Diagnosis & Management of LTBI

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Objectives

• US (& rural) TB epidemiology indicates treating LTBI is appropriate strategy

• Differentiate LTBI from active TB

• Understand the latest treatment recommendations for latent TB.

• Recognize how new technology affects LTBI diagnosis (eg, IGRA, QFT-G, T-Spot. TB)
Epidemiology of Tuberculosis
TB in Foreign-Born Immigrants to US

• Proportion of TB cases foreign-born increased from <25% to 57% (1986-2006)
• US-born TB cases decreased by 45% (1993-2006)
• ~70% MDR TB occur among Foreign-born
  – Anticipate XDR TB & TDR TB
• SE Asians, Sub-Saharan Africans, & Latin Americans
• Concentrated in NY, NJ, Ca, Fl, IL, Tx
• Active cases most often arise from prior infection
• ~55% occur within 5 yrs of immigration
  ≤ 2 yrs in US 75/100,000
  > 2 yrs in US 16/100,000

CDC; Cain et al: JAMA 2008
How do Rural TB rates compare to the National TB rates?
US vs. Foreign-Born TB Cases – Iowa 2010

US: 3.4 TB cases/100,000
Iowa: 1.3 TB cases/100,000
~1/yr drug resistant
TB Nomenclature

• Latent TB Infection (~90% TB infections):
  – Positive TST (or IGRA eg, QFT-G)
  – No symptoms
  – Negative or chronic CXR changes
  – Can not transmit disease to others.

• Active TB Infection (~10% TB infections):
  – TST (or IGRA) may be positive
  – Symptoms present
  – CXR changes & sputum smear positive in most cases
  – Disease transmission to others

• Treatment for both latent and active infections

↓ Prophylaxis, preventive therapy
TB Pathogenesis
Progression to Disease

Infection (LTBI)

3-4% First Year
1-2% Second Year
~0.1% per year thereafter

Disease (Active Infection)

No Active Disease (~90%)
Outcome for those Infected by TB

- **Active infection**: ~5% of infected become active in 1st 2 yrs.
  - Sick (coughing, no energy, losing weight, fevers)
  - Spreads TB to others

- **Latent infection**: ~90% of infected individuals have latent infection
  - Healthy
  - Can not spread TB to others
  - Latent TB Infection accounts for majority of TB

...But 2-5% with latent infection progress to active after 1st two years
Focus of TB Control in the US: Targeted Testing & Rx for LTBI

• Few cases due to transmission from other active cases (↓ HIV related cases)
• High rates of TB among foreign-born immigrants to US (including rural locales) from high incident countries
• “Targeted tuberculin testing” is the theme of the LTBI guidelines
• One of the main targets must be the foreign-born immigrants from high incident countries
Targeted TB Testing
Decision to Test = Decision to Treat

- Patients at highest risk for progression to active TB
- Patients with medical conditions that increase risk for active TB
- Patients in whom active TB is more prevalent
Targeted TB Testing
Decision to Test = Decision to Treat

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Targeted TB Testing
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Patients at highest risk for progression to active TB:

• HIV infection, or risk factors for HIV infection
• Close contact of persons with infectious TB (e.g., pulmonary, laryngeal TB)
• New TB infection (TST conversion within prior 2 years)
• Old fibrotic lesion on chest x-ray consistent with prior pulmonary TB
• IV drug abuser (HIV negative)
• Receiving TNFα antagonist for RA or Crohn’s
Targeted TB Testing
Decision to Test = Decision to Treat

- Patients at highest risk for progression to active TB
- Patients with medical conditions that increase risk for active TB
- Patients in whom active TB is more prevalent
Targeted TB Testing
Decision to Test = Decision to Treat

Patients with medical conditions that increase risk for progression to active TB:

- Jejunoileal bypass surgery or gastrectomy
- Silicosis
- Solid organ transplant (e.g. renal, heart)
- Chronic renal failure/hemodialysis
- Head/neck carcinoma
- Hematologic malignancies (e.g. leukemia, Hodgkin’s)
- Immunosuppressed, particularly steroid treatment ($\geq 15$ mg/day, $\geq 1$ month)
- Substantial weight loss: $>10\%$ ideal body weight
- Diabetes mellitus
Targeted TB Testing

Decision to Test = Decision to Treat

- Patients at highest risk for progression to active TB
- Patients with non-HIV medical conditions that increase risk for active TB
- Patients in whom active TB is more prevalent
Targeted Skin Testing
Decision to Test = Decision to Treat

Patients in whom active TB is more prevalent:

• Recent arrivals (< 5 years) from high TB prevalence countries (Africa, SE Asia, Pacific Isles, Latino, E. Europe, Russia)

• Resident or employee of high-risk congregate settings: prisons, jails, nursing homes & other long term facilities for elderly, hospitals and other health care facilities, residential facilities for AIDS patients, and homeless shelters

• Mycobacteriologiy lab workers
Case S. B.

- 56 yo female
- Asymptomatic
- TST+ (estranged husband had TB 20 years ago)
- On no drugs, no HIV risk factors, no EtOH
- Chest x-ray unremarkable
What is the diagnosis?

Latent TB Infection (LTBI)
New technology replacing old…
Mantoux Tuberculin Skin Test (TST)

- Standard (old) method of skin testing for *M. tuberculosis* infection
- Produces delayed-type hypersensitivity reaction
- TST is useful for:
  - Detecting LTBI
  - Contact investigation: Determining how many people in a group are infected
  - Evaluating persons who have symptoms of active TB
Administering the TST

• Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-gauge needle
• Produce a wheal 6 to 10 mm in diameter
Low (Old) Tech... TST
Delayed-type Hypersensitivity Reaction @ 48-72 hrs

- Positive: 18 mm Induration
- A positive test may be measured up to 7 days out
- A negative reaction can be read accurately @ 48-72 hrs
Ballpoint Pen Technique
Reading a TST

• Measure induration, not erythema by 48 to 72 hours

• Record induration size in millimeters, in addition to interpretation (“negative” or “positive”)

• Ensure trained health care professional measures & interprets the TST

• Educate patient & family about the significance of a positive test
TST Interpretation

Positive classification based on pre-test probability of TB:

≥ 5 mm = positive
  • HIV positive
  • Household or close contact to patient with infectious, active TB
  • CXR consistent with old/healed TB
  • Organ transplant or other immunosuppressed patient

≥ 10 mm = positive
  • Foreign born (e.g. Africa, SE Asia, Hispanic, India, China, E Europe)
  • IV drug abusers
  • Residents or employee of high risk congregate setting
  • Non-immunosuppressive medical conditions known to increase risk of active TB
  • Mycobacteriology lab workers

≥ 15 mm = positive
  • Persons in regions of low TB incidence
Factors Causing False-Negative TST

- **Anergy** = Weakened immune system ⇒ Inability to react to TST
  - Anergy testing utility in TST-negative persons not demonstrated in clinical trials
- New TB infection (eg, 2-10 weeks post exposure)
- Newborns
- Live virus vaccination (eg, measles, smallpox) suppresses TST response
- Overwhelming disease (eg, miliary TB)
- Poor TST administration technique
Other Limitations for TST

- Interpretation variability; False positives: NTM, BCG...

- BCG Vaccine effect on TST Interpretation
  - Induces 3-19 mm TST reaction in 1st few mos.
    - Reaction wanes significantly by 10 years
    - Reaction size does not correlate with protection
  - Positive TST most likely due to TB infection:
    - Persons from regions of high TB prevalence (eg. hispanic, asian)
    - Large reaction (>15 mm)
  - Prior BCG, should be Tested and Treated if positive

- Booster Phenomenon
  - False negative TST, becomes positive as a result of skin testing
  - Most common situations:
    - Initial TB infection many years previous
    - Prior BCG immunization
  - Two Step Skin Testing (TST x 2, one week apart)
    - Elderly nursing home population
    - Prior BCG immunization
TB Testing Upgrade...A Reality
Interferon Gamma Release Assay (IGRA)

Measures interferon-gamma (IFN-γ) released by lymphocytes in response to TB antigens

• QuantiFERON® Family:
  – QuantiFERON®-TB test 1999
  – QuantiFERON® - Gold 2005
  – QuantiFERON® -G-IT 2007

• New in US Aug ‘08: T-Spot. TB®
Presentation of TB antigens

- TST (multiple = PPD)
- IGRA (TB specific = ESAT6, CFP10)

IGRA Results include control wells

- Negative (Nil) – no antigen (subtract from pt value)
- Positive – mitogen stimulation

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<thead>
<tr>
<th>Step</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>1</strong></td>
<td>Collect the blood sample and centrifuge to separate Peripheral Blood Mononuclear Cells (PBMCs)</td>
</tr>
<tr>
<td><strong>2</strong></td>
<td>Wash and count the PBMCs</td>
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<td><strong>3</strong></td>
<td>Add PBMCs to wells with antigens and incubate overnight (37°C, CO₂)</td>
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<td><strong>4</strong></td>
<td>Wash and add secondary antibody</td>
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<tr>
<td><strong>5</strong></td>
<td>Add substrate and count any resulting spots. One spot = one T cell</td>
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**T-Spot. TB™**

- Nil Control
- Infection
- Positive Control (Mitogen Stimulation)
- Oxford Immunotec
LTBI Testing Upgrade...Generalizations
Interferon-γ Release Assay (IGRA)

• Accurate blood testing is a reality; Substitute for TST
• QuantiFERON-TB Gold® & T-Spot. TB®
  – Commercially available, costly
  – Measures Interferon-γ production by sensitized lymphocytes (T-cells)
  – Does not cross-react with BCG or MAC (antigens: ESAT-6, CFP-10)

• Advantages/Indications
  – Patients in whom false positive TST likely (eg BCG, NTM)
  – F/u not necessary in 48-72 hours; Ideal for patients unlikely to return
  – Equal Sensitivity, Increased Specificity compared to TST

• Limitations: Blood must be processed w/in 12h*; Multi-popn. data limited (HIV, Elderly, Children); Serial testing performance uncertain; Cost
• Does not distinguish latent from active disease
• Newest: *QFT-GIT (in tube...↓time factor)

Indeterminate IGRA Results

- Poor response to mitogen that resolves with repeat assay
  - Delayed specimen processing
  - Technical errors
- Persistent poor response to mitogen
  - Anergy from immunosuppression
  - May occur in healthy persons
- High background IFN-γ levels (high NIL response)
  - Often persistent, reasons unclear
  - IGRA not useful
Key Recent References

CDC. Updated Guidelines for Using IGRAs to detect M tuberculosis infection, US 2010. MMWR Recommendations and Reports June 25, 2010

At-risk person

TST (or IGRA) & symptom review

Negative

Positive

Chest x-ray

Normal

Potential candidate for Rx of latent TB

Treatment not indicated

Abnormal

Evaluate for active TB
...Back to SB, the case of LTBI

- Obtained:
  - TST (Mantoux) Positive
  - Chest x-ray Negative

- Do you need sputum smear and culture?
  
  Only if suspicious for active disease
  Not necessary in asymptomatic patient, positive TST, normal CXR
What Treatment for S. B.?
Treatment of Latent TB Infection

• ATS/CDC/IDSA sanctioned guidelines released 5/2000 (AJRCCM & MMWR)

• Evidence-based recommendations

• 9 months of therapy represent re-interpretation of old data, not failure of previously recommended 6 month regimen.
TB Case Rates vs. No. of Months INH Treatment (Bethal Data)

Comstock GW: Int J Tuberc Lung Dis 1999
Treatment of Latent TB Infection
HIV Neg. & Pos. Adults
(Dept of Public Health provides meds)

1. Daily INH for 9 months (270 doses w/in 12 mos)*,+ 
2. Daily INH for 6 months (100 doses w/in 9 mos)+
   Exclude any w/ old healed fibrotic TB lesions on CXR
3. 1*,+ or 2+ above, administered as DOT, twice weekly
   76 doses w/in 12 months or 52 doses w/in 9 months
4. Daily rifampin for 4 months (120 doses w/in 6 m)
   Alternative for those who are known contacts with INH
   resistant TB or INH not feasible

Completion = Total # doses, not duration alone
If > 2 month interruption, re-evaluate for active TB before
restarting

*Recommended for children < 18 years
+Recommended for pregnant women.

ATS/CDC/IDSA 5/2000; Update 8/2003
Even Shorter Treatment = Reality…

- **New regimen**: INH 900 mg plus Rifapentine 900 mg weekly x 3 months (12 doses, DOT)
- Open Label, Randomized Noninferiority trial 2011
  - **New regimen** (DOT) vs INH x 9 mos (not DOT)
  - N ~ 8000 US & Canada x 33 mos (few HIV, children)
  - Target population: TST converters & +TST old healed TB chest x-ray
  - Result: **New Regimen** equivalent to 9 mos INH
    - Drug d/c d/t adverse events 4.9 vs 3.7%
    - Increased hypersensitivity (**New**) vs hepatotoxicity (INHx9)
    - Trend toward **New regimen** better than INHx9
      - **New Regimen** group: TB rate ~50% lower
      - Rx completion rate 82% vs 69%

Sterling TR et al. *NEJM* 2011;365:2155-66
New Regimen vs INHx9

Sterling TR et al. NEJM 2011;365:2155-66
Real World Recommendation

- *New Regimen* (DOT) does not replace INHx9, but equal option for Rx LTBI
- Iowa Dept Public Health (IDPH) provides INHx9 at no cost for anyone diagnosed w/ LTBI
- IDPH agrees *New Regimen* equivalent to INHx9
  - *New Regimen* costs 10x the standard INHx9 regimen
  - IDPH unable to cover high cost of *New Regimen* & DOT
  - Notify IDPH if you dx LTBI & Rx w/ New Regimen (DOT)
- *New Regimen* not recommended for the following:
  - Child <2
  - HIV/AIDS taking HART
  - Pregnant women
  - Contacts of INH &/or Rif resistant TB
Treatment for S.B.

• INH daily x 9 months
• County public health department supervised treatment:
  – PHN performed Clinical Monitoring
  – 30 day supply aliquots of INH provided
  – Completed 9 months w/in 9 months
Summary Points

• Screen persons at high risk for TB (eg, foreign born)
• Seek to distinguish active vs. latent TB infection & drug regimen modifying issues
• LTBI diagnosis (TST) and Rx reviewed
  – Decision to test = Decision to treat!
  – Clinical Monitoring role for PHN
  – Drug toxicity issues
• New TB tests: IGRA, QFT-Gold, T-Spot. TB
• Iowa Department of Public Health provides TB Rx at no cost to patient (exception: new regimen)
• Call Iowa Department of Public w/ any TB question or suspect drug resistant LTBI (link MD TB experts)
Monitoring on INH Treatment

• Educate the patient
  – Liver disease symptoms & signs
  – Stop meds until contact made with health care

• The critical element for preventing INH toxicity is Clinical monitoring…PHN
  – Absolutely necessary to do, absolutely necessary to do well & absolutely necessary to document well.

• LFTs (ALT, AST) at baseline in selected cases
  – Hx of liver disease, EtOH, pregnancy, HIV
  – Repeat monthly if abnormal at baseline, symptomatic, or pregnant
  – Stop meds:
    • Symptomatic, LFTs 3x upper limit of normal (ULN)
    • Asymptomatic, LFTs 5x

ATS/CDC/IDSA 5/2000
Clinical Monitoring

• Instruct patient to report following adverse drug reactions (ADRs):
  – Rash
  – Anorexia, nausea, vomiting, or pain in RUQ
  – Fatigue or weakness
  – Dark urine
  – Persistent numbness in hands or feet

• Monthly visits should include review of:
  – Rationale for treatment
  – Adherence to therapy
  – Symptoms consistent with ADR(s)
  – Plans to continue treatment
Liver Safety Issues for INH

• Deaths from INH hepatitis in 1960s

• 1971-72 PHS Study (14,000 pts)
  – 1% overall rate of INH related hepatitis
  – Age related increase
    • 0.3% (<35)
    • 2.3% (>50)
  – 4x increase a/w EtOH
  – 8 deaths due to INH hepatitis

• Review of PHS data (Comstock JAMA 1986)
  – 7/8 deaths occurred in Baltimore
  – Death certificate review: XS deaths due to cirrhosis in 1972
  – Unidentified co-factor related to cluster of cirrhosis cases?

• Subsequent studies: risk is lower
Latest CDC Data on INH Liver Toxicity

• SAEs during LTBI Rx, 2004-2008
• 17 patients with SAEs, all hepatotoxicity
  – 2 children < 15 yrs of age; Adults median age 39
  – One patient HIV seropositive for Hep C, HIV
  – 5/17 liver transplant (one child), 5/17 died (one transplant)
• 10/17 patients with CDC on-site investigation
  – Prescribers followed ATS/CDC guidelines for Clinical Monitoring
  – Symptoms 1-7 months after INH started
  – Fatigue, nausea, abdominal pain in 7 patients who waited for jaundice to seek medical attention
  – 2 patients INH discontinued within 3 days of symptoms, 8 stopped at least one week after symptom onset; all after medical instruction
• Death & liver transplantation ~1/150,000 - 1/220,000
• SAEs idiosyncratic reaction, independent of dosing, possible anytime during treatment, can occur in children

MMWR 2010 59(08):224-229
Deaths from INH Hepatitis

• Rates in women increased
  – Pregnancy & immediate post-partum period (3 mos)

• Concurrent acetaminophen questionable

• INH death rate reduced by Clinical Monitoring
  – Stopping INH at symptom onset reduces deaths
  – 7/8 liver transplants for INH hepatitis: Pts continued INH >10 d beyond symptom onset
    (CDC: MMWR 1993)
Safety Issues for INH: Current Practice Outcomes

• Most PHD practice Clinical Monitoring vs. biochemical monitoring

• Clinical Monitoring:
  – Educate for Rx related ADRs & Reviews adherence
  – Stop INH if any question until consult with clinician
  – CDC: “Medical providers should emphasize to patients that INH treatment should be stopped immediately upon the earliest onset of symptoms (e.g. excess fatigue, nausea, vomiting, abdominal pain, or jaundice), even before a clinical evaluation has been conducted, and that initial symptoms might be subtle and might not include jaundice.”
Monitoring on Treatment

• Educate the patient
  – Liver disease symptoms & signs
  – Stop meds until contact made with health care

• Clinical monitoring monthly…PHN

• LFTs (ALT, AST) at baseline in selected cases
  – Hx of liver disease, EtOH, pregnancy, HIV
  – Repeat monthly if abnormal at baseline, symptomatic, or pregnant
  – Stop meds:
    • Symptomatic, LFTs 3x upper limits of normal (ULN)
    • Asymptomatic, LFTs 5x ULN

ATS/CDC/IDSA 5/2000
More Case Examples & Discussion
How Should Immunosuppressed Persons at Risk for TB Be Managed?

Empiric treatment for LTBI even when TST or IGRA neg on repeat testing 8-10 weeks after exposure

- Advanced HIV infected contacts
- Children < 5 years who are contacts
- Contacts with other causes of immunosuppression
- Persons at risk for exposure to TB who are to receive treatment with TNF alpha antagonists
TNFα Antagonists

- Block TNFα activity which is required for granuloma formation & containment of *M tuberculosis*
- Used for RA, Crohn’s disease, Psoriasis and a variety of other immune mediated diseases
  - Remicaid (inflixamab)
  - Embril (entanercept)
  - Humira (adalimumab)
  - Cimzia (certolizumab)
- Patients should be evaluated for LTBI with a TST.
- Treatment of LTBI should be initiated prior to therapy
Questions Remain

• Unknown
  – Does treatment of LTBI need to be completed prior to use of TNF-α antagonist?

• Unknown
  – Does a person at risk of TB who is TST negative need to be treated?
    • Consider treatment of high risk TST negative patients

• No need to continue INH after completion of treatment for LTBI
Case 2

• 36-year-old Native American female
• History of diabetes
• 35 weeks pregnant
• TST = 18 mm of induration
• No symptoms of TB disease
• CXR, CBC, LFTs normal
• No known contact with TB patient
Case 2

Questions

1. What are this patient’s risk factors for TB infection or disease?

2. What is the appropriate management for this patient?
Case 2

Discussion of risk factors

- Persons with diabetes mellitus are 2 to 4 times more likely to develop TB disease than those without diabetes.
- Risk may be higher in insulin-dependent diabetics and those with poorly controlled diabetes.
Discussion of management

- Pregnancy has minimal influence on the pathogenesis of TB or the likelihood of LTBI progressing to disease
- Pregnant women should be targeted for TB testing only if they have specific risk factors for LTBI or progression to disease
- Some experts prefer to delay treatment until after the early postpartum period, unless the woman has recent TB infection or HIV infection
Case 3

• 41-year-old Hispanic male
• Moved to U.S. from Mexico 4 years ago
• Known contact of infectious TB case
• TST = 5 mm of induration
• 3 months later TST = 23 mm of induration
• No symptoms of TB disease
• Normal CXR, CBC, AST, and bilirubin
Case 3

Questions

1. What are the patient’s risk factors for TB infection or disease?

2. Has the management of this patient to date been appropriate?
Case 3

Discussion of risk factors

• Patient is a contact of an infectious TB case
• Recent immigrant to the U.S. from a country with a high prevalence of TB. Such persons have increased rates of TB
• If the patient had not been a contact, the recent immigration (less than 4 years) would have made him a candidate for TB testing, but the 5-mm reaction would not be considered positive
Case 3

Discussion of management

• Should be treated for LTBI if TST reactions $\geq 10$ mm of induration

• As a contact of an active TB case, 5 mm of induration is considered positive

• This patient should have been treated for LTBI immediately after the first TST
Case 4

- 56-year-old White male
- Works in a mycobacteriology lab
- TST result negative 1 year ago
- *M. marinum* infection in his hand 8 months ago
- TST result 5mm
- QFT-G test positive
- No symptoms of TB disease, CXR normal
- No known contact with a TB patient & no known spills or accidents in the lab