DIAGNOSIS OF LATENT TB INFECTION
THE TUBERCULIN SKIN TEST

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After attending this lecture, participants should be able to describe:

- who should be screened for latent TB infection
- the performance characteristics of the TST
- how to administer and interpret a TST
QUESTIONS

• Who should be screened for LTBI?
• What is tuberculin and are all purified protein derivative products the same?
• What are the performance characteristics of the TST?
• How should the TST be administered and interpreted?
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SCREENING FOR TUBERCULOSIS: WHO SHOULD BE SCREENED

- USPSTF recommendation to screen for at risk individuals at higher risk for TB

- Screening should be targeted to those at higher risk of TB.

- Higher TB risk is seen in:
  - Persons or groups with increased risk of recent exposure to TB
  - Populations with increased rates of TB infection
  - Persons with increased risk of progression to active TB if infected
<table>
<thead>
<tr>
<th><strong>High-risk</strong></th>
<th><strong>Examples</strong></th>
</tr>
</thead>
</table>
| **Exposure** | • Contacts  
• Health care workers  
• Correctional officers |
| **Infection** | • Contacts  
• Born/lived extensively outside of the U.S. (>20/100,000)  
• Other (e.g., homeless) |
| **Progression** | • Recent contacts  
• HIV infection  
• Silicosis  
• Diabetes mellitus  
• Immunosuppressives  
• ESRD  
• Intestinal bypass  
• Post-gastrectomy  
• Malabsorption  
• Carcinomas of head/neck  
• < 10% below ideal weight  
• Smoking |
TUBERCULOSIS SCREENING FLOWCHART

At-risk person

Tuberculin test/IGRA + symptom review

Negative

LTBI treatment not indicated

Positive

Chest x-ray

Normal

Concerning symptoms?

Potential candidate for LTBI treatment

Abnormal

Evaluate for active TB
QUESTIONS

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• **What is tuberculin and are all purified protein derivative products the same?**
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Which of the following scientists was the first to develop the tuberculin skin test as a diagnostic test?

A. Robert Koch  
B. Clemens von Pirquet  
C. Florence Seibert  
D. Stefan Gryzybowski  
E. None of the above
TUBERCULIN SKIN TEST
IMPORTANT HISTORICAL POINTS

- 1890 - Robert Koch ("old tuberculin")
- 1907 - Clemens von Pirquet
- 1939 - Florence Seibert
- 1969 - Gryzybowski and Holden
- 1972 - Division of Biologic Standards
- 1976 - FDA appointed a Panel on Skin Test Antigens
  - Tubersol (Sanofi Pasteur Limited)
  - Aplisol (JHP Pharmaceuticals LLC)
PURIFIED PROTEIN DERIVATIVE (PPD)

- Mixture of denatured, but soluble proteins and peptides generated through autoclaving in vitro grown *M. tuberculosis* at 100° C for two hours.

- Chemical composition:
  - 93% proteins
  - 1% nucleic acid
  - 6% carbohydrate

- Proteomic analysis has shown significant overlap between *M. avium* and *M. tuberculosis* PPD.

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Braz J Infect Di 2006;10:427
### SPECIFICITIES OF THREE PPD PREPARATIONS

*N = 1555 persons at low risk of LTBI in 6 US cities*

<table>
<thead>
<tr>
<th>Test</th>
<th>Positive Defined as $&gt;10$ mm</th>
<th>Positive Defined as $\geq 15$ mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Positive</td>
<td>Specificity</td>
</tr>
<tr>
<td>PPD-S1</td>
<td>17</td>
<td>98.9</td>
</tr>
<tr>
<td>Aplisol</td>
<td>28</td>
<td>98.2*</td>
</tr>
<tr>
<td>Tubersol</td>
<td>13</td>
<td>99.2*</td>
</tr>
</tbody>
</table>

* $P = 0.02$

Mean ± SD: Aplisol $3.4 \text{ mm} \pm 4.2 \text{ mm}$ vs Tubersol $2.1 \pm 3.2 \text{ mm}$

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Sensitivity and Specificity of TST in Active TB

Pooled sensitivity: 65%
Range: 31-92%

Pooled specificity: 75%
Range: 48-93%

Sester M, et al. ERJ 2011
QUESTIONS

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TUBERCULIN SKIN TESTING
MANTOUX METHOD

5 TU of PPD

48 to 72 hours

Interpretation depends on person’s risk factors
Which of the following is considered a skin test converter?

A. 20 year nursing student whose TST is 20 mm, previous TST 9 mm
B. 35 year old secretary who TST is 15 mm, no previous history of TST
C. 10 year old contact to active TB case with a TST of 12 mm, no previous history of TST
D. 40 year old physician with TST of 12 mm, previous TST 6 mm
# TUBERCULIN SKIN TEST

## CRITERIA FOR A POSITIVE REACTION

<table>
<thead>
<tr>
<th>≥5 mm</th>
<th>≥10 mm</th>
<th>≥15 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>Recent immigrants</td>
<td>No risk</td>
</tr>
<tr>
<td>Contact to active TB case</td>
<td>Injection drug users</td>
<td></td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>Children</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>High-risk medical conditions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Residents and employees of jails/nursing homes, hospitals</td>
<td></td>
</tr>
</tbody>
</table>

Note: Skin test conversion is an increase of ≥10 mm to ≥10 mm within a 2-year period.
STABILITY OF REACTIONS AND INTER-READER VARIABILITY

- Biologic variation from test to test in the same patient is very small, approximately 1mm.
  - Chaparas et al. ARRD 1985;132:175.

- Same reader - Standard deviations of 1.3-1.9 mm

- Different readers - Standard deviations of 2.3-2.5 mm
  - Furcolow et al. ARRD 1967;96:1009.
INTERVAL FROM PRIMARY INFECTION TO TST CONVERSION

N = 172

Menzies D. AJRCCM 1999;159:15
TUBERCULIN SKIN TESTING
“BOOSTING”

- 14 mm
- 11 mm
- 12 mm

Years
0 5 10 15 20 30 31

Infection TST TST TST TST

Induration (mm)
0 5 10 15 20

Years
TUBERCULIN SKIN TESTING
TWO-STEP TESTING

4 visits

Place TST

Read at 48-72 hrs

Positive

Negative

Place 2nd TST at one week

Read at 48-72 hours

Positive (True positive)

Negative (True negative)

3 visits

Place TST

Read at 7 days

Positive

Negative

Place 2nd TST

Read at 48-72 hours

Positive (True positive)

Negative (True negative)
TUBERCULIN SKIN TEST

- False negative tests
  - Quality and stability of reagents
  - Poor technique
  - Anergy (common with HIV infection)
- False positive tests
  - Reader error
  - Presence of cross-reacting antigens
    - Nontuberculous mycobacteria
    - Recent BCG vaccination
SUMMARY

• Targeted testing should be performed in persons at high risk for LTBI and/or high risk of progression to TB

• Purified protein derivative is primarily composed of protein and there is significant variation between products

• The TST has low sensitivity and specificity when assessed in patients with TB. The TST has high specificity in low risk populations, particularly those who are non BCG vaccinated.

• The Mantoux method should be used to administer the tuberculin and induration should be read 48 to 72 hours later

• Boosting can occur from remote infection so an initial two-step method should be considered when annual screening is performed