Treatment of TB

David Griffith, MD
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TB for Community Providers
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Phoenix, Arizona

David Griffith, MD has the following disclosures to make:

• No conflict of interests
• No relevant financial relationships with any commercial companies pertaining to this educational activity
Medical Management of Tuberculosis

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University of TX Health Science Center, Tyler
Assistant Medical Director
Heartland National TB Center

Diagnosis of Tuberculosis

• Clinical suspicion is the single most important factor in the timely diagnosis of tuberculosis.
• The greatest risk for nosocomial transmission of tuberculosis is exposure to an undiagnosed case of TB.
• There is no diagnostic substitute for thinking about the diagnosis.
• Clinical judgment is second only to clinical suspicion in importance (know when to pull the trigger)
Reasons a Diagnosis of TB is Missed or Delayed

• Patient is diagnosed as a community acquired pneumonia and responds to a fluoroquinolone (more than one course required for FQ resistance)
• Atypical clinical and radiographic picture
• Extrapulmonary disease
• Clinician does not consider TB as a diagnostic possibility (PCP, ED, specialist, radiologist)
Standard Components of TB/LTBI Evaluation

- If TST or IGRA Positive
  - Patient History
  - Physical examination
  - Radiologic evaluation
  - Laboratory?

Patient History

- Symptoms
  - Fever
  - Chills
  - Night Sweats
  - Weight Loss
  - Cough
  - Productive Cough
  - Hemoptysis

- PMH:
  - Diabetes
  - HIV
  - Other Immunosuppression
  - Silicosis
  - Drug/alcohol/tobacco
  - TB exposures or Risk?
Clinical Evaluation: CXR

- Findings associated with higher risk of TB
  (require further evaluation and possible treatment for TB)
  - Noncalcified nodular lesions
  - Fibrotic scars

- Findings consistent with TB disease
  (require further evaluation and possible treatment for TB)
  - Enlarged hilar, mediastinal or subcarinal lymph nodes
  - Atelectasis
  - Alveolar consolidation
  - Interstitial infiltrates, cavitory and non-cavitary
  - Pleural effusion
  - Focal mass
  - Hyperinflation in children

- If CXR is abnormal, do not just treat for LTBI!
- You must rule out Active TB!

Atypical Presentation of TB

- HIV infection, chronic renal disease, diabetes, immunosuppression may alter presentation
  - CXR may be atypical; lower lobe infiltrate, adenopathy or completely normal
  - Negative TST or QTF Gold
  - Negative smear in up to 50%
  - Atypical clinical presentation
TB and AIDS: Radiographic Appearance

• The radiographic manifestations of HIV-associated pulmonary TB are dependent on the level of immuno-suppression.
  – Relatively intact cellular immune function (CD4 > 200): radiographic findings similar to non-HIV infected individuals (upper lobe, cavitary disease)
  – Severe immunosuppression (CD4 < 200): findings c/w primary disease or normal chest radiographs or dissemination with miliary pattern or extrapulmonary disease

PRIMARY TUBERCULOSIS
PRIMARY TUBERCULOSIS

MILIARY TUBERCULOSIS
REACTIVATION TB

21st Century Algorithm

1. Process Specimen
   - AFB Smear Microscopy: 24 hours

2. Inoculate Media
   - Amplification-based Tests
   - Species Identification: 2 - 6 weeks
     - Drug Susceptibilities: 2 - 3 weeks

3. Molecular DST
TB Diagnostic Methods Related to # of Bacilli in Sputum

Specimen Quality

• Accurate laboratory results are directly related to the quality of the specimen
• GOOD sputum
  – Recently discharged material from the bronchial tree, with minimal amounts of upper respiratory tract secretions
    • Well coached patient, collect at least 3ml
    • Label tube and form - indicate test:
      – initial Dx: NAAT
      – isolation release: smear only
      – drug resistance suspected?
• Transport to lab cool and quickly
Acid Fast Microscopy (AFB Smear)

- Rapid & universally available
  - Used to support diagnosis and identify need to isolate
  - Detects the most infectious cases
  - Helps monitor response to therapy
  - Identify priority cases for nucleic acid amplification (NAA)
- Not sensitive
  - misses ~50% of TB
- Not specific in low TB prevalence areas (e.g. Texas)
  - Positive smear may be NTM
- Highly specific where TB is highly prevalent

AFB Smear

<table>
<thead>
<tr>
<th>CAP</th>
<th>ATS</th>
<th>Interpretation</th>
<th>AFB/ml sputum</th>
<th>Infectiousness of patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative</td>
<td>negative</td>
<td>negative</td>
<td>&lt;5,000</td>
<td>probably not infectious</td>
</tr>
<tr>
<td>1 or 2 per smear</td>
<td>1 or 2 per smear</td>
<td>weakly positive</td>
<td>~5,000</td>
<td>probably infectious</td>
</tr>
<tr>
<td>&lt;1 per field</td>
<td>1+</td>
<td>moderately positive</td>
<td>~10,000</td>
<td>probably infectious</td>
</tr>
<tr>
<td>1-10 per field</td>
<td>2+</td>
<td>moderately positive</td>
<td>~100,000</td>
<td>probably infectious</td>
</tr>
<tr>
<td>&gt;10 per field</td>
<td>3+</td>
<td>strongly positive</td>
<td>~1,000,000</td>
<td>probably very infectious</td>
</tr>
<tr>
<td></td>
<td>4+</td>
<td>strongly positive</td>
<td>&gt;1,000,000</td>
<td>probably very infectious</td>
</tr>
</tbody>
</table>
Nucleic Acid Amplification Tests (NAAT)

• Tiny amounts of DNA/RNA are amplified (copied) until there is enough for easy detection

• DNA/RNA is examined
  • Identification
  • Detection of Drug Resistance

• Test turnaround time measured in hours

Nucleic Acid Amplification Tests (NAAT)

• Detects *M. tuberculosis* complex nucleic acids; does not distinguish between live and dead bacilli
  • For initial Dx specimens only
  • Not suitable for follow-up specimen or monitoring

• Sensitivity
  • >95% for AFB smear-positive TB patients
  • 55-75% of AFB smear-negative, culture-positive TB

• Does not replace culture
**CDC Recommendations for NAAT**

*MMWR, 2009, 58:7-10*

- “NAAT should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities”

- NAAT now recommended as standard practice!

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**Why Use A NAAT ?**

- Confirms AFB + case as M TB

- If AFB + case is NAAT negative on 2 specimens
  - **Suspect this is not M TB**
    - Suspend Contact investigation and
    - Hold TB treatment unless TB strongly suspected.

- If patient is not strongly suspected as M TB and is NAAT negative x 2,
  - **Remove from isolation.**
Who Should be Tested?

• CDC recommends NAAT on 1st sputum of every TB SUSPECT for whom the test result would alter case management or TB control activities
  
  – NAAT should NOT be ordered routinely if:
    • Hospital/commercial lab already has NAAT+
    • Clin. Susp. is extremely high, e.g. pt. symptomatic, smear+, Dx=TB, on Rx
      – i.e. when NAAT+ or – result would not change actions
    • Clin. Susp. very low, e.g. other Dx probable, spec is to r/o TB
  
• Definition of a “TB suspect” case can vary among providers

• TB programs, clinicians, and laboratorians must collaborate to develop criteria/definitions & policy for patients to be tested

How Do I Get a NAAT from the State Lab?

DSHS automatically performs NAAT on smear positive respiratory specimens, effective 3/1/2013
Cepheid GX MTB/Rif

- Practical NAAT
  - 15 minute entry-level technician versus 3-4 hrs using a highly skilled technician
- Highly accurate for smear positive TB
- Sensitivity uncertain for smear negative TB
- Limited data
  - Rifampin-R
  - Extra-pulmonary (CSF, gastric..)

AFB Culture

- Broth based system
  - MGIT, Trek, MB/BacT
- Solid medium
  - Purity
  - Middlebrook agar & LJ
### AFB Culture

- More sensitive than smear
  - 5,000 to 10,000 AFB/ml for smear
  - 10 to 100 AFB/ml for culture
- Required for drug susceptibilities & genotype
- Requires a quality specimen
- Positive for only ~85-90% of PTB
  - May be negative due to contamination
- Lengthy
  - 1-6 weeks by liquid media
  - 2-8 weeks by solid media

### Rapid Culture Identification

- DNA probes
  - GenProbe
- HPLC (High performance liquid chromatography)
- Amplification-based tests
  - Lab Developed Tests (“home brew”)
    - Real time PCR
    - Molecular Beacons
  - DNA Sequencing
  - Line Probes
# How Do NAAT and Culture Compare?

<table>
<thead>
<tr>
<th></th>
<th>NAAT</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial diagnosis</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Detect Non-viable Mtb</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Suitable to Monitor Treatment</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Detect Drug Resistance</td>
<td>Some</td>
<td>Yes</td>
</tr>
<tr>
<td>Detect Drug Susceptible</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Genotype for Epidemiology</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Current NAATs are not sensitive enough to rule-out TB and they cannot replace culture.

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## M. tuberculosis complex

- All positive by NAAT & AccuProbe

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of Texas strains 2005-2010*</th>
</tr>
</thead>
<tbody>
<tr>
<td>– <em>M. tuberculosis</em></td>
<td>8,058 (98.6%)</td>
</tr>
<tr>
<td>– <em>M. bovis</em></td>
<td>79 (1.0%)</td>
</tr>
<tr>
<td>– <em>M. bovis</em> BCG</td>
<td>15 (0.2%)</td>
</tr>
<tr>
<td>– <em>M. africanum</em></td>
<td>17 (0.2%)</td>
</tr>
<tr>
<td>– <em>M. caprae</em></td>
<td></td>
</tr>
<tr>
<td>– <em>M. microti</em></td>
<td></td>
</tr>
<tr>
<td>– <em>M. canettii</em></td>
<td></td>
</tr>
<tr>
<td>– <em>M. pinnipedii</em></td>
<td></td>
</tr>
</tbody>
</table>

* Data: Texas DSHS Laboratory Genotype Database
Drug Susceptibility Testing (DST) of *Mycobacterium tuberculosis* Complex

Current Recommendations

- Initial isolate should be tested against primary or first-line drugs (FLD)
  - INH, RMP, EMB, PZA
- For isolates resistant to RMP or to any 2 FLDs, test all second-line drugs
  - To include FQ, AMK/KAN, CAP, ETH, PAS
  - Not cycloserine; unreproducible

Turnaround Time for MTBC Drug Susceptibility Testing (DST)

- Specimen receipt to 1st line DST by rapid broth: 4 to 5 weeks
- 2nd line drugs by rapid broth or agar proportion: additional 2 to 4 weeks
- Referral to reference lab adds more time
- Molecular methods can detect resistance to 1st & 2nd line drugs within 1 to 2 days
Detection of Genetic Mutations Causing Resistance

- Examining DNA of specific genes for mutations known to be associated with conventional phenotypic resistance
- Rapid - analysis takes less 1 day
- Can be done on isolates or directly on NAA+ specimens!

MTBC Molecular Drug Resistance Testing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>% of Resist.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>rpoB</td>
<td>97%</td>
</tr>
<tr>
<td>INH</td>
<td>katG &amp; inhA</td>
<td>86%</td>
</tr>
<tr>
<td>EMB</td>
<td>embB</td>
<td>79%</td>
</tr>
<tr>
<td>PZA</td>
<td>pncA</td>
<td>86%</td>
</tr>
<tr>
<td>F-quinolones</td>
<td>gyrA</td>
<td>80%</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>rrs</td>
<td>~75%</td>
</tr>
</tbody>
</table>
CDC Molecular Detection of Drug Resistance (MDDR)

- Implemented Sept 2009 for isolates
- Expanded June 2012 for NAA+ specimens
- Test Indications
  - Known/suspect DR case or contact to DR case
  - Previous TB Treatment
  - Patient from area with high rate of DR TB
  - Mixed or nonviable culture

CDC Molecular Detection of Drug Resistance (MDDR)

- Provides 48-72 hr DNA sequence analysis for drug resistance prediction
- MDDR supplements, not replaces, conventional DST
  - Used alone, MDDR and conventional DST are imperfect
  - Used together, accuracy of the detection of drug resistance can be improved.
- Conventional DST results are still essential to confirm susceptibility to individual drugs.
21st Century Algorithm

- Process Specimen
  - 24 hours
  - AFB Smear Microscopy

- Amplification-based Tests
- Inoculate Media
- 2 - 6 weeks
- Species Identification
- 2 - 3 weeks
- Drug Susceptibilities
- Molecular DST

When should I consider my specimen delayed?

- Specimen received in the lab
- At 24 hours, expect smear results
- At 48 hours, expect results of NAAT or Molecular DST
- At 21 days, expect a culture ID (TB or NTM) (TB or NTM)
- At 28 days, expect 1st line susceptibility results, expect 2nd line 4 weeks after requested
- At 6-8 weeks, expect the culture to be finalized if negative

Day: 0 1 2 3 21 28 42-56
Treatment of Tuberculosis

American Thoracic Society, CDC, and Infectious Diseases Society of America

USPHS/IDSA Evidence-Based Rating Scale

- Strength of Recommendation
  - A = preferred
  - B = acceptable alternative
  - C = offer when unable to give A or B
  - D = should generally NOT be offered
  - E = should NEVER be offered

- Quality of Supporting Evidence
  - I – randomized clinical trial
  - II – clinical trial, not randomized
  - III – expert opinion
Short course treatment of drug susceptible TB

• Intensive phase
  – 4 drugs INH, rifampin, PZA, ethambutol
  – 8 weeks
    • Daily
    • Daily then BIW / TIW
    • TIW
• Continuation phase
  – 2 drugs INH, rifampin
  – 18 or 31 weeks
    • Daily
    • TIW
    • BIW

Duration of treatment

• 6 months
  – Requires INH, rifampin throughout and PZA during the initiation phase

• 9 months
  – If PZA was not used
  – Silico-TB
  – Prolongation to decrease risk of relapse
Treatment of Culture Positive Pulmonary Tuberculosis

**Regimens Rated A-I (HIV Uninfected)**

**Initial Phase**
2 mo H,R,Z,E *daily* (56 doses, 8wks) or
2 mo H,R,Z,E *5x/wk* (40 doses, 8wks) *then*

**Continuation Phase**
- 4 mo - H,R *daily* (126 doses, 18 wks) or
- 4 mo – H,R *5x/wk* (90 doses, 18 wks) or
- 4 mo – H,R, *2x/wk* (36 doses, 18 wks)

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**Regimens Rated A-II (HIV Uninfected)**

**Initial Phase**
2 weeks H,R,Z,E *daily* (14 doses) *then*
6 Weeks H,R,Z,E *twice weekly* (12 doses) *then*

**Continuation Phase**
4 months  H, R *twice weekly* (36 doses, 18 weeks)

Intermittent dosing by DOT only!
Treatment of Culture Positive Pulmonary Tuberculosis

Regimens Rated **A-II** (HIV Uninfected)

**Initial Phase**
2 weeks H,R,Z,E  5x per week  (10 doses) then
6  Weeks H,R,Z,E twice weekly (12 doses) then

**Continuation Phase**
4 months  H, R twice weekly (36 doses, 18 weeks)

Intermittent dosing by DOT only!

---

Treatment of Culture Positive Pulmonary TB

– THRICE WEEKLY – “HONG KONG” REGIMEN
  » Regimen Rated **BI** (HIV uninfected)

**Initial Phase**
• 2mo – H,R,Z,E 3x/week (24 doses, 8weeks)

**Continuation phase**
• 4mo – H,R 3x/wk (54 doses, 18 weeks)

Intermittent dosing by DOT only!
Newer drugs for treatment of TB

- Newer rifamycins
  - Rifabutin
    - HIV – TB
    - Unable to tolerate rifampin due to side effects
  - Rifapentine – long half life
- Fluoroquinolones: levofloxacin, moxifloxacin
  - Resistance to first line agents
  - Intolerance to first line drugs

Strategies to promote good outcome

- Patient centered care
- DOT provided by health department
- Monthly clinical evaluation in outpatient setting
  - Early detection of side effects
  - Educate and promote adherence to therapy
  - Address comorbidities that impact treatment response
- Monthly sputum until 2 consecutive negative cultures
Strategies to promote good outcome

• Assess patient related risk factors for poor outcome
  – Severity of disease
    • High bacillary burden
  – Co-morbid conditions
    • Liver disease
    • HIV
    • Poorly controlled DM
    • Malignancy
  – Adherence to therapy

Useful strategies

• Prolongation of treatment in delayed responders
• Increase frequency of dosing
• Evaluation and management of delayed response
• Serum drug level monitoring
Populations of Mycobacteria

Importance of the Intensive Phase

- Actively dividing bacterial subpopulation
  - INH
    - Most potent drug for killing actively dividing bacteria
    - Associated with decrease in infectiousness
Importance of the Intensive Phase

• Persisters
  – Revert back and forth to other subpopulations
  – Source of relapses
  – Rifampin is the only first line drug with activity against persisters

• Optimizing bactericidal and sterilizing activity early will minimize overall bacterial load present during continuation phase

2 month culture conversion

• Surrogate marker of sterilizing activity of drug regimen
• Used to predict likelihood of relapse
• Commonly considered to be 80% in 4 drug regimens
• More recent TBTC studies show lower rates
  – 71% Moxifloxacin vs Ethambutol*
  – 60% Moxifloxacin vs INH**

*Study 27 AJRCCM 2006
** Study 28 AJRCCM 2009
Adverse outcomes

• Delayed response
  – Culture conversion after 3 months effective regimen

• Treatment failure
  – Persistent + culture after 4 months treatment

• Relapse
  – Symptoms or culture positive after completion of treatment

• Development of drug resistance

Delayed Response
Culture Positive at 3 Months

• TB lab should automatically repeat susceptibility studies on last positive culture - check to be sure

• Assess adherence

• Consider serum drug levels

• Evaluate response to therapy
  – Clinically and radiographically

By the time you know this it is 4 months into therapy!
Treatment Failure
Culture Positive at 4 Months

Clinical evaluation
Repeat susceptibility studies
• On last positive culture
• And request on a “new sputum culture” now
  – Ask for molecular detection of drug resistance

Serum drug levels if not previously done

Augment therapy
• Add at least two and preferably three new drugs to which the isolate is likely to be susceptible
• Even if no clinical or radiographic evidence of failure

MMWR Treatment of Tuberculosis 2003; 52

Relapse

• Circumstance in which a patient becomes and remains culture-negative while receiving antituberculosis drugs but at some point after completion of therapy, either becomes culture-positive again or experiences clinical and radiographic deterioration consistent with active tuberculosis

• Try to identify “WHY” your patient relapsed so you can do it right this time!
TBTC STUDY 22: RATE OF FAILURE or RELAPSE, BY REGIMEN, SPUTUM CULTURE, AND CHEST RADIOGRAPH

End of Therapy (EOT) Cavity: A Risk Factor for Relapse

Figure 2: Proportion of subjects with tuberculosis relapse by findings on early and EOT CXR. EOT = end of treatment; CXR = chest radiograph.
Lack of Weight Gain and Relapse Risk, TBTC Study 22

- Relapse risk high in those underweight at diagnosis 19.1% versus 4.8%

- Among pts underweight at diagnosis, if weight gain ≤ 5% after 2 months of treatment:
  - Relapse risk 18.4% vs. 10.3%
  - If also cavitary disease: 18.9%
  - If cavitary and + 2 month culture: 50.5%


Risk factors for relapse

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Rate</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cavitary and culture positive 8 weeks</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Cavitary</td>
<td>4.7%</td>
<td>4.7</td>
</tr>
<tr>
<td>Culture positive 8 weeks</td>
<td>5.9%</td>
<td>5</td>
</tr>
<tr>
<td>Non Hispanic White race</td>
<td>13.5</td>
<td>2.4</td>
</tr>
<tr>
<td>* &gt;10% ideal body weight and failure to gain weight &gt; 5% at 8 weeks</td>
<td>18.4%</td>
<td>3.8</td>
</tr>
<tr>
<td>^ Beijing strain in Asia Pacific Islander</td>
<td></td>
<td>OR:11</td>
</tr>
</tbody>
</table>

Lancet 2002; 360:528
*AJRCCM 2006; 174:344
^Emerging Infect Dis 2009; 15:1061
Treatment Related Risk Factors for Early Relapse of TB

- Evaluation of 113 cases of relapsed TB, matched with case controls
  - Non-cavitary TB, thrice weekly, 6 mo relapse rate: 1.1%

- Cavitary TB relapse rates:
  - Thrice weekly, 6 mo: 7.8%
  - Daily, 6 mo: 3.3%
  - Extended thrice weekly: 0.5%
  - Extended daily: 0.4%
    - Either intensive phase or CP was beneficial

Am J Respir Crit Care Med. 2004; 170: 1124-30

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Treatment Related Risk Factors for Early Relapse - Dosing Intensity

Risk of relapse of 6 month regimen and dosing schedule, controlling for initial cavitation and 2 month sputum culture

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily IP, thrice weekly CP</td>
<td>1.6 (0.6 – 4.1)</td>
</tr>
<tr>
<td>Daily IP, twice weekly CP</td>
<td>2.8 (1.3 - 6.1)</td>
</tr>
<tr>
<td>Thrice weekly IP, CP</td>
<td>2.8 (1.4 – 5.7)</td>
</tr>
<tr>
<td>Daily IP, weekly rifapentine</td>
<td>5.0 (3.3-.15.3)</td>
</tr>
</tbody>
</table>

Am J Respir Crit Care Med 2006; 174: 1153
Treatment Related Risk Factors for Early Relapse-Dosing Intensity

• In cavitary disease (regardless of 2 month culture), risk of relapse of 6 month regimen > 5% except,
  – Daily IP, CP
  – Daily IP, thrice weekly CP

• In cavitary disease and 2 month culture +, risk of relapse is 6% in
  – Daily IP, CP
  – Daily IP, thrice weekly CP

Am J Respir Crit Care Med 2006; 174: 1153

Treatment of TB and Optimal Dosing Schedules

Kwok Chiu Chang, Chi Chiu Leung, Jacques Grosset, Wing Wai Yew
Thorax 2011 66:997-1007

Systematic Review of 32 articles – 9 systematic reviews, 8 controlled studies, 9 PK-PD studies, and 6 animal studies.

Levels of evidence and grades of recommendations assigned according to clinical evidence with reference to Scottish Intercollegiate Guidelines
Non HIV related TB (11 studies)

- Suggests that intermittent dosing reduces TB treatment efficacy shown by a higher risk of relapse or failure

- Negative impact most prominent in presence of cavities

- Standard 6 mo regimen - no significant difference between daily throughout and daily in initial phase

**Level of evidence: 1+**

**Grade of recommendation: “A”**

- Avoid intermittent doses, especially in initial phase and in presence of cavities

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TB With INH Resistance (2 studies)

- Suggests that dosing intermittency reduces TB treatment efficacy as shown by:
  - Higher risk of treatment failure, relapse or acquired drug resistance

**Level of evidence 1+**

**Grade of evidence: “A”**

- Avoid dosing intermittency, especially in the initial phase in the presence of INH resistance
HIV related TB (3 studies)

• Suggests intermittent Rx, especially in initial phase reduces treatment efficacy as shown by
  – a higher risk of treatment failure, relapse, or acquired Rifampin resistance

Level of evidence 1+
Grade of recommendation “A”
  – Avoid intermittency, especially in the initial phase in HIV TB

Prolongation of Continuation Phase

Continuation phase increased to 7 mo if initial CXR is cavitary & culture is positive at 2 mo

Treatment of Tuberculosis MMWR 2003

• Rational for Extending Therapy
  – Continuation of PZA for an additional 2 months was not helpful in drug susceptible disease

  – Prolongation of continuation phase by 2 months decreased relapses in silico-tuberculosis from 20% to 2%
Effect of Prolonging Therapy on Treatment Failure or Relapse

**Treatment of Silico-tuberculosis**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SHRZ - 6mo*</th>
<th>SHRZ – 8mo*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=49)</td>
<td>(n=50)</td>
</tr>
<tr>
<td>Relapse</td>
<td>20%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Three times weekly therapy

Am Rev Respir Dis 1991;143:262-267

Factors Associated with Relapse of Tuberculosis

**Disease related**
- Cavitation
- Bilateral disease
- Sputum culture at 2 months
- Low body weight
- Lack of weight gain
- Drug resistance
- ?Beijing strain in Pacific Islander
- Other comorbidities

**Treatment related**
- DOT
- Adherence
- Dosing intensity
- Duration of therapy
- Use of rifamycin
In the Treatment of TB, You Get What You Pay For...

• “A consistent theme has begun to appear: more extensive disease requires more treatment, and the fewer total doses, the higher the risk that treatment will prove inadequate”
  
  - What should we conclude?
    • First: More treatment means more cures
    • Second: Programs need to consider some individualization of therapy
    • Third: Should not deter us from intermittent therapy but should remind us of need for sophisticated management based on case-specific circumstances
      - Should not be surprised that individuals differ in their response.


Tailoring Treatment Regimens

• **Prolong** continuation phase when:
  - Positive 2 month culture with cavitary disease
  - Extrapulmonary disease
    • Meningitis
    • Disseminated disease in children
  - HIV TB in children and adolescents

ATS, CDC, IDSA: Treatment of Tuberculosis 2003
Tailoring Treatment Regimens

- **Consider** - Prolongation of continuation phase:
  - Slow clinical or radiological response
  - Positive 2 month culture **OR** cavitary disease?
  - End of therapy (EOT) cavity present
  - >10% below ideal body weight?

  ATS, CDC, IDSA: Treatment of Tuberculosis 2003

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Tailoring Treatment Regimens

- Daily IP
  - cavitary disease
  - HIV TB
  - INH resistance
Relapsed Tuberculosis Management Strategies

- Most relapses occur within the first 6 – 12 months after stopping therapy but some occur 5 or more years later
- Microbiological Confirmation of Relapse Should be Pursued Vigorously
  - Confirm relapse bacteriologically
  - Identify drug susceptibility pattern of isolate
  - Use DNA fingerprinting to identify new infection causing the disease versus relapse

ATS, CDC, IDSA: Treatment of Tuberculosis 2003

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Relapsed Tuberculosis Management Strategies

- Nearly all drug susceptible patients who were treated with a rifamycin and received DOT will relapse with drug susceptible organisms

Treat with standard RIPE regimen

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Relapsed Tuberculosis Management Strategies

• If culture & susceptibility studies (those treated in other countries) were not done but treatment given by DOT
  – Usual treatment with RIPE
    • Watch carefully for clinical deterioration -
  – Consider an expanded regimen if immune suppressed, significantly ill, or extensive disease
    • Use at least 2 drugs to expand the regimen
    • (Molecular testing for drug resistance)

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Relapsed Tuberculosis Management Strategies

• Suspect drug resistance if:
  – Patients treated with self administered therapy
  – Patient was poorly adherent
  – Patient deteriorates clinically or radiographically during initial weeks of treatment

• Do molecular testing for drug resistance
  • Consider expanded regimen, especially if immune suppressed
  • Add at least 2 (fluoroquinolone and an injectable)
Treatment in Special Situations

Active TB During Pregnancy

• Diagnosis may be difficult
  – Respiratory symptoms common in late pregnancy
  – Reluctance to do a CXR
  – Extra-pulmonary disease is even more difficult

• Outcomes for BOTH mom and baby are improved with treatment during pregnancy

• Infection control is important at time of delivery if mom is still infectious
Active TB During Pregnancy

• Treatment:
  – INH, Rifampin, Ethambutol x 9 months
    • Stop ethambutol if susceptible to INH and rifampin
  – PZA only if drug resistance is present
    • PZA regarded as safe by most countries in world

• Follow carefully for hepatotoxicity- risk is increased
  – During pregnancy
  – Three months postpartum
TB and DM

• 65 male, HbA1C, former smoker
  – Large soft tissue abscess R thigh
  – Abnormal CXR – RUL thick walled cavity
  – Sputum smear negative x3
  – Bronch: chronic inflammation and +AFB
  – Pansensitive
  – Standard therapy one week later and discharged

TB and DM

• Slow clinical improvement and cultures remained positive
• Switched to INH-rifampin after 8 weeks IP
• On 5th month – sputum turned smear + and later reported INH R
• Rifampin, Ethambutol, PZA, fluoroquinolone and streptomycin
• Side effects from strep and capreomycin with nausea, cramps and aches
TB and DM

- Endocrine attending started on insulin therapy
- Strep and capreomycin stopped due to adverse effects
- PZA stopped due to uric acid 9
- DST: only INH resistance
- Rifampin, FQ, ethambutol continued to 9 months after INH R developed
- Continued to complain of muscle pain in the limb girdles
Tuberculosis Drug Serum Level Monitoring Recommended

- Delayed response to therapy
- Advanced AIDS with evidence of malabsorption
- Seriously ill patient to maximize therapy
- ? Diabetics
- Toxicity evaluation
- Use of second line drugs
- Acquired drug resistance
- Relapse
- Potential for drug-drug interactions
- Renal and hepatic insufficiency

Management of TST + Persons With an Abnormal CXR and – AFB Smear

- Isolated CXR with nodules and/or fibrotic lesions:
  - If no symptoms - wait
    - Collect sputum culture
    - Evaluate for symptoms
    - Repeat CXR
  - If CXR stable at 2 – 3 months and cultures are negative, treat as LTBI

- Isolated CXR with nodules and/or fibrotic lesions:
  - If patient has any signs or symptoms of TB disease: patient is a TB suspect
    - Start 4 drugs
  - Never start a single drug in a patient with possible active TB
Culture Negative TB

- TB suspect with positive TST or IGRA
  - Risk factors for TB
  - Abnormal CXR
    - Usually – clinical symptoms

- All cultures are negative

- Classify based on clinical and/or radiograph response to treatment at 2 months
  - **Clinical or CXR improvement – Culture Negative TB**
  - Treat for 4 months (children and HIV + 6 months)
  - RIPE for 2 months, then RIE +/- PZA dependent on INH resistance

Management of Treatment Interruptions

- **Initial phase** of therapy
  - <14 days – complete standard # of doses
  - >14 days – restart from the beginning

- **Continuation phase**
  - >80% doses by DOT – if initial smear–, may stop
  - < 80% doses by DOT and/or initial smear +
    - Repeat culture
      - Management based on clinical and bacteriological factors.
Where to Get More Information

- HEARTLAND NATIONAL TB CENTER
  - 1-800-TEX LUNG: Medical Consultation and Technical Assistance Line
  - Future training courses
- CDC
- TB Educate
- TBresources.com