Latent Tuberculosis: Risk Factors, Treatment and New Tools

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Disclosures

• Will discuss off-label use of rifampin for latent TB infection
• No affiliation or financial relationship with any of the tests or companies mentioned in this presentation
• This presentation does not necessarily represent the official position of the US Centers for Disease Control and Prevention
Objectives

• Establish importance of testing and treatment for latent tuberculosis infection (LTBI)
• Discuss patient populations to be tested
• Review tests currently available
• Explore treatment options
PART 1: WHY TEST?
Tuberculosis Cases and Case Rates California, 1991–2015

Number of TB Cases

Case Rate per 100,000

TB Cases

TB Rate


1991
1996
2001
2006
2011
2015

2137
2134

0 1,000 2,000 3,000 4,000 5,000 6,000

0 2 4 6 8 10 12 14 16 18 20

1,000 2,000 3,000 4,000 5,000 6,000

0 1,000 2,000 3,000 4,000 5,000 6,000

0 2 4 6 8 10 12 14 16 18 20


2137
2134
Population:
39 million
• > 10 million immigrants
• ~25% of foreign-born in U.S.
• ~25% of TB in U.S.

From Public Policy Institute of California (http://www.ppic.org/main/publication_show.asp?i=258)
Reported TB in California, 2015

Foreign-born 81%  US-born 19%

Each person = 1 TB case (Total = 2137)
10% of TB Cases Die

Each person = 1 TB case (Total = 2137)
Consequences of Active TB

If TB disease is curable, why is prevention so important?

1. Mortality
   – ~10% of patients with TB do not survive
     Pascopella, Open Forum Infect Dis, 2014

2. Morbidity
   – After treatment, patients have shorter life expectancy

3. Cost of treating active TB disease
   – Hospitalization and outpatient case management

4. Public Health
   – Treatment of latent TB infection reduces future TB transmission
How do TB Cases Occur in California? - or - Why test for latent TB infection?

* France et al, Am J Epidemiol. 2015
When do TB cases occur?

- or -

Years in US at TB Diagnosis, California 2010-2014
Years in US at TB Diagnosis
California, 2010-2014

75% in US > 5.9 years
50% in US >16 years
Burden of TB in California

~2,000 cases of active TB disease

~2.4 million with latent TB infection

CDC, Annual Report, 2015
Miramontes, PLOS One, 2015
American Community Survey, 2014
2.4 Million Estimated TB Infections, California 2014

Estimated by applying nativity and race/ethnicity-specific TB infection prevalence from NHANES (Miramontes, 2015) to the California ACS population estimates using TST for US born and IGRA for foreign born.
Latent TB Infection: Number, awareness, and treatment —California, 2014

- LTBI prevalence: 1.8M
- Aware of LTBI: 20%
- Treated for LTBI: 12%

Part 1: Key Points

• Most TB cases in the U.S. are due to reactivation and are therefore preventable
• TB disease remains a substantial contributor to morbidity and mortality
• Historical barriers have impeded adoption in many practice settings
PART 2: HOW TO TEST?
Case

• 34 yo male born in India
• Came to the US at age 15 on a student visa
• Healthy with no other medical problems
• He is now starting a new job and changing visa to employment visa for lawful permanent residence
• He sees a civil surgeon for the first time
• What test would you do?
Tuberculin Skin Test (TST) aka PPD
Tuberculin Skin Test (TST)

• Delayed-type hypersensitivity reaction
• How to read:
  – Measure induration (not erythema) at 48-72 hrs
  – Record millimeters
## Interpreting the TST

<table>
<thead>
<tr>
<th>Induration of $&gt; 5 \text{ mm}$ is considered positive for:</th>
<th>Induration of $&gt; 10 \text{ mm}$ is considered positive for:</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected persons</td>
<td>Recent arrivals (&lt;5 yrs) from high-prevalence areas (Asia, Africa, Russia, Eastern Europe, and Latin America)</td>
</tr>
<tr>
<td>Recent contacts of persons with infectious TB</td>
<td>Injection drug users</td>
</tr>
<tr>
<td><strong>Persons with fibrotic changes on chest radiograph consistent with prior TB</strong></td>
<td>Residents and employees of high-risk congregate settings</td>
</tr>
<tr>
<td>Patients with organ transplants and other immunosuppressed patients</td>
<td>Mycobacteriology laboratory personnel</td>
</tr>
<tr>
<td></td>
<td>Persons with conditions that increase risk for progression to TB disease</td>
</tr>
<tr>
<td></td>
<td>Children younger than 4 years of age</td>
</tr>
<tr>
<td></td>
<td>Infants, children, and adolescents exposed to adults in high risk categories</td>
</tr>
</tbody>
</table>
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 vs. TST

• Advantages over TST
  – Not affected by BCG vaccination
  – Not affected by most non-tuberculous mycobacteria
  – Interpretation is more objective
  – No return visit needed for interpretation of test
  – 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>

# QuantiFERON®-TB Gold Test (4): Report of Results

<table>
<thead>
<tr>
<th>QFT-G Result</th>
<th>Report/Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>TB infection <strong>likely</strong></td>
</tr>
<tr>
<td>Negative</td>
<td>TB infection <strong>unlikely</strong>, but cannot be excluded especially if patient has TB signs and symptoms</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>Test inconclusive about the likelihood of TB infection. Either: 1. Repeat QFT-G 2. Administer a TST 3. Evaluate quantitative QFT result</td>
</tr>
</tbody>
</table>
# Reading QFT-GIT Results

**NIL:** 0  
**TB Antigen-NIL:** 7.03  
**Mitogen-NIL:** >10.00

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Nil*</th>
<th>TB Response†</th>
<th>Mitogen Response§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive‡</td>
<td>Any</td>
<td>≥0.35 IU/ml and ≥50% of Nil</td>
<td>Any</td>
</tr>
<tr>
<td>Negative**</td>
<td>≤0.7</td>
<td>&lt;0.35 IU/ml</td>
<td>≥0.5</td>
</tr>
<tr>
<td>Indeterminate††</td>
<td>≤0.7</td>
<td>&lt;0.35 IU/ml</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>&gt;0.7</td>
<td>&lt;50% of Nil</td>
<td></td>
<td>Any</td>
</tr>
</tbody>
</table>

Source: Dr. Meza
CDC Guidelines for Selecting a TB Screening Test

• IGRAs are the preferred method for:
  – People with poor rates of return for TST reading
  – Persons who have received BCG vaccination

• TST is the preferred method for testing for:
  – Children under the age of 5 years
Testing Foreign-Born Patients

• Using a test with poor specificity will result in many false-positive results

• Among foreign-born patients (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>

Pai, Clin Micro Rev, 2014
Miramontes, PLOS One, 2015

This interactive website provides detailed information on current and past BCG policies and practices for over 180 countries. The Atlas is designed to be a useful resource for clinicians, policymakers and researchers alike, providing information that may be helpful for better interpretation of TB diagnostics as well as design of new TB vaccines.

The rationale and methodology for this Atlas is described in a paper in PLoS Medicine.

Please select a Country from the drop down box, or use the map to select a country to view all available information concerning that country’s BCG policies and practices.
### Country: India

- **Region**: South Asia
- **TB Incidence (per 100 000 per year)**: 168
- **TB Incidence (Count)**: 200000
- **TB Prevalence (per 100 000 per year)**: 249
- **TB Prevalence (Count)**: 300000
- **Income group (World Bank)**: Low income
- **Current BCG vaccination?**: Yes
- **BCG Recommendation Type**: A
- **Which year was vaccination introduced?**: 1948
- **Year BCG stopped**: N/A
- **Timing of 1st BCG?**: At birth
- **Is TST done post BCG?**: No
- **Year of BCG coverage estimate**: 2006
- **BCG coverage (%)**: 99%
- **Year of changes to BCG schedule**: 1948: BCG intro as pilot project, 1949: Immunization program in schools, 51-59 Mass immunization campaigns, 1978: extended program of immunization to be given at birth or within 1st mo, 1985: universal immunization program BCG vaccine policy continued as earlier.

### BCG Recommendation Types

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>This country currently recommends BCG vaccination for everyone at a certain age. (Example: BCG at birth or for school-age children, etc.)</td>
</tr>
<tr>
<td>B</td>
<td>This country used to recommend BCG vaccination for everyone, but currently does not.</td>
</tr>
<tr>
<td>C</td>
<td>BCG vaccination was never recommended for everyone in this country, (i.e.: never gave BCG or given only to high risk groups such as health care workers.)</td>
</tr>
</tbody>
</table>

### Data Availability

<table>
<thead>
<tr>
<th>Entry</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>This entry is not applicable to this country.</td>
</tr>
<tr>
<td>(Blank)</td>
<td>This data was not available.</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
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\'s have advantages over TST in certain situations
PART 3: HOW TO TREAT?
Case

- 60 yo woman born in Vietnam
- Daughter who was born in the US recently had a baby and patient wants to permanently move to US to spend time with family.
- IGRA positive with normal CXR
- Never been treated for TB in the past
- Would you treat her for LTBI?
# 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>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>
<tr>
<td>Isoniazid (INH)</td>
<td>Daily</td>
<td>6–9 months</td>
<td>180 - 270</td>
</tr>
</tbody>
</table>
Rifampin

- Daily for 4 months
  - Good adherence (78% RIF vs. 60% INH)
  - Low hepatotoxicity

- Efficacy data limited but study ongoing
  - Recent network meta-analysis suggests 4RIF efficacious compared to placebo

Menzies, 2011 IJMR; Ziakas, CID 2009; Staff, Annals Internal Medicine 2014
INH and Rifapentine

The NEW ENGLAND JOURNAL of MEDICINE

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection
### 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>

Sterling, NEJM, 2011
## 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>Effectiveness</td>
<td>1.9 per 1,000</td>
<td>4.3 per 1,000</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>Completion</td>
<td>82.1%</td>
<td>69.0%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>0.4%</td>
<td>2.7%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Sterling, NEJM, 2011
Further Studies of INH-RPT

• Children (≥2 yrs)
  – Non-inferior to 9 months of INH
• Self-administered therapy (SAT)
  – Completion rates: SAT 78% vs. DOT 85% (non-inferior)
• HIV
  – Non-inferior to 9 months of INH
  – Unable to receive ART in first 90 days

INH-RPT without DOT

Figure: Differences in Completion Rates for DOT minus SAT and DOT minus eSAT: Total and U.S. only

Belknap, Abstract presented at 2015 CROI
Isoniazid (INH)

- 60 – 90% effective depending in adherence

- Completion rates of 50% or less

- Side Effects
  - Hepatotoxicity: Incidence 0.1% but increases with age
  - Rash and neuropathies

Nolan, JAMA, 1999
Smieja, Cochrane Database Syst Rev, 2000
Menzies, Ann Int Med, 2008
What about age?

- Younger persons have longer expected life during which TB progression could occur
- 25-30% of TB cases in 65+ age group
- LTBI prevalence increases with age
- Older age is a risk factor for death if active TB develops
- No upper limit of age has been set for TB screening
  - Consider individual TB risks, comorbidities, and life expectancy

Part 3: Key Points

- Short course regimens have higher completion rates and are less hepatotoxic

- INH-RPT (12 doses) is as efficacious as INH (9 months)

- INH can still be used but not preferred method
PART 4: TB ELIMINATION

-OR-

YOUR CRUCIAL ROLE
Elimination Definitions

<table>
<thead>
<tr>
<th>Goal</th>
<th>Goal Rate</th>
<th>Cases in California*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-elimination</td>
<td>&lt; 10 cases/million</td>
<td>388</td>
</tr>
<tr>
<td>Elimination</td>
<td>&lt;1 case / million</td>
<td>39</td>
</tr>
</tbody>
</table>

California Dream is to get to TB Elimination by 2040

*Based on 2014 US Census Estimate of California Population: 38.8 million
WHO. Framework towards TB Elimination in Low-Incidence Countries. 2014
Years of TB pre-elimination and elimination in California

Extrapolation based on current rate of decline

- Actual
- 3 year decline (-1.6%)
- 10 year decline (-4%)
- 2040 Elimination (-14%)
- Pre-Elimination
- Elimination

Years:
- 1985
- 1995
- 2005
- 2015
- 2025
- 2035
- 2045
- 2055
- 2065
- 2075
- 2085
- 2095
- 2105
- 2115
- 2125

Rate per 1 Million
- 0
- 1
- 10
- 100
- 1000

Years of TB pre-elimination: 47 years

Elimination in California in 2025:
- 2025
- 2014

Elimination in 2057:
- 2057
- 2114

2040:
- 2040

2025:
- 2025

2057:
- 2057
- 2257
Testing Foreign Born
Alex Goodell, Jim Kahn and UCSF/Berkeley/Stanford CAPE Investigators

Interventions
- Base case (4% tested)
- Use QFT/3HP
- 2x testing (FB)
- 4x testing (FB) ~1.6M
- 10x testing (FB)

TB Cases in California

Year

2015 2020 2025 2030 2035 2040 2045 2050 2055

2x, 4x, 10x use QFT/3HP
Dotted lines represent pre-elimination and elimination
### 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)

OPPORTUNITIES FOR PREVENTION
SUMMARY
Summary

• Most TB cases in the U.S. are preventable

• TB disease still causes substantial morbidity and mortality

• Age and years since U.S. entry are not contraindications to testing or treatment
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 certain situations (BCG-vaccinated)
Summary: How to treat?

- Short course regimens have higher completion rates and are less hepatotoxic.

- INH-RPT (3 months) is as efficacious as INH (9 months).

- INH has extremely low treatment completion rates.
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
Acknowledgments

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Jenny Flood
Sundari Mase
UCSF CAPE Team

CDC DTBE
CDPH TBCB
Local TB Control Programs

NShah6@cdc.gov
Use the California TB Risk Assessment
References and Resources

• California DPH TB Control Branch:
  http://www.cdph.ca.gov/programs/tb/Pages/default.aspx

• CDC
  – INH+Rifapentine Guideline: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm
  – NAAT Guideline: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5801a3.htm?s_cid=mm5801a3_e
  – Xpert MMWR: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6241a1.htm

• California TB Controllers Association

• TST in 3D: http://www.tstin3d.com/en/calc.html

• Curry International Tuberculosis Center (Warmline Consultation Service)
  http://www.currytbcenter.ucsf.edu/ 877-390-6682 or 510-238-5100