Screening and Treating Latent Tuberculosis Infection: New Options for an Old Disease

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Dr. Cook currently works with a largely Spanish-speaking patient population at Westwood Clinic, one of nine community health center sites that Denver Health maintains in neighborhoods throughout the city. He earned his medical degree from the University of Southern California (USC) School of Medicine, Los Angeles (now the Keck School of Medicine of USC), and completed a family medicine residency at North Colorado Medical Center, Greeley. He also earned a master’s degree in international health and tropical medicine and a Diploma in Tropical Medicine & Hygiene from the London School of Hygiene and Tropical Medicine, England. This training led to work in several areas related to infectious disease. For six years, he served as a county tuberculosis and sexually transmitted infection (STI) control officer and a physician in Ventura County, California, where he also oversaw the travel health clinic. Dr. Cook continues to pursue his interest in the interface between infectious diseases and family medicine through work on STI control at Denver Public Health and work on hepatitis B and C at Denver Health. In addition, he currently works with Project Echo Colorado, an effort to use video-conferencing technologies to extend training in the treatment of chronic hepatitis C to family physicians in underserved rural and urban communities.
Learning Objectives

1. Identify asymptomatic adults at increased risk for TB infection, and screen according to current USPSTF recommendations.

2. Identify symptoms and risk factors associated with active tuberculosis and conduct appropriate physical exam and laboratory testing.

3. Diagnose LTBI and provide indicated treatment to reduce future risk of progression to active TB.

4. Educate patients on the importance of completing the full round of antibiotic treatment to prevent drug resistance and recurrence of infection, and be familiar with concept of directly-observed therapy (DOT).

5. Counsel infected patients on how to prevent transmission of tuberculosis.

Audience Engagement System

Step 1

Step 2

Step 3
Mycobacterium tuberculosis

• Acid-fast bacillus
• Lipid-rich cell wall
• Slow growth in culture media
• Granuloma formation

Tuberculosis epidemiology: global

• ~ 2 billion people have latent TB infection
• ~ 10 million new active TB cases/year
• ~ 1.6 million deaths/year
• ~ 4.4 million active cases in SE Asia
• ~ 2.4 million active cases in Africa
• Leading cause of infectious disease death
• HIV-TB: causes 40% of HIV-related deaths
Poll Question #1

Which one of the following statements regarding the current epidemiology of TB in the US is false?

A. Overall, the number of active TB cases are declining annually.
B. An estimated 2 million people in the US have latent TB infection.
C. Currently, there are more active TB cases amongst foreign-born people living in the US than amongst US-born people.
D. Over 80% of active TB cases are due to reactivation of latent TB infection.

Tuberculosis epidemiology: USA

• Active TB disease: 9,105 cases in 2017
• Active TB cases progressively declining for many years
• Latent TB infection: ~ 13 million
• 70% active cases foreign-born
• Racial-ethnic differences in US-born cases
• ~ 87% active cases due to reactivation of latent TB infection
Active TB incidence and rates: USA

TB in US foreign-born population
• 6,346 cases in 2017; 70% of active cases
• Top five countries of origin and TB rates in country of origin (cases/100,000):

<table>
<thead>
<tr>
<th>Country</th>
<th># of cases</th>
<th>% of cases</th>
<th>TB rate</th>
</tr>
</thead>
<tbody>
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<td>1,204</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Philippines</td>
<td>783</td>
<td>12</td>
<td>554</td>
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<td>India</td>
<td>595</td>
<td>9</td>
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<td>Vietnam</td>
<td>526</td>
<td>8</td>
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<tr>
<td>China</td>
<td>400</td>
<td>6</td>
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</tbody>
</table>
Racial-ethnic disparities, active TB

• Differences in US-born active TB rates:

<table>
<thead>
<tr>
<th>Race/ethnicity</th>
<th>Cases/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawaiian/Pacific Islander</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Black</td>
<td>2.8</td>
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<tr>
<td>Asian</td>
<td>2.0</td>
</tr>
<tr>
<td>Hispanic</td>
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</tr>
<tr>
<td>White</td>
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</tr>
</tbody>
</table>

TB: the chain of transmission

• Infectious source case
  • Pulmonary and laryngeal TB are contagious
  • Patients with cavitary lung lesions and sputum AFB smear positivity most contagious

• Susceptible host
  • Duration and proximity of exposure increase risk of infection; household contacts at highest risk of infection
Preventing transmission of active TB

• Hospital setting: respiratory isolation; negative pressure room; N95 mask staff and visitors
• Outpatient setting: home isolation until sputum AFB smear negative
• Criteria for being considered non-contagious:
  • 3 negative sputum AFB smears 8 to 24 hours apart
  • 2 weeks adequate anti-TB therapy and appropriate clinical response (improved symptoms)

Pathophysiology of TB infection

• Aerosolized infectious secretions inhaled into alveolar airspaces
• Ingestion by alveolar macrophages
• Lymphatic and hematogenous spread to hilar lymph nodes and throughout body
• Immune control (latent TB) vs disease progression
Risk factors for active TB infection

- Latent TB infection: ~ 87% of active TB is “reactivation” of latent TB infection
- Residence in TB-endemic countries
- Household contacts of active TB case
- Very young (< 5 y/o) and very old
- Immune compromise: HIV, cancer, chemotherapy, immunotherapy, CKD, DM

Active TB infection

- Pulmonary TB
  - Majority of cases
  - Contagious
  - Cavitation
- Extra-pulmonary TB
  - Symptoms and clinical presentation specific to site of infection
Extra-pulmonary TB

• Most common sites and associated symptoms
  • Cervical lymphadenitis: adenopathy
  • Pleural: effusion
  • Bone-joint: Potts disease (TB of spine)
  • Genito-urinary: “sterile pyuria”
  • Miliary: multi-organ involvement
  • Abdominal: ascites

Diagnosis of active TB

• History and physical
• Epidemiologic context: exposure risk, LTBI
• Positive tuberculin skin test (TST) or IGRA blood test
• Imaging
  • CXR or CT for pulmonary
• Sputum, body fluid or tissue specimen
  • AFB stain
  • Culture and rapid diagnostic techniques
Imaging: active pulmonary TB

• Findings variable using CXR or chest CT
  • Nodules
  • Infiltrates
  • Cavitary lesions

Active pulmonary tuberculosis
Treatment of active TB

• Most common treatment: 4 drug regimen; 6 months total treatment
  • INH, rifampin, pyrazinamide and ethambutol x 2 months
  • INH, rifampin x 4 months
• Compliance with treatment critical to prevent development of drug resistance; directly-observed therapy (DOT) commonly used

Latent TB infection

• ~87% of active TB cases due to reactivation of latent TB
• Great majority of new TB infections result in latent TB
• Treatment of latent TB infection reduces risk of progression to active TB disease
Diagnosis of latent TB infection

• Positive TST or IGRA in person at risk for TB infection
• No signs or symptoms suggestive of active pulmonary or extra-pulmonary TB
• Normal CXR
  • CXR with small nodule (up to a few mm) also consistent with latent TB infection

Evidence for TB latency

• Pathologic evidence: viable TB bacteria found post-mortem in lymph nodes and other tissues of patients who did not have active TB
• Epidemiologic evidence: people with positive TST have much higher rates of subsequent active TB than people with negative TST; treatment of LTBI lowers risk of progression to active TB
Poll Question #2

What is the estimated lifetime risk that a person with latent TB infection and without immune-compromising conditions will progress to active TB disease?

A. 50 %  
B. Less than 1 %  
C. 5 to 10 %  
D. 20 to 25 %

Risk factors for progression from LTBI to active TB

• Recent infection within last 2 years: 5 to 10% lifetime risk  
• Close contact to active case  
• Children under 5  
• Previous residence in TB-endemic area  
• Immune suppressing drugs: TNF blocker, cancer chemotherapy  
• HIV infection: 10% per year!  
• Chronic kidney disease/dialysis  
• Diabetes mellitus
Targeted screening for latent TB infection: CDC/USPSTF

• People from high-prevalence countries
• People residing in large group settings
• Contacts to active TB
• HIV and immune-compromising illnesses
• Health workers
• Prior to use of certain medications: TNF blockers; high-dose steroids; others

Poll Question #3

Which one of the following statements concerning TB testing is true?

A. With the development of IGRA testing, tuberculin skin testing (TST) is no longer recommended.
B. BCG vaccination often causes false-positive IGRA test results.
C. The TST can be false negative in active TB in up to 20% of cases.
D. BCG vaccination does not affect TST results.
TB screening

• Tuberculin skin test (TST)
• Interferon gamma-release assay (IGRA)
• BCG vaccine and screening

Tuberculin skin test (TST)

• Tuberculin: extract of inactivated culture of M. tuberculosis
• PPD: purified protein derivative = protein precipitate of tuberculin
• 5 Tuberculin Units (TU) standard dose = 0.0001mg PPD in 0.1ml solution
• Sensitivity/specificity originally determined in very high and very low prevalence populations: 16-17mm reaction in sanatorium patients vs 0-5mm in children from non-infectious environment
Tuberculin skin testing

• 5 TU PPD intradermal injection volar forearm
• Correct injection: raised, blanched wheal; technique important
• Read in 48-72 hours; patient must return to clinic for reading
• Measure induration, not redness; intra-observer variability problematic
• Interpretation:
  • 5mm: immunocompromised, recent contact to active case
  • 10mm: other groups

Positive PPD/TST

![Positive PPD/TST Image]
TST accuracy

• False positivity: infection with non-tuberculous Mycobacteria and BCG vaccination
• False negative: ~20% of active TB cases have negative PPD

Interferon gamma-release assay (IGRA)

• T cells sensitized to TB bacteria in people with latent or active TB produce interferon-gamma
• IGRA test: whole blood exposed to in-vitro TB antigens; sensitized T cells produce interferon-gamma which can be measured
• More accurate than TST in patients vaccinated with BCG
• Quantiferon™ and T Spot™ are common commercial test kits
IGRA accuracy

• Theoretically not affected by BCG
• False negative: immune compromise, elderly
• “Indeterminate” results
• Children: Red Book (AAP infectious disease guidelines) recommends TST in children under 2

BCG vaccination

• Bacille Calmette-Guerin: inactivated extract of Mycobacterium bovis given as vaccine
• Used as public health strategy in many high prevalence countries; low cost
• Efficacy variable; many studies
• Prevention of miliary and meningeal TB in children
• May cause false-positive TST
Evidence for efficacy of LTBI treatment

• US Public Health Service TB branch INH prevention randomized trials, 1960s
  • 2,750 PPD positive children; 88% reduction TB “complications” such as XPTB
  • 25,000 household contacts to active TB cases; ~70% reduction in number of cases of subsequent active TB disease

Treatment for LTBI

• Current medications recommended by CDC:
  • INH x 9 months
  • Rifampin x 4 months
  • INH-rifapentine once-weekly x 12 weeks
  • Shorter course options now considered preferable in many patients due to improved adherence and completion of treatment
Rifampin vs INH for LTBI treatment

• Randomized, open-label trial for ~6000 adults with LTBI in 9 countries
• 4 months daily rifampin not inferior to 9 months INH after ~ 2 years of follow-up
• 78% of RIF completed treatment vs 63% INH
• Less hepatotoxicity with RIF (0.3% vs 1.8% INH)
• NEJM 2018; 379:440-453

INH-rifapentine vs INH for LTBI

• Randomized, open-label trial for ~7700 adults with LTBI in 4 countries
• INH-rifapentine once-weekly for 12 weeks as effective as 9 months INH (7 active TB cases vs 15 for INH in 33 months f/u)
• 82% completed treatment vs 69% for INH
• Less hepatotoxicity: 0.4% vs 2.7% for INH
• NEJM 2011; 365:2155-2166
Poll Question #4

Which of the following statements about INH for LTBI treatment is false?

A. INH-rifapentine can be administered without directly-observed therapy in most patients.
B. Approximately 10% of patients taking INH for LTBI treatment develop clinical hepatitis.
C. Vitamin B6 (pyridoxine) may help prevent INH-induced peripheral neuropathy.
D. INH should be stopped if the patients liver enzymes increase to 5 times upper limit of normal.

Isoniazid (INH): LTBI treatment

• 9 month regimen
• Adult dose: 300mg daily
• Child dose: 10-15mg/kg daily
INH and the liver

• 0.1% adults developed clinical INH hepatitis
• 10%-20% adults develop asymptomatic liver enzyme elevation
  • D/C INH if LFT 5x upper limit of normal with no symptoms or 3x upper limit of normal with symptoms

INH and peripheral neuropathy

• Occurs in less than 0.2% adult patients
• Vitamin B6 (pyridoxine) may prevent; use in pregnant/breastfeeding women and patients with other risks for neuropathy (DM, HIV+, renal failure, alcoholism)
Rifampin (RIF): LTBI treatment

• Now the preferred regimen for many patients: shorter course, improved compliance
• 4 month regimen
• Adult dose: 600mg daily
• Child dose: 10-20mg/kg daily for 6 months

Rifampin: cautions

• 0.6% risk hepatotoxicity
• 6% risk of pruritis +/- rash: may be able to continue therapy
• Orange discoloration of body fluids
• Drug-drug interactions due to induction of cytochrome 450 isoenzymes:
  • May reduce concentrations of contraceptives, phenytoin, methadone, warfarin, some anti-retrovirals
INH-Rifapentine: LTBI treatment

- 12 week regimen; once-weekly dosing
- Improved compliance!!
- Newly approved for self-administered treatment in many patients (previously by DOT)
- Dose by weight: 900 mg INH and 900 mg rifapentine for most adults; dose by weight for others: CDC website
- Similar cautions regarding drug interactions as with rifampin due to isoenzyme 450 induction

Drug interactions with rifampin/rifapentine

- Consider using INH for LTBI treatment in patients also treated with:
  - Methadone
  - Warfarin
  - Many HIV anti-retrovirals
  - Direct-acting antivirals for hepatitis C
  - Hormonal contraceptives
Monitoring patient on LTBI treatment

• Baseline visit with provider, RN or pharmacist for patient education, determining appropriate regimen
• Consider LFT monitoring in adults on INH regimens if underlying liver disease
• Monitoring for side-effects and compliance: patient visits vs phone

LTBI: pregnancy and breastfeeding

• Treat during pregnancy if HIV+ or recent contact to active case
• Delay until 2-3 months after pregnancy otherwise; possible higher risk of hepatotoxicity with INH
• Breastfeeding: treat and supplement with pyridoxine (vitamin B6) 10-25mg/day if using INH
LTBI: infants and children

• Often indicates recent infection
• High rate of progression to active TB
  • 50% in infant 0 to 1 year of age; risk decreases up to age 5 where risk same as older individuals
  • Higher risk of CNS infection
• Inform local TB control: adult contact with active disease?
• Tolerate INH very well: minimal hepatitis risk; monitoring LFT not indicated
• Children also candidates for newer, shorter course regimens

Ensuring compliance with TB treatment

• Importance of compliance with TB and LTBI therapy; patient education critical; use clinical judgment to assess likelihood of compliance
• DOT= directly-observed therapy; mainstay of treatment for active TB
• Self-treatment with monitoring for LTBI
TB and public health

• Local public health department should be notified of possible or confirmed cases of active TB.
• Urban and high-prevalence counties’ public health departments often have dedicated TB clinics. Get them involved early!

Practice recommendations

• Make a commitment to screen your at-risk patients for LTBI.
• Make a commitment to counsel patients with LTBI about risks and benefits of treatment and encourage treatment.
• Make a commitment to develop a protocol for treating LTBI in your practice and provide treatment using approved therapies.
TB resources

- CDC TB Centers of Excellence
  - “Warmline” consultation
  - 4 regional centers:
    - Curry Center (San Francisco)
    - Heartland Center (San Antonio)
    - Southeaster Center (Gainesville)
    - Global TB Institute (Newark)

TB resources

• CDC LTBI website: https://www.cdc.gov/tb/publications/ltbi/ltbi_resources.htm
• CDC TB 101: https://www.cdc.gov/tb/webcourses/tb101

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