Updates on the management of latent tuberculosis infection

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Div. of Infectious Diseases, University of Virginia
TB Consultant, Virginia Department of Health
Outline

• Definition and Pathogenesis of latent TB
• Global burden of infection
• Who to screen and how
• Review the various treatment options for LTBI and their side effects
• What’s on the horizon for LTBI
Latent tuberculosis infection

• Immunologic and clinical diagnosis
• Sensitization to mycobacterial proteins
  – Reactive tuberculin skin test
  – Positive interferon-gamma release assay
• Without clinical signs/symptoms of active disease.
M. tuberculosis infection

The spectrum of TB

<table>
<thead>
<tr>
<th></th>
<th>Infection eliminated</th>
<th>Latent TB infection</th>
<th>Subclinical TB disease</th>
<th>Active TB disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**TST**
- Negative
- Positive

**IGRA**
- Negative
- Positive

**Culture**
- Negative
- Negative

**Sputum smear**
- Negative
- Negative

**Infectious**
- No
- No

**Symptoms**
- None
- None

**Preferred treatment**
- None
- Preventive therapy

Note: *With innate immune response

The spectrum of TB

Global Epidemiology of LTBI

- 23% of people are infected with TB (1.7 billion)
  - 80% reside in Asia and Africa
  - ~1-5% reside in USA
  - 6% are children <15 years of age
  - ~1% recently infected
Active TB in Virginia

- 83% are foreign-born:

*Figure 6: Top Five Countries of Birth of Tuberculosis Cases, Virginia, 2017*

- Develop TB ~9.7 years after being in US
A) Time of onset of TB in 128 immigrants who neither left the UK nor had known contacts with TB in the UK before receiving a diagnosis of TB.

B) Time of onset of TB in 59 immigrants who visited their home countries and had no known contacts with TB in the UK before their diagnosis of TB. Time to onset is based on the time of initial UK entry.

C) Same group shown (B), but with the time to onset measured by the time from re-entry into the UK after their Asian visits.

M Behr et al. BMJ 2018;362
McCarthy, B J Dis Chest. 1984, 78
TB screening guidelines

• Targeted testing and treatment
• Focus on individuals who would benefit from treatment
• “Decision to test is a decision to treat”
Screen people at “high risk”

Of infection:
• environmental/behavioral risks
  – Recently exposed/infected (contacts of people with active TB)
  – People in homeless shelters/correctional facilities
  – Health care workers
  – Immigrants from high-burden countries
  – People who use illicit substances

Of progression to active TB:
• host-related risk
  – Age <5 years
  – HIV infection
  – Immunocompromised by organ transplant, chemotherapy (incl. prednisone 15mg daily >1 month) or malignancy, use of TNF-α blockers
  – Abnormal chest radiograph (apical fibro/nodular changes, “old healed TB”)
  – Silicosis
  – Advanced renal failure
  – Diabetes mellitus
How to test? TST vs IGRAs

**Tuberculin skin test**
- ~Century old
- Delayed-type hypersensitivity reaction
- Purified Protein Derivative
  - Mycobacterial antigens from *M.tuberculosis* (M.tb), *M. bovis* BCG, NTM

**Interferon-γ release assays**
- Available since 2005
- Measures IFN-γ response to TB antigens from RD-1 region of *M.tuberculosis* in CD4+ T cells
  - Proteins are absent from *M. bovis* BCG vaccine
IGRAs

• **T-SPOT.TB:**
  - ESAT-6 and CFP-10
  - Number of T cells producing IFN-γ

• **QuantiFERON-Gold In Tube (QFT-GIT):**
  - ESAT-6, CFP-10, TB7.7 (test) & pos/neg controls
IGRAs

- **T-SPOT.TB:**
  - ESAT-6 and CFP-10
  - Number of T cells producing IFN-γ

- **QuantiFERON-Gold In Tube (QFT-GIT):**
  - ESAT-6, CFP-10, TB7.7 (test) & pos/neg controls

- **QuantiFERON-Plus (4th generation):**
  - 2 “TB” tubes, measuring CD4⁺ and CD8⁺ T cell responses
Which test to use: TST vs IGRA?

• 2017 Guidelines:
  – **Low to intermediate risk**: IGRA preferred over TST
    • Infected with no known risk factors, smokers, DM, systemic steroid treatment.
  
  – **High risk**: either can be used, consider dual testing
    • HIV/AIDS, transplantation, immuno-suppressant therapy, silicosis, hemodialysis, recent TB, head/neck cancer, abnormal CXR,
Which test to use in children?

- Children <5 years (CDC/IDSA/ATS): TST preferred
- Children ≥2 years (AAP): either TST or IGRA
  - BCG-vaccinated? Prefer IGRA
  - BCG-vaccinated/TST+? Can check IGRA
- Children <2 years (AAP): TST preferred
- Children <3-6 months (AAP): neither are reliable
### Priority candidates for LTBI treatment

<table>
<thead>
<tr>
<th>TST ≥ 5mm or IGRA+</th>
</tr>
</thead>
<tbody>
<tr>
<td>People living with HIV</td>
</tr>
<tr>
<td>Recent contacts of infectious TB</td>
</tr>
<tr>
<td>People with fibrotic changes on CXR (“old TB”)</td>
</tr>
<tr>
<td>Organ transplant recipients</td>
</tr>
<tr>
<td>Otherwise immunosuppressed (TNF-α blockade, steroids, chemo)</td>
</tr>
</tbody>
</table>
## Priority candidates for LTBI treatment

<table>
<thead>
<tr>
<th>TST&gt;5mm or IGRA+</th>
<th>TST&gt;10mm or IGRA+</th>
</tr>
</thead>
<tbody>
<tr>
<td>People living with HIV</td>
<td>People from high-TB-prevalence countries</td>
</tr>
<tr>
<td>Recent contacts of infectious TB</td>
<td>Children &lt;4 years of age</td>
</tr>
<tr>
<td>People with fibrotic changes on CXR (&quot;old TB&quot;)</td>
<td>At high risk of reactivation (DM, end-stage renal disease, silicosis, some malignancies, injection drug use)</td>
</tr>
<tr>
<td>Organ transplant recipients</td>
<td>Residents/employees in high-risk congregate settings (corrections, shelters, health care)</td>
</tr>
<tr>
<td>Otherwise immunosuppressed (TNF-α blockade, steroids, chemo)</td>
<td>Mycobacteriology laboratory personnel</td>
</tr>
</tbody>
</table>
The Online TST/IGRA Interpreter
Version 3.0

The following tool estimates the risk of active tuberculosis for an individual with a tuberculin skin test reaction of 10 mm, based on a history of clinical profile. It is intended for adults tested with standard tuberculin (5 TU PPD-S, or 2 TU RT-23) and a commercial Interferon Gamma release assay (IGRA). For more details about the algorithm used, go to the About page. The current version of the algorithm contains modifications of the original version, which was detailed in a paper by Merzeg, et al. (2003). For further information see references, or contact dick.menzies@mcmill.ca.

Please select the best response for each field:

**TST:**
- Select...
- IGRA Result:
- IGRA Not Done

**Age:**
- Select...
- N/A

**Country of birth:**
- Select...

**BCG status:**
- Select...

**Recent contact with active TB:**
- No Contact

Please select all the conditions that currently apply to the patient:
(If none of these conditions apply, please leave boxes unchecked)

- AIDS
- Abnormal chest x-ray, fibromatous disease
- Chronic renal failure requiring hemodialysis
- Diabetics Mellitus (all types)
- Recent TB Infection (TST conversion x 2 years ago)
- Slippets
- Tumor Necrosis Factor (TNF)-alpha inhibitors (e.g. infliximab, etanercept)
- Young age when infected (0-4 years)
- Abnormal chest x-ray, granuloma
- Carcinoma of head and neck
- Cigarette smoker (>1 pack/day)
- HIV infection
- Transplantation (requiring immune-suppressant therapy)
- Treatment with glucocorticoids
- Underweight (< 90% of ideal body weight or a body mass index (BMI) < 20)

Submit
## LTBI Regimens

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (+B6)</td>
<td>9 months</td>
<td>Daily self-administered or twice-weekly administration via DOT</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>4 months</td>
<td>Daily administration.</td>
</tr>
<tr>
<td>INH + Rifapentine (+B6)</td>
<td>3 months</td>
<td>Weekly administration, DOT preferred (self administered therapy is acceptable)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not approved for &lt;2yrs or pregnant women</td>
</tr>
</tbody>
</table>
INH for LTBI: 6, 9, or 12 months?

Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial

International Union Against Tuberculosis Committee on Prophylaxis

• Rates of completion are inversely related to treatment duration
• 12 months of treatment was associated with 75%-93% reduction in TB incidence

Ferebee et al, Ann NY Acad Sci. 1963
IUAT Committee, WHO Bull Health, 1982
• ~50% of hepatitis occurred in first 3 months

• Although 52-wk regimen prevented more cases, the 24-wk regimen prevented more cases of TB per case of hepatitis caused
How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults?

G. W. Comstock

Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, Maryland, USA

Figure  Tuberculosis case rates (%) in the Bethel Isoniazid Studies population according to the number of months isoniazid was taken in the combined programs. Dots represent observed values; thin line, the calculated curve \( y = a + b/x \); and dotted lines, the calculated values based on the first four and last five observations \( y = a + bx \).
Open label, non-inferiority RCT:
• 3mo weekly INH+RPT under DOT versus
• 9mo daily INH alone Self-administered
• ~8000 children >12yrs and adults
• US, Canada, Brazil, Spain
3HP: 7 cases/3986 participants (0.19%)  82% completion
9H: 15 cases/3745 participants (0.43%)  69% completion

3HP: more dropouts due to hypersensitivity & “other” reaction
9H: more dropouts due to hepatotoxicity
Three months of weekly rifapentine and isoniazid for treatment of *Mycobacterium tuberculosis* infection in HIV-coinfected persons

Timothy R. Sterling, Nigel A. Scott, Jose M. Miro, Guilherme Calvet, Alberto La Rosa, Rosa Infante, Michael P. Chen, Debra A. Benator, Fred Gordin, Constance A. Benson, Richard E. Chaisson, M. Elsa Villarino, the Tuberculosis Trials Consortium, the AIDS Clinical Trials Group for the PREVENT TB Trial (TBTC Study 26/ACTG 5259)*

- ~400 participants >12 years of age
- US, Canada, Spain, Brazil, Peru, Hong Kong
- 3HP: 1% TB incidence in 33 months of follow up
- 9H: 3.5% TB incidence

Table 3. Safety and tolerability of the study regimens.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3HP, N = 207, n (%)</th>
<th>9H, N = 186, n (%)</th>
<th>P value</th>
<th>% Difference (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment completion (MITT)</td>
<td>183/206 (89)</td>
<td>123/193 (64)</td>
<td>&lt;0.001</td>
<td>25.0 (17.0, 33.0)</td>
</tr>
<tr>
<td>Discontinuation because of adverse drug reaction</td>
<td>7 (3)</td>
<td>8 (4)</td>
<td>0.79</td>
<td>-1.0 (4.7, -2.9)</td>
</tr>
<tr>
<td>Grade 3 toxicity</td>
<td>14 (7)</td>
<td>18 (10)</td>
<td>0.36</td>
<td>-3.0 (-8.4, 2.5)</td>
</tr>
<tr>
<td>Grade 4 toxicity</td>
<td>4 (2)</td>
<td>10 (5)</td>
<td>0.10</td>
<td>-3.0 (-7.2, 0.3)</td>
</tr>
<tr>
<td>Grade 5 (death)</td>
<td>6 (3)</td>
<td>5 (3)</td>
<td>1.00</td>
<td>0.2 (-3.0, 3.5)</td>
</tr>
<tr>
<td>Discontinuation due to hepatotoxicityb</td>
<td>2 (1)</td>
<td>8 (4)</td>
<td>0.05</td>
<td>-3.0 (-6.5, -1.1)</td>
</tr>
<tr>
<td>Flu-like/systemic drug reaction</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>0.50</td>
<td>1.0 (-0.4, 2.3)</td>
</tr>
</tbody>
</table>
Treatment for Preventing Tuberculosis in Children and Adolescents
A Randomized Clinical Trial of a 3-Month, 12-Dose Regimen of a Combination of Rifapentine and Isoniazid

- ~900 participants 2-17 years of age
- US, Canada, Spain, Brazil, Peru, Hong Kong
- 3HP: 0% TB incidence
- 9H: 0.74% TB incidence

Table 2. Tolerability and Reasons for Discontinuation Among Children in the Modified Intention-to-Treat Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Isoniazid (n = 434)</th>
<th>Rifapentine Plus Isoniazid (n = 471)</th>
<th>P Value(^a)</th>
<th>Difference (95% CI)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment completion</td>
<td>351 (80.9)</td>
<td>415 (88.1)</td>
<td>.003</td>
<td>-7.2 (-12.0 to -2.5)</td>
</tr>
</tbody>
</table>

Reason for not completing treatment

<table>
<thead>
<tr>
<th>Reason for not completing treatment</th>
<th>Isoniazid (n = 83)</th>
<th>Rifapentine Plus Isoniazid (n = 56)</th>
<th>P Value(^a)</th>
<th>Difference (95% CI)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All reasons</td>
<td>83 (19.2)</td>
<td>56 (11.9)</td>
<td>.003</td>
<td>7.2 (2.5 to 12.0)</td>
</tr>
<tr>
<td>Discontinuation because of AE(^c)</td>
<td>2 (0.5)</td>
<td>8 (1.7)</td>
<td>.11</td>
<td>-1.2 (-2.6 to 0.1)</td>
</tr>
<tr>
<td>Withdrawal of informed consent</td>
<td>5 (1.2)</td>
<td>4 (0.9)</td>
<td>.74</td>
<td>0.3 (-1.0 to 1.6)</td>
</tr>
<tr>
<td>Lost for ≥3 mo during treatment</td>
<td>26 (6.0)</td>
<td>5 (1.1)</td>
<td>&lt;.001</td>
<td>4.9 (2.5 to 7.4)</td>
</tr>
<tr>
<td>Physician decision to cancel other than AE</td>
<td>7 (1.6)</td>
<td>3 (0.6)</td>
<td>.21</td>
<td>1.0 (-0.4 to 2.4)</td>
</tr>
<tr>
<td>Participant refusal</td>
<td>15 (3.5)</td>
<td>16 (3.4)</td>
<td>&gt;.99</td>
<td>0.1 (-2.3 to 2.4)</td>
</tr>
<tr>
<td>Total dose count and/or administration period outside of protocol guidelines(^d)</td>
<td>28 (6.5)</td>
<td>20 (4.3)</td>
<td>.18</td>
<td>2.2 (-0.7 to 5.2)</td>
</tr>
</tbody>
</table>
Directly observed vs Self administered?

**iAdhere Study**

<table>
<thead>
<tr>
<th></th>
<th>DOT</th>
<th>SAT + monthly checks</th>
<th>SAT with weekly text reminders + monthly checks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Completion:</strong></td>
<td>87%</td>
<td>74%</td>
<td>76.4%</td>
</tr>
<tr>
<td><strong>In the USA:</strong></td>
<td>85%</td>
<td>78%</td>
<td>77%</td>
</tr>
</tbody>
</table>

— If DOT not available, OK to use SAT.
(recommendations for SAT/parent administered treatment extended to children ≥ 2yrs)

## INH + RPT weekly dosing for children and adults

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight based dose</th>
<th>Comments</th>
<th>Administration</th>
</tr>
</thead>
</table>
| INH  | 2-12 yrs: 25 mg/kg                     | - Max dose: 900mg                             | - Empty stomach preferred.  
- May crush tablet & mix in a soft food or liquid, or starch-based pudding |
|      | >12 yrs: 15 mg/kg                      | - Round up to nearest 50 or 100 mg dose       |                                                                               |
|      |                                        | - Max dose: 900mg                             |                                                                               |
| RPT  | 10 to 14 kg: 300 mg                    | - With meals preferred                        |                                                                               |
|      | >14 to 25 kg: 450 mg                   | - Tablets may be crushed and added to a small amount of semi-solid food and consumed immediately (reduces bioavailability) |                                                                               |
|      | >25 to 32 kg: 600 mg                   |                                               |                                                                               |
|      | >32 to 50 kg: 750 mg                   |                                               |                                                                               |
|      | >50 kg: 900 mg                         |                                               |                                                                               |

LexiComp  
Cruz et al, Pediatrics. 2018;141(2)  
Peloquin et al, CID, 2007;45(4)
Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults


• ~6800 adults, 9 countries, open-label, RCT
• 4R is non-inferior to 9H in preventing TB
• Treatment completion higher in 4R (79% vs 63%)
• 4R: less adverse events
• SAEs noted:
  – rash/allergy, hematologic, GI upset, drug interactions

NEJM, August 2, 2018
~850 children with LTBI or TB exposure (<5yrs)
- Treatment completion higher in 4R (87% vs 77%)
- Minor side effects were common (94% in both)
- No Grade 3+ SAEs noted
- 0 TB cases in 4R, 2 TB cases in 9H
Selecting a regimen?

• Drug interactions (especially with rifamycins)
• Adverse effects
• Adherence
• Concerns with pill burden
  – 9H + B6 : 2 pills/day
  – 4R: 2 pills/day
  – 3HP + B6: upto 10 pills weekly
• Costs
• Pregnancy
• Preferences (patient, provider, system)
Adverse effects: rifamycins

• Hypersensitivity reactions (<0.5-1%)
  – Rash, angioedema, syncope
  – thrombocytopenia/hemolytic anemia
• Cutaneous reactions (mild, 6%)
• Flu-like illness/myalgias (~3%), arthralgias
• GI upset: pain, nausea, vomiting,
• Hepatotoxicity (<1%)
• Orange discoloration of body fluids
Adverse effects: isonazid

• **Hepatotoxicity** (10-20%: asymptomatic, <1% symptomatic)
  – Underlying liver disease, alcoholism, other hepatically-metabolized medications,
  – Age:
    • <20 yrs: 1/1000
    • 20-34 yrs: 3/1000
    • 35-49 yrs: 12/1000
    • 50-64 yrs: 23/1000
    • >65 yrs: 8/1000

• **Peripheral neuropathy** (0.2%)
  – DM, HIV, renal failure, alcoholism, meat-deficient diet

• **CNS:** headaches, insomnia
Ongoing management

• Lab testing at baseline/during treatment
  – If at risk of hepatotoxicity (underlying liver disease)
  – Abnormal LFT results at baseline
  – Anyone with symptoms: fatigue/malaise, anorexia, abd pain, n/v, pale stools, dark urine, fevers/chills

• Follow up visits:
  – Symptom screening
  – Adherence checks, refills
• LTBI testing:
  – “incipient TB” biomarkers

• LTBI treatment:
  – Daily 1HP “ultra short course”:
    • non-inferior to 9H among ~3000 HIV+ adults from TB-endemic regions or TST+. (CROI, 2018)
  – Pediatric-friendly dispersable formulations

• Prevention:
  – New TB vaccines?

• Treatment:
  – Active TB in children: Shorter duration for mild forms of disease in children (SHINE study, 4 mos vs 6 mos)
Thank you

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