Photo shown:

Who is ???

TB “JA PERDY”
<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Latent TB</th>
<th>Clinical TB</th>
<th>Special Features</th>
<th>Drugs</th>
<th>TB Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>100</td>
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<tr>
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<tr>
<td>500</td>
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<td>500</td>
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<td>500</td>
</tr>
</tbody>
</table>
This adds 5% to 10% in yield in diagnosis
What is sputum induction; direct observed sputum evaluation; Bronchial lavage?
Sputum evaluation

Spontaneous Sputum

Supervised Sputum
“DOSE”

Induced Sputum

Related to pooling of specimens: Refrigeration OK
IUAT April 2011

Chang et al Eur Resp J 2008 May; (5) 1085-90
The issues

- Little supervision; the “give the cup” approach
- Bacterial contamination
- Only 30% positivity in the first sputum although incremental yield beyond 3 is doubtful
- (S:47%/C:74% to S:58%/ C: 90%)  
- Depends upon cavitary disease or non-cavitary disease
- Single vs. 24-72 hour pooled specimen: No difference except increased bacterial contamination (2%) increased to 15%

ILH data
451 times 3 sputum submitted on 426 patients since Nov 2008

**Smear Positive Inpatients (n=53):**
- 83% positive on first smear, 90.5% positive with 2 smears
- 9.4% (5 pts) not positive until 3rd smear (of these 5, 2 had TB)
  - Of the 5 pts who were not smear positive until 3rd sputum:
    - 2 with TB
      - 1 high suspicion (would have remained in isolation)
      - 1 low suspicion (HIV positive, discharged to hospice before 3rd sputum returned with diagnosis of PCP. He died the day the smear result became available)
    - 1 with M. kansasi
    - 2 with RG/MAC

**Culture Results**
- 26 (49%) with TB: 23 TB only, 2 TB/RG, 1 TB/MAC
- 15 (28.3%) with MAC: 12 MAC only, 3 MAC/RG
- 8 (15.1%) with M. kansasi
- 3 (5.7%) RG
- 1 (1.9%) Szulgai

# of sputum samples: Debate
Bullets

- 2 sputum smears as good as 3 even for infection control purposes but....
- Volume of sputum 5cc or more improves sensitivity
- If ES negative; SI adds up to 19–30 % in sensitivity in suspected cases
- FOB with Bronchial washing if less than 50 cc, there is no difference in sensitivity
- FOB with BAL better if return more than 50 cc and sensitivity increased if PCR also done

Ref: Thorax 2002: 57 1010
Nelson et al J Clin Micro 1999 36 (2)
Extraction of DNA; hybridization of labeled PCR products with oligonucleotide probes; according to the CDC, this must be performed on at least one respiratory specimen from each patient with clinical suspicion of TB, where diagnosis has not yet been established.
What are nucleic acid amplification tests?
3% to 7% of sputum specimens have this, 
Less than 50% of labs do this
What are tests for NAA inhibitors?
Molecular Methods

• STEPS
  1. Extraction of DNA
  2. PCR
  3. NA sequence amplification
  4. Hybridization of labeled PCR products with Oligo nucleotide probes

CID 2011 :52

“No home grown brew”
CDC recommends that standardized NAA testing be performed on at least one respiratory specimen from each patient with clinical suspicion of TB, where Dx has not yet been established, and for whom the result will alter management and TB control measures/contact investigations.

MMWR Jan 2009/58(01);7-10
NAA

Ampl MTB direct test
MTD (Gen-probe)
Enhanced Amplicor (Roche) test

Greater PPV /NPV and SS in smear positive cases ) 80-95%
Lower sensitivity and PPV in smear negative cases  50% appx
Earlier Detection
Less inappropriate use of FQ as empiric monotherapy for pneumonia
Reliance by MDs: 20-50% of cases
NAA testing should be considered as Critical test value notification
Report time less than 48 hours.
If clinical suspicion is low, do not do NAA as PPV low
If clinical suspicion moderate or high: single NAA negative should not be relied upon

MMWR Jan 2009
NAA inhibitors: Importance

- 3–7% sputum specimens have inhibitors
- 50–75 % labs do this test; probably less
### Interpretation

<table>
<thead>
<tr>
<th>CLINICAL SUSPICION</th>
<th>AFB smear</th>
<th>NAA result</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
<td>positive</td>
<td>positive</td>
<td>MTB (PPV 95%) Rx Isolate and Contact investigation</td>
</tr>
<tr>
<td>HIGH</td>
<td>Negative</td>
<td>positive</td>
<td>Repeat NAA; if positive or clinical suspicion high: Rx as TB as above</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>negative</td>
<td>Repeat; test for Inhibitors, if none This is probably MOTT If Inhibitors present NAA no use Decision to Rx ??</td>
</tr>
</tbody>
</table>

Adapted from AJRD 1997 #155 pg 1804
This is based on mycobacterial genomics and antigen specific T cell response. Antigenic targets include ESAT-6 and CFP-10.
What is IGRA test based on?
This is performed in homeless/transient resident population and has a higher PPV and NPV.
What is IGRA?
TIGRA* update

Advantages

- TIGRA preferred but TST acceptable for Homeless/Transitional Care/Substance abusers
- TST is preferred
- Equally acceptable:

Disadvantages

- Children less than 5 years of age
- Contact screening* (although higher PPV and NPV seen (3% vs 13% and 99% vs 100% when compared with TST)

ILH current priority list

- 5mm
- 1. Employees
- 2. Immune compromised patients
- 3. Patients with Hx of BCG
- 4. Specific cases where differential Dx of pneumonia includes TB or MAC
- 5. Referral from Transitional Homes/Shelters to UCC

Ref: MMWR/CDC Rep 2010: 59 (RR-5:1-28)
INTERFERON GAMMA RELEASE ASSAYS (IGRAs)

AN OVERVIEW
Two Disclosures

PERSONAL

Juzar Ali MB.,BS (MD); FRCP(C); FCCP

Interim LSU Public Hospital (ILH) & CLINICS System
Interim CEO /
Medical Director ; UMOB, 2025 Gravier St., 7th Floor NEW ORLEANS, LA 70112
Off: (504) 903 4900, 4907, 4917, Fax : 504 903 4952
Email: jali@lsuhsc.edu Cell : 504 444 3975

**Russell C. Klein, LSU-Alumni Professor of Clinical Medicine) ; **Faculty: Section of Pulmonary & Critical Care Medicine, LSUHSC 1901 Perdido, Suite 3205, MEB, New Orleans, LA 70112 LSUHSC Academic Office: 504 568 4634 Fax 504 568 4295

** Adjunct Professor, School of Nursing , LSUHSC
** Medical Director : Region 1 OPH ; Metro- Wetmore TB Clinics
** Adjunct Professor, Dept of Tropical Medicine, Tulane University School of Public Health and TM & Faculty:
Tulane University Dept of Preventive Medicine & Community Medicine
** Guest Faculty: Ege University & Hospital, Chest Unit , IZMIR Turkey
websites www.tbeducation.org www.tbinfo.lsuhsc.edu

INSTITUTIONAL

ACKNOWLEDGEMENTS

WETMORE TB CLINIC TEAM ; TB CONTROL OFFICE LEADERSHIP
Ms Maureen Vincent , Clinic Coordinator;
Drs Dean Ellithorpe & Louis Trachtman
Mr Charles DeGraw et team
Timeline of Advancements in TB Screening

- 1900
  - Tuberculin skin test developed by Dr. Charles Mantoux

- 2000
  - 2004 – US launch of QuantiFERON®-TB Gold
  - 2007 – US launch of QuantiFERON®-TB Gold In-Tube
  - 2008 – US launch of the T-SPOT®.TB test

- 2001
  - 2010 – US launch of approved overnight storage protocol for the T-SPOT®.TB test

T-SPOT is a registered trademark of Oxford Immunotec, Ltd.
Quantiferon is a registered trademark of Cellestis, Inc.
Tuberculin Skin Test (TST) vs Interferon-Gamma Release Assays (IGRAs)

Tuberculin Skin Test
- 2 visits required (minimum)
- Method: injection into skin
- Results affected by BCG
- Results in 48–72 hours
- Subjective results

IGRAs
- 1 visit required
- Method: blood draw
- Results not affected by BCG
- Next-day results
- Objective results
Updated CDC Guidelines

CDC guidelines allow the use of IGRA or TST for screening healthcare workers:

- “An IGRA or a TST may be used without preference for periodic screening of persons who might have occupational exposure to *M. tuberculosis* (eg, surveillance programs for healthcare workers).”
  - IGRA preferred testing for groups with low rates of return
  - IGRA preferred testing for individuals who have received BCG

- “Prior to implementing IGRAs, each institution and tuberculosis-control program should evaluate the availability, overall cost, and benefits of IGRAs for their own setting.”

- LSU/ILH guidelines: When DDx includes Pneumonia/MAC/MOTT
- & with employees screening

Commercially Available IGRAs

QuantiFERON®-TB Gold In-Tube
- ELISA technology
- Measures IFN-γ release
- “One and done”
- PI sensitivity: 88.2%
- PI specificity: 99.1%
- 3 specialized tubes
- Provides qualitative results
- Sample stability: 16 hours
- Can be run in hospital lab
- Available nationally through reference laboratories (eg, Quest)

The T-SPOT®.TB Test
- ELISpot technology
- Enumerates effector T cells
- “One and done”
- PI sensitivity: 95.6%
- PI specificity: 97.1%
- 1 standard tube
- Provides quantitative and qualitative results
- FDA-approved borderline category
- Sample stability: 32 hours
- Can be run in hospital lab
- Available nationally through Oxford Diagnostic Laboratories®

QuantiFERON®-TB Gold (QFT) Kit

• ELISA-based assay in a 96-well format
  – 1-mL control, mitogen, and TB antigen collection tubes for each patient
  – 3 wells used per patient; 26 wells per plate

• Uses specialized collection tubes requiring 0.8–1.2 mL of blood per tube

Blood Collection for QFT Testing

- Collection tubes include:
  - Nil control (grey cap)
  - TB antigen (red cap)
  - Mitogen control (purple cap)

- Tubes require shaking (10 times each) to mix blood with antigens coated on the inside of the tubes, but too much shaking could cause aberrant results.

- Blood in collection tubes must be incubated for 16–24 hours at 37°C within 16 hours of collection.

References:
The Science Behind QFT Technology

- Blood samples are incubated with antigen to stimulate IFN-γ release
- Plasma containing IFN-γ is harvested
- Plasma, standards, and conjugate are added to appropriate wells of QFT ELISA plate and incubated
- Substrate is added to each well and incubated
- Stop solution is added to all wells and absorbance read
- Computer software is used to interpret results

## Interpreting QFT Results

<table>
<thead>
<tr>
<th>QFT Result</th>
<th>Nil (IU/mL)</th>
<th>TB Ag-Nil (IU/mL)</th>
<th>Mitogen-Nil (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>≤ 8.0</td>
<td>≥ 0.35 and ≥ 25% Nil value</td>
<td>Any</td>
</tr>
<tr>
<td>Negative</td>
<td>≤ 8.0</td>
<td>&lt; 0.35</td>
<td>≥ 0.5</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>≤ 8.0</td>
<td>≥ 0.35 and &lt; 25% of Nil value</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>&gt; 8.0</td>
<td>Any</td>
<td>Any</td>
</tr>
</tbody>
</table>

---

T-SPOT.®TB Test Kit

- Flexible, 96-well format
  - 12 eight-well strips
  - 4 wells used per patient; 24 patients per kit
  - Positive and negative control for each patient test
  - A minimum of 1 patient test can be run

- Uses standard blood collection tubes

- No special lab equipment required

Blood Collection for T-SPOT.TB

- No special phlebotomy training required
- Uses a standard lithium or sodium heparin tube
- Less sensitive to preanalytical variables than QFT
  - Time from collection to analysis
  - No specialized tubes needed
  - No specific order of draw
  - No shaking of tubes
  - No incubation required
  - Specimens maintained at room temperature for up to 32 hours

The Science Behind T-SPOT.TB Technology

- Density gradient isolation of mononuclear cells
- Quantitation of cells and adjustment of concentration
- Incubation with specific antigens on ELISPOT microtiter plate


Ficoll™ and Ficoll-Paque™ are trademarks of GE Healthcare, Ltd.
Interpreting T-SPOT.TB Results

Panel A
- Nil Control
- ESAT-6
- CFP10

Panel B
- Positive Control

Negative Result

Positive Result

Interpreting T-SPOT.TB Results

• The test result is **Positive** if Panel A-Nil and/or Panel B-Nil ≥ 8 spots

• The test result is **Borderline** (equivocal) where the higher of Panel A-Nil or Panel B-Nil spot count is 5, 6, or 7 and retesting by collecting another sample is recommended

• The test result is **Negative** if Panel A-Nil and/or Panel B-Nil ≤ 4 spots. This includes values less than zero.

## Consideration of TB Blood Test Logistics

<table>
<thead>
<tr>
<th>Phlebotomy Steps</th>
<th>QuantiFERON®-TB Gold In-Tube&lt;sup&gt;1&lt;/sup&gt;</th>
<th>T-SPOT&lt;sup&gt;®&lt;/sup&gt;.TB Test&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collection tubes</td>
<td>3 specialized tubes</td>
<td>Standard tube</td>
</tr>
<tr>
<td>Tubes drawn in specific order</td>
<td>Required; Nil, TB antigen, mitogen</td>
<td>N/A</td>
</tr>
<tr>
<td>Blood volume</td>
<td>1 mL (0.8–1.2 mL); under- or overfilling outside the 0.8- to 1.2-mL range may lead to erroneous results</td>
<td>Fill 6-mL tube</td>
</tr>
<tr>
<td>Shake collection tubes</td>
<td>Required; vigorously shake the tubes up and down 10 times</td>
<td>Not required</td>
</tr>
<tr>
<td>Purge tube with butterfly</td>
<td>Required when a butterfly needle is used</td>
<td>Not required</td>
</tr>
<tr>
<td>Sample stability</td>
<td>Specimens must be incubated as soon as possible but within 16 hours</td>
<td>Up to 32 hours</td>
</tr>
</tbody>
</table>

---


T-SPOT is a registered trademark of Oxford Immunotec, Ltd. QuantiFERON is a registered trademark of Cellestis, Inc.
Study objective: To compare the diagnostic performance of an IGRA (T-SPOT.TB) to the TST in children seen in US tuberculosis clinics.

A prospective study of 210 children (ages 1 month to 18 years) from 3 pediatric TB clinics in Houston, Texas.

4 levels of epidemiologic risk:
- Low (no identifiable risk factor, n = 27)
- Intermediate (birth in or travel to high-prevalence country or contact with adults with risk factors, n = 78)
- High (recent contact with a person with TB, n = 74)
- Active disease (n = 31)

BCG vaccine status was also used to compare the performance of the 2 tests.
TB Screening in Children Using TST and T-SPOT.TB

Children NOT Vaccinated with BCG

- Confirmed TB
- Clinically Diagnosed TB
- High Risk
- Intermediate Risk
- Low Risk

TB Screening in Children
Using TST and T-SPOT.TB

TB

TB Screening in Children and Adolescents Using QFT and T-SPOT.TB

- **Study objective:** To evaluate the impact of age on the performance of various IGRAstrs when used in a hospital setting among children tested for suspected active or latent TB

- A retrospective study of 496 children (ages 0 to 19 years of age) at the University of Modena in Italy who had been tested with the TST and at least one IGRA:
  - 181 with QuantiFERON-TB Gold only
  - 315 with QuantiFERON-TB Gold In-Tube only
  - 87 with QuantiFERON-TB Gold & T-SPOT.TB
  - 67 with QuantiFERON-TB Gold In-Tube & T-SPOT.TB

TB Screening in Children and Adolescents

Using QFT and T-SPOT.TB

Indeterminate IGRA Results in Children

- **Results:** Compared with T.SPOT.TB, the rates of “indeterminate” results were significantly higher for both QuantiFERON-TB tests, because of low mitogen response. Indeterminate results were seen more frequently in children < 4 years old than in those ≥ 4 years old.

- **Conclusion:** Different TB blood tests in children seem to perform differently, because both QuantiFERON-TB tests were more likely than T.SPOT.TB to give indeterminate results in children < 4 years old.

---

No cross-reactivity to BCG and most NTMs

<table>
<thead>
<tr>
<th>Tuberculosis Complex</th>
<th>Antigens</th>
<th>Environmental Strains</th>
<th>Antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESAT-6</td>
<td>CFP 10</td>
<td>ESAT-6</td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>+</td>
<td>+</td>
<td>M. abcessus</td>
</tr>
<tr>
<td>M. africanum</td>
<td>+</td>
<td>+</td>
<td>M. avium</td>
</tr>
<tr>
<td>M. bovis</td>
<td>+</td>
<td>+</td>
<td>M. branderi</td>
</tr>
<tr>
<td>BCG substrain</td>
<td></td>
<td></td>
<td>M. celatum</td>
</tr>
<tr>
<td>gothenburg</td>
<td>-</td>
<td>-</td>
<td>M. chelonae</td>
</tr>
<tr>
<td>moreau</td>
<td>-</td>
<td>-</td>
<td>M. fortuitum</td>
</tr>
<tr>
<td>tile</td>
<td>-</td>
<td>-</td>
<td>M. gordonae</td>
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<td>-</td>
<td>M. intracellulare</td>
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<td>danish</td>
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<td>-</td>
<td>M. kansasii</td>
</tr>
<tr>
<td>glaxo</td>
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<td>M. malmoense</td>
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<tr>
<td>montreal</td>
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<td>M. marinum</td>
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<td>pasteur</td>
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<td>-</td>
<td>M. oenavense</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M. scrofulaceum</td>
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<td></td>
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<td></td>
<td>M. smegmatis</td>
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<td></td>
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<td></td>
<td>M. szulgai</td>
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<td></td>
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<td>M. terrae</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>M. vaccae</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>M. xenopii</td>
</tr>
</tbody>
</table>
IGRA responses are higher in active disease than in LTBI

However, there is a very large overlap in the results so it will not be possible to use IGRA to differentiate between active disease and latent infection


T-SPOT. TB spot numbers in subjects with active disease compared to LTBI

Janssens et al ERJ (2007)

T-SPOT. TB spot numbers in subjects with active disease compared to LTBI (TST+ve and TST-ve)
OTHER CONSIDERATIONS

• COST BENEFIT ANALYSIS
The SWITCH Study
Screening Health Care Workers with Interferon-γ Release Assay Versus Tuberculin Skin Test: Impact in Costs and Adherence to Testing

Authors: Wrighton-Smith, P.; Sneed, L.; Humphrey, F.; Tao, X.; Bernacki, E.
Publication: Journal of Occupational and Environmental Medicine. 54(7):806-815, July 2012
Study Sites: Johns Hopkins Healthcare System (JHHS) and Johns Hopkins Medical School, Baltimore, MD
Cost Modeling

CLINICAL PATHWAY FOR ANNUAL SCREENS USING TST

Key
Red text denotes probabilities of taking a particular branch at each decision point.
Blue numbers are used to label each of the possible final pathways that an employee could take during screening. The costs of these pathways were individually determined.

For example, pathway 5 has the following costs associated with it: TST placement (material and labor cost), TST reading (labor cost), chest X-ray (material and labor cost), INH treatment (drug costs, monitoring test costs, etc.).
Highlights:

• First study to analyze the actual cost of a TB screening program using both the TST and the T-SPOT.*TB test by obtaining direct measurements of all program components.

• Study exposes the “false economics” of the TST, demonstrating that it actually costs $73.20 per test to perform when taking into account all the components of a TST program.

• Using the T-SPOT.*TB test resulted in 99% compliance (with no follow-up required).

• Cost savings were realized when the material cost of the T-SPOT.*TB test is at or below $54.83 per test.
Results:

• 75/113 prior positive TST employees were T-SPOT.TB negative

• 10x more employees preferred the T-SPOT.TB test over the TST

• The average cost of using the TST at JHHS for their TB screening program costs an average of $73.20 per employee

• The TST screening adherence rate was 70.8% without EH staff follow-up, and modeled to be 98.5% with staff follow-up (at an additional cost of $20.59 per employee)
Discussion:

- 9/10 significant costs associated with TST screening programs were related to staff times.

- With TST, institutions are forced to weigh costs against the desired adherence rate. When using the T-SPOT.\textit{TB} test, that decision is not necessary.

- 10\% of the TST non-returners were positive with the T-SPOT.\textit{TB} test, demonstrating a risk to the hospital if the staff did not follow-up with the non-returners.

- SWITCH study results demonstrating TST screening costs of $52 to $73 per employee are similar to results from a study conducted by Lambert et al (\textit{ICHE}, 2003) that found TST costs.
What is your current case rate and volume of testing?

- Louisiana reported 218 cases with a 5.2 case rate in 2009
- Performed 4,901 PPDs
  - 90 HIV positives
  - 2,625 in high risk contacts
  - 427 in foreign-born
  - 1,849 in low risk screening

Cost Comparison

- Mantoux PPD: Clinic $23.80 Field $52.20
- Private Laboratories (QFG-IT): $150 to $260
- State Laboratory (T-SPOT): $85.00
- Oxford Diagnostic Laboratories (T-SPOT): $60.00

Implementation

• Guidelines
• Supplies
• Forms
• FedEx
• Venipuncture training
• Reports - Submitter and TB Control Program
• Payment

# Evaluation

9 Months: **2898 T-SPOT.TB** tests performed

<table>
<thead>
<tr>
<th></th>
<th>2009 (PPD)</th>
<th>2010 (T-SPOT.TB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contacts</td>
<td>23%</td>
<td>21%</td>
</tr>
<tr>
<td>Foreign-born</td>
<td>98%</td>
<td>38%</td>
</tr>
<tr>
<td>PPD Positive</td>
<td>83%</td>
<td>65%</td>
</tr>
<tr>
<td>HIV Positive</td>
<td>45%</td>
<td>54%</td>
</tr>
</tbody>
</table>

Presented May 16, 2011 at the Southeastern National TB Center, [http://sntc.medicine.ufl.edu/Webinars.aspx](http://sntc.medicine.ufl.edu/Webinars.aspx)
Evaluation (cont.)

9 Months: 113 T-SPOT. TB tests performed

<table>
<thead>
<tr>
<th>Cases</th>
<th>2009 (PPD)</th>
<th>2010 (T-SPOT. TB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture +</td>
<td>76%</td>
<td>89%</td>
</tr>
<tr>
<td>HIV Positive</td>
<td>85%</td>
<td>100%</td>
</tr>
<tr>
<td>Culture +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>75%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Summary of Benefits

• Restructure contact investigations
  – Eliminated second visit
  – Time to identify additional contacts
  – Increase the number of contacts placed on DOT for LTBI

• Place more HIV positives to DOPT

• Improve prevention services and reduce overall budget

Questions We Ask?

- TST and IGRAs: predictors of disease: General
- Does quantifying help in either case?
- Specific Quantification in TB spot test: Culture filtrate protein 10 spot count, but not early secretary antigenic target 6 spot count, was significantly associated with subsequent TB development. (Hongkong study in silicotic pts)
- Issue of discordance & Borderline data
- IMPORTANCE OF DEFINITION OF CONVERTORS OR REVERSION SPECIALLY IN HCWs
  Challenges of IGRAs conversion in serial testing of HCW: Fong et al. *Chest* 2012;142 (1): 55-62
Issue of Borderline results

• Both IGRAs are biological assay so results will have some variation around the cut-off
• Using a cut-off reduces fluctuations in results that are near the cut-off
• Benefit of cut-off is highlighted by CDC in 2010 guidelines:
  • “Use of a borderline category might address test variation and uncertainty for results near a dichotomous cut point.”
• Re-testing borderline results 2 weeks later should give definitive result
• Bordeline zones used by IGRAs:
  • T-SPOT.TB has a borderline of 5, 6 and 6 spots throughout the world
  • QFT only has borderline zone in Japan (0.1 - 0.35 IU/IFN gamma)
“These findings support the extensive literature showing that measurement of TB-specific T-cells using the ex vivo ELISPOT technique (upon which the T-SPOT.TB test is based) is more accurate than the TST, as it has closer correlation to exposure history and is unaffected by prior BCG vaccination.”

Zellweger et al., Int J Tuberc Lung Dis (2005)

<table>
<thead>
<tr>
<th></th>
<th>T-SPOT.TB</th>
<th></th>
<th>OR</th>
<th>P value</th>
<th>95%CI</th>
<th>TST</th>
<th></th>
<th>OR</th>
<th>P value</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Being in high exposure group</td>
<td>5.00</td>
<td>0.029</td>
<td>1.05–23.86</td>
<td>1.85</td>
<td>0.161</td>
<td>0.78–4.36</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Having received BCG vaccine</td>
<td>1.32</td>
<td>0.733</td>
<td>0.27–6.56</td>
<td>n/a*</td>
<td>0.0003</td>
<td>n/a</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age of subject†</td>
<td>3.31</td>
<td>0.116</td>
<td>0.70–15.80</td>
<td>2.66‡</td>
<td>0.041</td>
<td>1.02–6.92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Explaining discordant results; Contact tracing

Zellweger et al., Int J Tuberc Lung Dis (2005)

Setting: contact tracing in an institution for alcoholics in Lausanne, Switzerland

Index case:
- 47-year old female, born in Brazil
- Smear-positive pulmonary TB, infectious for 1 month
- She had stopped TB treatment 3 years before so possibility of MDR-TB

Background
- Preventive treatment associated with liver toxicity (most contacts >35 years old, residents all had history of alcoholic liver disease)
Vassilopoulus et al., J Rheumatology (2008)

- 70 subjects attending a rheumatology clinic in Athens
- All candidates for anti-TNF therapy
- 43/70 on immunosuppressive drugs
- 15/70 had co-morbid conditions (e.g. chronic liver disease, diabetes, COPD)
- Results of TST and the T-SPOT.TB test compared, multivariate analysis used to analyse discordant results

"(BCG) vaccination was associated with TST+/Elispot– discordant results (p = 0.01), whereas steroid use was linked to TST–/Elispot+ discordant results (p = 0.04)."
Borderline results

- Both IGRAs are biological assay so results will have some variation around the cut-off.

- Using a cut-off reduces fluctuations in results that are near the cut-off.

- Benefit of cut-off is highlighted by CDC in 2010 guidelines:
  - “Use of a borderline category might address test variation and uncertainty for results near a dichotomous cut point.”

- Re-testing borderline results 2 weeks later should give definitive result.
Indeterminate results occur when nil or positive controls fail. Caused by:

- Errors during processing (usually resolved when re-tested)
- Maybe patient specific (not usually possible to resolve)

Indeterminate results should be repeated 2 weeks later
- ~ two thirds will then give a reportable result
Black and white and Grey
The discussion about discordant results
<table>
<thead>
<tr>
<th>A: DATA</th>
<th>B: EVALUATE</th>
<th>C: SCAN</th>
<th>D: RECAP</th>
<th>E: TREAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>QUANTIFY ASSESS</td>
<td>RULE OUT ACTIVE DISEASE</td>
<td>RULE OUT EXTRA-PULM DISEASE</td>
<td>SIZE OF TST: is it helpful?</td>
<td>Dx; LTBI Should we offer Rx? Based on many factors</td>
</tr>
<tr>
<td>BORDERLINE INDETERMINATE</td>
<td></td>
<td></td>
<td>IN CHILDREN; Degree of IGRA ??</td>
<td></td>
</tr>
<tr>
<td>DISCORDANT RESULTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOCUMENT</td>
<td>SYMPTOMS H/P</td>
<td>ROS LN EXAM</td>
<td>GO BACK to STEPS B&amp;C IF IN DOUBT</td>
<td>RISK OF ADR*</td>
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<td>CHECK HIV</td>
<td>CXR CT Scan if needed</td>
<td>CORRELATE with Chest imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STRATIFY RISK, CHECK SOURCE CASE WHY??</td>
<td>SPUTUM INDUCE if needed</td>
<td></td>
<td>IF SURE GO TO STEP E</td>
<td></td>
</tr>
<tr>
<td>CONCLUDE AFTER FULL</td>
<td>PRE-TEST PROBABILITY?</td>
<td>TREAT FOR TB ?</td>
<td></td>
<td>TREAT FOR LTBI ASSESS RISK BENEFIT RATIO</td>
</tr>
<tr>
<td>EVALUATION: IF POSITIVE STEPS B-E</td>
<td>PRE-TEST PROBABILITY?</td>
<td>TREAT FOR TB ?</td>
<td>MONITOR SIDE EFFECTS* AND Rx</td>
<td></td>
</tr>
</tbody>
</table>

*ATS 2006 DILI consensus statement
TEŞEKKÜRLER

teşekkür ederim/ sağ olun for your kind attention

JA

And ... You all are welcome to LSU and New Orleans, USA
Hoş geldin to USA
ILH /Bogalusa MC data

- 1130 tests performed last 6 months *
- 55/1130 4.9 % positive... HOP and 4W
- 982/1130 86.9 % negative
- Rest either invalid, borderline, other causes

- ** previous year 3063 performed
Is it better to get LTBI than not?

- Relative to risk of developing progressive TB after reinfection compared to uninfected individuals.
- In a review of 23 cohort studies prior to LTBI Rx (1950’s) 79% lower risk of developing progressive TB.
NTM/MOTT
BCG
Technique
What are the drawbacks of TST/Mantoux test/PPD?
TST phenomenon
Two step
Confusion to treat or not
What is the booster phenomenon?
Granulomas
TST/TIGRA
Th1 response
Not infectious
What is latent TB?
Check for active TB
What do you do before starting treatment for latent TB?
Must be DOT and it is not treatment for active TB
What is chemoprophylaxis for latent TB by intermittent therapy?
TB
MOTT
Nocardia
Leprosy
What is a Positive AFB smear?
<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>5 mm</td>
</tr>
<tr>
<td>Contact</td>
<td>5 mm</td>
</tr>
<tr>
<td>Congregate setting</td>
<td>10 mm</td>
</tr>
<tr>
<td>No risk</td>
<td>15 mm</td>
</tr>
</tbody>
</table>
What are the criteria for a positive TST requiring consideration for chemoprophylaxis?
Normal chest x-ray
What is the CXR finding in 15% of HIV patients with TB?
13% to 22% of cohort can acquire disease form this group
What is Smear negative TB?
The hidden reservoir of TB

- Smear negative cases: 13–22% of cohort can acquire disease from smear negative contacts
- Undocumented immigrants with prolonged symptoms with poor access to health care

(CID 2008 Tostmann et al)
(Achkar et al Clin Infec Dis 2008 Nov)

Delay in Dx, Index of suspicion (Surgical specialties)


Note:
Infectious period 3 months prior to onset of symptoms
Only 20% of contacts with LTBI complete Rx.; Need to expand contact screening for Smear negative TB
Suspect cases

ILH data

- Suspect TB cases require Resp Isolation
- Average cost of care 20 K per pt
- ALOS : 22.7 days
When to hospitalize and when to discharge

Basis: NYC Health Dept criteria

When to discharge:
- Avoid weekends
- Check pt infection and clinical factors
- Co morbid conditions
- Home and follow up situations
- Depends upon where discharged to

When to admit:
- Cavitary disease / Hx Substance abuse
- Unstable medical / psych / social or societal or follow up situations

Latent TB
Low Suspicion
TB
For TB
Compliance

No DOT

Increase bacterial burden

Development of secondary resistance

Malabsorption of Drugs

Host variation in response to drugs

“lab error”
What are the causes of delayed sputum conversion and/or treatment failure?
Reasons for delayed conversion and/or treatment failure

- Compliance/ No DOT used; though 16% failure rates in DOT programs too (**)
- Increased bacterial burden; cavitary disease
- Development of secondary resistance
- Malabsorption of drugs
- Host variation in response
- “lab error”

Region 1: 28.6%
No SM
No PZA in USA
9 months at least
Vitamin B6 a must
What is TB treatment in pregnant women?
Rx protocols

- SAT
- Proxy SAT
- Modified DOT
- DOT
- Enhanced DOT

Guardian
Proxy
Clergy
Village lead

Single drugs versus FDC
No inferiority
JAMA 2011;305 (14):1415-1423
And then……
LFTS become abnormal (multiple Criteria)
Skin rash develops…Culprit ? * PZA /Rif in HIV
Now What?

LFT Pathways

Step Rx, Review Rx, Choose second line drugs, Re initiate in a step wise manner; choose drugs based on likely culprit etc. , Modify and de-escalate
Therapy

- Ideal Rx: DOT “RIPE”
  Duration: 6 months .....* 9 months in special case scenarios

* When sputum culture is still positive at the end of 2 months
* CXR showed cavitary disease/ Initial high bacterial load
* When initial induction phase did not include PZA
* When induction phase was not “standard” i.e. once weekly doses
## TB Pleural effusion**

<table>
<thead>
<tr>
<th>Test</th>
<th>Sens</th>
<th>Spec</th>
<th>ADA*</th>
<th>PCR</th>
<th>INFγ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>88%</td>
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<td>97.1%</td>
<td>90%</td>
</tr>
<tr>
<td>*</td>
<td></td>
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</table>

**Confirmed by culture or pleural bx

17% cases had Pleural fluid lymphocyte count of less than 50% And this count was inversely related to positive culture (63 % positive culture on liquid medium) Thorax March 2012

* May be helpful to remember in other fluid evaluation

The Pleural fluid triad*

ADA,LDH,L:N ratio of > 0.75

*Ghanei et al 2004
Asian CT Annals, Iran

**Villegas et al: Chest 2000 118:1355-1364

17% cases had Pleural fluid lymphocyte count of less than 50% And this count was inversely related to positive culture (63 % positive culture on liquid medium) Thorax March 2012

* May be helpful to remember in other fluid evaluation
Extra pulmonary TB

- 1993–2006 US data; 18.7%
- 40% Lymph nodes, 20% Pleural effusion
- 10% combined
- Female sex, foreign birth
- Not associated with usual Pulm TB risk factors
- Relationship between *MTB* and phylogenetic lineage and clinical site!!

- CID 2009;49:1350-7
- CID 2012;54(2): 211-9
23% of MDR-TB are this
What is XDR-TB?
RISK Factors for DR; MDRTB and XDR-TB

- Inadequate Rx protocols and non-compliance
- Question of low level resistance and importance thereof
- Previous TB Rx OR 11; HIV OR 3, Homelessness OR 3, ETOH abuse OR 2 (Annals June 2009)
- Rifampin Resistance is an excellent marker for MDRTB
XDR-TB in the limelight, but this has existed.....up to 34% of MDRTB

Lancet 2006: Gandhi et al from the Natal Province South Africa

- Dx – Death period: 16 days; mortality 85–98%
- HIV population; median CD4: 64 with only 34% receiving ART
- Epidemiological survey: 41% MDRTB; 23% of these were XDR-TB
It is not coming soon

It is here

90% sensitive/specific
What is

The XPERT Test?
Where are we moving forward?

- Old drugs; Newer drugs and newer class of drugs (*focus has moved to out of USA to Japan, India*)
- Other approaches: targeting *MTB* proteins*
- Drug delivery: Inhaled administration
- **Revisit Rifampins** (Dose, toxicity concerns (immunologic and idiosyncratic), association with PZA, Drug levels, D–D interaction)
- Caution about Fluoroquinolones

*Mitnick et al NJMRC Denver Expert Opinion Pharmacoth 2009

(*Nature 2009: Lin et al*)
Not recommended in USA generally
May be considered in special circumstances of continued exposure/MDR-TB exposure
Not recommended in HIV/impaired immunity/Pregnancy
What is BCG?
Rifapentine
Rifabutin
What are Other forms/types of rifamycin?
KatG gene
aphC gene
What are the genetic basis of INH resistance?
Detecting drug resistance

- **Rifampicin resistance:** Mutations in β subunit of RNA polymerase
  - >90% of mutations in 81 base pair region

- **Isoniazid resistance** – more complex
  - katG gene (peroxidase) mutations
  - inhA gene mutations – cell wall synthesis
  - others - aphC gene mutations

- **PZA:** mutations in gene pncA

- **PCR-based detection line probe assay**
  - GenoType MTBDRplus (Hain Lifescience)
TB: 2012 update of contemporary topics
Exposed ... Now what?

** transmission factors

NID = Non-Imm Defenses

ID = Imm Defenses

Exposure

- NID=Non
- Imm Defenses

Early progression 5%
- ID=Imm Defenses
- Containment 95%

Late progression 5%
- Continued
- Containment 90%
Latent TB Infection
Definition?

- A paucibacillary infection with no detectable bacilli present
- Animal models: Bacilli “stunted” due to nutritional depletion, hypoxia or genetic factors

Ref: Mol Micro 2002; 43: 717
The triple issues of LTBI

TST

* Poor Specificity in BCG vaccinated persons
* Low sensitivity in Immune compromised hosts
* Logistical drawbacks
* Overall no show rate for reading test is 40-60%
A “positive” TST / IGRA : suggested plan

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<td></td>
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*ATS 2006 DILI consensus statement*
IGRA tests

- LTBI: low burden of dormant bacilli, which are not directly detectable or quantifiable
- No gold standard for LTBI, surrogate marker used such is active TB
- Strong cellular immune response: LTBI serves as an amplified signal
- TST: first measure: DTH
- Whole blood: ELISA (Q TB gold in Tube)
- T cell secretion Enzyme - linked immunospot ELISpot assay (T-SPOT TB)
Quantiferon TB Gold

- Unaffected by BCG and NTM
- TB-specific antigens are only present in M.TB
- INF-Gamma in whole blood with an ELISA measurement
- 90% SENSITIVITY IN Culture + TB
- 98% SPECIFICITY IN Culture + TB

www.cellestis.com

Further references: lancet 2004 Dec Volume 4;
QUANTIFERON - GOLD
INF-Gamma based assay

• Advantages: More Specific ,( BCG/MOTT), One visit; good correlation with TST
• Disadvantages: Technical, Analysis software, Blood, Cost, Usage, Refrigerated
• Components: Early secretory antigen target (ESAT-6 antigen), Culture Filtrate protein (CFP)-antigens and others
ELISPOT & ELISA

- Both tests have higher specificity than TST
- Higher diagnostic sensitivity than TST (70-97%)
- Further increase in sensitivity with T cell INF γ release assay (IGRA)
- ?? Decreased levels as a marker for treatment response???
- Excellent specificity, but we still need higher sensitivity

Ref: Lalvani Chest 2007;131:1898-1906
Pai et al Annals 2008; 149: 177-184 (meta analysis)
IGRAs & TB progression

- Of 41 QFT-G pos – 6 (14.6%) developed TB
- Of 219 TST pos – 5 (2.4%) developed TB
- Of 545 QFT-G neg – 0 developed TB
- Of 181 QFT-G neg/TST pos – 0 developed TB
- Of 358 TST neg – 1 developed TB

Diel et al. AJRCCM 2008;177:1164
IGRA* update

Advantages
Disadvantages
IGRA preferred but TST acceptable  Homeless/Transitional Care/ Substance abusers
TST is preferred  Children less than 5 years of age
Equally acceptable:  contact screening

ILH priority list under consideration
1. Employees
2. Immune compromised patients
3. Patients with Hx of BCG
4. Specific cases where differential Dx of pneumonia includes TB or MAC
5. Referral from Transitional Homes/shelters

Ref MMWR/CDC Rep 2010: 59 (RR-5:1-28)
Why Rx?
Rx options

- INH 6 months
- INH 9 months
- RIF 4 months
- RIF & INH 4 months
- RFT / INH
- If index case MDRTB or XDRTB, then a big problem
CDC recommends that NAA testing be performed on at least one respiratory specimen from each patient with clinical suspicion of TB, where Dx has not yet been established, and for whom the result will alter management and TB control measures/contact investigations.

MMWR Jan 2009/58(01);7-10
NAA contd

Ampl MTB direct test
MTD (Gen-probe)  
Enhanced Amplicor (Roche) test

Greater PPV
Earlier Detection
Less inappropriate use of FQ as empiric monotherapy for pneumonia
Reliance by MDs: 20-50% of cases
NAA testing should be considered as Critical test value notification
Report time less than 48 hours.
If clinical suspicion is low, do not do NAA as PPV low
If clinical suspicion moderate or high: single NAA negative should not
NAA inhibitors

- 3-7% sputum specimens have inhibitors
- 50-75% labs do this test; probably less
- AFB positive, NAA negative x2 and no inhibitors present…it is probably NTM
- If AFB positive, NAA negative and Inhibitors detected, NAA test is of no use
- If AFB is negative, NAA negative, Inhibitors negative, use clinical judgement as sens of NAA in smear negative, culture positive cases is 50-80% only
<table>
<thead>
<tr>
<th>CLINICAL SUSPICION</th>
<th>AFB smear</th>
<th>NAA result</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>positive</td>
<td>positive</td>
<td>positive</td>
<td>MTB (PPV 95%)</td>
</tr>
<tr>
<td>Negative</td>
<td>positive</td>
<td></td>
<td>Repeat NAA; if positive or clinical suspicion high: Rx as TB</td>
</tr>
<tr>
<td>Positive</td>
<td>negative</td>
<td></td>
<td>Repeat; test for Inhibitors ….will discuss</td>
</tr>
</tbody>
</table>
# Pleural effusion**

<table>
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<tr>
<th></th>
<th>ADA</th>
<th>PCR</th>
<th>INFγ</th>
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<tbody>
<tr>
<td>*Sens</td>
<td>88%</td>
<td>85.7%</td>
<td>73.8%</td>
</tr>
<tr>
<td>*Spec</td>
<td>85.7%</td>
<td>97.1%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>*Maintained over a wide range of prevalence</td>
<td></td>
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</tr>
</tbody>
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**Confirmed by culture or pleural bx > 90 % s/s


ADA, LDH, L:N ratio of > 0.75

*Ghanei et al 2004

Asian CT Annals, Iran
Sputum evaluation

Spontaneous Sputum

Supervised Sputum
“DOSE”

Induced Sputum

Chang et al Eur Resp J 2008 May ; (5) 1085-90
Supervised and induced sputum among patients with smear-negative pulmonary tuberculosis

K. C. Chang1, C. C. Leung1, W. W. Yew2 and C. M. Tam1

ERJ 2008

From a cohort of 660 patients; prospectively for collection of one specimen each of supervised and induced sputum in succession. Among 78 patients with culture-proven pulmonary tuberculosis, analysis of matched sputum culture results showed that: 1) induced sputum outperformed supervised sputum; 2) the second unsupervised sputum was significantly inferior to the first and redundant in the presence of the others; 3) adding one specimen each of supervised and induced sputum to two unsupervised specimens increased culture yield significantly; and 4) patients with either extent of disease less than right upper lobe or no respiratory symptoms were more likely to benefit.
The issues

• Little supervision; the “give the cup” approach
• Bacterial contamination
• Only 30% positivity in the first sputum although incremental yield beyond 3 is doubtful
• (S:47%/C:74% to S:58%/C:90%)
• Depends upon cavitary disease or non cavitary disease
• Single vs. 24-72 hour pooled specimen: No difference except increased bacterial contamination (2%) increased to 15%

Bullets

• 2 sputum smears as good as 3 even for infection control purposes but....
• Volume of sputum 5cc or more improves sensitivity
• If ES negative; SI adds up to 19-30 % in sensitivity in suspected cases
• FOB with Bronchial washing if less than 50 cc, there is no difference in sensitivity
• FOB with BAL better if return more than 50 cc and sensitivity increased if PCR also done

Ref: Thorax 2002 : 57 1010
Nelson et al J Clin Micro 1999 36 (2)
The Real Life Algorithm*  
.. 2/4 or 2/7 or 3/3

Dx of TB (Class 3 or 5)  Start RIPE DOT DAILY/Bi weekly*

RIPE***
*******

Culture back  
************

Pan sensitive  
***RIP(drop E)

2 month Sputum culture negative

***Drop PZA  
|  

0……  2-4 weeks……..6 weeks  8-12 wks …….6mths  ……….9mths

* Check dosage; ***Watch for ADR/LFTs/DILI
Therapy

- Ideal Rx: DOT “RIPE”
  - Duration: 6 months .....* 9 months in special case scenarios
  - (a) When sputum culture is still positive at the end of 2 months
  - (b) CXR showed cavitary disease
  - (c) When initial induction phase did not include PZA
  - (d) When induction phase was with once weekly drugs i.e. INH/Rifapentine
Rx protocols

SAT

Proxy SAT

MM SAT **
Haiti study
2002-2003
Int J Tub

Modified DOT

DOT

Enhanced DOT
Completion range of Rx strategies

JAMA 1998; 279: 943-948
Yield of continued monthly sputum evaluation after culture conversion

- Retrospective analysis
- Pan sensitive disease
- RI containing regimens
- 56% initial smear positive
- At the end of 5 month 5.3% smear positive
- 1.3% culture reversions

NY city Health Dept IUATLD 2002 6 (3)

National data: 10% of cases culture positive after 12 weeks of Rx
You start RIPE

- And then……
- LFTS become abnormal (multiple Criteria)
- Now What?

Pathways

Stop Rx, Review Dx, Choose second line drugs, Reinitiate in a stepwise manner; choose drugs based on likely culprit etc., Modify and deescalate
A problem or multiple problems?
Reasons for delayed conversion and/or treatment failure

- Compliance/ No DOT used; though 16% failure rates in DOT programs too (**)
- Increased bacterial burden; cavitary disease
- Development of secondary resistance
- Malabsorption of drugs
- Host variation in response
- “lab error”

**Region 1: 28.6%**
Drug levels

- Body weight or Body surface* especially in children
- **Low 2 hr serum conc was 46% INH and Rifampin mainly associated with dose/kg weight
- INH associated with acetyl INH/INH ratio and ETH associated with Cr Cl;
- However significant scatter noted and clinical relevance unclear

*Thee et al In J Tuberc 2007
**Um et al In J Tuberc 2007

Done at wetmore
Relapses

• In nearly all patients with TB caused by drug susceptible organisms and who are treated with Rif–containing regimens using DOT Rx, relapses occur with susceptible organisms
High risk for treatment failure or relapse

**Cavitation on initial CXR**

**Positive Sputum Culture after 8 weeks of Rx.**

**When PZA is not used in the Intensive phase**

US PHSS 22 TB Consortium trial 1993-2002 cohort and ATS guidelines
Relapse of PTB after sputum conversion after SCC

- Followed for 3 years
- 3.29%
- Those who became smear negative after 3 months of Rx had a relapse rate of 8.8%

CDC data from NC Public health dept
Latest National Statistics* MMWR 2007

- 13767 TB cases in 2007 @ 4.6 per 100K
- 3.2% decline from 2005
- Less decline than previously (7.3%)
- Highest rates in foreign born individuals
- Blacks 8.4 times higher
- Asians 2 times higher
- Hispanics 7.6 times higher than whites
Figure 1

FIGURE 1. Rate* of tuberculosis (TB) cases, by state/area — United States, 2008†

* Per 100,000 population.
† Data updated as of February 18, 2009. Data for 2008 are provisional.
§ TB rate cutoff points were based on terciles: 18 states had TB case rates of <2.0 (range: 0.46–1.99) per 100,000, 17 states had TB case rates of 2.0–4.0 (range: 2.03–3.92) per 100,000, and 15 states and the District of Columbia had TB case rates of >4.0 (range: 4.02–9.63) per 100,000.
• LOUISIANA TUBERCULOSIS (TB) CASES / RATES FOR 2008
• cases by parish/ case rates per 100,000
• State Total = 227 cases/ 5.4 cases per 100,000*
### LA 2008 examples

<table>
<thead>
<tr>
<th>Parish</th>
<th># of case</th>
<th>Rate/100K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jefferson</td>
<td>25</td>
<td>5.6</td>
</tr>
<tr>
<td>Orleans</td>
<td>28</td>
<td>12.2</td>
</tr>
<tr>
<td>E Baton Rouge</td>
<td>20</td>
<td>4.5</td>
</tr>
<tr>
<td>St. Bernard</td>
<td>2</td>
<td>15.4</td>
</tr>
<tr>
<td>Terrebonne</td>
<td>4</td>
<td>3.6</td>
</tr>
<tr>
<td>5 parish here</td>
<td>55</td>
<td>7.7</td>
</tr>
</tbody>
</table>
Drug Resistance

**Primary** drug-resistance is said to occur in a patient who has never received antituberculosis therapy.

**Secondary** resistance refers to the development of resistance during or following chemotherapy, for what had previously been drug-susceptible tuberculosis.
Detecting drug resistance

- **Rifampicin resistance**: Mutations in β subunit of RNA polymerase
  - >90% of mutations in 81 base pair region

- **Isoniazid resistance** – more complex
  - katG gene (peroxidase) mutations
  - inhA gene mutations – cell wall synthesis
  - others - aphC gene mutations

- **PCR-based detection**
  - GenoType MTBDRplus (Hain Lifescience)

USED THIS IN ONE CASE RECENTLY AT WETMORE
This report summarizes the results of that survey, which determined that, during 2000--2004, of 17,690 TB isolates, 20% were MDR and 2% were XDR.

Population-based data on drug susceptibility of TB isolates were obtained from the United States (for 1993--2004), Latvia (for 2000--2002), and South Korea (for 2004), where 4%, 19%, and 15% of MDR TB cases, respectively, were XDR.

MMWR 3/2006
55(11);301-305
• **DRTB**: The term "drug-resistant tuberculosis" refers to cases of tuberculosis caused by an isolate of Mycobacterium tuberculosis, which is resistant to one of the first-line antituberculosis drugs: isoniazid, rifampin, pyrazinamide, or ethambutol.

• **Multidrug-resistant tuberculosis (MDR-TB)** is caused by an isolate of M. tuberculosis, which is resistant to at least isoniazid and rifampin, and possibly additional chemotherapeutic agents.

• **Extensively drug-resistant tuberculosis (XDR-TB)** is caused by an isolate of M. tuberculosis, which is resistant to at least isoniazid, rifampin, fluoroquinolones, and either aminoglycosides (amikacin, kanamycin) or capreomycin, or both.
The Story of MDRTB

• Exists and ongoing throughout the world over the years. Russia, Far East, South Asia;
• Globally 400K cases reported
• 1990s Several outbreaks in hospitals and correctional facilities in NY and Florida; Mostly HIV, 80% mortality; Dx-Death time 4-16 weeks
• Nosocomial transmission; not more contagious but more difficult to treat
• Lower cure rate and Cost differential
Mainly from Mexico, Philippines, Vietnam, China and India
124 MDRTB in 2005
Foreign born 81% of MDRTB
XRDTB: 17 cases reported between 2000 - 2006
RISK Factors for MDRTB

- HIV, clusters, inadequate Rx protocols and non compliance
- Rifampin Resistance is an excellent marker for MDRTB
XDRTB in the limelight, but this has existed.....up to 34 % of MDRTB

Lancet 2006: Gandhi et al from the Natal Province South Africa

• Dx - Death period: 16 days; mortality 85-98%

• HIV population; median CD4 : 64 with only 34 % receiving ART

• Epidemiological survey: 41 % MDRTB; 23 % of these were XDRTB
FIGURE 2.12
Countries that had reported at least one case of XDR-TB by the end of 2008

- Red: ≥1 case reported
- Gray: No case reported
FIGURE. Number of reported cases of extensively drug-resistant tuberculosis (XDR TB)* — United States, 1993–2006

* XDR TB defined as resistance to at least isoniazid, rifampin, any fluoroquinolone, and at least one second-line injectable drug (kanamycin, amikacin, or capreomycin).
† Excludes New York City.
Newer Drugs……in the pipeline

TB vaccine developments

- **Boosting BCG responses**
  - Subunit vaccines, combined with novel T-cell adjuvants
  - Ag85B-ESAT6 (or Ag85B-TB10.4) fusion molecules
  - Immunogenic and safe in phase I study
  - MTB72f
  - MVA85A
  - Modified vaccinia virus expressing Ag 85A

Hoft. Lancet 2008;372:164
Side effects may be due to longer intervals of dosing rather than the actual dose. We may be using a lower dose than is needed.
What is Rifampin and ? issues with standard dosage?
Dec levels Reported in TB patients

Receptor polymorphism associated with increased susceptibility to MTB

Can suppress intracellular growth of MTB in vitro

Induces expression of autophagy, phagosomal maturation, antimicrobial peptides such as cathelicidin

Enhances the activity of PZA
What is Vitamin D?
TB and nutritional deficiency: A historical fact

- Vit D deficiency reported in TB pts
- Vit D receptor polymorphism associated with increased susceptibility to *MTB*
- Vit D can suppress intracellular growth of *MTB* in vitro
- Vit D also induced expression of autophagy, phagosomal maturation, antimicrobial peptides (cathelicidin,
- Enhanced activity of PZA

Seen in at least one TB drug in about 46% of cases

Data shows significant scatter
What are Low drug levels?
Drug levels

- Due to PK and PD variability it is better to use Body surface* area, especially in children to decide dosage and achieve better therapeutic levels.
- **Low 2 hr serum conc of at least one Anti TB drug was seen in about 46%**
- INH associated with acetyl INH/INH ratio and ETH associated with Cr Cl;
- However significant scatter noted, many variables such as ETOH use, fixed combination etc and hence clinical relevance unclear. Importance of looking at the therapeutic level range.

References:
- *Thee et al In J Tuberc 2007* 
- **Um et al In J Tuberc 2007**
- ***Kimerling et al Chest 1998***
Drug levels? Some questions

- Present practice; why the doses? RIF specially*
  - (Ingen et al CID 2011: 3 reasons
  - Drug conc above MIC, Fear of side effects, economic
  - 600mg is at a lower end of the dose response curve; side effects not dose related: idiosyncratic and immunological more, cost?)
  - Weight/gender/genetic variations/BSA may determine different dose

- Any reason to change practice since in most cases of Rx failure, causes are multifactorial

- Side effects may be due to longer intervals of dosage rather than dose

- Importance of tailoring Rx

- Do we re-set the clock?

* Some questions
TUBERCULOSIS DISEASE: DRUG LEVEL TESTING

CRITERIA FOR TESTING

1) Recurrent MTB disease of any site
2) MTB cases not converting to negative sputum smear @ 4 weeks
3) MTB cases not converting to negative sputum culture @ 8 weeks
4) MTB case with known drug resistant organisms
5) MTB case with HIV co-infection
Continued

6) MTB cases with abnormal Drug Blood Level results

7) Other MTB cases with administrative approval

Drug levels that should be tested include INH, Rifampin or Rifabutin, PZA and
Drug Level Testing in TB Patients
2009 - 2012

# Pts tested = 47
Positive Culture Conversion to Negative:
Nml Levles vs Low Drug Levels

- Conversion data not avail/Xtra Pulm
- Low level Conversion > 3 mos
- Low level Conversion <= 3 mos
- Nml level Conversion > 3 mos
- Nml level Conversion <= 3 mos

# Pts tested = 47
HIV & DRUG RESISTANCE

# Pts tested = 47

HIV & DRUG RESISTANCE

HIV POS
HIV NEG
DRUG RESIST
HIV POS & DRUG RESIST
Over the course of 4 years, data were collected on Mycobacterium tuberculosis and MOTT, basically to compare the number of patients infected with each of these organisms. Patients with MTB are provided treatment at no cost through the Public Health System. However, those unlucky patients diagnosed with MOTT are on their own when it comes to seeking treatment for their condition.
DUAL INFECTIONS

• As noted in the previous chart, there were 10 dual infections. Eight (8) of these were MTB and Mycobacterium Avium Complex (MAC), one (1) was MTB and Mycobacterium fortuitum and one (1) was MTB and Mycobacterium kansasii.
MTB
M. bovis
M. africanum
M. microti
M. canetti
M. Mungi
What is MTB Complex?
What are

The factors that caused an increase in TB post 1981?
Sputum culture is positive after 2 months
Cavitary, heavy smear positive disease
PZA of RIPE not used.
When

Do you extend treatment beyond 6 months?
Relapse of PTB after sputum conversion after SCC

- Followed for 3 years
- 3.29 %
- Those who became smear negative after 3 months of Rx had a relapse rate of 8.8 %

CDC data from NC Public health dept
High risk for treatment failure or relapse

**Cavitation on initial CXR**

**Positive Sputum Culture after 8 weeks of Rx.**

**When PZA is not used in the Intensive phase**

*US PHSS 22 TB Consortium trial 1993–2002 cohort and ATS guidelines*
HIV
Silicotic lung disease
Immunocompromised
Diabetes
Congregate settings
Travel to high endemic countries
What are the conditions in which there is increased risk of infection to disease?
Proximity, frequency, duration of exposure

Environmental concentration

Infectiousness of index case

Susceptibility of exposed person
What are Factors that increase transmission of TB?
FINAL Jeopardy TOPIC History
Final Jeopardy

The monster that is associated with tuberculosis.
What are Vampires?
Tempting the enemy !!

Sender: JassimAbul@HotMail.Com