TB Intensive
Tyler, Texas
June 5-8, 2007

TB Drug Review
David E. Griffith, MD
June 8, 2007

TB Drugs
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Statements and recommendations consistent with ATS/CDC guidelines.


ANTITUBERCULOSIS DRUGS
(ATS/CDC/IDSA)

- First-Line drugs
  - Isoniazid
  - Rifampin
  - Rifapentene
  - Rifabutin*
  - Ethambutol
  - Pyrazinamide

- Second-Line Drugs
  - Cylcoserine
  - Ethionamide
  - Levofoxacin*
  - Moxifloxacin*
  - PAS
  - Streptomycin
  - Amikacin/Kanamycin
  - Capreomycin

*Not FDA approved for TB
ISONIAZID (INH)

- “Profound early bacteriaceidal activity…”
- Adults: 5mg/kg (300 mg/daily), 20-30 mg/kg (900 mg) twice or three times weekly
- Children: 10-15 mg/kg daily, 20-30 mg/kg (900 mg) twice weekly

INH Hepatotoxicity

- Asymptomatic elevation of aminotransferases: 20% of patients
- Clinical hepatitis: 0.6% of patients
- Fulminant hepatitis (hepatic failure): Approximately 4/100,000 persons completing therapy (continued INH with symptoms of hepatitis, prior INH hepatotoxicity, malnutrition).
An Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy
American Journal of Respiratory and Critical Care Medicine
2006; Vol. 174: 935-952

“DILI”
Drug Induced Liver Injury
Isoniazid Hepatotoxicity
(AJRCCM, 2006; 174: 935-952)

• Mechanism Unknown
• Generally occurs after weeks to months (rather than days to weeks)
• Risk factors: Age, alcohol consumption, pregnant and post-partum women, active hepatitis B, other hepatotoxic drugs
• ?Non-risk factors: Race, gender, quiescent hepatitis B, hepatitis C, HIV

Isoniazid Hepatotoxicity: Pretreatment Evaluation (New)
(AJRCCM, 2006; 174: 935-952)

• Physical examination: liver tenderness, hepatosplenomegaly, jaundice, caput medusa, spider angiomata, ascites, edema
• Screening for viral hepatitis: IV drug users, patients from endemic areas of the world, household and work contacts, undiagnosed liver disease
Isoniazid Hepatotoxicity: Treatment Choice
(AJRCCM, 2006; 174: 935-952)

• “For those with ALT elevation more than 2.5 to 3 times the ULN, chronic alcohol consumption, or severe liver disease manifested by low albumin and coagulopathy or encephalopathy, the risks of LTBI may outweigh benefits. If LTBI is undertaken, close monitoring is indicated.”

Isoniazid Hepatotoxicity: Monitoring
(AJRCCM, 2006; 174: 935-952)

• “Face-to-face clinical assessments are the cornerstone of clinical monitoring for treatment adherence and adverse events.”
• “Baseline and follow-up serum ALT and bilirubin are recommended for patients with a possible liver disorder; those with a history of chronic liver disease...patients with chronic alcohol use, those with HIV infection treated with HAART, pregnant women and those who are up to 3 months post partum.”
Isoniazid Hepatotoxicity: Monitoring
(AJRCCM, 2006; 174: 935-952)

• Consider baseline testing for patients receiving other medications or for those with chronic medical conditions.
• “Some experts” recommend biochemical testing for “healthy individuals” over the age of 35.
• ALT is preferred (AST less liver specific)

Isoniazid Hepatotoxicity: Interventions
(AJRCCM, 2006; 174: 935-952)

• “Isoniazid should be withheld if ALT is at least three times the ULN when jaundice and/or hepatitis symptoms are reported, or if ALT is at least five times the ULN in the absence of symptoms”
• “A rapid increase in ALT may be an indication for more frequent monitoring…”
• Consider rechallenge (many caveats)
INH Toxicity Monitoring

• The critical element for INH toxicity monitoring is CLINICAL MONITORING.
• Clinical monitoring of patients on INH is absolutely necessary to do, absolutely necessary to do well and absolutely necessary to document well.

INH Peripheral Neurotoxicity

• Dose Related
• Uncommon (< 0.2%) at conventional doses
• Increased risk with other conditions associated with neuropathy: malnutrition, diabetes, HIV, renal failure, alcohol
• Pyridoxine 25 mg/kg recommended patients with above conditions
RIFAMPIN (Rif)

- Activity against rapidly dividing and against semi-dormant bacterial populations.
- Adults: 10 mg/kg (600 mg) daily, twice weekly or three times weekly
- Children: 10-20 mg/kg (600 mg) daily or twice weekly

Rifampin Toxicity

- Cutaneous Reactions: 6%, generally self-limited
- Gastrointestinal symptoms: nausea, anorexia, abdominal pain
- Flulike symptoms: < 1% of patients on intermittent therapy.
- Hepatotoxicity: nearly 0% as monotherapy, 2-3% with INH, cholestatic
Rifampin Toxicity

- Severe immunologic reactions: thrombocytopenia, hemolytic anemia, acute renal failure and thrombotic thrombocytopenic purpura (each < 0.1% of patients)
- Drug interactions due to induction of hepatic microsomal enzymes

Rifampin Drug Interactions

- Interactions due to induction of hepatic microsomal enzymes that accelerate metabolism of multiple drugs
- Major concern is reduction in serum concentrations of common drugs (BCP’s, warfarin, etc.) to ineffective levels
- Bidirectional interactions between rifamycins and antiretroviral agents
Rifampin Drug Interactions

- Very high severity: delavirdine, nevirapine
- High severity: anti-retroviral protease inhibitors, amiodarone, diltiazem, itraconazole, phenytoin, tamoxifen, verapamil, warfarin
- Moderate severity: corticosteroids, digoxin, efavirenz, fluconazole, metoprolol, thyroid hormone

It is imperative to be aware of all medications a patient is taking when that patient is placed on rifampin.
PYRAZINAMIDE (PZA)

- Greatest activity against dormant or semi-dormant organisms within macrophages or caseous foci.
- Adults: 20-25 mg/kg (2.0 g) daily, 50 mg/kg (4.0 g) twice weekly
- Children: 15-30 mg/kg (2.0 g) daily, 50 mg/kg (2.0 g) twice weekly

Pyrazinamide (PZA) Toxicity

- Hepatotoxicity: Unusual (1%) at 25 mg/kg
- Gastrointestinal symptoms: nausea and vomiting mild at standard doses.
- Nongouty polyarthralgia: Up to 40% of patients.
- Asymptomatic hyperuricemia: Expected
- Acute gouty arthritis: Unusual except in patients with pre-existing gout.
Ethambutol (EMB)

- Included in first-line treatment regimens to prevent the emergence of Rif resistance when INH resistance may be present.
- Adults: 15 mg/kg daily, 50 mg/kg twice weekly (max dosage based on wt, AJRCCM, 2003; 167: 603-662)
- Children: 15-20 mg/kg daily, 50 mg/kg (2.5 g) twice weekly

Ethambutol Toxicity

- Retrobulbar neuritis: decreased visual acuity or red-green color discrimination, dose related, unusual at dose 15 mg/kg. Increased risk with renal insufficiency. Safe at higher doses given intermittently.
- Peripheral neuritis
- Cutaneous reactions: < 1% of patients
Ethambutol Toxicity: Monitoring

- All patients should have baseline visual acuity (Snellen chart) and testing of color vision discrimination (Ishihara tests).
- Monthly symptom check (blurred vision scotoma)
- Monthly testing: high doses, treatment longer than 2 months, renal insufficiency
- PATIENT EDUCATION

Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active TB (Yee, AJRCCM 2003; 167: 1472)

430 Patients treated for TB in Canada 1990-1999
Major side effect: Any adverse reaction resulting in discontinuation of one or more drugs, and or resulting in hospitalization.
Almost all patients received IRZ (75% E)
Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active TB

Yee, AJRCCM 2003; 167: 1472

37 Patients had major side-effects: 9 had a second major adverse event (46 total events)

- Rash/drug fever 21
- Hepatitis 12
- Severe Gl upset 11
- Visual Toxicity 1
- Arthralgia 1

Associated with Female sex, age >60, Birthplace in Asia and HIV status

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>Rash</th>
<th>Hepatitis</th>
<th>Gl</th>
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<tr>
<td>INH</td>
<td>5.2</td>
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<td>5</td>
<td>4</td>
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<tr>
<td>RIFAMPIN</td>
<td>10.2</td>
<td>9</td>
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<td>4</td>
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<tr>
<td>PZA</td>
<td>24.2</td>
<td>8</td>
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<td>3</td>
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<tr>
<td>EMB</td>
<td>16.8</td>
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</table>
Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active TB
(Yee, AJRCCM 2003; 167: 1472)

PZA: 1.48/100 person months of exposure
INH: 0.49/100 person months
Rif: 0.43/100 person months
EMB: 0.07/100 person months

“The drug most likely responsible for the occurrence of hepatitis or rash during therapy for active TB is PZA”

**Fluoroquinolones**

- Levofloxacin: 500-750 mg/day, no data to support intermittent dosing
- Moxifloxacin: 400 mg/day, no data to support intermittent dosing
Fluoroquinolones

• Preferred oral agents for treating drug resistant TB that is susceptible to this class of drugs or for patients intolerant of first-line drugs
• Activity against MTB: Moxifloxacin > levofloxacin > ofloxacin/ciprofloxacin
• Cross resistance

Fluoroquinolone Hepatotoxicity

• Moxifloxacin metabolized in part by the liver, levofloxacin excreted unchanged by the kidneys
• Reversible transaminase elevation among the fluoroquinolones in 2 to 3% of cases
• Moxifloxacin: transaminase elevation >1.5 times ULN in 0.9% of cases
• Levofloxacin: severe hepatotoxicity-RARE
Fluoroquinolone Toxicity

- Gastrointestinal disturbance: nausea/bloating 0.5-2%
- Neurologic effects: dizziness, insomnia, tremulousness, headache 0.5%
- Cutaneous reactions: rash, pruritus, photosensitivity 0.2-0.4%
- Musculoskeletal effects: myalgias, tendonitis/tendon rupture

Fluoroquinolones in the Treatment of TB

  - Until there are data from the TB Trials Consortium studies evaluating the role of moxifloxacin in the initial intensive phase of treatment for patients with active TB as a substitute for EMB or INH, fluoroquinolones should not be considered first-line agents for the treatment of drug-susceptible TB…”
Rifapentine

- Long acting rifamycin that can be used once weekly (600 mg) with INH in the continuation phase of treatment for TB
- Should not be used: HIV seropositive, cavitary disease, positive sputum smears after the initiation phase of therapy
- Adverse effects similar to rifampin
- Investigation underway as an agent for treatment of LTBI (TBTC trials)

Rifabutin

- A substitute for rifampin for patients who are receiving drugs, especially antiretroviral drugs, that have unacceptable interactions with rifampin.
- Adverse effects: hematologic toxicity, uveitis, gastrointestinal symptoms, polyarthralgias, pseudojaundice, hepatotoxicity, rash, flu-like syndrome
### Second-Line TB Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
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<tbody>
<tr>
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<td><strong>Cycloserine</strong></td>
<td>- Rash&lt;br&gt;- CNS toxicity, may include seizure, depression, suicidal ideation, psychosis&lt;br&gt;- Peripheral neuropathy&lt;br&gt;- Skin changes (lichenoid eruptions, Stevens-Johnson Syndrome)</td>
</tr>
<tr>
<td><strong>Para-Aminosalicylate (PAS)</strong></td>
<td>- Rash&lt;br&gt;- GI upset, may be significant&lt;br&gt;- Hepatotoxicity&lt;br&gt;- Reversible hypothyroidism</td>
</tr>
<tr>
<td><strong>Clofazimine</strong></td>
<td>- Rash&lt;br&gt;- GI upset&lt;br&gt;- Discoloration and dryness of skin&lt;br&gt;- Photosensitivity&lt;br&gt;- Retinopathy</td>
</tr>
<tr>
<td><strong>Linezolid</strong></td>
<td>- Rash&lt;br&gt;- Myelosuppression&lt;br&gt;- Nausea and diarrhea&lt;br&gt;- Optic neuropathy&lt;br&gt;- Peripheral neuropathy</td>
</tr>
</tbody>
</table>

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**20**
Antituberculosis Drugs in Pregnancy

• INH: Approved, risk of hepatitis increased in peripartum period. Biochemical monitoring indicated
• Rifampin: Approved
• Ethambutol: Approved
• PZA: Controversial, FDA vs WHO and IUTLD, ATS

Antituberculous Drugs in Pregnancy

• Used with caution: rifabutin, cycloserine, para-Aminosalicylic acid
• Contraindicated: ethionamide, amikacin, streptomycin, kanamycin, capreomycin, quinolones
• Unknown: rifapentine
Antituberculous Drugs in Renal Disease

- INH: No dosage adjustment in patients with renal insufficiency and failure (900 mg TIW post hemodialysis).
- Rifampin: No dosage adjustment (600 mg TIW post hemodialysis).
- PZA: dose reduction with renal insufficiency, (25-35 mg/kg TIW post hemodialysis).
- Ethambutol: cleared by the kidneys, significant dose reduction with renal insufficiency (15-20 mg/kg TIW post hemodialysis)

Antituberculous Drugs in Renal Disease

- Fluoroquinolones: Cleared primarily by the kidney, dosage adjustment required
- Streptomycin/Amikacin/Capreomycin: Cleared primarily by the kidney, dosage adjustment, post hemodialysis dosing
- Ethionamide: dosage adjustment with daily therapy
- Cycloserine: Should not be used with CC < 50 ml/min unless dialysis (500 mg TIW, 250 mg/day)
Treatment of TB in Advanced Hepatic Disease

- Treatment without INH: Rif/EMB/PZA, still potentially hepatotoxic, 6 months regimen
- Treatment without PZA, 9 months regimen
- One potential hepatotoxic drug: Rif + EMB, fluoroquinolone, injectable
- No potentially hepatotoxic drugs (“liver friendly”): injectable, EMB, fluoroquinolone + second line oral drug, 18-24 months
- Initial “liver friendly” followed by challenge with hepatotoxic drug (Rif).

Antituberculosis Drugs for TB Meningitis

- INH: Excellent CSF penetration, CSF concentrations similar to serum
- PZA: Excellent CSF penetration, CSF concentrations similar to serum
- Rif: Concentrations in CSF 10-20% serum concentrations, increased with inflammation, adequate for efficacy
Antituberculosis Drugs for TB Meningitis

- EMB: Penetrates inflamed meninges, role in TB meningitis therapy not established
- Cycloserine: Excellent CSF penetration, CSF concentrations similar to serum
- Ethionamide: Excellent CSF penetration, CSF concentrations similar to serum
- Streptomycin: Slight penetration of inflamed meninges

Antituberculosis Drugs for TB Meningitis

- Capreomycin: Does not penetrate inflamed CSF
- PAS: 10-50% serum concentration in CSF with inflamed meninges, marginal efficacy
- Levofloxacin: CSF concentrations 16-20% serum concentrations
- Linezolid: Good CSF concentration
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

TB Disease: Baseline Testing and Monitoring
AJRCCM 2006; 174: 935-952

- Baseline transaminases, bilirubin, alkaline phosphatase, creatinine and platelet count for all adults beginning TB therapy
- Routine measurements during treatment: baseline abnormalities, chronic alcohol consumption, other hepatotoxic drugs, viral hepatitis or history of liver disease, HIV infection, prior DILI
- Screen for viral hepatitis in at risk patients
Laboratory Monitoring

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

Adverse Drug Events

Hepatotoxicity

- Drugs:
  - INH
    - Most likely to cause hepatitis (?)
    - Hepatotoxicity appears to be increased when used with rifampin
  - Rifampin/Rifabutin
  - PZA
  - Levofoxacin
  - (Ethionamide)
  - (PAS)
Adverse Drug Events
Hepatotoxicity

Who is most at risk?

- Those with underlying liver disease
  - Alcoholics
  - Hepatitis B and C
- Women
  - Pregnancy (last trimester)
  - Immediate (3 months) post-partum period
- Those on other hepatotoxic medications
- HIV-infected

Treatment of TB: Elevated ALT
AJRCCM 2006; 174: 935-952

- Consider 9 month regimen (INH, Rmp, EMB) without PZA
- Consider Rmp, EMB, fluoroquinolone without INH for patients with cirrhosis
- Consider EMB, fluoroquinolone, aminoglycoside (? Fourth agent) for patients with liver failure (“liver friendly”)
Interventions for Hepatotoxicity

AJRCCM 2006; 174: 935-952

- Transaminase levels either 3X ULN with symptoms or 5X ULN without symptoms: stop hepatotoxic medications.
- Obtain serologic tests for viral hepatitis; evaluate biliary disease, use of alcohol, other hepatotoxic drugs
- Consider (severity of TB, length of therapy interruption) “liver friendly” regimen (EMB, fluoroquinolone, aminoglycoside)

Interventions for Hepatotoxicity

AJRCCM 2006; 174: 935-952

- After ALT <2X ULN: restart RMP ± EMB
- After 3-7 days: restart INH
- If symptoms recur: stop last drug added
- If RMP and INH tolerated: do not restart PZA
- Consider alternative regimens as necessary: RMP, EMB, fluoroquinolone (9 months); RMP, EMB, PZA (6 months)
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

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
Oral Desensitization to Rif and EMB in Mycobacterial Disease
(Matz, AJRCCM, 1994;149:815)

- Patients with hypersensitivity reaction to either rifampin or ethambutol
- Not for patients with: hepatitis, hemolytic anemia, purpura, nephritis, ocular toxicity, anaphylaxis, hypotension, bronchospasm, laryngeal angioedema

- INH: Chest, 1990; 98: 1518

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>DESENSITIZATION PROTOCOL</th>
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<td>Time from Start (hr:min)</td>
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<td>11:00</td>
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</tr>
<tr>
<td>Next day</td>
<td>06:30 A.M.</td>
</tr>
</tbody>
</table>
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
  – Acuity testing with Snellen, Illiterate or Kindergarten charts
  – Color discrimination testing with Ishihara plates
  – Educate patient to report any changes in vision, erythema or eye pain

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
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, pricking, 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
Ototoxicity

– Amikacin, kanamycin, capreomycin

– Toxicity is related to total dose and is cumulative (not possible to predict the dose any one patient will not tolerate)

If tinnitus and unsteadiness develop, stop the injectable agent

• Drug–induced vestibular toxicity is not reversible
• Persistent vertigo, unsteadiness, ataxia and tinnitus will develop if the drug or another injectable agent is continued

Adverse Drug Events
Ototoxicity

• Auditory toxicity
  – Perform audiometry at baseline and repeat monthly
    • Identify pre-existing hearing loss
    • Refer for evaluation if any decrease from baseline
  – High frequency hearing loss occurs first
    • Effects speech discrimination
  – Monitor patient’s ability to engage in normal conversation
    • Answering inappropriately
    • Asking speakers to repeat what they have said
    • Increasing volume of radio/TV
    • Withdrawal/isolation
  – Toxic effects are cumulative
  – Hearing loss may be reversible or permanent
Adverse Drug Events
Nephrotoxicity

- Drugs: amikacin/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
Adverse Drug Events

- GI upset: PZA, rifabutin, fluoroquinolones, ethionamide, PAS, (any drug)
- Central Nervous System: INH, fluoroquinolones, amikacin, ethionamide, cycloserine
- Musculoskeletal: PZA, fluoroquinolones, rifabutin

NEW DRUGS FOR TREATMENT OF TUBERCULOSIS
New Drugs for Treatment of Tuberculosis
8- Methoxy-Fluoroquinolones
Moxifloxacin

• Moxifloxacin, Rmp, PZA reduces time to eradicate MTB from lungs of mice by up to 2 mos compared with INH, Rif, PZA
• Bactericidal activity in humans greater than Rmp (comparable to INH); MTB MICs for Moxi 4-fold lower than Levaquin.
• Moxifloxacin in multi-drug regimens may shorten duration of treatment needed

TBTC. Moxifloxacin vs EMB in the First 2 Months of Treatment for Pulmonary TB
Burman et al AJRCCM 2006; 174; 331.

• Effect of Moxi vs EMB with I,R,Z on sputum culture conversion to negativity at 2 mos
• Conversion rates 71% for both agents (Moxi patients more likely negative cultures at 4 wks)
• Moxi tolerated well
• No unequivocal conclusions about sterilizing activity of moxifloxacin
• Limitations of study
LINEZOLID

- Oxazolidinone → Inhibit protein synthesis by binding to the 70 S ribosomal initiation complex
- Antimicrobial spectrum includes drug resistant staphylococci, enterococci, pneumococci and mycobacteria
- Intravenous and oral forms

Linezolid for Treatment of TB (Alcala, AAC, 2003; 47: 416)

- 117 M. Tuberculosis Isolates
  - 73 Drug susceptible
  - 44 Resistant to first line drugs
- All isolates with Linezolid MIC
  - < 0.023 μg/ml
Linezolid for Treatment of TB
(von der Lippie, Infection, 2005; e-pub)

10 consecutive patients with MDR-TB: 7 pulmonary, one HIV with dissemination
• All TB isolates susceptible to linezolid
• Linezolid 600 mg BID and at least 3 other drugs
• Linezolid 6-10 weeks: 7 patients cured, 2 lost, one died
• 7 Patients serious adverse events: 6 peripheral neuropathy, 5 bone marrow suppression

Linezolid for Treatment of Tuberculosis

- Very active against MTB
- Can be given orally
- Frequent, severe adverse events:
  bone marrow suppression- dose dependent/reversible
- Peripheral Neuropathy- Not dose dependent
  ? not reversible
- Optimal dose not known
New Drugs for Treatment of Tuberculosis

Diarylquinolines (R207910)


- Structurally and mechanistically different from Fluoroquinolones and other Quinolines (Mefloquine)
- Unique site of action: Targets the portion pump of ATP Synthase
- High tissue penetration
- Very low MICs: Drug susceptible/resistant
- No cross resistance with other drugs

Table 1. MICs of R207910 that inhibited 99% of the growth of different mycobacterial species.

<table>
<thead>
<tr>
<th>Mycobacterial species</th>
<th>Number of strains</th>
<th>Range of MICs for multiple strains (µg/ml)</th>
<th>Median MIC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. tuberculosis, H37Rv</td>
<td>1</td>
<td>0.030</td>
<td>0.030</td>
</tr>
<tr>
<td>M. tuberculosis, fully susceptible clinical isolates</td>
<td>6</td>
<td>0.030–0.120</td>
<td>0.060</td>
</tr>
<tr>
<td>M. tuberculosis resistant to isoniazid</td>
<td>7</td>
<td>0.003–0.060</td>
<td>0.010</td>
</tr>
<tr>
<td>M. tuberculosis resistant to rifampin</td>
<td>1</td>
<td>—</td>
<td>0.030</td>
</tr>
<tr>
<td>M. tuberculosis resistant to isoniazid and rifampin</td>
<td>2</td>
<td>0.030–0.030</td>
<td>0.030</td>
</tr>
<tr>
<td>M. tuberculosis resistant to isoniazid and streptomycin</td>
<td>1</td>
<td>—</td>
<td>0.010</td>
</tr>
<tr>
<td>M. tuberculosis resistant to ethambutol</td>
<td>1</td>
<td>—</td>
<td>0.010</td>
</tr>
<tr>
<td>M. tuberculosis resistant to pyrazinamide</td>
<td>1</td>
<td>—</td>
<td>0.030</td>
</tr>
<tr>
<td>M. tuberculosis resistant to fluoroquinolone</td>
<td>2</td>
<td>0.060–0.120</td>
<td>0.090</td>
</tr>
<tr>
<td>M. bovis</td>
<td>1</td>
<td>—</td>
<td>0.003</td>
</tr>
<tr>
<td>M. avium/M. intracellulare (MAC)</td>
<td>7</td>
<td>0.007–0.010</td>
<td>0.010</td>
</tr>
<tr>
<td>M. kansasii</td>
<td>1</td>
<td>—</td>
<td>0.003</td>
</tr>
<tr>
<td>M. marinum</td>
<td>1</td>
<td>—</td>
<td>0.003</td>
</tr>
<tr>
<td>M. fortuitum</td>
<td>5</td>
<td>0.007–0.010</td>
<td>0.010</td>
</tr>
<tr>
<td>M. abscessus</td>
<td>1</td>
<td>—</td>
<td>0.250</td>
</tr>
<tr>
<td>M. smegmatis</td>
<td>7</td>
<td>0.003–0.010</td>
<td>0.007</td>
</tr>
<tr>
<td>M. ulcerans</td>
<td>1</td>
<td>—</td>
<td>0.500</td>
</tr>
</tbody>
</table>
New Drugs for Treatment of Tuberculosis

Diarylquinoline (R207910)

- In mouse model R207910 exceeds the bactericidal activity of INH and Rif
- Substitution of R207910 for INH or Rif in mouse model accelerates bactericidal activity
- Phase I Studies in Humans:
  - Well absorbed Orally
  - Long half-life (24 months)
  - Peak levels exceed MIC for MTB
  - Well Tolerated

New Drugs for Treatment of Tuberculosis

Nitroimidazopyrans (PA-824)

Novel mechanism of action
Antimycobacterial activity highly specific for MTB
MIC 0.015 to 0.25 µg/ml for susceptible/resistant MTB
Comparable activity to INH, Rif, Moxi in mouse model
Potential for oral administration
No phase I data from humans yet.