Tuberculosis: What the Family Practitioner Needs To Know

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Disclosures

Dr. Starke is a member of a Data Safety Monitoring Board for Otsuka Pharmaceuticals concerning pediatric trials of delamanid. This will not be discussed during this talk.

Dr. Starke will not discuss off-label use of drugs or diagnostic tests during this talk.
TUBERCULOSIS IS A SOCIAL DISEASE WITH MEDICAL IMPLICATIONS
MYCOBACTERIIOLOGY

- non-motile, nonspore-forming, weakly Gram-positive rods; often appear slightly bent or beaded
- obligate aerobes; simple growth requirements
- cell wall: 20 to 60 percent lipids
- generation time of 12 to 48 hours (except rapid growers)
- acid-fastness: form stable mycolate complexes with arylmethane dyes (carbolfuchsin, crystal violet, auramine, rhodamine)
### ACID-FAST STAINS

<table>
<thead>
<tr>
<th>Stain</th>
<th>Color and Fluorescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziehl-Neelsen</td>
<td>Fuchsin (Red)</td>
</tr>
<tr>
<td>Kenyoun</td>
<td>Fuchsin (Red)</td>
</tr>
<tr>
<td>Crystal Violet</td>
<td>Purple</td>
</tr>
<tr>
<td>*Truant</td>
<td>auramine rhodamine (yellow-green fluorescence)</td>
</tr>
</tbody>
</table>
TRANSITIONS IN TUBERCULOSIS

Susceptible → Exposed
Exposed → Infected
Infected → Diseased
Diseased → Sick
Sick → Diagnosed
Diagnosed → Treated
Treated → Cured

Prevent Infection → Prevent Disease → Register, Record, Report
STAGES OF TUBERCULOSIS

**Exposure**

- Defined by contact investigation - recent (< 3 months) contact with an infectious case
- Negative TST or IGRA, physical exam and chest radiographs
- Period during which the skin test may be negative in an infected person
- Children < 5 years old should be treated (usually INH) because they may develop disease rapidly
- Older children and adults often not treated, but repeat skin test 3 months after exposure over
STAGES OF TUBERCULOSIS

Infection
- Hallmark is a “positive” skin test
- “Germs in the body”
- Chest radiograph is normal or shows only one or more granulomas or fibrotic lesions
- No symptoms, physical exam is normal
- Anyone with infection should be treated when the risk of disease outweighs the risk of serious adverse reactions to the medication
LTBI and the Risk of Tuberculosis Disease

- On average, 50% of close contacts become infected [range 0-100%]
- Lifetime risk of disease after infection – 2% to 10%
- One-half of risk is in the first 2 years after infection
- Risk of disease in infected infants – 40%
- Risk of disease in HIV-infected persons (prior to use of HAART) – 5% to 10% per year
STAGES OF TUBERCULOSIS

**Disease**

- Clinical and/or radiographic manifestations of progressive tuberculosis infection
- Primary: complication of initial infection
- Reactivation: disease occurs after period of dormancy of the infection
- TST is negative in 10% of disease cases (50% of meningeal or miliary disease)
WHO 2016 Global TB Report

- 10.4 million new cases: 5.9 million in men, 3.5 million in women, 1.0 million in children
- This is an increase from 2014, accounted for mostly by new surveillance and survey data from India
- Only 6.1 million cases were detected and notified, a gap of 4.3 million cases
- The gap is caused by underreporting of TB cases in countries with large unregulated private sectors, and under-diagnosis in countries with major barriers to accessing care
WHO 2016 Global TB Report

- 480,000 new cases of MDR-TB and 100,000 cases of rifampicin resistance newly eligible for MDR treatment regimens
- Only 1 of 5 people eligible for second-line therapy were able to access it
- 1.4 million deaths, with an additional 400,000 deaths resulting from TB disease among people living with HIV
- 210,000 deaths occurred among children
- Number of TB-related deaths fell 22% between 2000 and 2015, but TB remains in the top 10 causes of mortality
Estimated incidence of MDR/RR-TB in 2015, for countries with at least 1000 incident cases. Areas that are not applicable are in grey.
Reported TB Cases
United States, 1982–2015*

*2015 data are provisional.

No. of Cases

Year

2015: 9,563 cases
Childhood Tuberculosis in the United States

- 460 Cases in 2014
Number of TB Cases in U.S.-born vs. Foreign-born Persons, United States, 1993–2015*

*2015 data are provisional.
Countries of Birth of Foreign-born Persons Reported with TB, United States, 2014

- Mexico (21%)
- Philippines (12%)
- India (8%)
- Vietnam (8%)
- China (7%)
- Guatemala (3%)
- Haiti (3%)
- Other Countries (39%)
SOME REASONS WHY TB RESURGED FROM 1984 TO 1992

- HIV Co-epidemic
- Immigration – increased pool of infection and disease
- Congregate settings
- Poor tuberculosis control
Tuberculosis in Texas - 2015

- 1,334 cases – up 4.3%
- 398 cases in Region 6 [Harris County]
- 4.9/100,000 case rate [US: 3.0]
- 76 cases in children < 15 years old
- Homeless – 90 cases
- Correctional institutions – 150 cases
- 773 [58%] cases among foreign-born
- 9 cases of MDR-TB
RISK FACTORS FOR TUBERCULOSIS

**Increased risk of acquiring or having infection**
- Foreign born from high prevalence country
- Intravenous drug or crack cocaine user
- Family history of TB (2-3 generations)
- Contact with HIV-infected individuals
- Contact with inmates of prison or jail (past or present)
- Some nursing homes, residential living
- Some healthcare workers

**Increased risk of developing disease after infection**
- HIV-infected
- Immune suppression - drugs or disease
- Recent (<3 years) infection
- Certain diseases: silicosis, diabetes mellitus
- Extremes of ages: infants, elderly
MONOCLONAL ANTIBODIES AND TUBERCULOSIS

**Remicade (Infliximab)**
- monoclonal antibody against tnf–alpha
- black box warning for tuberculosis – 84 cases by 10/01
- severe pulmonary, G-I and disseminated tuberculosis
- must do at least a TB risk assessment and TST prior to use

**Humira (adalimumab), Enbrel (etanercept)**
- less information known
- strong warning to assess for TB risk and place a TST
PATHOGENESIS OF TUBERCULOSIS

- Organisms contained in droplet nuclei land in the alveoli

- Infectious dose probably < 10 organisms

- Organisms ingested by macrophages, transported to regional [hilar, mediastinal, cervical] lymph nodes

- Lymphohematogenous dissemination of organisms occurs early – meninges, apices of lungs, lymph nodes, other organs
FEATURES OF CONTAGIOUS TUBERCULOSIS

- **Positive acid-fast stain of sputum smear**
- Cavitary lung lesion
- Sputum production
- Bronchoscopy
- Draining lesions or surgical drainage of an abscess
All existing diagnostic tests for TB infection have significant shortcomings.

The utility of most tests is further diminished in patients with immune compromise [especially HIV infection].
DIAGNOSTIC TESTS FOR TUBERCULOSIS INFECTION

- The sensitivity and specificity of the available tests are inherent in the tests.
- However, the positive and negative predictive values are inherent in the population on whom the tests are used.
- Therefore, all tests are more accurate when used on patients with a high index of suspicion [epidemiology – HISTORY OF RECENT CONTACT TO A TB CASE - or suspicious symptoms]
Sensitivity = Specificity = 95%

90% prevalence
PPV = 99% (1% false+)

1% prevalence
PPV = 15% (85% false+)
MANTOUX TUBERCULIN SKIN TEST

- uses 5 TU [2 TU if R23] of purified protein derivative
- interpret in 48 – 72 hours
- record size of induration in mm
- if it makes a reaction at >72 hrs, it counts!

false negatives: 10% to 20% in disease
INDURATION SIZE – POSITIVE TUBERCULIN SKIN TEST

$\geq 5 \text{ mm}$

- HIV co-infection
- Immune compromise
- Recent contact to TB
- Suspected disease

$\geq 10 \text{ mm}$

- Foreign-born from a HR country
- Drug users
- Living in HR congregate setting
- Specific HR groups
- Children $< 4$ yrs old (AAP)

$\geq 15 \text{ mm}$

- No risk factors
- Previous BCG vaccination?
Problems With the Tuberculin Skin Test

- Hundreds of antigens leads to poor specificity
- Low PPV when BCG-vaccinated or exposure to environmental mycobacteria – false positives
- 10% false negatives with pulmonary disease, up to 50% with meningitis and disseminated TB
- Requires two patient visits
- Requires training to place and interpret
- High inter-observer variability in interpretation
- Digit preference: tendency to round up or down to a significant value to affect the result [observer bias]
INTERACTION OF BCG VACCINES WITH THE TUBERCULIN SKIN TEST

50% of vaccinated infants do not react to a TST; most of the rest stop reacting within 5 years

Most non-infants who get one or more BCG vaccinations will react to a TST (usually < 15 mm), but effect wanes over 5 – 10 years

Previous Dogma: outside infancy, “positive” TST more likely to indicate infection with *M. tuberculosis* than be residual from BCG
INTERACTION OF BCG VACCINES WITH THE TUBERCULIN SKIN TEST

**H1N1 influenza** – Which makes you feel better?
- 99.9% get no serious complications
- If 1 million people in Houston get it, 1,000 will develop serious complications

**BCG vaccination**
- By 5 years post-vaccination, 90% will have a negative TST
- Millions of children get BCG
Interferon-γ Release Assays [IGRAs] – Quantiferon & T.Spot

- MTB specific antigens:
  - Genes in region of difference (RD1) on MTB genome
  - Culture filtrate protein 10 (CFP-10)
  - Early secretory antigen target 6 (ESAT-6)
  - TB7.7(p4) in QuantiFERON Gold In-Tube

- Identify LTBI &/or disease
- Does not cross react with BCG vaccine or most other mycobacteria

- Requires:
  - single medical visit [for LTBI, not for exposure]
  - blood collection
  - laboratory equipment and personnel

- Results in 24-48 hrs
# TECHNICAL REPORT

## Interferon-γ Release Assays for Diagnosis of Tuberculosis Infection and Disease in Children

### TABLE 1 Comparison of the TST and IGRA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TST</th>
<th>IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigens used</td>
<td>Many; PPD</td>
<td>3 (QFT) or 2 (T-SPOT)</td>
</tr>
<tr>
<td>Sample</td>
<td>Intradermal injection</td>
<td>Blood draw</td>
</tr>
<tr>
<td>Patient visits required</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Distinguish between LTBI and TB disease</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Cross-reactivity with BCG</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cross-reactivity with NTM</td>
<td>Yes</td>
<td>Only rare species&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Differing positive values by risk</td>
<td>Yes (5-10-15)</td>
<td>No</td>
</tr>
<tr>
<td>Causes boosting</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Subject to boosting by previous TST</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Durability over time (stays positive with or without treatment)</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Difficulties with test reproducibility</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Relative cost</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Location of need for trained staff</td>
<td>“Bedside”</td>
<td>Laboratory</td>
</tr>
<tr>
<td>Estimated specificity in BCG-unvaccinated children</td>
<td>95% to 100%</td>
<td>90% to 95%</td>
</tr>
<tr>
<td>Estimated specificity in BCG-vaccinated children</td>
<td>49% to 65%</td>
<td>89% to 100%</td>
</tr>
<tr>
<td>Estimated sensitivity (confirmed TB disease)</td>
<td>75% to 85%</td>
<td>80% to 85%</td>
</tr>
<tr>
<td>Estimated sensitivity (clinical TB disease)</td>
<td>50% to 70%</td>
<td>60% to 80%</td>
</tr>
</tbody>
</table>

<sup>a</sup> M marinum, M kansasii, M szulgai, and M flavescens.
CDC expert panel recommended:

1. No preference for one test over the other
2. Should replace the TST for most adults and older children, except, perhaps, for immune compromised; less clear for children < 5 years of age
3. Can be used in contact investigations [even in contact investigations, many adults with a positive TST and history of BCG likely do not have LTBI]
<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Suggested Uses of TST and IGRA in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TST preferred</strong></td>
<td></td>
</tr>
<tr>
<td>- Children younger than 5 y&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>IGRA preferred, TST acceptable</strong></td>
<td></td>
</tr>
<tr>
<td>- Children 5 y or older who have received BCG vaccine</td>
<td></td>
</tr>
<tr>
<td>- Children 5 y or older who are unlikely to return for the TST reading</td>
<td></td>
</tr>
<tr>
<td>Both the TST and an IGRA should be considered when:</td>
<td></td>
</tr>
<tr>
<td>- The initial and repeat IGRA results are indeterminate/invalid</td>
<td></td>
</tr>
<tr>
<td>- The initial test (TST or IGRA) result is <em>negative</em> and:</td>
<td></td>
</tr>
<tr>
<td>- There is clinical suspicion of TB disease&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>- The child has a TB risk factor and is at high risk of progression and poor outcome (especially therapy with an immunomodulating biologic agent, such as a TNF-α antagonist)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>- The initial TST is <em>positive</em> and:</td>
<td></td>
</tr>
<tr>
<td>- The patient is 5 years or older and has a history of BCG vaccination</td>
<td></td>
</tr>
<tr>
<td>- Additional evidence is needed to increase adherence with therapy</td>
<td></td>
</tr>
</tbody>
</table>

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**TNF-α, tumor necrosis factor α.**

<sup>a</sup> Some experts will use an IGRA in children 2 to 4 years of age, especially if they have received a BCG vaccine but have no other significant risk factors. Most experts do not use an IGRA for children younger than 2 years because of lack of data for this age group and the high risk of progression to disease.

<sup>b</sup> A positive result of either test is considered significant in these groups.
IGRAs AND THE 2015 [and 2018] AAP “RED BOOK”

- Can use IGRAs in immunocompetent children > 4 years of age in all situations when a TST would be used
- Particularly useful/preferred for children who have received a BCG vaccination
- Same recommendations as TST for risk factors and frequency of testing
- Use with caution in children < 5 years of age, many experts endorse down to 2 years of age
- Neither IGRAs nor the TST are perfect; always need clinical judgment!
Most Common Systemic Symptoms of Tuberculosis

- Fever
- Chills
- Night Sweats
- Weight Loss
- Loss of appetite
- Fatigue
- Malaise
Most Common Symptoms of Pulmonary Tuberculosis

- Cough lasting 3 or more weeks
- Coughing up sputum
- Coughing up blood [late]
- Chest pain [less common]
Signs and Symptoms of Tuberculosis in Children

- Children have a relative paucity of signs and symptoms
- The chest x-ray is often “sicker” than the patient
- Children are more likely to have extrapulmonary TB – a complete exam is important!
HOW IS TUBERCULOSIS DIAGNOSED?

**Adults – Mycobacterial-based diagnosis**
- positive sputum AFB smear - 60% - 75%
- positive sputum culture - 90%
- positive tuberculin skin test - 80% [HIV <50%]

**Children**
- positive sputum or gastric AFB smear - 10%
- positive sputum or gastric culture - 10% - 40%
- positive tuberculin skin test - 50% - 80%
Traditional Lab Methodology: a stepwise approach

1. Obtain culture: gastrics
2. Speciate as TB vs. NTM: HPLC
3. Perform drug-susceptibility testing

Accelerated Diagnostics

- Induced Sputa
- Traditional PCR
  - MODS: 7-10 days
  - Xpert: 90 minutes

6-8 wks
Xpert MTB/RIF

- Cartridge-based NAAT & closed sample preparation
- Better than microscopy for children
Evaluation of an Adult With Suspected Pulmonary Tuberculosis

- Thorough history and physical exam
- Risk factor/exposure history
- Infection control precautions
- Chest radiograph
- Sputum for AFB smear and culture
- + TST or IGRA
- Baseline AST/ALT, platelets
- Notify the health department
The development of drug resistance in *M. tuberculosis* is the result of a **conspiracy** among the organism, the patient, the doctor and the healthcare system!
DRUG RESISTANCE IN MYCOBACTERIUM TUBERCULOSIS

- genetic loci for resistance on chromosome, unlinked
- resistance of drugs independent
- frequency of mutations at loci is known
- more likely to have mutations when mycobacterial population is larger: infection vs. disease
- primary - resistance present when infection acquired
- secondary - resistance develops while on therapy
### U.S. Preventive Service Task Force - 2016

<table>
<thead>
<tr>
<th>Population</th>
<th>Asymptomatic adults at increased risk for infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendation</td>
<td>Screen for latent tuberculosis infection (LTBI).</td>
</tr>
<tr>
<td></td>
<td>Grade: B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Assessment</th>
<th>Populations at increased risk for LTBI include persons who were born in, or are former residents of, countries with increased tuberculosis prevalence and persons who live in, or have lived in, high-risk congregate settings (e.g., homeless shelters and correctional facilities). Local demographic patterns may vary across the United States; clinicians can consult their local or state health departments for more information about populations at risk in their community.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Tests</td>
<td>Screening tests include the Mantoux tuberculin skin test and interferon-gamma release assays; both are moderately sensitive and highly specific for the detection of LTBI.</td>
</tr>
<tr>
<td>Balance of Benefits and Harms</td>
<td>The USPSTF concludes with moderate certainty that the net benefit of screening for LTBI in persons who are at increased risk for tuberculosis is moderate.</td>
</tr>
</tbody>
</table>

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to http://www.uspreventiveservicestaskforce.org.
Key Risk Groups in the U.S.

- Racial/ethnic minorities: 85% of cases; case rates 7-17 times higher than whites
- Foreign-born: 67% of cases; case rate 11 times higher than US-born
  - Mexico, Philippines, Vietnam, China, India top 5 countries
- HIV infected: ~ 7% of cases
- Homeless: ~ 6% of cases
- Incarcerated: ~ 4% of cases
- Substance abuse: 7-12% of cases
All risk assessment questionnaires should ask:

1. Was your child born outside the U.S? Where?
2. Has your child traveled (non-tourist, 1 wk) outside the U.S.? Where?
3. Has your child been in contact with anyone with TB?
4. Does your child have contact with anyone with a positive tuberculin skin test?
5. **Were the parents born in a high-prevalence country?**
TREATING TUBERCULOSIS EXPOSED CHILDREN

- Very high rate of and rapid progression to disease
- Takes up to 3 months for the TB skin test or IGRA to turn positive
- U.S. studies – 10% to 20% of childhood TB cases can be prevented if children exposed in a household receive isoniazid
Treatment of Tuberculosis Infection

Established therapies include:

- Isoniazid for 9 months – U.S.
- Isoniazid for 6 months - WHO
- Rifampin for 4 months
- Isoniazid and rifampin for 3 months
- Isoniazid and rifapentine once weekly for 12 weeks [under directly observed therapy]
TREATMENT OF TUBERCULOSIS DISEASE

- Start with 4 drugs, usually INH, RIF, PZA, EMB
- If drug susceptible, PZA and EMB dropped after 2 months, and INH & RIF given for 6 total months
- Drugs given every day at first, then twice or thrice a week
DIRECTLY OBSERVED THERAPY FOR TUBERCULOSIS

- Means a dispassionate 3rd party is actually present when medications are taken with every dose

- “Standard of care” in U.S. for treating tuberculosis disease

- Best for high risk infections - newborns and infants, household contacts, HIV-infected or immune compromised
Interactions Between the Clinician and the Health Department

- Must report immediately the *suspicion* of tuberculosis disease
- Contact investigation finds other cases and infected individuals
- Refer cases to experts and proper settings [infection control]
- DOT provided for free by health departments – monitor side effects
Roles and Responsibilities of Specific Private Sector Providers

Role of Clinicians

- Understand prevalent medical conditions of their patient populations
- Be aware of local TB reporting laws
- Know procedures for suspected TB: diagnose, hospitalize, report case, plan treatment
- Follow current guidance for screening, diagnosis, treatment of TB and LTBI
- Be able to administer TB tests, rule out TB disease, administer treatment
Main Challenges to TB Elimination in the U.S.

- **Political commitment**
  - As cases continue to decrease, seems less of a priority to general public and policymakers
  - Resources at risk – “U-shaped Curve of Concern”

- **Loss of expertise and experience**
  - Clinical [nurses and MDs], laboratory, program

- **Drug and biologic shortages because of lack of market**
  - Regulatory requirements (FDA) limit access to larger global market, e.g. child-friendly formulations

- **Concentration of remaining cases and outbreaks in more difficult-to-reach populations**
  - Foreign-born, homeless, etc.

- **How to address the large pool of persons with latent tuberculosis infection (LTBI)**
  - <10 thousand TB cases; up to 13 million persons with LTBI