TB IN SAN FRANCISCO: INNOVATIONS & COLLABORATIONS

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Flu and Infectious Disease Forum
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Outline

- Background / TB elimination
- TB Testing / Screening
- LTBI Treatment
Global Tuberculosis, WHO 2015 report

10.4 million new cases*

1.8 million deaths

Leading Infectious Killer in the World and Leading Killer of People Living with HIV

* Additional one-third of the world’s population are infected
San Francisco TB Case Rate

- 2016: 100 new cases (11.8 cases / 100,000 population)
- CA: 5.3 cases / 100,000
- US: 3 cases / 100,000
Natural History of TB

- Exposure to infectious TB
- Latent TB infection (LTBI)
  - Rapidly develop active TB disease

- Not infected

- Active TB disease (years)
## TB Disease vs. (Latent) Tuberculosis Infection (LTBI)

<table>
<thead>
<tr>
<th>Active TB disease</th>
<th>Latent TB infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough, fever, weight loss, night sweats</td>
<td>No symptoms</td>
</tr>
<tr>
<td>Abnormal chest x-ray</td>
<td>Normal chest x-ray</td>
</tr>
<tr>
<td>Infectious</td>
<td>Not infectious</td>
</tr>
<tr>
<td></td>
<td>May progress to active TB disease</td>
</tr>
</tbody>
</table>

- Active TB disease: Infections that can cause symptoms and spread to others.
- Latent TB infection: Infections that are not active but can progress to active TB disease.
TB as a spectrum of disease

- Evidence of progression / regression of FDG-avid granulomas in non-human primates
- Re-think binary definitions: LTBI vs Active Disease
- Nomenclature change?: (Latent) Tuberculosis Infection
TB in the U.S.- what lies beneath

9557 cases

10-15 million persons with LTBI

1 out of 5 non-U.S. born has LTBI

1 out of 7 Asian-born has LTBI
2.4 Californians with latent TB infection—most are unaware and untreated

NHANES 2011-2012 applied to California population
How far are we from elimination?

TB elimination: <1 case per million

**United States, 2015**
- 30 cases per million (all)
- 12 cases per million (U.S.-born)
- 151 cases per million (non-U.S.-born)

**San Francisco, 2016**
- 116 cases per million (all)
- 23 cases per million (U.S. born)
- 291 cases per million (non-U.S.-born)
TB elimination: Key Points

1) TB disease remains a substantial contributor to morbidity and mortality

2) Most TB cases in California are due to progression of LTBI and are therefore preventable

3) In order to move forward in elimination, LTBI needs to be diagnosed and treated
TB Testing / Screening

TB Skin Test (TST)

Interferon-gamma release assays (IGRAs, e.g. Quantiferon, T-spot)
Screening for Latent Tuberculosis Infection in Adults
US Preventive Services Task Force Recommendation Statement

Recommendation:
Screen for latent tuberculosis infection in asymptomatic adults at increased risk of infection

Grade: B
Check appropriate risk factor boxes below. LTBI testing is recommended if any of the 3 boxes below are checked. If LTBI test result is positive and active TB disease is ruled out, LTBI treatment is recommended.

- **Foreign-born** person from a country with an elevated TB rate
  - Includes countries other than the United States, Canada, Australia, New Zealand, or Western and North European countries.
  - If resources require prioritization within this group, prioritize patients with at least one medical risk for progression (see Fact Sheet for list)
  - Interferon Gamma Release Assay is preferred over Tuberculin Skin Test for foreign-born persons

- **Immunosuppression, current or planned**
  - 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

- **Close contact** to someone with infectious TB disease at any time

See the California Tuberculosis Risk Assessment Fact Sheet for more information about using this tool.
LTBI Testing and Treatment Guidelines for SF

- **High Priority:** Focus on risk factors for progression
  - Foreign born with **diabetes**
  - Foreign born with **active tobacco** use
  - Foreign born with **ESRD**
  - Foreign born / US born with **immune suppression**
    - Medications (biologics, organ transplant)
    - Cancer
    - HIV
  - Converters
  - Contacts

- **Medium Priority:** Foreign Born < 50

  * Recent arriver criteria has been eliminated
Tuberculin Skin Test (TST)

• 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

• QuantiFERON®-PLUS is replacing QFT-Gold

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

<table>
<thead>
<tr>
<th>TST (e.g. PPD)</th>
<th>IGRA (e.g. QFT, T-spot)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential for false positive in BCG vaccinated</td>
<td>Preferred in prior BCG vaccinated individuals</td>
</tr>
<tr>
<td>vaccinated individuals</td>
<td></td>
</tr>
<tr>
<td>Subjective</td>
<td>Less subjective (although issue with indeterminate)</td>
</tr>
<tr>
<td>Booster effect</td>
<td>No booster effect</td>
</tr>
<tr>
<td>Injection, ≥2 visits</td>
<td>Blood draw, single visit</td>
</tr>
<tr>
<td></td>
<td>Limited in young (2-5 yo)</td>
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</tbody>
</table>
Diagnosing Latent TB Infection

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

• Patients with positive TST or IGRA must be evaluated for active TB disease
Case

• 35 yo US-born nurse works in a long term care facility
• Contact to active TB cases 3 years ago → TST positive → completed 9 mo of INH

• Now
  – Smear positive, cavitary, INH resistant TB
  – Review of prior CXR shows “faint irregular 1cm density” in area of current cavity

• Genotype matches prior cases (INH sens)
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
TST / IGRA Interpreter

- Estimates risk of active TB
- Limited to up to age 80
- Accounts for risk factors
The likelihood that this is a true positive test (PPV) is: 98%

The annual risk of development of active tuberculosis disease is estimated to be 1.99%

The cumulative risk of active tuberculosis disease, up to the age of 80, is 19.89%

If treated with INH, the probability of clinically significant drug-induced hepatitis is 5%, and the associated probability of hospitalization related to drug-induced hepatitis is 2.4%.
Testing: Key Points

1) Use a risk based approach to testing
2) Patients should be evaluated for TB risk factors regardless of age or time since entry into the U.S.
3) Either IGRA or TST can aid in the diagnosis of latent TB infection
4) Neither test can distinguish between LTBI and active TB disease
5) IGRA s have advantages over TST in certain situations
LTBI Treatment Options

- Isoniazid
- Isoniazid + Rifapentine (3HP)
- Rifampin
## 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>Isoniazid (INH)</td>
<td>Daily</td>
<td>6–9 months</td>
<td>180 - 270</td>
</tr>
<tr>
<td>INH + Rifapentine (RPT)</td>
<td>Weekly</td>
<td>3 months</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Daily</td>
<td>4 months</td>
<td>120</td>
</tr>
</tbody>
</table>
Isoniazid (INH)

• Advantages
  – Efficacy is 60%–90%, depending on duration of treatment
  – Fewer drug-drug interactions

• Disadvantages
  – Adherence: Completion rates <50%
  – Hepatotoxicity: Incidence 0.1%, but increases with age
  – Clinic time required for 6-9 monthly visits
3HP (INH+RPT)

- INH + Rifapentine, Qweek x 12 weeks
- Recommended as an equal alternative to INH x 9 mo in healthy patients $\geq 12$ yo
- Not recommended in the following:
  - Children <2yo
  - HIV-infected patients on any ART
  - Pregnant or planning to become pregnant
  - Contact to INH/RIF resistant cases
  - Prior adverse events / hypersensitivity to INH/RIF
## 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</td>
<td>4.3 per</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>Completion rate</td>
<td>1,000</td>
<td>1,000</td>
<td></td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>82.1%</td>
<td>69.0%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>0.4%</td>
<td>2.7%</td>
<td></td>
</tr>
</tbody>
</table>

3HP- Adverse Reactions

- Possible hypersensitivity (3.8%)
- Rash (0.8%)
- Hepatotoxicity (0.4%)
- Thrombocytopenia (rare)
- Other toxicities (3.2%)

- Monitoring- similar to INH or RIF
- RFP drug-drug interactions similar to RIF

Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection. MMWR 2011;60:1650–1653
3HP

- **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%)
  - Directly Observed Therapy
Video Directly Observed Therapy

- Observation of medication ingestion by video
  - Live vs Recorded
  - Smartphone application, cloud based
- Can be used for active disease and LTBI
- Cost-effective and ensures adherence

http://www.calit2.net/newsroom/release.php?id=2211
Rifampin

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

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

- Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. MMWR 2000; 49 (No. RR-6)
- Guidelines on the management of latent tuberculosis infection, WHO, 2015
- American Academy of Pediatrics, Red Book 2015
Rifampin- Adverse reactions

- Hepatotoxicity
  - Rare severe hepatitis, more common when combined with other medications
- Asymptomatic hyperbilirubinemia (0.6%)
- Dermatologic: Pruritis, rash (up to 6%)
- Hypersensitivity reaction (0.07-0.3%)
- GI: nausea, anorexia, abdominal pain
- Immune-mediated: thrombocytopenia, TTP, hemolytic anemia (<0.1%)
- Orange discoloration of body fluids
Rifampin - Need for additional data

- Cost
- Efficacy
- Adverse events
- Development of resistance
- HIV
- Pediatrics
Monitoring

ATS/CDC LTBI guidelines, 2000

- Routine baseline / follow-up laboratory testing
  → Not needed

- Except for:
  - HIV infection
  - Pregnancy / Early postpartum (<3mo)
  - History of liver disease / hepatitis
  - Regular EtOH use

Also consider for: Statin/other hepatotoxic meds, age >50
Monitoring

Evaluate monthly for:

- Adherence
- Symptoms of hepatitis or other side effects
  - Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
  - Fatigue or weakness
  - Dark urine
  - Rash
  - Persistent numbness in hands or feet
Management of side effects: Drug-induced liver injury

- Review hepatotoxic meds (tylenol, statins, etc), ETOH use, prior hepatitis risk/screen
- HOLD Treatment if:
  - AST/ALT > 3 times the upper limit of normal + symptoms of hepatotoxicity
  - AST/ALT > 5 times the upper limit of normal + asymptomatic
- If less than parameters above, continue treatment with plan to repeat labs in 1-4 weeks.
- Depending on above, consider alternate therapy with close LFT monitoring.
LTBI Treatment: Key Points

1) INH has low treatment initiation and completion rates

2) Short course regimens have higher completion rates and are less hepatotoxic

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

4) All patients should have at least a monthly symptom review for hepatotoxicity and adherence.
SFDPH TB Prevention & Control (Ward 94)

- Provide services to patients / providers within health network and the rest of SF, regardless of insurance or immigration status
- **TB Clinic**
  - Manage all cases of suspected / confirmed active TB cases
  - Perform Directly Observed Therapy
  - Complicated TB infection
  - TB program clearance for at-risk settings (shelters, methadone program, rehab, etc)
- **TB Control**
  - Contact investigations
  - Technical assistance and policies on TB screening, diagnosis, and treatment
  - Research
Assistance is right around the corner…

- TB Control & Prevention, SFDPH
  - 415-206-8524
  - Report of confirmed/suspected case: 415-206-3398
- TB Warmline Consultation (Curry International TB Center): 1-877-390-6682
- California Dept of Public Health, TB Control Branch, [https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/TBCB.aspx](https://www.cdph.ca.gov/Programs/CID/DCDC/Pages/TBCB.aspx) (510) 620-3000
THANK YOU!

Special thanks to CDPH/TBCB for additional slides

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