OUR RECENT CASE

• This patient, 30 year old, G4 P2 presented to the OB clinic for her prenatal visit;
  • TST was 25 mm,
  • CXR shown;

• She was totally asymptomatic; had no history of contact with any TB patient personally or professionally; Had a negative TST 8 yrs. ago;

• 3 sputum tests of 6 were positive for AFB

• T-Spot TB TEST WAS NEGATIVE
PATHWAY OF PATHOGENESIS IN NON-IMMUNE COMPROMISED PATIENTS WITH A CONNECTION AND YET A DISCONNECT BETWEEN INFECTION, IMMUNE RESPONSE AND DISEASE

- Inhalation
- Macrophage phagocytosis
- Shedding and macrophage turnover
- Alveolar Dendritic Cell migration to regional LN
- MTB Antigens ESAT-6; CFP-10 with CD4 /CD8 interaction
- Differentiate into INF-G, TNF TH1 or cytotoxic Tc1 cells respectively IL 17 21, 22
- DTH Reaction- positive TST with Intragranuloma necrosis called Ghon Complex  LATENT PHASE
  ➢ Ghon Complex is not necessarily limited to lung
- Post Primary IL-4 IL-13 TH 2 response with central caseation and DISEASE

LATENT TB AKA LTBI AKA LASTING TB IMMUNITY HAS NO CLINICAL ACTIVITY BUT GRANULOMAS ARE DYNAMIC LESIONS WITH CONTINOUS TURNOVER AND VARIABLE BACILLARY POPULATION AND DISEASE ACTIVITY RANGING FROM DORMANCY TO STUNDED GROWTH TO ACTIVE MULTIPLICATION

TB INFECTION FLOW CHART (DIAGRAM 1)

- Exposure → Infection → Immune Response
- Elimination of Bacteria → Latent TB
- No Treatment
- Treatment

- Positive TST/IGRA
- TB INFECTION (LTBI)
- PAUCIBACILLARY DORMANT STATE

- Normal Immune System
- Weakened Immune System (HIV+)

- 10% Lifetime Risk
- 7-10% Annual Risk

Adapted from Core Curriculum on Tuberculosis: What the Clinician Should Know, 5th ed. Atlanta, GA: US Department of Health and Human Services, CDC; 2011. with addenda and modifications by authors.
Pregnancy suppresses the T-helper 1 (Th1) proinflammatory response, which may mask symptoms while increasing susceptibility to new infection and reactivation of tuberculosis (like Influenza). After delivery, Th1 suppression reverses—similar to immune reconstitution syndrome in HIV patients starting antiretroviral therapy (ART)—and symptoms are exacerbated.

A large study recently found that early postpartum women are twice as likely to develop tuberculosis as non-pregnant women.

• Prevalence of active TB in pregnancy 0.25 – 7 % In low burden countries

• Prevalence of LTBI probably matches the population (4.2 % LTBI)


Kenneth H. Mayer, Section Editor
Jyoti S. Mathad and Amita Gupta
Tuberculosis increases mortality during pregnancy or postpartum, especially in HIV-positive women. Pregnant women with pulmonary or extrapulmonary tuberculosis, other than lymphadenitis, also have increased risk of complications including antenatal hospitalization and miscarriages.

MODIFIED PUBLIC HEALTH CLASSIFICATION

- 0  No Exposure; Not Infected
- 1  Exposure; Not Infected
- 2  Infected; No Active Disease
- 3  Active Disease Pulmonary and or Extra-Pulmonary
- 4  Old Disease or “UDA”
- 5  Under Evaluation for Active TB
- 6  “TB wannabes”/Atypical/NTM
- 7  Associate Involvement
- 8  Exposed Contacts
"To Be or Not To Be"

Risk, Signs, Symptoms, Micro (Smear, Culture, Probe, Final Culture) Images Tissue Dx

...BUT IS IT?

Based on 2003 – 2007 Medicare data
Projected 8% annual increase in prevalence
Estimated 86,244 cases in 2010 at an annual cost $815 million;
87% inpatient
70% of NTM disease cases occurred in oceanic coast line & gulf states
Medication cost: 76% of all total cost

Number of TB related deaths

Number of NTM related deaths

BCG – Does that matter?
NTM - Is that important?
WHICH NTM THE MOST : MAC
TESTS FOR IMMUNE RESPONSE

TB Skin Testing

- **In vivo** measurement of cell-mediated immunity to mycobacterium antigens in the form of a delayed-type hypersensitivity reaction
- Previous exposure to mycobacterium results in production of **sensitized lymphocytes**
- Sensitized lymphocytes secrete cytokines to attract neutrophils, **memory CD4 T cells, CD8 T cells**, which cause induration and erythema
- Induration measured 48–72 hours post implantation
- Sensitivity of the tuberculin skin test is limited in **immunocompromised** individuals
- Specificity is limited because of cross-reactivity due to prior infection with **environmental mycobacteria or BCG vaccination**

Interferon-Gamma Release Assay

- **In vitro** measurement of INF-gamma released by effector T cells responding to specific TB antigen stimulation, such as ESAT-6 and CFP10
- Previous exposure to *M. tuberculosis* results in production of **sensitized T cells**
- Sensitized T cells secrete IFN-γ (cytokine) when they reencounter specific *M. tuberculosis* antigens
- IFN-γ secreted by effector T cells measured ~20 hours poststimulation
- **Antigens used in IGRAs (ESAT-6, CFP10, TB7.7) are not present M. bovis BCG and in most environmental mycobacteria**

TESTING METHODOLOGIES FOR IMMUNE RESPONSE

Tuberculin skin testing (TST) Interferon-gamma release assay (IGRA)

- Mantoux test, Purified Protein Derivative (PPD)
- T-SPOT®. TB test
- QuantiFERON®-TB Gold/Plus

Advantages & Disadvantages
NTM/MOTT
BCG
Technique
Anergy?
What are the drawbacks of TST/Mantoux test/PPD?
ISSUES AFFECTING THE USE OF TST

Limitations
- Need for trained personnel to administer the intradermal injection and also interpret the test
- Inter- and intra-reader variability in interpretation
- Need for a return visit to have the test read
- False-positive results due to cross-reactivity of antigens within the PPD to both BCG and nontuberculous mycobacteria
- False-negative results due to infections and other factors, rare adverse effects, and complicated interpretation

False-Negative Results
- In persons with clinical conditions associated with immunosuppression or overwhelming illness
- After recent viral and bacterial infections
- In association with treatment with immunosuppressive drugs

False-Positive Results
- Repeat TST can restore reactivity in persons whose TST reactivity has decreased over time
- Cross-reactivity with BCG vaccine
- Cross-reactivity for non-tuberculous mycobacteria (NTM) is increased for persons living in areas where nontuberculous mycobacteria is common
- Errors in TST placement or reading

This is based on mycobacterial genomics and antigen specific T cell response, Antigenic targets include ESAT-6 and CFP-10
This is performed in homeless/transient resident population and has a higher PPV and NPV
What is IGRA and what is it based on?
**TB-SPECIFIC ANTIGENS USED IN IGRAS**

- Produce measurable immunologic responses in TB-infected persons
- Are present in
  - *Mycobacterium tuberculosis* complex organisms, including *M. tuberculosis*, *M. bovis*, *M. africanum*, *M. microti*, and *M. canetti*
  - *M. kansasii*, *M. szulgai*, and *M. marinum* (nontuberculous mycobacteria)
- Are absent in and do not cross-react with
  - *M. bovis* BCG sub strains
  - *M. avium* and most other nontuberculous mycobacteria

JA note: except "KMSGF"

*In vitro* measurement of INF-gamma released by effector T cells responding to specific TB antigen stimulation, such as ESAT-6 and CFP10.
IGRAs demonstrate only fair concordance with the TST in pregnancy. Two US studies screening pregnant women for latent tuberculosis found that most discordance was IGRA negative/TST positive attributed to previous BCG vaccination among the foreign-born.

In contrast, in India, discordance was largely IGRA positive/TST negative. Epidemiological (eg, recent tuberculosis exposure) and biological factors (eg, malnutrition, immune changes of pregnancy) may explain this, although the significance of this discordance needs further study.
TARGETED TST OR IGRA: CAN BE PERFORMED IN PREGNANCY

- Identified increased risks
- Foreign born
- Recent immigrants
- Frequent travelers
- HIV / immune compromised

TARGETTED TST

Clin Inf Disease 2012; 55:1532/ATS etc …but what happened to our case
OTHER APPROACHES

- Counselling
- \LTBI\ testing prior to pregnancy if indicated
• Silicosis** ..................... 30% ** silica exposure
• DM .................................. 2-4 %
• CRF .............................. 10-25%
• Gastrectomy ................. .2-5%
• J-I Bypass ...................... 27-63%
• Solid Organ Transplant .... 37% / 70%
• Carcinoma of head or neck 16%
What is the relative Increased Risk for developing Active TB by selected conditions:

- NOT PREGANCY
J 7 200
HIV  5 mm
Contact  5mm
Congregate setting  10 mm
No risk  15mm
What are the criteria for a positive TST requiring consideration for chemoprophylaxis?
JEOPARDY 1

Must check for active TB

Do not forget to look for Extrapulmonary TB
What do you do before starting treatment for latent TB/TB Infection?

…Remember the one definitive contraindication**
### Suggested Traffic Light Plan

<table>
<thead>
<tr>
<th>A: DATA</th>
<th>B: EVALUATE</th>
<th>C: SCAN</th>
<th>D: TREAT LTBI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quantify:</strong> Assess Borderline Indeterminate Discordant Results</td>
<td><strong>Rule Out:</strong> Active TB Disease Based on Symptoms and Risk</td>
<td><strong>Rule out Extra-Pulmonary Disease</strong></td>
<td><strong>Dx; LTBI Infection</strong></td>
</tr>
<tr>
<td><strong>Document</strong></td>
<td><strong>Symptoms History / Physical</strong></td>
<td><strong>Detailed Review of Systems: “ROS 101”; Repeat Physical exam specially LN Exam</strong></td>
<td><strong>Should we Offer Rx? Assess Risk Benefit Ratio and patient engagement, understanding and adherence to treatment.</strong></td>
</tr>
<tr>
<td><strong>Check HIV Other Immune status</strong></td>
<td><strong>Chest Radiograph CT Scan if needed</strong></td>
<td><strong>Correlate with Chest and other imaging if applicable</strong></td>
<td><strong>Pre-Rx start: Lab Check</strong></td>
</tr>
<tr>
<td><strong>Risk Stratify Check Source Case Culture/ Sensitivity</strong></td>
<td><strong>Sputum Smear/NAAT; Induce Sputum if needed May need Direct Observed Sputum Evaluation (DOSE)</strong></td>
<td><strong>Assess Background History again?</strong></td>
<td><strong>Treat for TB Infection based on Risk Benefit Ratio</strong></td>
</tr>
<tr>
<td><strong>Conclude after Full Evaluation: Proceed to Steps B-E</strong></td>
<td><strong>Assess Pre-Test Probability; Treat for active TB disease index of suspicion is high</strong></td>
<td><strong>Treat for active TB disease index of suspicion is high</strong></td>
<td><strong>Monitor Side Effects; Drug-Drug Interaction; Establish Care Coordination with Primary Care Team</strong></td>
</tr>
</tbody>
</table>

*Designed by JA*
RX FOR LTBI IN PREGNANCY IF RECENT INFECTION/ CLOSE HOUSEHOLD CONTACTS SEVERE IMMUNE COMPROMISED HOSTS HIV

OTHERWISE DEFER**** BUT REPEAT PROCESS AND RULE OUT ACTIVE TB PROCESS POST DELIVERY******

***** WHY? RISK OF INH HEPATOTOXICITY POST PARTUM

*****ADHERENCE TO FOLLOW UP LOW 42 % ..CRUZ ET AL AM J OBST GYN 2005;192:1455

***** HOWEVER NEEDS STRICTER STRUCTURED POST PARTUM FOLLOW UP CLOSE THE LOOP BY CARE COORDINATION

****** USE OF RIF AND D-D INTERACTION RELATED TO CONTRACEPTION MEASURES
RX OPTIONS; USUALLY RX DEFERRED, BUT IF STARTED PRIOR TO PREGNANCY, THAT SHOULD BE CONTINUED; WATCH LFTS AND FOR HIV HEP B/C

- INH 6 months*
- INH 9 months*
- RIF 4 months**
- RIF & INH 4 months
- RPT and INH weekly**

*Completion rate 20-60%

If index case MDRTB or XDRTB, then a big problem

** DOT
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*** (RIF INH PZA ETM)

*******

Culture back

**********

Pan sensitive

***RIP(drop E)

2 month Sputum culture negative

***Drop PZA

| 0…… 2-4 weeks……..6 weeks  8-12 wks  …….6mths  
| 12mths 18mths

* Check dosage; ***Watch for ADR/LFTs/DILI
J 14 300
No SM
No PZA in USA
9 months at least
Vitamin B6 a must
What is TB treatment in pregnant women?
DRUGS FOR RX IN PREGNANCY

REF **ATS GUIDELINES** **MMWR 2003**
VERSUS **IUAT AND WHO**

**NO PZA,**
**NO SM OR ANY AMINOGLYCOCIDES;**
**FQS … ONLY IF NO OTHER ALTERNATIVES**

- **INH HEPATOXICITY**
- **RIF *** Watch for hemorrhagic complications peri delivery**
- **RB in case of HIV & Pregnancy and use of PI ; watch levels**
Rare

- Associated with maternal HIV infection, miliary disease and tuberculous endometriosis**
- ** needs a high index of suspicion ..a true ILH/UMC story
- Hematogenous spread
- Multiorgan involvement with low APGAR
- TST unhelpful
- High mortality
• What is Congenital TB?

• **Note Neonatal TB on the other hand follows exposure to mother’s resp secretions.**
• Not contraindicated; concentrations small; no toxic effects
• AVOID Rifabutin AND FQs
• Not recommended when treatment with second line drugs
GUIDELINES ABOUT BREAST FEEDING
OUR RECENT CASE AND THE REST OF THE STORY

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University Medical Center NTM (Non-Tuberculosis Mycobacterial) Disease Program Clinic, New Orleans
UMC CLINIC NURSE 504 702 4574 ; fax 504 702 -5728
WETMORE TB CLINIC /Office of Public Health Region 1 New Orleans Phone : 504 826 2063 FAX 504 826 2052
TB/Mycobacterial Disease program HOT LINE: Ms. Maureen Vincent 504 568 4581 or CELL 504 638 7053

REFER TO
1. Wetmore Clinic Fax referral print through Epic
2. NTM - ELD/UMC Clinic EPIC direct
Use TB Hot line 504 638-7053 Ms. Maureen JA 504 875 7680 jali@lsuhsc.edu

DOTS YES, BUT ALSO ………………………..

http://www.medschool.lsuhsc.edu/tb/
http://ntm.lsuhsc.edu