Opportunities for TB Prevention in College Students

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Young adults with TB in U.S.

- 18 year old who arrived from Guatemala 3 years previously
  - Presents with fever and cough to ER
  - Bronchitis diagnosed
  - Returned to ER with massive hemoptysis

- 22 year old in U.S. since college entry
  - TB in lymph nodes around his airway
  - With treatment lymph nodes may get larger before resolving

Q. “Is there anything I could have done to prevent this from happening?”
Natural History of TB

Exposure to infectious TB

- Not infected
- Latent TB infection (LTBI)

Latent TB infection (LTBI)

- 90% Remain latently infected
- 5% Progression to active TB disease "Reactivation"

5% Develop "primary" active TB disease
Failure to Prevent TB

- 1 in 10 individuals who develop TB die
- TB disease is costly ($40K - $1 million)
- TB spreads through the air
Questions

• What is the frequency of TB disease and latent TB infection in young adults?
• What strategies are most effective to detect and treat TB infection?
• How can TB disease be rapidly identified when it occurs in college settings?
What is the frequency of TB disease and infection?
TB Cases in the United States
1982–2015

First increase in 23 yrs

CDC, Annual Report, 2015
Salinas, et al. MMWR, 2016

No. of Cases

Percentage

Number of Cases

Percent of Total Cases
How do TB Cases Occur in California?

7.5% Importation

13% Recent Transmission

79.5% Reactivation of remote infection

~2,000 TB Cases Per Year
International Students at U.S. Colleges and Universities

In 2013/14

886,052

International students studied at U.S. colleges and universities

The number of international students studying in the U.S. grew by 8% over the prior year and is now at a record high.
Top 10 States with International Students

The top 10 states together host 61% of all international students.

Top 3 states:
- California
- New York
- Texas

host 32%.
Places of Origin for International Students

- China: 31%
- India: 12%
- South Korea: 8%
- Saudi Arabia: 6%
- Other: 32%

50% of international students come from China, India and South Korea.
WHO 22 High Burden TB Countries
Overseas Screening Requirement

**NO TB screening** is required for the following groups:

- Visitor/tourist
- **Student**
  - Work
  - Unauthorized (undocumented)

**Required for:**

- Immigrant
- Refugees
- Permanent resident applicants
- Asylees
- Status adjusters
## TB Disease in Persons

### Ages 18-24 in United States, 2011

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>878</td>
<td>2.8/100,000</td>
</tr>
<tr>
<td>US born</td>
<td>629</td>
<td>0.9/100,000</td>
</tr>
<tr>
<td>Foreign-born</td>
<td>249</td>
<td>19/100,000</td>
</tr>
</tbody>
</table>
TB Exposures on College Campuses in U.S.

- ~ 900 TB cases in 18-24 year olds

Potential for ~1 TB exposure every day on a college campus in US
### Reason for presentation: TB Cases among Adults 18-24 years old in United States, 2011

<table>
<thead>
<tr>
<th>Reason for TB evaluation</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL</strong></td>
<td>878</td>
</tr>
<tr>
<td><strong>TB Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>TB Symptoms</td>
<td>671 (76%)</td>
</tr>
<tr>
<td>Contact investigation</td>
<td>57 (7%)</td>
</tr>
<tr>
<td>Targeted testing</td>
<td>48 (5%)</td>
</tr>
<tr>
<td>Occupational screen</td>
<td>23 (3%)</td>
</tr>
<tr>
<td>Immigrant medical exam</td>
<td>27 (3%)</td>
</tr>
<tr>
<td>Other (HCW, incidental lab result, unknown)</td>
<td>52 (6%)</td>
</tr>
</tbody>
</table>
### TB Case Characteristics in Foreign-born Adults 18-24 years old, U.S., 2011

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Foreign-born</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td><strong>Years in US at TB diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>288</td>
</tr>
<tr>
<td>2 – 5 years</td>
<td>231</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>110</td>
</tr>
<tr>
<td><strong>Location of Birth</strong></td>
<td></td>
</tr>
<tr>
<td>Mexico</td>
<td>125</td>
</tr>
<tr>
<td>Guatemala</td>
<td>46</td>
</tr>
<tr>
<td>India</td>
<td>43</td>
</tr>
<tr>
<td>China</td>
<td>40</td>
</tr>
<tr>
<td>Philippines**</td>
<td>40</td>
</tr>
<tr>
<td>Vietnam</td>
<td>36</td>
</tr>
<tr>
<td>Other</td>
<td>299</td>
</tr>
</tbody>
</table>
## Clinical Characteristics TB Case: Adults 18-24 years old, U.S., 2011

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectiousness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smear positive, culture positive</td>
<td>346</td>
<td>39%</td>
</tr>
<tr>
<td>Smear negative, culture positive</td>
<td>193</td>
<td>22%</td>
</tr>
<tr>
<td><strong>Site of Disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary only</td>
<td>165</td>
<td>19%</td>
</tr>
<tr>
<td>Pulmonary only</td>
<td>616</td>
<td>70%</td>
</tr>
<tr>
<td>Both extrapulmonary and pulmonary</td>
<td>95</td>
<td>11%</td>
</tr>
<tr>
<td><strong>Abnormal chest radiograph</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cavitary chest radiograph</td>
<td>278</td>
<td>32%</td>
</tr>
<tr>
<td>Abnormal chest radiograph</td>
<td>694</td>
<td>79%</td>
</tr>
</tbody>
</table>
## Latent TB Infection in 18-24 year olds, U.S. 2011

<table>
<thead>
<tr>
<th></th>
<th>IGRA positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>US-born</td>
<td>1.3%</td>
</tr>
<tr>
<td>Foreign-born</td>
<td>8.7%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2.5%</strong></td>
</tr>
</tbody>
</table>

~ 800,000 young adults

Source: Estimated using NHANES and 2011 census data
Most are unaware of their TB infection and untreated!
American College Health Association

- All incoming students should be screened for risk factors for TB through a screening questionnaire

- Students with identifiable risks factors should be tested

- Treatment for LTBI should be recommended and completion should be a high priority
Barriers to TB Prevention

Patient
- Patient feels well
- Perception of risk: uncertain and not urgent
- Worried about medicine side effects

Provider
- Not considered important clinical problem
- Unclear who to test/treat
- Suboptimal tests/treatment options
Opportunities for TB Prevention in College Setting

• Young healthy adults
• Student enrollment procedures may facilitate screening
• Recent testing and treatment advances (specific test, shorter treatment)
• Can be monitored through treatment
• Risk of TB spread in dorm and classroom setting is a motivating factor
Part 1: Key Points

- Most TB cases in the U.S. are due to reactivation of LTBI and are preventable.
- TB disease continues to cause death.
- TB disease disproportionately affects the foreign-born.
- Latent TB infection is nearly 10 X higher in foreign-born.
- Historical barriers have impeded LTBI treatment adoption in many practice settings.
What are the effective strategies for detection and treatment?
What is Risk-based Testing?

• Only test patients who have “TB risk factors”

• Treatment decisions routine:

“\textit{A decision to test is a decision to treat}”
Why not Test Everyone?

- Testing populations with low prevalence will result in many false-positive results.

- Among low-risk U.S.-born patients:

<table>
<thead>
<tr>
<th>Prevalence of latent TB infection</th>
<th>False-positive rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.8%</td>
<td>46%</td>
</tr>
</tbody>
</table>

Miramontes, PLOS One, 2015
Pai, Clin Micro Rev, 2014
# U.S. Preventive Services Task Force

## Draft: Recommendation Summary

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>The USPSTF recommends screening for latent tuberculosis infection (LTBI) in populations that are at increased risk.</td>
<td>B</td>
</tr>
</tbody>
</table>

### Population

Adults who are at increased risk for tuberculosis:
- persons born in, or former residents of, countries with increased tuberculosis prevalence
- persons who live in, or have lived in, high-risk congregate settings (such as homeless shelters and correctional facilities)

California Tuberculosis Risk Assessment
A tuberculosis (TB) screening tool for College and University Students

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Foreign-born</strong> person from a country with an elevated TB prevalence</td>
<td>All countries within Africa, Asia/Pacific, Eastern Europe (including Russia), Latin America (including Mexico). Interferon Gamma Release Assay (IGRA) is preferred over Tuberculin Skin Test (TST) for foreign-born persons.</td>
</tr>
<tr>
<td><strong>Current or planned</strong> immunosuppression</td>
<td>HIV infection, organ transplant recipient, treated with TNF-alpha antagonist (e.g., infliximab, etanercept, others), steroids (equivalent of prednisone ≥15 mg/day for ≥1 month) or other immunosuppressive medication</td>
</tr>
<tr>
<td>Close <strong>contact</strong> to someone with infectious active TB disease at any time</td>
<td></td>
</tr>
<tr>
<td>Volunteered, worked or lived in a <strong>healthcare, homeless or correctional</strong> facility</td>
<td></td>
</tr>
<tr>
<td><strong>Travel or residence of &gt; 1 month</strong> in a country with an elevated TB prevalence</td>
<td>All countries within Africa, Asia/Pacific, Eastern Europe (including Russia), Latin America (including Mexico)</td>
</tr>
</tbody>
</table>

If LTBI test result is positive and active TB disease is ruled out, LTBI treatment is recommended.
Tuberculin Skin Test (TST)

• Delayed-type hypersensitivity reaction

• How to read:
  – Measure induration (not erythema) at 48-72 hrs
  – Record millimeters

• Positive test:
  – ≥ 5mm for immunosuppressed including HIV, recent contacts
  – ≥ 10mm for all others with TB risk
Interferon-Gamma Release Assays (IGRAs)

• QuantiFERON®-TB Gold (QFT)
  – Reported as positive, negative, or indeterminate

• T-SPOT.TB (T-Spot)
  – Reported as positive, borderline, negative, or indeterminate
IGRA advantages

• Advantages over TST
  – Not affected by BCG vaccination
  – Not affected by most non-tuberculous mycobacteria
  – Interpretation is more objective
  – No return visit needed for test interpretation
  – Patients and providers may lack confidence in TST results
# TST and QFT Specificity

<table>
<thead>
<tr>
<th></th>
<th>Specificity</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST without BCG</td>
<td>97</td>
<td>95–99</td>
</tr>
<tr>
<td>TST with BCG</td>
<td>59</td>
<td>46–73</td>
</tr>
<tr>
<td>QFT</td>
<td>96</td>
<td>94–98</td>
</tr>
</tbody>
</table>

Testing Foreign-Born Patients

- Using a test with poor specificity will result in many false-positive results
- Among foreign-born patients with prevalence 16%:

<table>
<thead>
<tr>
<th>Test</th>
<th>False-positive rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFT</td>
<td>12%</td>
</tr>
<tr>
<td>TST</td>
<td>73%</td>
</tr>
</tbody>
</table>
Diagnosing Latent TB Infection

- TSTs and IGRAs cannot distinguish between latent TB infection and active TB disease

- Active TB disease must be evaluated if IGRA or TST is positive
Rule out Active Disease Before Starting LTBI Treatment!

- Symptom screen + chest radiograph
- If abnormal collect sputum:
  1. AFB smear and culture
  2. TB PCR/NAAT
- If sputum collected:
  - Either start empiric treatment for active disease
  - Or await final culture results before starting LTBI Rx
Part 2: Key Points

• Either IGRA or TST can aid in the diagnosis of latent TB infection
• Neither test can distinguish between latent TB infection and active TB disease
• IGRA have advantages over TST in foreign-born (BCG vaccinated)
LTBI Treatment Regimens
## Treatment Regimens for Latent TB Infection

<table>
<thead>
<tr>
<th>Medication(s)</th>
<th>Frequency</th>
<th>Duration</th>
<th>Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isonizaid (INH)</td>
<td>Daily</td>
<td>6–9 months</td>
<td>180 - 270</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Daily</td>
<td>4 months (vs 3 months)</td>
<td>120</td>
</tr>
<tr>
<td>Rifapentine (RPT) + INH</td>
<td>Weekly</td>
<td>3 months</td>
<td>12</td>
</tr>
</tbody>
</table>
Isoniazid (INH)

- **Advantages**
  - Longstanding treatment for latent TB infection
  - Efficacy is 60%–90%, depending on duration of treatment
  - Fewer drug-drug interactions

- **Disadvantages**
  - Adherence
    - Initiation and completion rates <50%
  - Hepatotoxicity
    - Incidence 0.1%, but increases with age
  - Clinic time required for 9 monthly visits

Rifampin

• Advantages:
  – Less hepatotoxicity (~5x less than INH)
  – Greater adherence (78% RIF vs. 60% INH)

• Disadvantages:
  – Less evidence of efficacy
  – Multiple drug interactions
    • Warfarin, oral contraceptives, methadone, protease inhibitors

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

<table>
<thead>
<tr>
<th></th>
<th>INH-RPT</th>
<th>INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3,986</td>
<td>3,745</td>
</tr>
<tr>
<td>Frequency</td>
<td>Weekly</td>
<td>Daily</td>
</tr>
<tr>
<td>Duration</td>
<td>3 months</td>
<td>9 months</td>
</tr>
<tr>
<td>Administration</td>
<td>Directly-observed</td>
<td>Self-administered</td>
</tr>
</tbody>
</table>
## Prevent TB Study Results

<table>
<thead>
<tr>
<th></th>
<th>INH-RPT</th>
<th>INH</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effectiveness</strong></td>
<td>1.9 per 1,000</td>
<td>4.3 per 1,000</td>
<td>Non-inferior</td>
</tr>
<tr>
<td><strong>Completion</strong></td>
<td>82.1%</td>
<td>69.0%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Hepatotoxicity</strong></td>
<td>0.4%</td>
<td>2.7%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Sterling, NEJM, 2011
INH-RPT

• Advantages:
  – Less hepatotoxicity (~ 7x less than INH)
  – Greater adherence (82% INH-RPT vs. 69% INH)

• Disadvantages:
  – Multiple drug interactions
  – Pill burden
  – Flu-like / hypersensitivity syndrome (2.2%)

Bliven-Sizemore, Int J Tuberc Lung Dis, 2015
Sterling, Clin Infect Dis, 2015
Part 3: Key Points

- INH has been front line drug, but has low treatment initiation and completion rates
- Short course regimens now preferred given higher completion rates and lower hepatotoxicity
- INH-RPT (12 doses) is as efficacious as INH (9 months)
TB Diagnosis
Clinical Presentation: Signs and Symptoms

- Cough (dry/productive sputum) 75-80%
- Weight loss 45-75%
- Fatigue 60-70%
- Fever 50-60%
- Night sweats 50-55%
- Hemoptysis 25-35%
- Pleuritic chest pain
- No symptoms 10-20%

Barnes 1988, Miller 2000
# Radiographic Patterns of Pulmonary TB

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltrate</td>
<td>Majority of Cases (80%) 85% upper</td>
</tr>
<tr>
<td>Cavitation</td>
<td>Minority of Cases (20%) Rare in children and primary TB</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>Uncommon More common in children and primary TB</td>
</tr>
<tr>
<td>Effusion</td>
<td>May be present</td>
</tr>
</tbody>
</table>
Sputum AFB smear

• Smear positive $\geq 10^4$ bacilli per ml
• Smear AFB amount correlates with infectiousness
• 40-60% of culture positive cases will be smear negative

*Three smear negative specimens does not “rule out” TB!*
What is the Added Value of NAAT?

• **For AFB smear (−):**
  - 50-70% of smear −/culture + cases will be + by NAAT → start treatment (earlier)
  - If NAAT (−), the likelihood of TB lower
    • Release from isolation earlier (2 Xpert results finds all smear +)
    • Still start treatment if suspicion is high

• **For AFB smear (+):**
  - NAAT can confirm TB quickly
  - If NAAT negative, prevent falsely diagnosing TB
    (likely NTM if inhibitors are ruled out and result repeated)
Xpert MTB/RIF Test Performance Compared with Culture, U.S. Patients

<table>
<thead>
<tr>
<th>Smear Status</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear (+)</td>
<td>96.7% (59/61)</td>
<td>100% (62/62)</td>
</tr>
<tr>
<td>Smear (−)</td>
<td>59.3% (16/27)</td>
<td>71.4% (20/28)</td>
</tr>
</tbody>
</table>

Luetkemeyer *Clin Infect Dis* 2016
Use of NAATs!

- NAAT should be used unless results would not impact clinical or public health management.
- Xpert results showing Rif resistance should:
  - Be confirmed using sequencing and/or culture.
  - Trigger suspicion for MDR TB (not Rif monoR).

CDC MMWR October 18, 2013 / 62(41);821-824
Part 4: Key Points

- Most but not all patients have TB symptoms
- Most patients do not have a cavity on CXR
- Use NAATs
- Clinical suspicion is crucial → don’t be afraid of empiric TB treatment
- Discuss with state/local TB control program
Summary

- Most TB cases in the U.S. are preventable
- TB disease persists as a cause of preventable morbidity and mortality
- College students should have risk-base testing and treated if positive
- Foreign birth/travel, immunosuppressed, TB contact are the main risks for TB
Summary

• Both IGRAs or TSTs can be used to support the diagnosis of latent TB infection
• Neither test can distinguish between latent TB infection and active TB disease
• IGRAs have advantages over TST in foreign-born (BCG vaccinated)
Summary: How to treat?

• Short course regimens have higher completion rates and are less hepatotoxic.
• INH has very low treatment completion rates.
• INH-RPT (3 months) is as efficacious as INH (9 months).
TB Elimination is achievable

- New tools can help simplify and improve management of latent TB infection
  1. Simple TB risk assessment
  2. IGRAs
  3. Short course regimens
END

TB

Know Your Risk
Thank you!
Acknowledgements

- Pennan Barry
- Joanna Lu
- Neha Shah
- Jim Scott
Resources to look forward to:

• ATS/IDSA/CDC LTBI guidelines
• NTCA companion document
• ATS diagnostic standards
• Up to Date revisions