Updates in TB for the PCP: Opportunities for Prevention

Advances in Infectious Diseases:
New Directions for the Clinic and the Hospital
March 23, 2018

Pennan Barry, MD, MPH
Chief, Surveillance and Epidemiology,
California TB Control Branch
Assistant Clinical Professor,
Division of Infectious Diseases, UCSF
pennan.barry@cdph.ca.gov

Disclosures
No conflicts
Will discuss off-label use of rifampin for latent TB infection

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
• Discuss diagnosis of active TB

PART 1: WHY TEST?
Natural History of TB

- Not infected
- Exposure to infectious TB
- Latent TB infection (LTBI)
  - 90% Remain latently infected
  - 5% Develop "primary" active TB disease
  - 5% Progression to active TB disease "Reactivation"

TB Cases in the United States 1982–2015

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

TB Cases in the United States 1982–2015

- First increase in 23 yrs

10% of TB Cases Die

- Each □ = 1 TB case (Total = 2073)
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?

- 7.5% Importation
  835 of 11,149 cases occurred within 1 year of arrival in U.S. (2010-2014)

- 79.5% Reactivation
  of remote infection
  Cases not from importation or recent transmission

>2,000 Cases Per Year

* France et al, Am J Epidemiol. 2015

~2.3 Million Estimated TB Infections California, 2015

<table>
<thead>
<tr>
<th>U.S. Born</th>
<th>Foreign Born</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 Million</td>
<td>1.8 Million</td>
</tr>
</tbody>
</table>

Estimated by applying nativity and race/ethnicity-specific TB infection prevalence from NHANES (Miramontes, 2015) to the California population estimates using TST for US born and IGRA for foreign born

Estimated TB Infection prevalence, awareness, treatment —California, 2015

NHANES 2011-2012 applied to California population

- LTBI prevalence
- Aware of LTBI
- Treated for LTBI

Millions of persons

U.S.-born
Foreign-born
Barriers to Treatment of Latent TB Infection

- Nonspecific guidelines
- Confusion about which groups should (or should not) be tested and treated
- Limited resources in busy clinical settings
- Suboptimal tests and treatment options
- Not considered an important clinical problem

Why Test?: 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: WHO TO TEST?

Case

- 32 yo Female at health maintenance visit
- Born in Fresno, works as a secretary for a small insurance company
- Has 2 children, ages 2 and 4
- Uses public transportation
- Heard a story about TB on the radio
- Requests TB skin test (TST)
  
  What do you do?
What is targeted testing?

- Only test patients who have “TB risk factors”
- Treatment decisions routine: “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

<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>

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

Natural History of TB

Risk for infection

Exposure to infectious TB

Latent TB Infection (LTBI)

Develop “primary” active TB disease

Risk for progression

90% Remain latently infected

5% Progression to active TB disease “Reactivation”

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 has new insurance coverage
- He sees a physician for the first time
- Should he be screened for TB?
Risk Assessment

• For use by primary care providers
• Extensive feedback from diverse providers
• Simplicity, clarity over detail
• Companion Fact Sheet
• Pediatric, University, and Adult versions

http://www.cdph.ca.gov/programs/tb/Pages/RiskAssessment.aspx

Prioritize if necessary

• Foreign-born persons with medical risk for progression
  1. Diabetes mellitus
  2. Smoker within past 1 year
  3. End stage renal disease
  4. Leukemia or lymphoma
  5. Silicosis
  6. Cancer of head or neck
  7. Intestinal bypass/gastrectomy
  8. Chronic malabsorption
  9. Body mass index ≥20
  10. History of chest x-ray findings suggestive of previous or inactive TB (no prior treatment).

California Department of Public Health, 2016
US Preventive Services Task Force

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)


Case

- 67 yo woman born in Vietnam immigrated to US in her 40s
- Previous HbA1c=6.0 and osteoporosis on bisphosphonate
- Seen at primary care visit
- In addition to biannual mammogram and bone mineral density, should you screen for TB infection?

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

Years in U.S. at TB diagnosis
California, 2012-2016

- 75% in US >5 yrs
- >50% in US >16 yrs
What about “high risk”
congregate settings?
Homeless shelters, corrections

- Risk and epidemiology can vary
  - Geography, type of facility
- Regulatory and legal mandates may apply
- Screening programs integrated into sites
  - Shelter screening programs, corrections screening, occupational health
- Check with your local public health TB control program

Who to Test?: Key Points

- Use a risk assessment before testing
- A decision to test is a decision to treat
  (if tested because of risk)
- Patients should be evaluated for TB risk factors regardless of age or time since entry into the U.S.

PART 3: HOW TO TEST?

Natural History of TB
Tuberculin Skin Test (TST) aka PPD

• 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 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

**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>
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<tbody>
<tr>
<td>QFT</td>
<td>16%</td>
</tr>
<tr>
<td>TST</td>
<td>72%</td>
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**ATS/IDSA/CDC Guideline on TB Diagnosis**

- Use IGRA for all >5 yrs (TST acceptable)
- Use a second test if first test is positive in a person with no TB risk (if test required)
- Use a second test if first test is negative in a person with a high risk for progression (e.g., TNF- alpha, HIV)

**Diagnosing Latent TB Infection**

- TSTs and IGRA cannot distinguish between latent TB infection and active TB disease
- Active TB disease must be evaluated
Case

• 35 yo US-born nurse in a long term care facility
• Contact to active TB cases 3 years ago → TST positive → completed 9 mos of INH
• Now: Smear positive, cavitary, INH resistant TB
• Genotype matches prior cases (INH sens)
• Review of prior CXR shows “faint irregular 1cm density” in area of current cavity
• Repeat extended contact investigation including toddlers and immunosuppressed adult

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

How to Test?: 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 certain situations

PART 4: HOW TO TREAT?
Natural History of TB

- Exposure to infectious TB
- Latent TB infection (LTBI)
- 5% Develop "primary" active TB disease
- Treatment of LTBI
- 5% Progression to active TB disease "Reactivation"
- 90% Remain latently infected
  
  TST or IGRA

Treatment Regimens for Latent TB Infection

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

- **Advantages**
  - Gold standard of 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

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The New England Journal of Medicine

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

<table>
<thead>
<tr>
<th>INH-RPT</th>
<th>INH</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>3,986</td>
</tr>
<tr>
<td>Frequency</td>
<td>Weekly</td>
</tr>
<tr>
<td>Duration</td>
<td>3 months</td>
</tr>
<tr>
<td>Administration</td>
<td>Directly-observed</td>
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</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

• 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%)

Bivens-Sizemore, Int J Tuberc Lung Dis, 2015
Sterling, Clin Infect Dis, 2015

How to Treat?: Key Points

• INH is traditional gold-standard, but has low treatment initiation and completion rates
• Short course regimens have higher completion rates and are less hepatotoxic
• INH-RPT (12 doses) is as efficacious as INH (9 months)
**Case**

- 42 yo male born in the Philippines p/w cough x 1 month, 10 pound weight loss
- PMH: DM (Hgb A1c=8.0), Tobacco
- TST/PPD positive (16mm) 2 years before but not treated
- CXR shows RUL infiltrate, no cavity

**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>“Typical” (Reactivation)</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</td>
</tr>
<tr>
<td></td>
<td>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 ≥ 10⁴ 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?

• AFB smear (–):
  – 50-70% of smear –/culture + cases will be + by NAAT → start treatment (earlier)
  – If NAAT (–) likelihood of TB lower
    • Still start treatment if suspicion is high
• AFB smear (+):
  – NAAT (+) can confirm TB quickly
  – If NAAT (–), prevent falsely diagnosing TB (likely NTM if inhibitors ruled out; result repeated)
  • Release from isolation (2 Xperts finds all smear +)

NTCA /APHL Consensus Statement:

Luetkemeyer Clin Infect Dis 2016

Xpert MTB/RIF Test Performance Compared with Culture, U.S. patients

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 Xpert</td>
<td>2 Xperts</td>
</tr>
<tr>
<td>Smear (+)</td>
<td>96.7%</td>
<td>100%</td>
</tr>
<tr>
<td>Smear (–)</td>
<td>59.3%</td>
<td>71.4%</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 culture
  – Trigger suspicion for MDR TB (not Rif monoR)

CDC MMWR October 18, 2013 / 62(41):821-824
Active TB Diagnosis: 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

OPPORTUNITIES FOR PREVENTION
SUMMARY

Summary

• Most TB cases in the U.S. are preventable
• TB disease still causes substantial morbidity and mortality
• Patients should have a TB risk assessment
  – Foreign birth, immunosuppressed, contact
• Age and years since U.S. entry are not contraindications to testing or treatment

Summary

• Both IGRA s 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
• IGRA s have advantages over TST in certain situations (BCG-vaccinated)
**Summary: How to treat?**

- INH has extremely low treatment completion rates
- Short course regimens have higher completion rates and are less hepatotoxic
- 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. IGRA
  3. Short course regimens

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Christy Pak  
Pennan.Barry@cdph.ca.gov

Use the California TB Risk Assessment

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**References and Resources**

- California DPH TB Control Branch: [http://www.cdph.ca.gov/programs/tb/Pages/default.aspx](http://www.cdph.ca.gov/programs/tb/Pages/default.aspx)  
- Spor MDR: [https://www.cdc.gov/mmwr/pdf/rr/rr5801a3_e.pdf](https://www.cdc.gov/mmwr/pdf/rr/rr5801a3_e.pdf)
- ATS/IDSA/CDC Guidelines (new):  
  877-300-6885 or 510-238-5100