IGRAs and LTBI

Civil Surgeons Course
November 14, 2018

David Horne, MD, MPH
Harborview Medical Center
University of Washington

DISCLOSURES

• I have no disclosures or conflicts of interest to report
Outline

• Background
• Tests for LTBI
• TB diagnosis
• LTBI treatment

Variability in TB Outcomes

80% of U.S. TB cases due to reactivation: PREVENTABLE

~90% will not progress to TB

Small NEJM 2001
Global TB

U.S. TB incidence = 2.9 2.8/100,000 persons in 2017
Estimated that 23% of world is latently infected with TB

WHO 2017 Global TB Report
Houben PNAS 2016

Progress toward TB Elimination?

LoBue Lancet ID 2017

https://www.currytbcenter.ucsf.edu
LTBI Diagnosis Guidelines

Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children

Lewinsohn CID 2017

Diagnosing LTBI

Tuberculin Skin Test (TST)  Interferon Gamma Release Assays (IGRAs)

https://www.currytbcenter.ucsf.edu
**Diagnosing LTBI**

- **No gold standard** for diagnosing LTBI
- **All tests** assess T-cells for prior exposure to TB antigens

**Antigens: TST vs. IGRAs**

*M. tuberculosis* antigens shared with NTM, & BCG

Antigens specific to *M. tuberculosis*, e.g., ESAT-6 & CFP-

May get false positives due to infection with these uncommon pathogens

Ganguly et al, 2008: 88, 510-517
What’s Wrong with the TST?

- Specificity—poor to good
  - Mycobacteria besides *M. tuberculosis*
  - Bacillus Calmette-Guérin (BCG) vaccine
- Boosting
- Reliable tuberculin (PPD) antigen solution
- Technique—(skills)—poor to not-so-poor
  - Injection
  - Measurement and interpretation
- Two healthcare encounters for one result

LTBI Prevalence (US)

LTBI in US: 12.4 – 13.6 million individuals

Ghassemieh AJRCCM 2016

Table 2: Estimated frequency (95% Confidence Interval) of tuberculin skin test (TST) and QuantiFERON®-TB Gold In-Tube (QFT) test results among the U.S.-born population ≥ 6 years old.

<table>
<thead>
<tr>
<th>QFT 0.35 IU</th>
<th>TST 5 mm</th>
<th>TST 10 mm</th>
<th>TST 15 mm</th>
<th>Any TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>0.8%</td>
<td>2.0%</td>
<td>0.6%</td>
<td>2.2%</td>
</tr>
<tr>
<td></td>
<td>(0.5-1.3%)</td>
<td>(1.3-3.0%)</td>
<td>(0.3-1.0%)</td>
<td>(1.5-3.2%)</td>
</tr>
<tr>
<td>-</td>
<td>2.5%</td>
<td>94.8%</td>
<td>0.8%</td>
<td>96.4%</td>
</tr>
<tr>
<td></td>
<td>(1.4-4.3%)</td>
<td>(92.6-96.3%)</td>
<td>(0.4-1.6%)</td>
<td>(95.0-97.4%)</td>
</tr>
</tbody>
</table>

Table 3: Estimated frequency (95% Confidence Interval) of tuberculin skin test (TST) and QuantiFERON®-TB Gold In-Tube (QFT) test results among the foreign-born U.S. population ≥ 6 years old.

<table>
<thead>
<tr>
<th>QFT 0.35 IU</th>
<th>TST 5 mm</th>
<th>TST 10 mm</th>
<th>TST 15 mm</th>
<th>Any TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>11.6%</td>
<td>4.7%</td>
<td>9.1%</td>
<td>7.2%</td>
</tr>
<tr>
<td></td>
<td>(9.9-14.7%)</td>
<td>(4.5-6.4%)</td>
<td>(7.0-13.6%)</td>
<td>(5.5-9.4%)</td>
</tr>
<tr>
<td>-</td>
<td>25.5%</td>
<td>60.2%</td>
<td>11.2%</td>
<td>72.5%</td>
</tr>
<tr>
<td></td>
<td>(18.7-29.1%)</td>
<td>(53.0-67.1%)</td>
<td>(8.8-15.3%)</td>
<td>(66.5-77.8%)</td>
</tr>
</tbody>
</table>

Ghassemieh AJRCCM 2016
Test Accuracy

- **Sensitivity**: Probability of a positive test in someone with infection
- **Specificity**: Probability of a negative test in someone without infection
- **Positive Predictive Value**: Probability of infection in someone with a positive test
- **Negative Predictive Value**: Probability of no infection in someone with a negative test

Targeted Testing: Rationale

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>80%</td>
<td>97% (60% if BCG vaccinated)</td>
</tr>
<tr>
<td>QFT</td>
<td>80%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>T-SPOT.TB</td>
<td>90%</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

The formula for Positive Predictive Value (PPV) is:

\[
PPV = \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}
\]

For a US born patient (LTBI prevalence ~3%) with no other risk factors, the PPV of:

- + TST is 45%
- + QFT is 55%
- + T.SPOT. TB is 58%
Interferon-gamma Release Assays (IGRAs)

**QuantiFERON-GIT**
- Collect 1mL of blood in 3 tubes
- Incubate within 16 hr, at 37°C for 16–24 hr
- Collect plasma for ELISA

**TSPOT.TB**

Measure [IFN-γ]/Interpret

<table>
<thead>
<tr>
<th>Source of Variability</th>
<th>Impact on Assay Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing</td>
<td>QFT-GIT</td>
</tr>
<tr>
<td>Probabilities</td>
<td></td>
</tr>
<tr>
<td>Time of blood draw (h, min)</td>
<td></td>
</tr>
<tr>
<td>Thrombolytic blood draw</td>
<td></td>
</tr>
<tr>
<td>Blood volume (ml)</td>
<td>1.7 ml</td>
</tr>
<tr>
<td>T-cell and APC count</td>
<td>1</td>
</tr>
<tr>
<td>Stimulant concentration</td>
<td>1</td>
</tr>
<tr>
<td>Incubation delay</td>
<td>14-16 hr</td>
</tr>
<tr>
<td>Incubation temperature</td>
<td>37°C</td>
</tr>
<tr>
<td>Pheno-PAO in mg</td>
<td>No offset</td>
</tr>
<tr>
<td>Analyzed</td>
<td></td>
</tr>
<tr>
<td>White-run impurities</td>
<td>1</td>
</tr>
<tr>
<td>Between-run impurities</td>
<td>1</td>
</tr>
<tr>
<td>Between-laboratory impurities</td>
<td>1</td>
</tr>
<tr>
<td>Autoclave</td>
<td>1</td>
</tr>
<tr>
<td>Clinical error</td>
<td>1</td>
</tr>
<tr>
<td>Microbiologic</td>
<td>1</td>
</tr>
<tr>
<td>Mass detection failure</td>
<td>1</td>
</tr>
</tbody>
</table>

**QuantiFERON-Plus**

4th Generation QuantiFERON, FDA approved in 2017, uses same test principle, procedure and technology

**Added 2nd antigen tube (TB1, TB2), kept ESAT6/CFP10**
- Nil – same grey color, Mitogen – same purple
- TB1 – green, CD4 only
- TB2 – yellow: optimized to detect both CD4 and CD8!
- OR...Standard lithium heparin tube-> 16 hours to transfer to 4 tubes

Why CD8+ antigens? May incite stronger response in recent infection and remain relatively intact in immunocompromised patients

**Multicenter study of QFT Gold + in patients with active TB**
- 164 participants with active TB
- QFT-GIT sensitivity 94%
- QFT-Plus sensitivity 93%
- Kappa 0.89

**Home** *IJTLD 2018*

---

IGRAs for the Diagnosis of LTBI

https://www.currytbcenter.ucsf.edu
IGRAs for the Diagnosis of LTBI

https://www.currytbcenter.ucsf.edu
Those pesky indeterminates (both) & borderlines (TSPOT)

- **Indeterminate**
  - Optimally, an indeterminate result tells you that MTB infection data cannot be obtained from the QFT-IT test
  - Low lymphocyte count/low lymphocyte activation potential
  - Optimally, an improvement over the TST in which “anergy” cannot be diagnosed
  - Repeat test with valid result (pos/neg) in 68% (Banach IJTLD 2011)

- **Borderline**
  - Only in US (European test approved only with positive or negative
  - Interpret based on pre-test probability

**Bottom Line:** For indeterminate or borderline results no further testing and no CXR needed → Patients have completed process

---

**Age under 5**

**Preferred test: TST**

**Rationale**
- Limited evidence suggests TST more sensitive in children
- Prioritize sensitivity over specificity
- Allows for serial testing with TST during “window prophylaxis”

- Can use IGRAs in immunocompetent children > 2 years; some experts down to 1 year of age - Esp. if prior BCG vaccination

---

**IGRAs for the Diagnosis of LTBI**

https://www.currytbcenter.ucsf.edu
Are IGRAs Useful for Assessing Tx Response?

- Systematic Review of IGRAs and association with tx responses for LTBI and active TB

- 15 studies that evaluated LTBI responses
- No consistent pattern using reversions or quantitative IFN-gamma levels

Clifford Tuberculosis 2015

TB Diagnosis
IGRAs for the Diagnosis of LTBI

https://www.currytbcenter.ucsf.edu
Behind the scenes at LHJ…

TB diagnosis: Sputum Evaluations

- AFB Smears
  - Ziehl- Nielsen, auramine-rhodamine
  - Rapid, ~70% sensitive, nonspecific

- Molecular methods
  - PCR-based (e.g. GeneXpert) – rapid ID of smear positive samples but also better sensitivity than smear

- Culture

Behind the scenes at LHJ…

Laboratory Diagnosis: Culture

- Cultures may take several weeks for results
- May get earlier results with liquid media

<table>
<thead>
<tr>
<th>Culture media</th>
<th>Time to Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Egg-based media (e.g., Lowenstein-Jensen)</td>
<td>4-8 wks</td>
</tr>
<tr>
<td>Agar-based media (e.g., Middlebrook 7H10)</td>
<td>4-6 wks</td>
</tr>
<tr>
<td>BACTEC liquid medium</td>
<td>2-4 wks</td>
</tr>
<tr>
<td>Mycobacterial growth indicator tube (MGIT)</td>
<td>2-4 wks</td>
</tr>
</tbody>
</table>
LTBI Treatment

Medical Eval before LTBI Treatment

- Rule out active TB disease – CXR, symptoms
- History of previous LTBI treatment?
- Alcohol intake / liver disease/potentially hepatotoxic medications/pregnancy
- At risk for neuropathy (INH)?
  - diabetes, uremia, alcoholism, malnutrition, HIV infection, pregnancy, seizure disorders
Options for LTBI Treatment

INH (A)  Daily or twice-weekly

Rifampin (B)  Daily

INH + Rifapentine (A)  q7d

WEEKS  0  12  18  39

http://www.cdc.gov/tb/topic/treatment/ltbi.htm

More Likely to Complete Shorter Treatment Regimens

http://www.currytbc.or.edu
Rifampin for LTBI

- Recent RCT demonstrated efficacy of RIF daily for 4 months: 10 mg/kg, max 600 mg
- Non-inferior to INH
- Higher rate of treatment completion and safer
- Watch for drug-drug interaction
- Side effects: hepatotoxicity, rash, hypersensitivity

Menzies NEJM 2018

INH-Rifapentine for LTBI

- Not recommended for: < 2 years of age, HIV+ on ART, pregnancy, infection with presumed INH or RPT resistance
- Case by case ages 3-11 years
- DOT or Self-administered
- RPT (like RIF) may alter metabolism of many drugs
- Consider Vitamin B6, 50 mg with each dose
- Compared to INH: Higher completion Rx rate & less serious adverse events
INH for LTBI Treatment

- A single daily dose of 300 mg/d (child 10-15 mg/kg, not to exceed 300 mg)
- Consider Vitamin B6 25-50 mg with each dose
- General: 9 months for all incl children, HIV, abnl CXR
- 6 months of INH lower efficacy
- DOPT – Intermittent dosing
  - 9- and 6-month regimens may be given twice-weekly
  - When intermittent, INH should be administered only as directly observed preventive therapy (DOPT)

Choosing an LTBI Treatment

<table>
<thead>
<tr>
<th>Drug Regimen</th>
<th>Doseage</th>
<th>Efficacy vs. Placebo*</th>
<th>Efficacy vs. 6 Mo of Isoniazid*</th>
<th>Hepatotoxicity vs. 6 Mo of Isoniazid*</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid alone for 6 mo or 9 mo</td>
<td>Adults, 5 mg/kg; children, 10 mg/kg (maximum, 100 mg)</td>
<td>Not applicable for 6-mo regimen, and not available for 9-mo regimen</td>
<td>Not applicable for 6-mo regimen, and not available for 9-mo regimen</td>
<td>Drug-induced liver injury, nausea, vomiting, abdominal pain, rash, peripheral neuropathy, diarrhea, and exacerbation</td>
<td></td>
</tr>
<tr>
<td>Rifampin alone for 3 to 4 mo</td>
<td>Adults, 10 mg/kg; children, 10 mg/kg (maximum if &lt;45 kg, 650 mg; maximum if ≥45 kg, 1000 mg)</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Influence-like syndrome, rash, drug-induced liver injury, anemia, nausea, abdominal pain, neuropsychiatric, and renal reactions (e.g., acute tubular necrosis and interstitial nephritis)</td>
<td></td>
</tr>
<tr>
<td>Weekly rifampin plus isoniazid for 3 mo</td>
<td>Adults and children: rifampin, 15-30 mg/kg (maximum, 600 mg); isoniazid, 15 mg/kg (maximum, 900 mg)</td>
<td>Not available</td>
<td>0.44 (0.18-1.07)</td>
<td>0.16 (0.10-0.27)</td>
<td>Hyposensitivity reactions, psychiatric reactions, drug-induced liver injury, anemia, nausea, abdominal pain, and hypotensive reactions</td>
</tr>
</tbody>
</table>

Stagg Ann Int Med 2014; Getahun NEJM 2015
LTBI Treatment Monitoring

- Baseline and monthly education about adverse effects and what to do if they occur
- Monthly clinical evaluation for adverse effects
  - Common pitfalls: communication, fatigue
- Laboratory monitoring not routinely indicated
  - Consider baseline LFTs & monitoring if at high risk, e.g. HIV, daily alcohol, chronic liver disease, pregnant or recent delivery (< 3 months), taking meds with potential for liver toxicity
- Hold LTBI treatment when transaminases exceed 3x ULN if symptoms/5x ULN if asymptomatic

Questions/Comments?

Additional Resources

- Local health department
- State health department
- CDC TB Center of Excellence – Curry International TB Center
- Washington State TB ECHO
  https://www.doh.wa.gov/YouandYourFamily/illnessandDisease/Tuberculosis/TBProviderToolkit/TECHO