Overview

• Diagnosis
  o Clinical considerations
  o Laboratory considerations

• Treatment
  o Routine
  o Variants

TB Diagnosis: When to Suspect

• Cough illness ≥2-3 weeks +
  o Fever, night sweats, weight loss, and/or hemoptysis

• High risk for TB, unexplained illness, including respiratory symptoms of ≥ 2-3 weeks duration
  o Recent exposure, known (+) TST, HIV, drug use, immigrant <5 years from high-risk region, high-risk congregate setting, homeless, immunosuppressed, advanced CKD, silicosis, others

• HIV (+), unexplained cough, fever
• High risk and unresponsive CAP after 7 days
• High risk and worrisome CXR

Guidelines. MMWR 54:1 (2005)
Suggestive Radiologic Findings

- Infiltrates in upper lobes or superior segments of lower lobes
Sputum Analysis in TB

- Recommendations: Submit 3 specimens for AFB smears and cultures
  - Labs report that ~25% of requests for AFB smears and cultures are submitted as the one and only specimen.

- Culture (+)
  - #1: ~75%
  - #1 + #2: ~90%
  - #1 + #2 + #3: ~95%

- Smear (+) About 60% (45-80%) of patients
  - Roughly 40% of patients with culture-proven pulmonary TB never have a positive smear


Lab Evaluation: Sputum Analysis

- AFB smear microscopy
  - Sensitivity 45-80% (culture (+) cases)
  - Lower in children

- AFB culture
  - Sensitivity ~80% (most of rest are “smear-negative culture-negative” TB)
  - Specificity ~98% (false positives due to contaminated equipment, lab cross-contamination)

Rates of False (+) Cultures for Mycobacterium tuberculosis

<table>
<thead>
<tr>
<th>Study</th>
<th>False (+)</th>
<th>Total</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3/114</td>
<td></td>
<td>2.6%</td>
</tr>
<tr>
<td>2</td>
<td>9/496</td>
<td></td>
<td>1.8%</td>
</tr>
<tr>
<td>3</td>
<td>9/259</td>
<td></td>
<td>3.5%</td>
</tr>
<tr>
<td>4</td>
<td>12/441</td>
<td></td>
<td>2.7%</td>
</tr>
<tr>
<td>5</td>
<td>4/443</td>
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</tr>
<tr>
<td>6</td>
<td>24/306</td>
<td></td>
<td>7.8%</td>
</tr>
<tr>
<td>7</td>
<td>5/173</td>
<td></td>
<td>2.9%</td>
</tr>
<tr>
<td>8</td>
<td>3/105</td>
<td></td>
<td>2.9%</td>
</tr>
<tr>
<td>9</td>
<td>0/210</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>8/159</td>
<td></td>
<td>4.0%</td>
</tr>
<tr>
<td>11</td>
<td>48/1439</td>
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<td>3.2%</td>
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Burman W, Reves R., CID 2000;31:1390
## Nucleic Acid Amplification Tests

<table>
<thead>
<tr>
<th>TB/Total</th>
<th>Smear</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>1262/2241</td>
<td>+</td>
<td>94.3%</td>
<td>98.1%</td>
</tr>
<tr>
<td>75/170</td>
<td>-</td>
<td>70.8%</td>
<td>85.9%</td>
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</table>

Laraque F et al., CID 2009;49:46-54

<table>
<thead>
<tr>
<th>Smear</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>95%</td>
<td>98%</td>
</tr>
<tr>
<td>-</td>
<td>75-78%</td>
<td>95%</td>
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</tbody>
</table>

UpToDate 2009

### Predictive Value, Positive NAAT, in Smear (-) TB

<table>
<thead>
<tr>
<th>Test Parameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>TB Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>75%</td>
<td>86%</td>
<td>84%</td>
<td>70%</td>
</tr>
<tr>
<td>75%</td>
<td>95%</td>
<td>94%</td>
<td>87%</td>
</tr>
<tr>
<td>75%</td>
<td>95%</td>
<td>94%</td>
<td>62%</td>
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</table>

## Lab Evaluation: Nucleic Acid Amplification

- 2009 CDC guidelines recommend routine use when suspicion moderate to high
  - Some kits approved for smear (-) sputum, some not.
  - Can detect 50-80% of AFB smear-negative, culture-positive cases.
  - When clinical suspicion of TB is low, positive predictive value <50%.
- Guideline:
  - Routinely collect, process, and test.
  - At least one specimen, preferably the first, should be [appropriately process] and tested using an NAA test.

MMWR 2009 (January 16);58:7-10

## Treatment of Pulmonary TB

- How long?
- What drugs?
- How?
**TB Treatment: Duration (with Standard Regimen)**

- Most pulmonary: 6 months
- Lymph node: 6 months
- Pleural: 6 months
- Pericardial: 6 months
- Disseminated: 6 months
- GU: 6 months
- Peritoneal: 6 months

**TB Treatment: Duration (with Standard Regimen)**

- Special pulmonary situations
  - Sputum culture (+) at 2 months and cavity:
    - 9 months
  - Adult smear (-), culture (-):
    - 4 months
- Bone/joint: 6-9 months
- CNS: 9-12 months

**Hypothetical Model of TB Chemotherapy**

- 3 “Populations” of bacilli in cavity TB
- Variables of these populations: **avermicid or metronidazole**

**Bactericidal Activity and Sterilizing Effect**

- Pop A: Rapidly multiplying (bacilli)
- Pop B: Slowly multiplying (avermicid or metronidazole)
- Pop C: Sterilizing (avermicid or metronidazole)
**Preferred TB Regimen for Pan-Sensitive Isolates (Standard Regimen)**

- First 2 months: RIPE
  - Rifampin
  - Isoniazid
  - Pyrazinamide
  - Ethambutol (stop if RIF susceptible)
- Final 4 months: RI

**Effectiveness of Standard Regimen**

<table>
<thead>
<tr>
<th>Initiate</th>
<th>Mo.</th>
<th>Continue</th>
<th>Mo.</th>
<th>Relapse (%)</th>
<th>C (-) 2 mo.</th>
<th>n</th>
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<tr>
<td>RIF</td>
<td>2</td>
<td>RI</td>
<td>4</td>
<td>3.4</td>
<td>85</td>
<td>116</td>
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<td>RIF</td>
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<td>RI</td>
<td>4</td>
<td>4.1</td>
<td>--</td>
<td>330</td>
</tr>
<tr>
<td>RIF</td>
<td>2</td>
<td>RI</td>
<td>4</td>
<td>2.9</td>
<td>90</td>
<td>140</td>
</tr>
<tr>
<td>RIF</td>
<td>2</td>
<td>RI</td>
<td>4</td>
<td>3.5</td>
<td>80</td>
<td>206</td>
</tr>
<tr>
<td>RIF</td>
<td>2</td>
<td>RI</td>
<td>4</td>
<td>6.5</td>
<td>--</td>
<td>337</td>
</tr>
<tr>
<td>RIFPE</td>
<td>2</td>
<td>RI</td>
<td>4</td>
<td>2.5</td>
<td>--</td>
<td>132</td>
</tr>
</tbody>
</table>


**TB Recurrence Rates: Meta-Analysis**

Korenromp E et al; Clinical Infect Dis 2003;37:101
TB: Diagnosis and Treatment

October 212, 2009

**TB Relapses in 6-Month Regimen**

- Twice weekly RI in continuation phase
  - Cavity, culture (+) at 2 months: 21% (48)
  - Cavity, culture (-) at 2 months: 5% (150)
  - No cavity, culture (+) at 2 months: 6% (17)
  - No cavity, culture (-) at 2 months: 2% (181)

*Lancet* 2002;360:528-534; *MMWR* 2003;52:35

Similar findings also in two prior studies

**Extend Treatment to 9 Months**

- Combination of cavitary disease and positive culture at 2 months.

**Isolated or Combined INH Resistance**

- World-wide resistance to INH in 2005 was about 8%.
- Major outliers: Kazakhstan (43%); Tomsk Oblast (Russia); 29%; Latvia (29%); Israel (26%); Lithuania (25%); Liaoning Province (China) 25%; North Arcot (India) 23%; Estonia (23%)
- Indiana: Last 5 years 27/671 (4.0%); 2007 10/129 (7.8%)

INH Resistant TB: Can Still Use 6-Month Therapy

- As long as isolates remain susceptible to rifampin and two other drugs, six month regimens are effective.
- With rifampin + 2 or more other active drugs, in 12 studies done in Africa, Hong Kong, and Singapore, success rate for 6-month regimens was over 95%. (n ~ 246 patients)
- In 11 patients, rifampin resistance was present, and 5 failed treatment.


Moxifloxacin vs INH: 2-Month Results: Culture-Negative Sputa

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>S (+)/TOTAL</th>
<th>% S (+)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIPE</td>
<td>90/164</td>
<td>54.9%</td>
<td>0.37</td>
</tr>
<tr>
<td>RMPE</td>
<td>99/164</td>
<td>60.4%</td>
<td></td>
</tr>
</tbody>
</table>

Dorman S et al., AJRCCM 2009;180:273

Rifampin Resistance: 6-Month Course Not Adequate

- Short course (6-month) treatment cannot be used for any rifampin resistant isolate.
- For isolated rifampin resistance, use 12 – 18 months of INH, ethambutol, fluoroquinolone supplemented by pyrazinamide during first two months. INH + PZA + streptomycin for 9 months can work but is difficult for patients to tolerate.
- For INH and rifampin resistance, use 18 – 24 months of pyrazinamide, ethambutol, fluoroquinolone, streptomycin.

ATS/CDC/IDSA Guidelines. MMWR 2003;52:69
Culture-Negative Smear-Negative Pulmonary Tuberculosis in Adults

- U.S.: ~15% of pulmonary TB is culture (-)
- 4-month RI (rifampin + isoniazid) regimen → 99% success rate (1.2% relapse rate at ~44 months)  
  (Dutt et al., ARRD 1989;139:867-870)
- ATS/IDSA/CDC guidelines recommend RIPE for first 2 months then RI for 2 months.
- AFB smear (+) culture negative cases (clinically highly suspicious for TB) should be treated with 6-month regimen.

Time to Relapse in TB (HIV (-))

Korenromp et al; Clinical Infect Dis 2003;37:101

TB Risk of Relapse by Dosing Schedule

<table>
<thead>
<tr>
<th>IP</th>
<th>CP</th>
<th>N</th>
<th>Cavity</th>
<th>No Cavity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cl2m+</td>
<td>Cl2m-</td>
</tr>
<tr>
<td>Daily</td>
<td>Daily</td>
<td>1554</td>
<td>6.0%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Daily</td>
<td>3xW</td>
<td>410</td>
<td>6.1%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Daily</td>
<td>2xW</td>
<td>506</td>
<td>15.6%</td>
<td>5.7%</td>
</tr>
<tr>
<td>3xW</td>
<td>3xW</td>
<td>1853</td>
<td>14.5%</td>
<td>5.3%</td>
</tr>
<tr>
<td>2xW</td>
<td>2xW</td>
<td>108</td>
<td>2.5%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

Relative Relapse Risk All Patients

Chang KC et al., AJRCCM 2006;174:1154  
(Systematic Review)
TB Drugs: Pipeline

- Fluoroquinolones: moxifloxacin (Ph 3)
- Oxazolidinones: linezolid
- Diarylquinolone (TMC207) (Tibotec/J&J) (Ph 2)
- Nitroimadazoles (OPC67683; PA824) (Otsuka; Pathogenesis) (Ph 2; Ph 2)
- Pyrrole (LL3858) (Lupin) (Ph 1)
- Diamine (ethambutol-like) (SQ109) (Squibb) (Ph 1)

Summary

- Treatment is usually RIPE X 2 months then RI X 4 months
- Promising new drugs are in the pipeline