

Ocular toxicity (eyes): Optic Neuritis

Clinical Presentation
• blurred vision (decrease in the “sharpness” of objects)
• “spots” present in the patient’s field of vision
• red/green color blindness

Frequency/Characteristics
• uncommon and mild with a dose of 25mg/kg/day for 60 days, then decreased to 15mg/kg/day for the remainder of therapy
• optic neuritis has not been documented in children
• dose related (↑ dose = ↑ ocular toxicity)
• uncommon with intermittent therapy
• usually reversible if ethambutol is discontinued with the onset of initial symptoms
• permanent vision impairment may result if ethambutol is continued after symptoms occur

Management
• children with complaints of vision changes should be referred to the Flick Memorial Tuberculosis Clinic for evaluation
• discontinue ethambutol therapy
• refer to Optic Neuritis Management Guidelines, page 18

Neurotoxicity (nervous system)

Clinical Presentation
• peripheral neuropathy: prickling, tingling or burning sensation of the fingers and/or toes

Frequency/Characteristics
• rare
• consider ethambutol as the causative agents in patients who continue to experience peripheral neuropathy even after discontinuing isoniazid

Management
• refer to Peripheral Neuropathy Management Guidelines, page 17

Arthalgias (joint pain)

Clinical Presentation
• symptoms: pain, tenderness and/or swelling of joints (usually mild)
• signs: elevated serum uric acid concentrations secondary to inhibition of urate secretion
Frequency/Characteristics 1
• a majority of patients develop mild hyperuricemia while receiving ethambutol
• acute gouty arthritis is rare

Management
refer to Arthralgia Management Guidelines, pages 14-15

Hypersensitivity (immune mediated reaction)

Clinical Presentation
• hives (raised, itchy rash)
• fever may occur

Frequency/Characteristics 2
very rare

Management
refer to the Hypersensitivity Management Guidelines, pages 5-6

Drug Interactions 14,16

Antacids (aluminum and magaldrate containing)
• results in decreased ethambutol absorption
• separate administration times by ≥ 2 hours

Monitoring of ADEs

ATS recommendations 9
• symptom assessment
• measurement of baseline visual acuity and red-green color perception in adults
• repeat testing based on results of symptom assessment

CDC recommendations 8
baseline and monthly monitoring of visual acuity and color vision
Ethionamide

Adverse Drug Effects (ADEs)

Gastrointestinal (stomach)

Clinical Presentation
- nausea, vomiting, abdominal pain, diarrhea, metallic taste and loss of appetite

Frequency/Characteristics
- very common: occurs to some degree in the majority of patients receiving ethionamide
- may be severe enough to require discontinuation of drug therapy

Management
- administer with food
- consider starting therapy at a low dose and increasing as tolerated
- consider administering with an antiemetic at bedtime for severe symptoms
- refer to the Nausea/Vomiting and Diarrhea Management Guidelines on pages 7-11

Hepatotoxicity (liver)

Clinical Presentation
- symptoms: nausea, vomiting, abdominal tenderness, discomfort near the ribs on the right upper abdomen, jaundice (yellowing of skin and whites of the eyes)
- signs: hepatic enlargement, increased LFTs (refer to the Hepatotoxicity Management Guidelines, pages 12-13)

Frequency/Characteristics
- uncommon
- usually resolves after drug discontinuation

Management
- children who are suspected of developing hepatotoxicity should be referred to the Flick Memorial Tuberculosis Clinic for evaluation
- refer to the Hepatotoxicity Management Guidelines, pages 12-13

Hypersensitivity (immune mediated reaction)

Clinical Presentation
- hives (raised, itchy rash)
- fever may occur

Frequency/Characteristics
- rare

Management
- refer to the Hypersensitivity Management Guidelines, pages 5-6
Monitoring of ADEs

ATS recommendations
• monitor for symptoms
• monitor ALT/AST monthly

CDC recommendations
monitor LFTs
Isoniazid

Adverse Drug Effects (ADEs)

Neurotoxicity (nervous system)

Clinical Presentation

• peripheral neuropathy: prickling, tingling or burning sensation of the fingers and/or toes that usually occurs in a stocking glove distribution
• other: insomnia, restlessness, muscle twitching
• children: drowsiness, hyperactivity, dizziness, tonic/clonic seizures

Frequency/Characteristics

• peripheral neuropathy is uncommon with the recommended doses of isoniazid
• patients who are likely to be pyridoxine deficient are at greater risk of developing peripheral neuropathy:
  • pregnant women
  • patients with chronic liver disease
  • cancer patients
  • malnourished patients
  • uremic patients
  • elderly patients
  • diabetic patients
  • chronic alcoholics
• other nervous system effects are common at the recommended doses but are usually mild
• nervous system effects are uncommon in children unless:
  • isoniazid doses exceed 10mg/kg/day
  • patient is malnourished (vitamin B6 deficient)
• tonic/clonic seizures occur rarely in children

Management

• pyridoxine 10-50mg should be administered to adults receiving isoniazid to prevent peripheral neuropathy
• pyridoxine administration is not usually required in children unless their diet is deficient in vitamin B6
• refer to Neurotoxicity Management Guidelines, page 17

Hepatotoxicity (liver)

Clinical Presentation

• symptoms: nausea, vomiting, abdominal tenderness, discomfort near the ribs on the right upper abdomen, jaundice (yellowing of skin and whites of the eyes)
• signs: hepatic enlargement, increased LFTs (refer to the Hepatotoxicity Management Guidelines, pages 12-13)

Frequency/Characteristics

• overt hepatitis
  • occurs in 1% of patients receiving isoniazid
  • occurs in 4% of patients receiving rifampin and isoniazid
  • rarely develops in children
  • the risk of hepatitis increases with concomitant alcohol use and age > 35 years
  • usually develops within the first 1-2 months of therapy
asymptomatic increases in serum transaminases\textsuperscript{2,14}
- occurs in 10-20\% of patients
- usually occurs within the first 4-6 months of therapy
- transaminase levels usually return to pretreatment levels even if isoniazid is continued

Management
- children who are suspected of developing hepatotoxicity should be referred to the Flick Memorial Tuberculosis Clinic for evaluation
- refer to Hepatotoxicity Management Guidelines, pages 12-13

Gastrointestinal (stomach)

Clinical Presentation
nausea, vomiting, diarrhea

Frequency/Characteristics\textsuperscript{2}
- uncommon at recommended daily doses
- the likelihood of developing gastrointestinal effects increases with increasing doses (e.g. > 20mg/kg/d)

Management
- refer to the Nausea/Vomiting and Diarrhea Management Guidelines on pages 7-11

“Flushing Reaction”

Clinical Presentation\textsuperscript{2,3}
- flushing and/or itching of the skin with or without a rash
- hot flashes, palpitations, headache and/or increased blood pressure

Frequency/Characteristics\textsuperscript{2,3}
- some patients experience this reaction immediately after ingesting certain foods
  - tyramine containing foods: cheese, red wine
  - histamine containing foods: skipjack tuna
- reaction usually resolves within 2 hours

Management
- counsel patients not to ingest these foods while receiving isoniazid
- refer to Mild Cutaneous (“Flushing”) Reactions Management Guidelines, page 4

Hypersensitivity (immune reaction)

Clinical Presentation
- hives (raised, itchy rash)
- fever may occur
Frequency/Characteristics\textsuperscript{2,14}  
• uncommon  
• usually occurs 3-7 weeks after initiation of therapy

Management  
refer to the Hypersensitivity Management Guidelines, pages 5-6

Ocular toxicity (eyes): Optic Neuritis

Clinical Presentation  
• blurred vision (decrease in the “sharpness” of objects)  
• eye pain

Frequency/Characteristics  
uncommon\textsuperscript{17}

Management  
• children with complaints of vision changes should be referred to the Flick Memorial Tuberculosis Clinic for evaluation  
• refer to Optic Neuritis Management Guidelines, page 18

Arthalgias (joint pain)

Clinical Presentation  
pain, tenderness and/or swelling of joints

Frequency/Characteristics\textsuperscript{1}  
rare

Management  
refer to Arthralgia Management Guidelines, pages 14-15

Drug Interactions\textsuperscript{14,16}

Isoniazid may increase the serum concentrations/toxic effect of:  
• anticonvulsants: carbamezepine, phenytoin, primidone, and valproic acid  
• benzodiazepines  
• theophylline  
• warfarin

Monitoring for ADEs

ATS recommendations/ CDC recommendations\textsuperscript{8,9}  
• monthly symptom assessment  
• refer to “Routine Monitoring for Hepatotoxicity”, pages 12-13, for guidelines for monitoring LFT
Kanamycin (see aminoglycosides)
Levofloxacin (see quinolones)
Ofloxacin (see quinolones)
Para-aminosalicylic acid (PAS)

Adverse Drug Effects (ADEs)

Gastrointestinal (stomach)

Clinical Presentation
nausea, vomiting, abdominal cramps, loss of appetite, diarrhea

Frequency/Characteristics
• a majority of patients experience some degree of gastrointestinal side effects
• drug discontinuance may be required in some patients
• diarrhea may be severe enough to cause steatorrhea, malabsorption, secondary folic acid deficiency and megaloblastic anemia

Management
• administer with food
• consider administration of vitamin B₁₂ in patients receiving PAS > 1 month
• refer to the Nausea/Vomiting and Diarrhea Management Guidelines on pages 7-11

Hypersensitivity (immune mediated reaction)

Clinical Presentation
• itchy rash, fever, conjunctivitis (most common)
• immune induced hepatitis: above symptoms plus hepatomegally (enlarged liver), leukocytosis (increased white blood cell count), lymphadenopathy and/or eosinophilia.

Frequency/Characteristics
• 5-10% of patients experience hypersensitivity reactions
• usually occurs within the first 5 weeks of therapy
• immune related hepatitis usually occurs within the first 3 months of therapy and is commonly preceded by rash, fever, conjunctivitis and eosinophilia

Management
• discontinue and do not attempt to restart PAS if immune related hepatitis occurs
• refer to the Hypersensitivity Management Guidelines, pages 5-6

Drug Interactions

Digoxin
• PAS may decrease the absorption of digoxin
• decreased serum digoxin concentrations/therapeutic effect may occur
Monitoring for ADEs

ATS recommendations⁹
    symptom assessment

CDC recommendations⁸
    measure hepatic enzymes
Pyrazinamide

Adverse Drug Effects (ADEs)

Arthalgias (joint pain)

Clinical Presentation
- symptoms: pain, tenderness and/or swelling of joints
- affects fingers, shoulders, knees, etc.
- usually mild but can be severe (acute gouty arthritis)
- signs: serum uric acid concentrations may be elevated

Frequency/Characteristics\textsuperscript{2,14}
- 40\% of patients receiving pyrazinamide experience nongouty, polyarthalgias
- uncommon in children\textsuperscript{7}
- acute gouty arthritis is rare
- pyrazinamide decreases renal uric acid secretion

Management
refer to Arthralgia Management Guidelines, pages 14-15

Hepatotoxicity (liver)

Clinical Presentation
- symptoms: nausea, vomiting, abdominal tenderness, discomfort near the ribs on the right upper abdomen, jaundice (yellowing of skin and whites of the eyes)
- signs: hepatic enlargement increased LFTs (refer to the Hepatotoxicity Management Guidelines, pages 12-13)

Frequency/Characteristics\textsuperscript{2}
- uncommon with doses of 20-30mg/kg/d or with high dose intermittent regimens
- uncommon in children
- hepatotoxicity was reported frequently when doses of 40-50mg/kg/day were used for prolonged periods in the 1950s
- asymptomatic increases in LFTs may occur early in therapy

Management
- children who are suspected of developing hepatotoxicity should be referred to the Flick Memorial Tuberculosis Clinic for evaluation
- refer to Hepatotoxicity Management Guidelines, pages 12-13

Gastrointestinal (stomach)

Clinical Presentation
nausea, vomiting, loss of appetite
Frequency/Characteristics
- mild nausea and loss of appetite are common
- vomiting is uncommon

Management
refer to Nausea/Vomiting Management Guidelines, pages 7-9

“Flushing Reaction”
Clinical Presentation
flushing and/or itching of the skin with or without a rash

Frequency/Characteristics
- common
- uncommon in children

Management
refer to Mild Cutaneous (“Flushing”) Reactions Management Guidelines, page 4

Hypersensitivity (immune mediated reaction)
Clinical Presentation
- hives (raised, itchy rash)
- fever may occur

Frequency/Characteristics
- rare

Management
refer to the Hypersensitivity Management Guidelines, pages 5-6

Drug Interactions
Cyclosporin
- pyrazinamide may increase serum cyclosporin concentrations

Monitoring for ADEs
ATS recommendations/CDC recommendations
- symptom assessment
- baseline uric acid and LFTs; repeat based on symptom assessment
- refer to “Routine Monitoring for Hepatotoxicity”, pages 12-13, for guidelines for monitoring LFTs
Quinolones (levofloxacin, ofloxacin)

Adverse Drug Effects (ADEs)

Neurotoxicity (nervous system)

Clinical Presentation
headache, insomnia, dizziness, seizures

Frequency/Characteristics
• in Phase II/III clinical trials the following percentages of patients experienced these effects\textsuperscript{18,19}:
  • headache: ofloxacin 9\%, levofloxacin 5.4\%
  • insomnia: ofloxacin 7\%, levofloxacin 2.9\%
  • dizziness: ofloxacin 5\%, levofloxacin 2.5\%
• usually occurs in the first few days of therapy\textsuperscript{14}
• commonly resolves even with continued therapy\textsuperscript{14}
• theoretically, the once daily regimens utilized in TB regimens may produce more central nervous system effects (insomnia, dizziness) because of higher peak serum concentrations
• seizures occurred in <1\% of patients receiving ofloxacin and levofloxacin in Phase II/III clinical trials\textsuperscript{18,19}
• quinolones should be used cautiously in patients with seizure disorders or other CNS disorders

Management
• symptomatic therapy (e.g. analgesics for headache)
• administer in the morning to minimize the occurrence of insomnia
• consider administering doses twice daily if nervous system effects do not resolve

Gastrointestinal (stomach)

Clinical Presentation
nausea, diarrhea

Frequency/Characteristics
• in Phase II/III clinical trials the following percentages of patients experienced these effects\textsuperscript{18,19}:
  • nausea: ofloxacin 10\%, levofloxacin 6.6\%
  • diarrhea: ofloxacin 4\%, levofloxacin 5.4\%
• gastrointestinal effects are usually mild and transient\textsuperscript{14}

Management
refer to Nausea/Vomiting and Diarrhea Management Guidelines, pages 7-11
Arthropathy (joints)

Frequency/Characteristics\textsuperscript{20,21}
- quinolones cause damage to cartilage in weight-bearing joints in immature animals
- reviews of quinolone use in children have not found joint cartilage damage

Management
ofloxacin and levofloxacin should be used cautiously in children

Drug Interactions\textsuperscript{14,16}

Antacids, iron and calcium, products, sucralfate (Carafate\textsuperscript{®}) and multivitamins
- results in decreased absorption of levofloxacin and ofloxacin
- levofloxacin and ofloxacin should be administered 2 hours before or after these products

Theophylline, warfarin, cyclosporin A
- no significant alteration in serum levels or therapeutic effect of these drugs occurred when combined with levofloxacin or ofloxacin, unlike other quinolones
- monitor for symptoms of increased levels (theophylline, cyclosporin) or therapeutic effect (warfarin)

Monitoring for ADEs

ATS recommendations/CDC recommendations\textsuperscript{8,9}
symptom assessment
drug interactions
Rifamycins (rifampin, rifabutin, rifapentine)

**Rifampin**

**Adverse Drug Effects (ADEs)**

**Discoloration of Body Fluids**

Clinical Presentation
- reddish/orange discoloration of body fluids including urine, tears, saliva

Frequency/Characteristics
- common
- monitoring for discoloration of urine can be used to assess drug absorption and patient compliance

Management
- counsel patients to expect discoloration
- patients should be advised that contact lenses may be stained

**Gastrointestinal (stomach)**

Clinical Presentation
- nausea, vomiting, heartburn, abdominal cramps, loss of appetite
- diarrhea is less common than nausea and vomiting

Frequency/Characteristics
- most common adverse effect of rifampin
- rarely requires drug discontinuation

Management
- refer to Nausea/Vomiting and Diarrhea Management Guidelines, pages 7-11

“Flushing Reaction”

Clinical Presentation
- flushing and/or itching of the skin with or without a rash
- usually involves the face and scalp; may cause redness and watering of the eyes

Frequency/Characteristics
- uncommon in children
- up to 5% of patients experience the “flushing reaction”
- usually occurs 2-3 hours after drug ingestion
- the reaction is usually self-limited
Management refer to Mild Cutaneous ("Flushing") Reactions Management Guidelines, page 4

Hepatotoxicity (liver)

Clinical Presentation
- symptoms: nausea, vomiting, abdominal tenderness, discomfort near the ribs on the right upper abdomen, jaundice (yellowing of skin and whites of the eyes)
- signs: hepatic enlargement, increased LFTs (refer to the Hepatotoxicity Management Guidelines, pages 12-13)

Frequency/Characteristics
- up to 1% of patients develop rifampin-induced hepatitis
- 4% of patients receiving both rifampin and isoniazid develop hepatitis
- hepatotoxicity is uncommon in children
- asymptomatic increases in serum transaminases may occur in the first few weeks of therapy
- bilirubin levels may increase with initial therapy due to competition for excretion with rifampin; levels normalize with continued rifampin therapy

Management
- children who are suspected of developing hepatotoxicity should be referred to the Flick Memorial Tuberculosis Clinic for evaluation
- refer to Hepatotoxicity Management Guidelines, pages 12-13

Hypersensitivity-immune mediated reactions involving the skin

Clinical Presentation
- hives (raised, itchy rash)
- fever may occur

Frequency/Characteristics
- severe, generalized reactions are rare

Management
- refer to the Hypersensitivity Management Guidelines, pages 5-6

Hypersensitivity-immune mediated "influenza syndrome"

Clinical Presentation
- fever, headache, fatigue, bone pain

Frequency/Characteristics
- more common with high dose (>1200mg), intermittent therapy than with daily dosing
- occurs in 10% of patients receiving 600mg twice weekly
- may also occur with daily therapy when administered irregularly (e.g. in noncompliant patients)
• usually presents after 3-6 months of intermittent therapy
• usually occurs 1-2 hours after rifampin administration
• resolution of symptom usually occurs within 12 hours

Management
refer to “Influenza Syndrome” Management Guidelines, page 16

**Hypersensitivity-immune mediated hematologic (blood) disorders**

**Clinical Presentation**¹
• thrombocytopenic purpura: decreased platelet count, excessive bruising, nose bleeds, and/or other abnormal bleeding
• acute hemolytic anemia

**Frequency/Characteristics**¹²
• rare
• more common with high dose (>900mg), intermittent than daily dosing
• may occur with daily therapy when administered irregularly (e.g. in noncompliant patients)
• thrombocytopenia:
  ▪ the platelet count decreases within 3 hours of rifampin administration
  ▪ the platelet count usually return to normal levels 36 hours after rifampin is discontinued
• hemolytic anemia
  ▪ hemolysis may become evident within 2 to 3 hours after rifampin administration
  ▪ resolution occurs when rifampin is discontinued

Management
• discontinue rifampin
• thrombocytopenic purpura and hemolytic anemia are contraindications for further rifampin use

**Hypersensitivity-immune mediated acute renal failure (kidneys)**

**Clinical Presentation**²
• sudden onset of lower back pain, fever and decreased urine output

**Frequency/Characteristics**¹²
• rare
• most likely immune mediated
• occurs with intermittent therapy or in patients administering rifampin irregularly (e.g. in noncompliant patients)

Management
• discontinue rifampin
• acute renal failure is a contraindication for further rifampin use
Drug Interactions

• Rifampin is a potent inducer of the cytochrome P<sub>450</sub> hepatic enzyme system.
• Rifampin may increase the metabolism of many drugs resulting in decreased therapeutic effect.
• Rifabutin and rifapentine induce the cytochrome P<sub>450</sub> hepatic enzyme system to a lesser extent than rifampin (rifampin > rifapentine > rifabutin).
• Practitioners should always check for drug interactions when initiating rifamycin therapy.

Rifampin and the other rifamycins may decrease serum levels/therapeutic effects of (list is not all inclusive):

- antiarrhythmic agents: disopyramide, mexilitine, propaferone, tocainide
- antifungals: fluconazole, itraconazole, ketoconazole
- benzodiazepines: alprazolam, clonazepam, diazepam, estazolam, flurazepam, midazolam, quazepam, triazolam
- β-blockers: bisoprolol, metoprolol, propranolol
- calcium channel blockers: diltiazem, nifedipine, verapamil
- cyclosporin
- digoxin, digitoxin
- estrogen (e.g. oral contraceptives)
- non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine)*
- protease inhibitors (saquinavir, ritonavir, indinavir, nelfinavir)*
- phenytoin
- sulfonylureas: acetohexamide, chlorpropamide, glimepiride, glipizide, glyburide, tolazamide, tolbutamide
- tacrolimus
- theophylline
- tricyclic antidepressants
- warfarin

Drugs that decrease rifamycin serum concentrations/therapeutic effect
- ketoconazole

Drugs that increase rifamycin serum concentrations
- macrolides: erythromycin, clarithromycin

Monitoring for ADEs

ATS and CDC recommendations<sup>8,9</sup>
- symptom assessment
- refer to “Routine Monitoring for Hepatotoxicity”, pages 12-13, for guidelines for monitoring LFTs

* Concomitant rifampin and protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI) use is contraindicated. Rifabutin is the rifamycin of choice in patients receiving PI or NNRTI. Preferred PI for this combination are indinavir and nelfinavir. Preferred NNRTI are neviripine and efavirenz. Delavirdine and ritonavir should not be used in combination with any of the rifamycins.22
Rifabutin

Adverse Drug Effects (ADEs)\textsuperscript{2,9,23}

- Generally, adverse effects of rifabutin are similar to those of rifampin (refer to Rifampin Section, pages 42-45). The frequency and severity of adverse effects are ≤ to rifampin.
- In clinical trials with HIV infected patients, the most common reasons for discontinuing rifabutin were rash (4\%) and gastrointestinal intolerance (3\%).
- Uveitis appears to be a unique adverse effect of rifabutin that does not occur with rifampin.

Uveitis (inflammation of the eyes: iris, ciliary body, choroid)

Clinical Presentation
   eye pain, blurred vision

Frequency/Characteristics\textsuperscript{24}
- in clinical trials with HIV infected patients, uveitis occurred with increased rifabutin serum levels (doses > 300mg/d with concomitant use of clarithromycin or fluconazole)
- uncommon with doses of ≤ 300mg/day
- usually mild to moderate in severity

Management\textsuperscript{24}
- uveitis usually resolves with use of topical steroids and cycloplegics and mydriatics
- discontinuance of rifabutin is not required unless the uveitis recurs or is refractory to treatment

Drug Interactions\textsuperscript{15,23}

Rifabutin decreases the serum levels/therapeutic effect of:
- many of the same drugs as rifampin (refer to page 45)
- rifabutin will have less of an effect on these drugs than rifampin because it is a less potent inducer of the cytochrome P\textsubscript{450} hepatic enzyme system than rifampin
- monitor serum levels and/or therapeutic effect when these drugs are used concomitantly

Drugs that increase rifabutin serum concentrations:
clarithromycin, erythromycin

Monitoring for ADEs

ATS recommendations\textsuperscript{9}
- symptom assessment
Rifapentine

Rifapentine (Priftin®) received FDA approval for the treatment of pulmonary tuberculosis in June 1998.

Adverse Drug Effects (ADEs)

• In comparative clinical trials, the frequency of ADEs was similar for rifapentine and rifampin.
  ▪ ADEs were similar to those previously reported with rifampin (refer to Rifampin Section, pages 42-45)
  ▪ Differences between rifapentine and rifampin were seen with the occurrence of:
    • rash (rifapentine 3.6%, rifampin 6.1%)
    • itching (rifapentine 2.5%, rifampin 4.4%)
  ▪ Drug was discontinued secondary to ADEs more frequently in the rifampin group (5%) than the rifapentine group (2.5%)

Drug Interactions

Rifapentine decreases the serum levels/therapeutic effect of:

• Many of the same drugs as rifampin (refer to page 45)
• Rifapentine’s cytochrome P450 hepatic enzyme system induction potential is < rifampin but > rifabutin
• Monitor serum levels and/or therapeutic effect when these drugs are used concomitantly
Streptomycin (see aminoglycosides)
## Appendix 1

### Selected Antihistamines for the Prevention/Treatment of Cutaneous (“flushing”) Reactions

<table>
<thead>
<tr>
<th>Antihistamine*</th>
<th>Dosage Form</th>
<th>Adult Dose</th>
<th>Pediatric Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>diphenhydramine (Benadryl®) OTC</td>
<td>caps/tabs 25mg, 50mg syrup 12.5mg/5ml (120ml, 240ml)</td>
<td>25-50mg 1 hour before meds, then 25mg q 4-6hr prn max dose=300mg/24h</td>
<td>&lt;20 lbs: 6.25-12.5mg 1 hour before meds then 4-6hr prn</td>
</tr>
<tr>
<td>chlorpheniramine (Chlor-Trimeton®) OTC</td>
<td>tabs 4mg, 8mg, 12mg syrup 2mg/ml (120ml)</td>
<td>4mg 1 hour before meds, then q 4-6 hours prn max dose=24mg/24h</td>
<td>6-12yo: 2mg 1 hour before meds, then q 4-6 hours prn max dose=12mg/24h</td>
</tr>
<tr>
<td>loratidine (Claritin®) Rx</td>
<td>tabs 10mg solution 5mg/ml</td>
<td>10mg 2-3 hours before meds</td>
<td>&gt;6yo (not recommended &lt;6yo) 10mg 2-3 hours before meds</td>
</tr>
</tbody>
</table>

*Incidence of drowsiness: diphenhydramine > chlorpheniramine > loratidine
Appendix 2

Oral Desensitization Protocol for Isoniazid

Drug desensitization should not be attempted with severe skin reactions or those involving the mouth or mucous membranes (e.g. exfoliative dermatitis and Stevens-Johnson Syndrome).

1. Consideration should be given to desensitizing patients under monitored conditions for severe reactions.
2. Administer isoniazid as outlined in the table below (doses require adjustment in children).
3. Isoniazid syrup (50mg/ml) should be used for initial doses.
   a. Tubercillin syringes may be used to administer small volume doses.
4. Isoniazid tablets may be administered beginning with the 50mg or 100mg dose.
5. If a reaction develops during desensitization, decrease the dose to the highest dose (the previous dose) that did not cause a reaction and begin increasing the doses in smaller increments.

Protocol for Oral Desensitization of Isoniazid in Adults

<table>
<thead>
<tr>
<th>Time</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM</td>
<td></td>
</tr>
<tr>
<td>7:00</td>
<td>0.1</td>
</tr>
<tr>
<td>7:15</td>
<td>0.5</td>
</tr>
<tr>
<td>7:30</td>
<td>1.0</td>
</tr>
<tr>
<td>7:45</td>
<td>2.0</td>
</tr>
<tr>
<td>8:00</td>
<td>4.0</td>
</tr>
<tr>
<td>8:30</td>
<td>8.0</td>
</tr>
<tr>
<td>9:00</td>
<td>16.0</td>
</tr>
<tr>
<td>9:30</td>
<td>32.0</td>
</tr>
<tr>
<td>10:30</td>
<td>50</td>
</tr>
<tr>
<td>PM</td>
<td></td>
</tr>
<tr>
<td>12:30</td>
<td>100</td>
</tr>
<tr>
<td>2:30</td>
<td>150</td>
</tr>
<tr>
<td>3:00</td>
<td>150</td>
</tr>
<tr>
<td>AM</td>
<td>12:30</td>
</tr>
<tr>
<td></td>
<td>150</td>
</tr>
</tbody>
</table>

Continue 150mg q 12 hours
Appendix 3

Oral Desensitization Protocol for Rifampin and Ethambutol

Drug desensitization should not be attempted with severe skin reactions or those involving the mouth or mucous membranes (e.g. exfoliative dermatitis and Stevens-Johnson Syndrome).

1. Consideration should be given to desensitizing patients under monitored conditions for severe reactions.
2. Administer rifampin or ethambutol as outlined in the table below (doses require adjustment in children).
3. If a reaction develops during desensitization, decrease the dose to the highest dose (the previous dose) that did not cause a reaction and begin increasing the doses in smaller increments.
4. After completing the protocol, continue dosing BID (rifampin) or TID (ethambutol) for 3 days, then administer the total daily dose once daily thereafter.

Protocol for Oral Desensitization of Rifampin and Ethambutol in Adults

<table>
<thead>
<tr>
<th>Time from start (h:min)</th>
<th>Rifampin (mg)</th>
<th>Ethambutol (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:00</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>00:45</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>01:30</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>02:15</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>03:00</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>03:45</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>04:30</td>
<td>16.0</td>
<td>16.0</td>
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<tr>
<td>05:15</td>
<td>32.0</td>
<td>32.0</td>
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<tr>
<td>06:00</td>
<td>50.0</td>
<td>50.0</td>
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<tr>
<td>06:45</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>07:30</td>
<td>150</td>
<td>200</td>
</tr>
<tr>
<td>11:00</td>
<td>300</td>
<td>400</td>
</tr>
<tr>
<td>Next day, 06:30 am</td>
<td>300 bid</td>
<td>400 tid</td>
</tr>
</tbody>
</table>

Dosage Preparation for the Desensitization Protocol

Rifampin

1. Empty and mix 4 rifampin 300mg capsules with 120ml of cherry syrup (10mg/ml suspension).
2. Administer the specified amount of drug for each time period via an oral syringe.
   a. Shake well before drawing suspension into syringe.
   b. E.g. 0.1mg rifampin = 0.01ml of the rifampin suspension.
   c. Tubercillin syringes can be used to administer small volume doses.
3. Begin using rifampin capsules with the 150mg dose.

Ethambutol

1. Crush 1 ethambutol 400mg tablet and mix with 400ml of 70% sorbitol/water (1mg/ml suspension) and/or crush 10 ethambutol 400mg tablets and mix with 400ml of 70% sorbitol/water (10mg/ml suspension).
2. Administer the specified amount of drug for each time period via an oral syringe.
   a. Shake well before drawing suspension into syringe.
   b. E.g. for 1mg/ml suspension: 0.1mg of ethambutol = 0.1ml suspension.
      for 10mg/ml suspension: 0.1mg of ethambutol = 0.01ml suspension.
   c. Tubercillin syringes can be used to administer small volume doses.
3. Begin using ethambutol tablets with the 50mg or 100mg dose.
Appendix 4

Guidelines for Medication Administration

1. Tablets and capsules should be administered all together once a day except in very unusual situations (e.g. extreme side effects to the drugs). TB Control personnel should be consulted before dividing doses throughout the day.

2. If medication administration times are divided, the entire dose of each drug should be given at one time (e.g. isoniazid 300mg in the morning, rifampin 600mg in the evening).

3. Food and drug administration
   a. Isoniazid and rifampin should be administered 1 hour before or 2 hours after food ingestion for maximum drug absorption.
   b. If nausea and/or vomiting occurs, administer isoniazid and rifampin with food (better to give the drug with food and have some decreased absorption than to not have the patient ingest the drug at all because of the side effect).
   c. All other TB medications can be administered without regard to food.

4. Options for patients who can not swallow tablets and capsules (some adults and infants/children)
   a. Liquid preparations
      1) availability
         a) isoniazid is the only commercially available liquid product
         b) rifampin and pyrazinamide suspensions can be prepared from the tablets/capsules
         c) ethambutol suspensions can not be prepared because of drug stability problems
      2) limitations of liquid preparations
         a) the volume of the liquid required for each dose may be too large for the patient to tolerate (especially in infants and children)
         b) diarrhea may occur due to the lactose and sucrose content in liquid preparations
         b) prepared suspensions have limited stability
         c) some suspension are not palatable (bitter tasting)
   b. Crushing capsules and tablets
      1) preferred to administration of liquid formulations
         a) drug stability is not an issue
         b) administration of a large volume of liquid in children is avoided
      2) procedure
         a) open and empty capsule contents into mortar, place tablets in the mortar and crush to a fine powder with a pestle (or other suitable container and “crusher” if mortar and pestle are not available)
         b) mix the powder with a pleasant tasting substance to mask the taste of the pills
            i) juice
            ii) flavored syrup (e.g. cherry)
            iii) applesauce
            iv) pudding
            v) ice cream
            vi) chocolate syrup (seems to mask bitter tastes well)
            vii) whatever else works!
         c) administer immediately after mixing with a spoon, medication cup or syringe
         d) if the mixture does not taste good and is rejected by the patient, continue to mix medications with different substances until an acceptable mixture is found (especially with children)
   c. Administer medication through a nasogastric tube
      1) alternative for children who are unable or unwilling to ingest medications
Appendix 5

Technique for Medication Administration through an Oral (needleless) Syringe

The following administration technique helps to minimize the amount of liquid medication spilled because of infant “squirming” or the amount spit out once it had been administered.

1. The infant should be held in the arm or lap of the person administering medication. The infant’s arms closest to the caregiver should be extended behind the caregiver’s back. The infant’s other arm is held down by the caregiver’s arm as the medication is being administered.

2. The medication in the oral or needleless syringe should be injected into the infant’s cheek at the gums toward the back of the mouth. The volume of medication injected at one time should be determined based on the child’s size (the entire dose may not be able to be injected at one time).
Appendix 6

Tuberculosis: Drug Therapy in Pregnancy

Pregnancy Risk Categories

A. Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is not evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.

B. Either animal-reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

C. Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal, or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

X. Studies in animals or human beings have demonstrated fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.
### Tuberculosis: Drug Therapy During Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy Risk Category</th>
<th>CDC/ATS Recommendations for Use</th>
<th><em>Breast Feeding</em></th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>C</td>
<td>Safe</td>
<td>considered “compatible” with breast feeding</td>
<td>pregnant women may be at an increased risk of developing hepatitis when INH is administered as preventive therapy&lt;sup&gt;21,32&lt;/sup&gt; pyridoxine should be administered to pregnant women receiving INH</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>C</td>
<td>Safe</td>
<td>INH, acetylisoniazid are excreted into breast milk</td>
<td>milk:plasma ratio is 1:1 monitor baby for hepatitis and peripheral neuritis&lt;sup&gt;29&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rifampin</td>
<td>C</td>
<td>Safe</td>
<td>considered “compatible” with breast feeding</td>
<td>rifampin is excreted into breast milk milk:plasma ratio is 0.20</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>B</td>
<td>Safe</td>
<td>considered “compatible” with breast feeding</td>
<td>ethambutol is excreted into breast milk milk:plasma ratio is 1:1</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>B</td>
<td>Safe</td>
<td>ethambutol is excreted into breast milk</td>
<td>peak milk concentration is ≈1.4 mcg/ml after a 15 mg/kg dose</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>C</td>
<td>Avoid</td>
<td>PZA is excreted into breast milk</td>
<td>general PZA use is not recommended by U.S. organizations because of lack of teratogenicity data PZA is recommended for use by international TB organizations the risks vs. benefits of using PZA in pregnancy should be considered carefully if MDR-TB is suspected&lt;sup&gt;10,31&lt;/sup&gt; a few reports of PZA use in pregnancy have been published&lt;sup&gt;33,34,35&lt;/sup&gt; total of 15 patients when reports combined primarily during 3rd trimester (2-1st trimester, 3-not specified) 9 patients received PZA for 2 months, 6 patients-duration not specified no adverse effects to babies noted (5 patients-no mention of babies made at all) a review article written in 1992 by members of the Los Angeles TB control program recommends using PZA for the first two months of treatment in pregnancy&lt;sup&gt;36&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* If baby receiving treatment for TB, breast feeding should be avoided. Additional drug received by the baby through breast milk increases the risk of adverse drug effects.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy Risk Category</th>
<th>CDC/ATS Recommendations for Use</th>
<th>Breast Feeding</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofloxacin/Levofloxacin</td>
<td>C</td>
<td>Do Not Use (CDC)</td>
<td></td>
<td>• the peak milk concentration was 2.41 mcg/ml after 400mg po bid dosing (peak plasma level was 2.45 mcg/ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• ofloxacin has produced lesions of the articular cartilage in immature animals at doses 5-16 times the maximum human doses</td>
</tr>
</tbody>
</table>
|                      |                         |                                 |                | • a small observational study compared pregnancy outcomes in 38 women who received quinolones (28-norfloxacin, 10-ciprofloxacin) to 38 women who received a nonteratogenic antibiotic:  
|                      |                         |                                 |                | • doses=norfloxacin 800mg/d, ciprofloxacin 1 gm/d                                                                                                                                                  |
|                      |                         |                                 |                | • mean treatment duration was 7.7 ± 5.4 days                                                                                                                                                    |
|                      |                         |                                 |                | • 35/38 received the quinolone during the first trimester                                                                                                                                    |
|                      |                         |                                 |                | • 31/38 in the quinolone group and 30/38 in the control group had live births                                                                                                                  |
|                      |                         |                                 |                | • fetal distress and use of cesarean delivery was more common in the quinolone group than the control group                                                                                    |
|                      |                         |                                 |                | • no fetal malformations were found in the quinolone group                                                                                                                                     |
|                      |                         |                                 |                | • ofloxacin was administered at a dose of 200mg po bid to a woman during the 2nd trimester for 6 days; no teratogenetic effects were seen                                                                 |
|                      |                         |                                 |                | • a postmarketing surveillance of ofloxacin use included a report on 39 women who received ofloxacin during pregnancy:  
|                      |                         |                                 |                | • dose/duration of therapy was not included                                                                                                                                                |
|                      |                         |                                 |                | • 33 women delivered healthy babies (15 received ofloxacin <17 days after becoming PG, 9>17 days after PG, 9 unknown)                                                                 |
|                      |                         |                                 |                | • 1-miscarriage, 1-hydatidiform mole, 4-congenital malformations (3 of these judged not related to ofloxacin, there was insufficient information to evaluate the 4th)                                                                 |
|                      |                         |                                 |                | • another postmarketing study of ofloxacin, norfloxacin and ciprofloxacin was conducted in the UK using "prescription event monitoring":  
<p>|                      |                         |                                 |                | • dose/duration was not indicated (use for UTI, respiratory tract infections)                                                                                                                  |
|                      |                         |                                 |                | • outcome for patients receiving drug during 1st trimester reported (an additional 208 PG but data not reported)                                                                 |
|                      |                         |                                 |                | • total PG=32, normal birth=21, PG termination=5, spontaneous abortion=5, ectopic PG=1                                                                                                            |
|                      |                         |                                 |                | • total PG for ofloxacin=10, normal birth=8, PG termination=1, spontaneous abortion=1                                                                                                           |
|                      |                         |                                 |                | • no congenital abnormalities were reported                                                                                                                                                     |
|                      |                         |                                 |                | • no reports of using ofloxacin or levofloxacin (or other quinolones) in TB regimen in PG patients or for prolonged use in pregnancy were found by a MEDLINE search                                                   |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy Risk Category</th>
<th>CDC/ATS Recommendations for Use</th>
<th><em>Breast Feeding</em></th>
<th>Comments</th>
</tr>
</thead>
</table>
| Streptomycin         | D                       | Avoid                           | •considered “compatible” with breast feeding  
•streptomycin is excreted into breast milk  
•milk:plasma ratio is 0.5-1  
•ototoxicity is not expected since oral absorption of streptomycin is poor but it may cause modification of bowel flora | •streptomycin can cause eighth cranial nerve damage and result in congenital deafness  
•this effect can occur anytime throughout a pregnancy  
•kanamycin and capreomycin are expected to have similar effects (data is not available on use in PG) |  |
| Cycloserine          | C                       | Avoid                           | •considered “compatible” with breast feeding  
•cycloserine is excreted into breast milk  
•milk concentration after 250mg qid dosing ranges from 6-19mcg/ml (72% of serum levels) | •ATS recommends avoiding use when possible because of lack of information about teratogenicity  
•Briggs notes that 50,282 mother-child pairs were monitored during the Collaborative Perinatal Project. No adverse fetal effects were noted. Only 3 of these pairs had 1st trimester exposure to cycloserine  
•One study compared cycloserine, sulphadimidine or no AB for the management of asymptomatic bacteruria in PG:  
•patients received cycloserine 250mg bid x 2 weeks then 250mg every other day until delivery (total duration not noted)  
•31 patients received cycloserine: 3 stillbirths, untreated group: 1 stillbirth, 1 neonatal death  
•31 patients did not receive AB: 1 stillbirth, 1 neonatal death  
•An editorial review of an author’s 10 year experience with cycloserine(from 1970) stated that it he had used it in pregnant women to treat UTIs without adverse effect to the fetus (except for 1 spontaneous abortion not believed to be related). The number of PG women treated was not noted. |  |
| Ethionamide          | Not Classified          | Do Not Use/Avoid                | •information is not available about ethionamide excretion into breast milk | •a MEDLINE search of ethionamide and PG showed 5 citations (references are not available for review)  
•ATS recommends avoiding use when possible because of lack of information about teratogenicity |  |
| Para-aminosalicylic acid | C                  | Safe (CDC)                      | •PAS is excreted into breast milk  
•peak milk concentration after 1 gm was 1.1 mcg/ml (plasma concentration was 70 mcg/ml) | •Briggs review of clofazimine included ≈ 90 pregnant women reported from several different sources. No congenital anomalies were reported (however, in the largest report of 76 women, PG outcome was not noted by the author)  
•pigmentation may occur in the newborn (reports noted that pigmentation resolved over a 1 year period in some infants) |  |
| Clofazimine          | C                       | Avoid (CDC)                     | •excreted into breast milk  
•pigmentation may occur in the baby |  |  |

* If baby receiving treatment for TB, breast feeding should be avoided. Additional drug received by the baby through breast milk increases the risk of adverse drug effects.
References