Tuberculosis

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

UNCLASSIFIED
Acknowledgments

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Tuberculosis

TUBERCULOSIS ROBS YOU

PUBLIC HEALTH PROTECTS YOU

CHRISTMAS SEALS FINANCE THE CAMPAIGN AGAINST TUBERCULOSIS
Outline

• Global Burden of Tuberculosis
• Active vs. Latent TB Infection
• Diagnosis and Treatment of Active TB
• Diagnosis and Treatment of Latent TB
• Military screening policies
• Managing Exposure in a Deployed Environment
• Other issues
Global Burden of Tuberculosis

- 9.2 million cases and 1.7 million deaths yearly
- Associated with co-pandemic of HIV
- Drug-resistance increasingly common
- One third of the world’s population is infected with LTBI
  - Focus is on identification and treatment of active TB (DOTS)
  - Screening for LTBI is not routinely done in most countries
  - Increasing efforts to extend LTBI treatment to HIV populations
Global Burden of Tuberculosis

Estimated TB incidence rates, 2012
TB Pathophysiology

• Spread person-to-person through the air
• Droplet nuclei may remain in the air
• Primary infection
  o Inhale tubercle bacilli
  o Reach alveoli, engulfed by macrophages
  o Some multiply intracellularly and released
  o Immune system (cell-mediated) prevents progression

• Activation
  o Tubercle bacilli overcome immune system
  o “5% risk in 2 years, 10% lifetime” (may be lower – *Am J Respir Crit Care Med* 2014 NOV 1; 190: 1044)
Diagnosis of TB

- Clinical symptoms and signs
- CXR (not confirmatory)
- Detection of tubercle bacilli
  - AFB Smear (sensitivity 50%)
  - Culture and sensitivity testing
  - Nucleic Acid Amplification Tests
Symptoms of Active TB

- Fever
- Chronic cough
- Night sweats
- Hemoptysis
- Weight loss
- Fatigue
Active TB

• Chronic infection with *Mycobacterium tuberculosis*.

• Pulmonary most common (80%)
  – Pulmonary and laryngeal TB are contagious

• Extrapulmonary (20%)
  – Lymphadenitis (scrofula)
  – Skeletal
  – Renal
  – Meningeal
CXR

- Patchy or nodular infiltrate
- Apical- or subapical-posterior areas of the upper lobes or the superior segment of a lower lobe
- Especially if bilateral or associated with cavity formation
AFB Smear

Figure 9. Sputum specimen demonstrating acid fast bacilli (AFB) (arrow). Source CDC.
Treatment of **ACTIVE** TB

- “4 for 2 and 2 for 4”
  - INH, RIF, PYR, ETH X 2 months, **then**
  - INH, RIF X 4 months

- Modify regimen if necessary after antibiotic susceptibility results are available

- Check bacteriologic response monthly

- HIV test

- “**Never add a single drug to a failing regimen**”

INH = isoniazid
PYR = pyrimethamine
RIF = rifampin
ETH = ethambutol
Treatment of ACTIVE TB

• 4 Month Moxifloxacin based regimens for Drug-Sensitive TB
  – 1931 patients randomized into 1 of 3 treatment groups (1:1:1)
    • Control group (standard RIPE therapy) – 6 months
    • “INH” arm (Moxi, INH, RIF for 4 months to include 2 months PZA)
    • “ETH” arm (Moxi, RIF for 4 months to include 2 months PZA and ETH)
  
  – No significant safety differences
  – The regimens with 4 months of moxifloxacin did **NOT** meet criteria for noninferiority compared to the standard of care
    • Moxi groups had a more rapid decline in bacterial load compared to standard
    • Moxi groups had more likelihood of relapse at the end of therapy

NEJM Oct 2014; 371 (17): 1577-87
When are they non-infectious?

• On adequate therapy

• Clinical response

• Three consecutive negative sputum smears from sputum collected on different days
Infection Control

• Administrative controls
  – Primary strategy for infection control! *****
  – “Develop policies and protocols to ensure the rapid identification, isolation, diagnostic evaluation, and treatment of persons likely to have TB”

• Engineering controls (ventilation)
  – Isolation
  – Negative pressure rooms

• Personal respiratory protection (N95)
HIV and TB

• 10% risk of progression per year
• Atypical presentations, anergy
• Leading cause of death in HIV patients
• MDR and XDR TB
• Drug interactions
• Reconstitution syndrome
MDR and XDR

• MDR=INH and RIF resistance

• XDR=MDR+
  – Any fluoroquinolone; **AND**
  – 1 of 3 injectable second line drugs
    • Capreomycin
    • Kanamycin
    • Amikacin

MDR = multi-drug resistant
INH = isoniazid
RIF = rifampin
XDR = extremely drug resistant
LTBI vs. Pulmonary TB Disease

**LTBI**

- TST* or IGRA† positive
- Negative chest radiograph
- No symptoms or physical findings suggestive of TB disease

**Active Pulmonary TB**

- TST or IGRA usually positive
- Chest radiograph may be abnormal
- Symptoms *may* include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite
- Respiratory specimens *may* be smear or culture positive

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* Tuberculin Skin Test (TST)
† Interferon Gamma Release Assay (IGRA)
What defines a positive TB test?

a) 5 mm
b) 10 mm
c) 15 mm
d) It depends on the epidemiological characteristics and degree of TB exposure of the patient
**Table 7. Criteria for tuberculin positivity, by risk group**

<table>
<thead>
<tr>
<th>Reaction ≥5 mm of induration</th>
<th>Reaction ≥10 mm of induration</th>
<th>Reaction ≥15 mm of induration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human immunodeficiency virus (HIV)-positive persons</td>
<td>Recent immigrants (i.e., within the last 5 y) from high prevalence countries</td>
<td>Persons with no risk factors for TB</td>
</tr>
<tr>
<td>Recent contacts of tuberculosis (TB) case patients</td>
<td>Injection drug users</td>
<td></td>
</tr>
<tr>
<td>Fibrotic changes on chest radiograph consistent with prior TB</td>
<td>Residents and employees of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters</td>
<td></td>
</tr>
<tr>
<td>Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥15 mg/d of prednisone for 1 mo or more)*</td>
<td>Mycobacteriology laboratory personnel</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Includes patients taking TNF-α antagonists

*Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.
† For persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥15 mm induration is considered positive.

CDC Guidelines Call for Targeted Testing Only

• Targeted testing:
  – “…targeted tuberculin testing programs should be conducted only among groups at high risk and discouraged in those at low risk.” (MMWR 2000)
    – All military services conduct testing at accession

• CDC clearly considers high-risk:
  – Hospitals and health care settings
  – Prisons
  – HIV-infected
  – Homeless
  – Contacts of active case

*NOT Military*
Testing for *M. tuberculosis* Infection

**Mantoux tuberculin skin test (TST)**
Skin test that produces delayed-type hypersensitivity reaction in persons with *M. tuberculosis* infection

**Interferon Gamma Release Assays (IGRAs)**
Blood tests that measure and compare amount of interferon-gamma (IFN-γ) released by blood cells in response to *M. tuberculosis* antigens.

These include:
1. *Quantiferon® Gold-in-tube (QFT-GIT)*
2. *T-SPOT®.TB*
The Tuberculin Skin Test

- Cell-free purified protein fraction extracts obtained from a human strain of *M. tuberculosis*
- In use for over a century
- Problems with TST
  - *Positive predictive value is low if prevalence of infection is low*
  - Errors and variability in administration
  - False negatives and false positives

- Pseudoepidemics of TST reactions reported in hospitals, prisons, reservations, military populations
Administering the TST

- Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-gauge needle.

- Produces a wheal 6 to 10 mm in diameter.

Reading the TST

- Measure reaction in 48 to 72 hours

- Measure induration, not erythema

- Record reaction in millimeters, not “negative” or “positive”

- Ensure trained health care professional measures and interprets the TST

Boosting and Two-Step Testing

• Boosting
  o May have an initially negative test due to waning responsiveness
  o First test may stimulate immune response for second test
  o Second test positive=boosted reaction

• Two-step testing
  o Done on initial test if annual testing is planned
  o Prevents interpreting a subsequent annual TST as a new seroconversion
  o A negative first test with a positive second test should be evaluated for LTBI.
Interferon Gamma Release Assays (IGRA)

- Measures interferon-γ released from lymphocytes incubated with antigens to MTB
  - Unknown rate of progression to active TB
  - Lack of “gold standard” for LTBI prevents defining the sensitivity and specificity of the test

When should I use the IGRA?

• Depends who you talk to
  o CDC guidelines: may be used to replace TST, but don’t do both
  o UK, many other European countries: use IGRA as confirmatory test
  o Military policies conform with CDC, but Navy Great Lakes was using it as a confirmatory test

• Evolving issue, not resolved yet
  o More data
  o Evolving technology

• IGRA preferred among BCG vaccinated
Other LTBI Testing Issues

• Must maintain good quality testing program, whether TST or IGRA
  o Both are difficult in the field
  o **Should only be performed for contact investigations**
  o Useful QA/QC guidelines for TST quality control in Appendix F of: CDC. *MMWR* 2005;54(RR-17):138-9

• **Tubersol®** is the only TST that should be used
  o False positives with Aplisol®

HA Policy 08-012 (29 Sept 08)
Decision to treat

• “A decision to test is a decision to treat”
  o Don’t ignore a positive test
  o But be skeptical in low-risk populations (don’t test)

• Must rule out active TB first
  o Symptoms of active TB
  o Compatible chest x-ray findings
  o If symptoms → 3 sputum smear, culture, at least 1 NAAT test

• Look at criteria to determine cutoff

• Assess risks & benefits for each individual patient
  o Medical history (esp. liver disease, alcohol abuse)
  o How recent was TB exposure?
  o Pregnancy
  o Allergies
Decision to treat

• LTBI Treatment options:
  – Isoniazid x 9 months 5 mg/kg daily (max 300 mg daily)
  – Isoniazid x 9 months 15 mg/kg twice weekly (max 900 mg daily)
    • Don’t use the 6 month option if your patient can tolerate the longer option
  – Isoniazid 15 mg/kg (max 900 mg) + Rifapentine once weekly for x 3 months given once weekly
    • 10.0–14.0 kg 300 mg
    • 14.1–25.0 kg 450 mg
    • 25.1–32.0 kg 600 mg
    • 32.1–49.9 kg 750 mg
    • ≥50.0 kg 900 mg maximum
  – Rifampin 10 mg/kg (max 600 mg) x 4 months

When dosing, round up to the nearest 50-100 mg

TREATMENT DOSE NOT ELIMINATE THE RISK OF ACTIVE DISEASE*

*Am J Respir Crit Care Med 2014; 190: 1044
Screening for LTBI in the US Military

• Over 250,000 tests per year among recruits
• Accessions: all services do universal screening
  o Army (DA PAM 40-11; 20 Oct 2008)
  o Navy (BUMED Instruction 6224.8A; 12 Feb 2009)
  o Air Force (AFI 48-105; 1 Mar 2005)

• Prevalence of TST reactors
  o Navy: 5%
  o Army: 3%
  o Air Force: 1.5%
  o *Depends on proportion of foreign-born*

• Deployment-related screening
What about guidelines for travelers?

- **US Guidelines (CDC Yellow Book):** both pre- and post-travel testing for those with “prolonged exposure to tuberculosis…e.g. [routine contact with] hospital, prison, and homeless shelter populations”

- **IDSA Guidelines:** TST “should be performed for those with anticipated exposure to TB or long-term stays in developing areas or when requested by the traveler because of concern about exposure”

- **TRAVAX:** “travelers to countries with high risk (i.e., > 100 cases per 100,000) should have pre-departure testing if staying for > 1 month; travelers to countries with moderate risk (approximately 25-100 cases per 100,000) should have pre-departure testing if they plan on staying for > 3 months”

- **Canadian Guidelines:** a single, post-travel test based on duration of travel as well as TB incidence in the country visited.

What does the US military for deployers?

• Air Force
  – Targeted testing after deployment since ’05 (AFI 48-105)

• Navy
  – Used to test operational units yearly with TST
  – Now targets testing during PHA with questionnaire (BUMEDINST 6224.8A, 12 Feb 2009)

• Army
  – Used to test before deployment, after deployment, and then again 3-6 months after deployment (3 tests per deployment)
  – In 2008, moved to targeted testing after deployment using DD 2796 (OTSG Memo, 25 Sept 2008)
  – Testing SHOULD NOT be routinely performed during deployment

See http://www.pdhealth.mil/tuberculosis.asp
Recent Deployment TB Epidemiology

• Outbreaks on Navy ships—common in the 1960s
  o USS Wasp (1998): 21 infected from failure to diagnose index case
  o USS Ronald Reagan (2003): 1 reactivation despite prior INH Rx

• Active TB: lower rate of disease than in the US population

• TST reactors during deployment
  o Prevalence of TST conversion: 1-2% without specific exposure history (similar to prevalence in recruits)
  o Numerous false positives and pseudo-outbreaks reported

Camarca MM and Krauss MR. Mil Med 2001;166(5):452-6
Managing TB Exposure in a Deployed Setting

• Refer to Preventive Medicine
Managing TB Exposure in a Deployed Setting

FIGURE 1. Decision to initiate a tuberculosis (TB) contact investigation

- Site of disease
  - Pulmonary/laryngeal/pleural
  - Pulmonary suspect (tests pending, e.g., cultures)
  - Nonpulmonary (pulmonary and laryngeal involvement ruled out)

- AFB* sputum smear positive
  - NAA† positive or not performed
    - Contact investigation should always be initiated
  - NAA negative
    - Contact investigation not indicated

- AFB sputum smear negative or not performed
  - Cavitary disease
    - Contact investigation should always be initiated if sufficient resources
  - Abnormal CXR‡ non-cavitary consistent with TB
    - Contact investigation should be initiated if sufficient resources
  - Abnormal CXR not consistent with TB
    - Contact investigation should be initiated only in exceptional circumstances

* Acid-fast bacilli.
† Nucleic acid assay.
‡ According to CDC guidelines.
§ Chest radiograph.
Managing TB Exposure in a Deployed Setting

• Document TB symptoms (or the lack thereof)

• High or medium priority contacts should receive TST at initial encounter

• All contacts should have a TST at 8-10 weeks post-exposure

• A diameter >5 mm is positive for any contact

• Any contact with TB symptoms should be managed immediately regardless of skin test results
Other important management issues

• Directly observed therapy (DOT)
  o Standard of care for **Active** TB
  o May be used for LTBI, but uncommon
  o **Refer to Preventive Medicine**

• Disease reporting
  o **Active TB is a reportable disease**, LTBI is not
  o Positive TST or IGRA must be documented in an electronic registry (ALTHA, MEDPROS, etc)
  o Reportable diseases are reported to Preventive Medicine both in garrison and on deployment
THE NEXT TO GO

FIGHT TUBERCULOSIS!

Red Cross Christmas Seal Campaign
Summary

• Remember for TB testing, a decision to test is a decision to treat

• LTBI is not symptomatic and has normal Chest X-ray

• Targeted testing for TB with skin test or IGRA (“TB blood test”)

• Measure the swelling, not the redness on a TB skin test

• Consider IGRA for foreign born individual who may have receive BCG as child

• Always rule out active TB before treating for LTBI

• Active TB requires airborne isolation when possible

• Report active TB cases to preventive medicine

Directly observed minimum 4 drug therapy for active TB
Thank You

Questions?

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