Diagnosis & Treatment of Latent TB Infection

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I have no financial disclosures or conflict of interest related to this presentation.

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Objectives

• Evaluate current burden of LTBI worldwide
• Describe the current guidelines for LTBI treatment
  – Understand current target population
  – Describe where research is leading
  – Describe current treatment guidelines
• Describe monitoring recommendations for patients on LTBI treatment
• Review management strategies for TB patients with co-morbid conditions
• Review treatment and management strategies for specific populations
• Look at a few specific innovations that can be applied inexpensively to public health TB programs

- For the past twenty years, the worldwide estimate for LTBI has been stated as “one-third”
- Changes in demographics and national populations, the size and distribution of TB burden, as well as the availability of new data means re-estimation is needed
- Controlling LTBI is a critical part of the strategy for eliminating TB by 2050

<table>
<thead>
<tr>
<th>WHO region</th>
<th>All LTBI</th>
<th>Recent infection prevalence (within 2 y)</th>
<th>Proportion with INH-R infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevalence (%)</td>
<td>Proportion of infections in children &lt;15 y (%)</td>
<td>(%)</td>
</tr>
<tr>
<td>AMR</td>
<td>11.0 [7.0–20.0]</td>
<td>2.3 [1.3–3.7]</td>
<td>0.2 [0.1–0.2]</td>
</tr>
<tr>
<td>SEA</td>
<td>30.8 [28.3–34.8]</td>
<td>7.4 [6.3–8.2]</td>
<td>1.2 [0.9–1.6]</td>
</tr>
<tr>
<td>EMR</td>
<td>16.3 [13.4–20.5]</td>
<td>7.9 [6.0–9.4]</td>
<td>0.7 [0.5–1.0]</td>
</tr>
<tr>
<td>WPR</td>
<td>27.9 [19.3–40.1]</td>
<td>2.4 [1.7–3.5]</td>
<td>0.5 [0.4–0.7]</td>
</tr>
<tr>
<td>EUR</td>
<td>13.7 [9.8–19.8]</td>
<td>2.0 [1.3–2.7]</td>
<td>0.3 [0.2–0.3]</td>
</tr>
<tr>
<td>GLOBAL</td>
<td>23.0 [20.4–26.4]</td>
<td>5.9 [5.1–6.7]</td>
<td>0.8 [0.7–0.9]</td>
</tr>
</tbody>
</table>

What Do These Findings Mean?

• Approximately 1.7 billion individuals were infected with LTBI in 2014; just under a quarter of the global population

• If left unaddressed, the current LTBI burden alone will likely prevent achieving the global TB targets for TB elimination

• Research and development should focus on developing better tools to identify individuals who will benefit from LTBI treatment
Some of this research includes:

**PPD Induced Mitochondrial Damage**

How Does the BCG Vaccine Work?

Prospective cohort study \( N=2060 \) of Healthy Household Contacts (HHC) of patients with pulmonary tuberculosis

- 1,859 out of 2,060 samples showed monocyte death in response to PPD stimulation in vitro (201 samples not used due to low cell viability)
- Of these 1859:
  - 83.4% underwent mitochondrial damage (protective)
  - 50.9% had membrane damage.
- The membrane damage in response to PPD was higher in:
  - children under 4 years (OR: 1.57; (95% CI: 1.1 to 2.4)
  - HHCs who slept regularly in the same household has an index case of (OR: 1.54; 95% CI: 1.0 to 2.3)
  - the risk of developing active TB among BCG vaccinated HHCs with induction of mitochondrial damage was **HR = 0.19** (95% CI: 0.1 to 0.5)

Fig 2. Distribution of the percentage of monocytes with mitochondrial damage and membrane damage in peripheral blood mononuclear cells (PBMC) cultures from household contacts stimulated and non-stimulated with PPD.

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0171930
Table 2. TB incidence and non-adjusted Hazard Ratio (HR) that influences development of TB according to various factors related to households of smear-positive patients in Colombia.

<table>
<thead>
<tr>
<th>Factor</th>
<th>n/N</th>
<th>Person-years (PY)</th>
<th>Incidence × (1000 PY)</th>
<th>Non-adjusted HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD-induced mitochondrial damage</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11/308</td>
<td>808.57</td>
<td>13.6</td>
<td>0.45 (0.22–0.92)</td>
<td>0.029</td>
</tr>
<tr>
<td>Yes</td>
<td>23/1545</td>
<td>3897.31</td>
<td>5.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPD-induced membrane damage</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>20/909</td>
<td>2275.05</td>
<td>8.79</td>
<td>0.67 (0.34–1.32)</td>
<td>0.243</td>
</tr>
<tr>
<td>Yes</td>
<td>14/944</td>
<td>2430.82</td>
<td>5.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≤ 4</td>
<td>7/181</td>
<td>451.5</td>
<td>15.51</td>
<td>2.05 (0.88–4.79)</td>
<td>0.127</td>
</tr>
<tr>
<td>5–14</td>
<td>4/467</td>
<td>1230.2</td>
<td>3.25</td>
<td>0.71 (0.45–1.12)</td>
<td>0.095</td>
</tr>
<tr>
<td>≥ 15</td>
<td>23/1205</td>
<td>3024.3</td>
<td>7.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG scar</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>12/388</td>
<td>987.9</td>
<td>12.15</td>
<td>0.51 (0.25–1.03)</td>
<td>0.060</td>
</tr>
<tr>
<td>Yes</td>
<td>22/1428</td>
<td>3632.3</td>
<td>6.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21/1469</td>
<td>3795.5</td>
<td>5.53</td>
<td>2.30 (1.01–5.22)</td>
<td>0.046</td>
</tr>
<tr>
<td>Yes</td>
<td>8/265</td>
<td>655.0</td>
<td>12.21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>30/1760</td>
<td>4486.9</td>
<td>6.69</td>
<td>2.93 (0.70–1.23)</td>
<td>0.142</td>
</tr>
<tr>
<td>Yes</td>
<td>2/45</td>
<td>102.2</td>
<td>19.57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional status</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>20/998</td>
<td>2538.5</td>
<td>7.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>5/489</td>
<td>1270.0</td>
<td>3.94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>9/340</td>
<td>841.9</td>
<td>10.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximity to index case</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>HHC slept in other household</td>
<td>20/1388</td>
<td>3516.7</td>
<td>5.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHC slept in same household</td>
<td>7/189</td>
<td>479.7</td>
<td>14.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHC slept in same room</td>
<td>7/276</td>
<td>709.5</td>
<td>9.87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons per room</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Less than 3</td>
<td>21/1354</td>
<td>3454.8</td>
<td>6.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 or more</td>
<td>13/486</td>
<td>1217.1</td>
<td>8.08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Incidence Highest In:
- Children Under 4
- HHC without scar
- HHC with co-morbidity
- Particularly diabetic

TB Incidence rates:
- Similar in mitochondrial and cell membrane damage

BUT, risk of developing the disease higher in HHC where the response to PPD showed no mitochondrial damage
Current Guidelines for LTBI Treatment

Scope of Review 2016

- The USPSTF commissioned a systematic review of the evidence on screening for LTBI.
- Evidence dating from the inception of searched databases until August 3, 2015, was included.
- Directed at LTBI in asymptomatic adults seen in primary care settings.
- Specifically did not include evidence on screening in persons for whom LTBI screening would already be part of medical or public health screening.
U.S. Preventive Services Task Force recommends testing for TB as a part of standard preventive care for certain at-risk groups which fall into 2 categories:

- Those who have an increased likelihood of exposure to persons with TB disease
- Those with clinical conditions that increase their risk of progressing from LTBI to TB disease

This necessitates a careful interview— **TALK TO YOUR PATIENTS!**
### Evaluation of Persons with Latent Tuberculosis Infection Based on Risk of Infection, Risk of Progression to Tuberculosis, and Benefit of Therapy

<table>
<thead>
<tr>
<th>Group</th>
<th>Testing Strategy</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Likely to be Infected</strong></td>
<td><strong>High Risk of Progression (TST ≥ 5mM)</strong></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td><strong>Acceptable</strong>: IGRA OR TST</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider dual testing where a positive result from either result would be considered <strong>positive</strong></td>
<td></td>
</tr>
<tr>
<td>Children ≤ 5 years of age</td>
<td><strong>Preferred</strong>: TST</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Acceptable</strong>: IGRA OR TST</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider dual testing where a positive result from either would be considered <strong>positive</strong>¹</td>
<td></td>
</tr>
<tr>
<td><strong>Likely to be Infected</strong></td>
<td><strong>Low to Intermediate Risk of Progression (TST ≥ 10mM)</strong></td>
<td></td>
</tr>
<tr>
<td>Preferred</td>
<td>IGRA where available</td>
<td></td>
</tr>
<tr>
<td>Acceptable</td>
<td>IGRA or TST</td>
<td></td>
</tr>
<tr>
<td>Testing for LTBI is not recommended If necessary:</td>
<td>Preferred: IGRA where available.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acceptable: Either IGRA OR TST</td>
<td></td>
</tr>
<tr>
<td>For serial testing:</td>
<td>Acceptable: Either IGRA OR TST</td>
<td></td>
</tr>
<tr>
<td>Unlikely to be Infected</td>
<td>(TST &gt; 15mM)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider repeat or dual testing where a negative result from either would be considered <strong>negative</strong>²</td>
<td></td>
</tr>
</tbody>
</table>

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1. Performing a second diagnostic test when the initial test is negative is a strategy to increase sensitivity. This may reduce specificity, but the panel decided that this is an acceptable tradeoff in situations in which the consequences of missing LTBI (i.e., not treating individuals who may benefit from therapy) exceed the consequences of inappropriate therapy (i.e., hepatotoxicity).

2. Performing a confirmatory test following an initial positive result is based upon both the evidence that false-positive results are common among individuals who are unlikely to be infected with Mtb and the committee’s presumption that performing a second test on those whose initial test was positive will help identify initial false-positive results.
Beginning Treatment for LTBI

• Although IGRA and TST can determine whether a patient is infected, they are unable to differentiate between active TB and latent TB

• As a result, “the diagnosis of active TB must be excluded prior to embarking on treatment for LTBI”

• At minimum, this includes a careful screening for signs and symptoms and a recent chest film
When In Doubt About Active TB v Latent

- Tspot + contact to Sister in Law
- Infant in house had pulmonary TB after sleeping in same room as the aunt
- Because of work shift, “never in the same room”
- Had cough past 2 days after “being outside with no shoes”
- Did not want to miss work
- Worked in large, open space
- Seen in clinic Tues, CXR, home isolation begun, wrote orders for RIPE to begin Wed
- 2 sputum on Tues, 1 first morning of Wed
- Verbal report from radiologist Wed—”No Active Disease”
- Negative smears on Thursday
- Allowed back to work Monday
  - (5 doses RIPE)
- +Mtbf growth at 5 weeks on culture

"Given the public health implications of prompt diagnosis and effective management of tuberculosis, empiric multidrug treatment is initiated in almost all situations in which active tuberculosis is suspected. “ Official American Thoracic Society/centers for disease control and prevention/infectious diseases society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis." Clinical Infectious Diseases 63.7
Signs and Symptoms in Evaluation of TB/LTBI (until it is not)

- 48 y.o. woman, visiting from Florida
- Hurricane Harvey about to hit
- While in Michigan, was called by her Florida dermatologist to say that her IGRA was positive on 8/29/17 (previously negative 2016)
- Advised by that doctor to, “go to the public health clinic and get a skin test because it can tell you if you have active TB or not”
- Patient reported 3 day history of +temp $>100$ F, 3 week history of productive cough, with 6-8 weeks of SOB, 20# weight loss, night sweats, After a great deal of work-up, this was determined not to be TB

“The diagnosis of active TB must be excluded prior to embarking on treatment for LTBI”
Regimens

• Unlike active TB where four drugs are required in the intensive phase, the burden of bacteria in LTBI is quite low

• This allows for more flexibility in regimen choices

• But also emphasizes why it is so important to rule out active disease before beginning LTBI regimen so as not to potentiate drug resistance development
## Treatment Regimens for Latent TB Infection

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>52</td>
</tr>
<tr>
<td>Isoniazid &amp; Rifapentine</td>
<td>3 months</td>
<td>Once weekly</td>
<td>12</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>

**Note:** Rifampin (RIF) and Pyrazinamide (PZA) should not be offered to persons with LTBI. RIF and PZA should continue to be administered in multidrug regimens for the treatment of persons with TB disease.
Latent TB Infection Treatment Regimens
Isoniazid (INH)

• 6-month regimen is less effective and not recommended, but may be used if unable to complete 9 months
• Use directly observed therapy (DOT) for intermittent regimen
• Preferred regimen for children 2-11 years of age—per CDC (this may be changing!)
3HP
12 Doses of Once a Week DOT of Isoniazid and Rifapentine

• 3-month regimen of INH and RPT is an option equal to 9-month INH regimen for treating LTBI in certain groups:
  – “12 years of age and older, who were recently in contact with infectious TB or who had tuberculin skin test conversions or positive blood test for TB”
• Not recommended for:
  – children younger than 12 years of age,
  – HIV-infected people taking antiretroviral therapy
  – pregnant women, or women expecting to be pregnant within the 12-week regimen
• My experience: particularly beneficial for:
  • Hep C patients-safer
  • Patients in and out of congregate settings
  • College students home for summer
• Must use directly observed therapy (DOT)
High Rate of Treatment Completion in Program Settings With 12-Dose Weekly Isoniazid and Rifapentine for Latent Mycobacterium tuberculosis Infection

Amy L. Sandul,1 Nwabunike Nyama,1 J. Mike Holcombe,2 Mark N. Lobato,2,3 Suzanne Marks,1 Risa Webb,1 Shu Hua Wang,5 Brock Stewart,1 Phil Griffin,1 Garrett Hunt,1 Neha Shah,1,2 Aweeem Marco,1 Navleen Sethi,1 Leonard Ofokansi,2 Ruth N. Moro,6 John Leach,1 Sundar Mane,2 Terence Chakba,7 Sajna Banerjee-Morris,7 and Christine S. Ho8

- Published on-line May, 2017 (CID October, 2017)
- In clinic settings, found high rate of completion 87.2% with 3HP regimen among a diverse patient cohort
- Substantially higher than INH completion
- Factors associated with lower likelihood of discontinuation of 3HP treatment included:
  - age 2–17 years (12 children ages 2-11)
  - being the contact of a TB case
  - being a student
- Factors associated with increased risk of discontinuation homelessness and incarceration past 12 months

Treatment reason or population (patients might be in ≥1 category)9

- 821 (25.0%) Contactb
- 800 (24.3%) Converte
- 516 (15.7%) Corrections
- 181 (5.5%) Homeless
- 132 (4.0%) Refugee
- 1294 (39.4%) Foreign born
- 500 (15.2%) Healthcare worker
- 130 (4.0%) Student
- 211 (6.4%) Employment
- 47 (1.4%) Long-term-care resident
“Those who have an increased likelihood of exposure to persons with TB disease”

- Close contacts to person with infectious TB
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, health care facilities)
- Recent immigrants from TB-endemic regions of the world (within 5 years of arrival to the United States)
  - Question the 5 year rule!
  - Finding high activation in first two years, but then continued elevated risk of activation long after living in USA. May be a factor of aging, changing dietary profiles (increase DM) etc...
- But do not forget about business travelers, missionaries, remote history of living abroad!
- All of these people fall under the caution from the Official American Thoracic Society...Clinical Practice Guidelines: Diagnosis... “Individuals with LTBI who have been recently exposed have an increased risk of developing TB, whereas those with remote exposure have less risk over time unless they develop a condition which impairs immunity.
Close contacts to person with infectious TB

Certain circumstances may warrant additional steps. For example, contacts to MDR TB who refuse treatment, should be evaluated by serial radiographs for at least two years after exposure. Use Public Health Threat to Others for legal support in drug resistant cases.
On Third Serial Radiograph, HHC Developed LUL Infiltrate as Contact to MDR Patient

3.3 Emergency procedures available to the Manager/Health Officer shall not be limited to the procedures outlined in the Michigan Public Health Code. MCL 333.2453(1). Measures that may be employed by the Manager/Health Officer to prevent the spread of the imminent dangers are:

3.41 An order to quarantine individuals known or reasonably expected to pose a serious communicable disease risk to others.

3.42 An order for communicable disease treatment of infected individuals involved in an outbreak or epidemic of a serious communicable disease.

3.43 An order to immunize or provide preventive treatment for population groups at risk during an outbreak or epidemic of a serious communicable disease.

3.44 An order to ensure continuation of essential public health services and enforcement of health laws.

3.45 Other actions or directives consistent with the Department’s authority and judgement, including the development of environmental sanitation control measures, clinical interventions, exclusion notices, information, outreach and education programs.

Chest Radiograph:

Date 1/12/20**

CHEST

PA and lateral views of the chest were obtained and compared with a prior chest study dated 8/9/20**. There is some new soft infiltrate in the left upper lobe partially superimposing over the posterior aspect of the 4” rib. This infiltrative change, not present on the prior study, would be suspicious of active tuberculosis process and further investigation of this patient with CT scan may be needed. No clear evidence of focal cavitation is seen at this time.

IMPRESSION:

THERE IS SOME NEW INFLTRATE IN THE LEFT UPPER LOBE SUGGESTIVE OF ACTIVE TUBERCULOUS PROCESS. FURTHER INVESTIGATION OF THIS PATIENT IS NEEDED.

JOHN MELLEN, M.D.
“Those with clinical conditions that increase their risk of progressing from LTBI to TB disease”

• HIV-infected persons

• Those with a history of prior, untreated TB or fibrotic lesions on chest radiograph—Get sputum before treating!

• Children ≤ 5 years with a positive TST

• Substance abusers (such as smoking, alcohol abusers, or injection drug use)
Increased emphasis on persons living with clinical conditions that increase their risk of progressing from LTBI to TB disease cont...

- Those with certain medical conditions such as:
  - receiving TNF-α antagonists
  - Silicosis
  - Chronic renal failure or on hemodialysis
  - Diabetes mellitus
  - Solid organ transplantation (e.g., heart, kidney)
  - Carcinoma of head or neck
  - Gastrectomy or jejunoilial bypass
Methadone and LTBI

- 68 y.o. man
- Refugee with history of being given heroin for recreational use while imprisoned in a work camp in Asia.
- Now anxious to continue his regimen to wean off of methadone
- Chose 3HP due to less likelihood of drug interactions and quicker resolution, but still need to monitor carefully by s/s for unstable methadone levels.
- Incidentally, we also check hep B and C levels for all patients from Asia
Methadone and TB Treatment

- Rifampin is the most powerful known inducer of the hepatic cytochrome P450 enzyme system and other pathways as well
- This increases the metabolism of methadone, thereby reducing its efficacy
- Methadone seems to be the only opioid that is also a CYP inhibitor
- Isoniazid may increase the effect of methadone
- Necessitates close working relationship with methadone clinic physician
- Patient may need to be seen 1-2 days after each dose of 3HP (but usually not-monitor for symptoms of withdrawal)
Chronic Kidney Disease (CKD) and LTBI

• Immunodeficiency associated with CKD is multifactorial in etiology:
  – Inflammation
  – Vit D deficiency
  – Malnutrition
  – Functional abnormalities of many kinds of immune cells (including B, T, monocytes)
  – Changes in immunity begin as early as stage 3

• TST has a significantly higher rates of false-negative results in the ESKD population than in the general population and IGRA should be used

• Estimate that TB risk is increased 3- to 25-fold
  – But with adjusting for demographic factors, the risk appears to be about 3.6 (95% confidence interval 1.8–7.3)
  – Country of birth appears to be a particularly important TB risk factor in dialysis populations
    • Low incidence countries the rate is about 18 per 100,000 per year in dialysis and in those born in the highest TB incidence countries the rate was 698 per 100,000 per year
  – Critical to treat at LTBI because hemodialysis patients with active TB pose a great risk to other patients and health care workers, particularly given the frequency and proximity of shared air space.

Syndemic:

A set of linked health problems involving two or more afflictions, interacting synergistically, and contributing to excess burden of disease in a population. ... To prevent a **syndemic**, one must prevent or control not only each affliction but also the forces that tie those afflictions together.
Renal Disease Treatment Considerations

• Diagnosis can be a challenge due to nonspecific symptoms and a relatively high incidence of extrapulmonary tuberculosis

• Particularly easy to miss peritoneal disease in patients receiving renal replacement therapy with chronic ambulatory peritoneal dialysis

• Pharmacokinetics of TB drugs – some are cleared by kidney and/or dialysis, and must be adjusted:
  – Generally, do not decrease dose, increase interval between doses
  – But for LTBI, RIF and INH are metabolized by the liver—use these!
  – May need to measure serum concentrations at 2 and 6 hours after administration to assist with optimizing drug doses
  – Post-dialysis administration of all LTBI regimens to avoid premature clearance of the drugs
  – Monitor carefully for toxicity
Missed Opportunity in 67 Y.O. Man with CKD

2008—Converted TST; patient made aware of it, and solitary nodule found, Not offered treatment

2012—"Solitary Pulmonary Nodule" with history given as 63 y.o. male with weight loss, fatigue, night sweats, hx of pulmonary nodule in CT in 2008 Comment: No malignancy

CT granuloma clearly marked by radiologist. Patient already in Stage 3 Renal Disease. Not offered treatment
2016

presents with SOB produced by exertion or stress

“Improvement in prior pleural effusion, now small to moderate, extending into the fissures. Rt lower lobe airspace disease is difficult to assess. Some patchy airspace disease present within the right upper lung.” Told he could take LTBI treatment or be monitored
Persons at Risk of Progression to Active Disease: Diabetes, In More Detail

“Some evidence from observational studies has explored the association between poorly controlled diabetes and progression of LTBI to active disease. However, there is insufficient evidence on screening for and treatment of LTBI in persons with diabetes for the USPSTF to make a separate recommendation for this important subgroup.” USPSTF 2016
Diabetes Potentiates TB

- Causes relative immunocompromise
- Decreases macrophage and lymphocyte function, leading to decreased ability to contain the organism
- Produces local tissue acidosis and electrolyte imbalance that impairs repair
- Disturbed protein metabolism with subsequent decrease of antibody formation
- Disturbed fat metabolism leading to:
  - Ketosis which decreases bactericidal effect of lactic acid
  - Increase in glycerol in the blood that then favors growth of tubercle bacilli
- Associated hepatic insufficiency from fatty liver leads to low levels of vitamins A and D, which decrease integrity of epithelial tissue
Diabetes and Potential to Use Identification of Status to Increase LTBI Treatment Initiation

- DM is a risk factor for active TB disease
- Studies looking at whether DM predisposes to infection with Mtb are on-going
- Hensel, R.L. et al., out of Emory, describes an association of both DM and pre-DM with LTBI
- Oakland County initiated HbA1c testing in persons with LTBI:
  - identify persons at increased risk of activation
  - educate those clients at increased risk of conversion to active disease in order to increase uptake of treatment for LTBI

Known Status of Diabetes and Prediabetes among Latent and Active TB Cases at Oakland County Health Division

Overall significant increase in proportions between self-reporting and HbA1c testing
- Similar increase among both latent and active
- Reflects general unawareness of prediabetes
Treat as LTBI Because DM Modifies the Clinical Presentation of Pulmonary TB and Is Misdiagnosed

- Already difficult to remember to “Think TB” in low-incidence states
- Associated with atypical radiological presentation
  - Lower lungs, misdiagnosed as CAP
  - Increased cavitary disease
- Typical features such as cough and weight loss can be less common

46 year old man with DM and TB
Patients with Co-morbid Conditions - Diabetes
Metformin use reverses the increased mortality associated with diabetes mellitus during tuberculosis treatment
Nicholas R Degner et al., Clinical Infectious Diseases, 9 September 2017

• Patients with DM had 1.91 times higher of death during TB treatment than patients without DM
  – 2,416 patients
  – adjusted for multiple factors
• Metformin use in patients with DM was significantly associated with decreased mortality during TB treatment
  – hazard Ratio 0.56, CI 0.39-0.82
  – metformin users had similar mortality as patients without DM
• Metformin, a first-line drug for DM, has received significant attention recently as a potential adjunctive agent for TB, as it has been shown to enhance autophagy, an immune process crucial for the control of TB
Monitoring Recommendations for LTBI Treatment-per CDC

• Clinical monitoring, including a brief physical examination, should occur at monthly visits to assess adherence and to identify signs or symptoms of adverse drug reactions.

• Baseline and routine laboratory monitoring during treatment of LTBI are indicated when:
  – history of liver disease
  – HIV infection
  – pregnancy (or within 3 months post delivery)
  – regular alcohol use

• Baseline hepatic measurements of serum AST, ALT, and bilirubin are used in the situations mentioned above and to evaluate symptoms of hepatotoxicity such as:
  – Unexplained anorexia, nausea or vomiting, dark urine or icterus
  – Persistent weakness, fatigue, fever, or abdominal tenderness
  – Easy bruising or bleeding
Treatment and Management Strategies for Specific Populations-HIV-Infected Persons

• Consult an expert in managing HIV and TB
• INH daily for 9-months, err on the side of DOT
• RIF is generally contraindicated for persons taking protease inhibitors
• “Rifabutin with dose adjustments can sometimes be substituted for RIF”
• INH/RPT regimen not recommended for HIV-infected people taking antiretroviral therapy
THIS IS MR. TB GERM

He'd love to catch you with your RESISTANCE down

AMERICAN LUNG ASSOCIATION
One County’s Efforts (On-going)

- Based on literature review:
  - Initiation into treatment rather than completion of treatment was the major challenge. Goswami et al. (2012)
  - Streamline tuberculosis infection follow-up visits and use dedicated tuberculosis staff. Hill et al. (2010)

*Special thanks to Emily Smith, MPH, for her dedicated work at OCHD in data analysis and developing the questionnaires. She has set in motion further actions to promote LTBI treatment uptake*
To streamline and provide continuity of care to clients with LTBI, changes made in OC clinics in January, 2017:

• One dedicated nurse for LTBI in each clinic
  – Allows for “preferred arrival time” of clients in otherwise walk in clinic
  – Patient sees the same nurse for each visit:
    • builds patient/nurse relationship
    • patient has a phone number that directly calls someone they know
    • maintain continuity and expertise
    • allows for 3HP
  – Initiate follow up both for patients and to coordinate transfer of patients to other counties for follow up
  – Improve nursing satisfaction and understanding of the importance of LTBI treatment
Research Questions

1. Out of all TST tests given, how many clients are positive and initiate treatment?
2. Out of all TSPOT tests given, how many clients are positive and initiate treatment?
3. What is the country of origin for those patients who tested positive for tuberculosis infections?
4. Describe the demographic information for patients testing positive by TST at Oakland County Health Division.
5. Describe the demographic information for patients testing positive by TSPOT Oakland County Health Division.
6. Describe Oakland County residents who tested positive for TSPOT and/or TST and initiated treatment in 2016 in compared to January 3 to July 1, 2017.
• Investigated predictors of initiation/completion of tuberculosis infection treatment.
  – Examined data for TSPOT and TST tests completed at the Oakland County Health Division from January 3, 2017 to July 1, 2017.

• Questionnaire administered to clients evaluated for LTBI:
  – TB Infection Completed Treatment Questionnaire
  – TB Infection Declined Treatment Questionnaire
Key Findings:

- 41.66% of Oakland County Residents tested positive for tuberculosis infection by TST or TSPOT initiated treatment in 2016.

- 44.87% of Oakland County Residents tested positive for tuberculosis infection by TST or TSPOT initiated treatment from January 3 - July 1, 2017.

- 3.21% increase from 2016 to 2017

- Numbers at time of analysis were low, but we generally diagnose about 300 patients with LTBI a year
References Page 1

• Gray, E. L., and H. F. Goldberg. "Baseline abnormal liver function tests are more important than age in the development of isoniazid-induced hepatotoxicity for patients receiving preventive therapy for latent tuberculosis infection." Internal medicine journal 46.3 (2016): 281-287.
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- Emily Smith, MPH, our innovative epi intern this past summer, who pulled together sustainable tracking of outcomes for our LTBI program