Smear Negative PTB

Speaker: Previous Miri GH Medical Department Officer
Definition

1. Clinical & Radiological findings suggestive of TB
2. Smear AFB (at least 2): Negative
3. Decided by Physician to treat as PTB.
4. Smear negative, later confirmed by culture, biopsy or other investigations.
50 years old man
CXR on 16/7/2012 and 22/8/2012
Given augmentin X 1 week
LOA for 2 month, LOW 2kg in 2 months.
SAFB x6 negative, mantoux 25mm
Smear +: 5000-10 000 bacilli/ml of sputum
Culture+: 10-100 bacilli/ml of sputum
NAA technique: 1 bacilli.

Number of bacteria seen on microscopy and interpretation

<table>
<thead>
<tr>
<th>Number of AFB Seen by Staining Methods</th>
<th>Fluorochrome (250-fold magnification)</th>
<th>Laboratory report, Canadian&lt;sup&gt;104&lt;/sup&gt;</th>
<th>Laboratory report, IUATLD&lt;sup&gt;120&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 in 100 fields</td>
<td>0 in 30 fields</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>1-2 per 300 fields</td>
<td>1-2 per 30 fields</td>
<td>Indeterminate, repeat</td>
<td>Report exact number</td>
</tr>
<tr>
<td>1-9 per 100 fields</td>
<td>1-9 per 10 fields</td>
<td>1+</td>
<td>1+</td>
</tr>
<tr>
<td>1-9 per 10 fields</td>
<td>1-9 per field</td>
<td>2+</td>
<td>2+</td>
</tr>
<tr>
<td>1-9 per field*</td>
<td>10-90 per field</td>
<td>3+</td>
<td>3+</td>
</tr>
<tr>
<td>&gt; 9 per field†</td>
<td>&gt; 90 per field</td>
<td>4+</td>
<td></td>
</tr>
</tbody>
</table>

* Consistent finding in at least 50 fields
† Consistent finding in at least 20 fields
Burden of the disease

• There are 1.22 cases of smear-negative and extra-pulmonary TB for every case of smear-positive TB in developing countries¹.

• More common in children, elderly, immunocompromised (HIV, drugs, CKD etc).

• Low bacillary burden with minimal disease and no/less cavitation-escape clinical detection.

Local Data

![Bar chart showing the number of new cases from 2005 to 2011 for different categories of PTB Smear Positive, PTB Smear Negative, PTB Smear Unknown, and EPTB.](image)

<table>
<thead>
<tr>
<th>Year</th>
<th>PTB Smear Positive</th>
<th>PTB Smear Negative</th>
<th>PTB Smear Unknown</th>
<th>EPTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>8446</td>
<td>4313</td>
<td>549</td>
<td>1702</td>
</tr>
<tr>
<td>2006</td>
<td>9414</td>
<td>3977</td>
<td>359</td>
<td>1920</td>
</tr>
<tr>
<td>2007</td>
<td>9578</td>
<td>3828</td>
<td>258</td>
<td>2107</td>
</tr>
<tr>
<td>2008</td>
<td>10441</td>
<td>3643</td>
<td>180</td>
<td>2197</td>
</tr>
<tr>
<td>2009</td>
<td>9981</td>
<td>4143</td>
<td>453</td>
<td>2344</td>
</tr>
<tr>
<td>2010</td>
<td>11135</td>
<td>4122</td>
<td>216</td>
<td>2545</td>
</tr>
<tr>
<td>2011</td>
<td>11862</td>
<td>4446</td>
<td>55</td>
<td>2888</td>
</tr>
</tbody>
</table>
TYPE OF NEW TB CASES DETECTED,
SARAWAK 2005

<table>
<thead>
<tr>
<th>Type</th>
<th>PTB</th>
<th>EXTRA TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg</td>
<td>463</td>
<td>220</td>
</tr>
<tr>
<td>Pos</td>
<td>865</td>
<td>0</td>
</tr>
</tbody>
</table>
Transmission of disease

• The relative transmission rate from patients with smear-negative compared with smear-positive PTB is around 22%.

• Easier to treat. Better response, less relapse rate.

Behr MA. Transmission of MTB from patients smear negative for AFB. Lancet 1999;353:444
Clinical predictors

• History alone is not able to diagnose smear negative PTB confidently.

• LOA, fever, night sweat, chest pain, hemoptysis and breathlessness are more common in PTB patients compare to those without PTB.
Differential diagnosis of smear neg PTB

Other medical conditions
- Bacterial pneumonia
- Empyema
- Pulmonary nocardiosis
- *Pneumocystis carinii* pneumonia
- Cryptococcal pneumonia
- Histoplasmosis
- Pulmonary Kaposi’s sarcoma
- Interstitial pneumonitis
- Cytomegalovirus pneumonitis
- Gram-negative bacteraemia
- Carcinoma
- Lymphoma
- Congestive cardiac failure
- Asthma, chronic obstructive lung disease
- Allergic bronchopulmonary aspergillosis
- Occupational lung diseases (e.g., silicosis)
- Extrinsic allergic alveolitis
- Psittacosis

1. OLD PTB
2. CAP
3. Old Scar-previous infection
4. Cancer
5. Bronchiectasis
6. ILD
7. Other infection-Meliodosis, fungal infection. (esp if HIV +)
Sensitivity of AFB smear microscopy

- Smear microscopy sensitivity: 22-80% in culture proven cases\(^1\).
- Specificity>96%, PPV 50-80%
  - False positive
  - NTM
- Quality of the smear microscopy performance underlies differences in sensitivity.

<table>
<thead>
<tr>
<th>No. of bacilli observed</th>
<th>Estimated concentration of bacilli per ml of specimen</th>
<th>Probability of a positive result</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 in 100 or more field</td>
<td>&lt;1000</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>1-2 in 300 fields</td>
<td>5000-10000</td>
<td>50%</td>
</tr>
<tr>
<td>1-9 in 100 fields</td>
<td>about 30 000</td>
<td>80%</td>
</tr>
<tr>
<td>1-9 in 10 fields</td>
<td>about 50 000</td>
<td>90%</td>
</tr>
<tr>
<td>1-9 per field</td>
<td>about 100 000</td>
<td>96.2%</td>
</tr>
<tr>
<td>10 or more per field</td>
<td>about 500 000</td>
<td>99.95%</td>
</tr>
</tbody>
</table>

Reason for smear negative

• Poor quality of specimen
• Low bacilli load.
• Inexperience laboratory technician-\textit{false negative}.
• Immunocompromised state ie HIV
• Extra-pulmonary TB
• Not TB
What can we do to improve microscopy yield?

• Ensure at least 2/3 good quality sputum (5-10mL) are sent.

• Lab enhancement: Ensure adequate training, quality assessment and facilities.

• Use of other microscopy techniques: - Fluorescence/LED microscopy.
Induced sputum for microscopy

- 90% sensitivity.
- Gastric lavage = 77% sensitivity
- Bronchoscopy = 77% sensitivity.

- Induced with 3% saline, using ultrasonic nebulizer to adm 5-6mL/min over 15 minutes.
- Almost all patients will produce sputum.
A Minimum 5.0 ml of Sputum Improves the Sensitivity of Acid-fast Smear for *Mycobacterium tuberculosis*

JOHN R. WARREN, MONDIRA BHATTACHARYA, KLEPER N. F. DE ALMEIDA, KATHY TRAKAS, and LANCE R. PETERSON

Departments of Pathology and Medicine, Northwestern University Medical School, and the Clinical Microbiology Laboratory, Northwestern Memorial Hospital, Chicago, Illinois

Sensitivity
- ≥5ml: 92%
- All specimens were processed regardless of volume: 72.5%

Procedure
1. Decontamination: 2.0% NAOH+mucolytic agent NAC.
2. Incubation
3. Centrifugation/cytocentrifugation
4. Auramone-rhodmine fluorochrome staining
5. Entire smear examined.
Mycobacterial culture

- The Gold standard of diagnosis
- Sensitivity of 3 cultures >90%.
- False positive: contamination, NTM.
- Solid vs liquid culture media.

- All patients who are suspected of having TB should have at least one TB culture done.
Algorithm 1: Laboratory Diagnosis of *Mycobacterium tuberculosis*

1. **Risk Minimal**
   - All laboratories
     - Microscopy
       - Positive
       - Negative or no results
         - **CULTURE (Solid or Liquid)**
           - Positive
           - Negative or contamination
             - **DRUG SUSCEPTIBILITY TESTING – First-line (Solid or Liquid)**
               - Not MDR-TB, resistant other drugs
               - Susceptible
             - **IDENTIFICATION (SPECIATION) (Conventional/Commercial)**
               - MTB or NTM
             - **LPA**
               - **DRUG SUSCEPTIBILITY TESTING – Second-line (Solid or Liquid)**
                 - XDR-TB
                 - Not MDR-TB, resistant other drugs
                 - Susceptible
                 - Negative result
               - **Microscopy**
                 - AFB
                 - TB/NTM Drug resistance
               - **State/NR**
                 - **MDR-TB**
               - **NRL/Regional**
                 - **NRL/SRL**
               - **Risk high**
Mycobacterial Culture

Local culture center

Culture resemble mycobacterium identified

National culture center: Sungai Buloh(MKAK): Identification and sensitivity

Negative

Report

Report Via MKAK Website
http://www.los.moh.gov.my/result/
Tuberculin skin test: Mantoux Test

Positive TST may be due to:

1. TB infection: both Latent or Active
2. Previous BCG vaccination
   - Reaction >15mm of induration, esp if BCG was given >15 years ago, are not likely caused by BCG.
   - BCG given at infancy unlike causing positive TST esp in adult.
3. Atypical mycobacterium exposure.

Figure 3  Percentage reactors versus skin test results in mm with 5 TU PPD (576 BCG+, 1145 BCG–).

Figure 4  Percentage reactors versus skin test results in mm with 2 TU RT23 (2880 BCG+, 1425 BCG–).
TST-mantoux test

• Unable to differentiate between infection vs disease. (Same for IGRA: Quantiferon/T-spot TB test)

• For the diagnosis of active disease, TST and IGRA are NOT recommended.
TST

• False negative (20-30% of active TB cases at the time of initial diagnosis)
  – Elderly
  – Severe hypoalbuminemia
  – Disseminated tuberculosis
  – Immunocompromised host
  – Recent acute infection
  – Recent vaccination with live virus
  – Chronic illness-CKD
uncertain. At present, most clinicians appear to interpret tuberculin test results from personal experience of the local population. The pattern of tuberculin test reaction in the local setting will serve a useful guide for interpreting them. The aim of this study was to determine the usefulness of tuberculin skin tests in helping make a diagnosis of tuberculosis in Malaysian subjects.

Materials and Methods

The results of 468 Mantoux tests done in out-patients and in-patients is often done as an aid to diagnosis.

Materials and Methods

- In patient and outpatient setting.
- 1988
- Mantoux Test: 0.1ml of PPD-RT25 (2TU).
- Positive mantoux: 10mm.
- 85 cases of active TB cases: sputum direct smear, biopsy or culture.
- 30 cases of old TB: based on history, CXR, direct smear and culture.
- 17 of the 30 cases of old TB had positive mantoux.

10mm or more was considered as positive Mantoux reaction.

Eighty-five cases of active tuberculosis (detection of Mycobacterium on sputum direct smears, gastric lavage, biopsies, cultures etc.) and 30 cases of ‘old’ tuberculosis diagnosed in this hospital were then reviewed for their Mantoux reactions. The diagnosis of old tuberculosis was made when the patient gave a history of past tuberculosis and the chest X-ray showed evidence of bilateral apical fibrosis but examination for Mycobacteria including cultures was negative.

Sensitivity: 73/112=65%
Specificity: 344/356=96%
ESR

- Too non-specific
- Should not be depend on in the diagnostic algorithm.
CXR

• 92% of PTB cases in low TB/HIV prevalent countries have typical appearances on CXR\(^1\)

• Only 8% have atypical appearances: Lower lobe infiltrates, hilar lymphadenopathy, miliary pattern, normal)

• **Sensitivity=70-80% based on typical CXR Changes.**
• **Specificity=60-70%.**

• A survey in Malawi: MO misdiagnosed 1/3 of clinical vignettes which described typical radiographic signs of TB\(^2\)

• Old vs active TB

2. Harries AD. Bull World Health Organ 1998;76:651
1. Typical findings: a triad of classic findings are seen in non-immunocompromised adults.
   - Position – apical-posterior segments of upper lobes or superior segment of lower lobes in 90%.
   - Volume loss – this is a hallmark of TB disease as a result of its destructive and fibrotic nature.
   - Cavitation – this is seen at a later stage and depends upon a vigorous immune response. Therefore, it may not be seen in severely immunocompromised individuals.

2. Atypical features: these will be seen in patients with immunocompromising conditions such as HIV infection, diabetes, renal failure or corticosteroid use.
   - Hilar and mediastinal lymphadenopathy, particularly in HIV-infected individuals.
   - Non-cavitary infiltrates and lower lobe involvement.
Management

1. Take a good history and clinical examination.
   • Look for alternative diagnosis.

2. Sputum are really negative
   • Consider 3% NS neb for sputum induction, NG aspirate for AFB in children, poor GCS patients.

3. Sputum is sent for TB culture and sensitivity.
   • If you don’t send, it will NEVER come back.

4. CXR is reported by “radiologist”
   • Trace old CXR

5. Refer physician for decision on treatment.
## Clinical Decision Analysis

<table>
<thead>
<tr>
<th>Symptoms/Signs</th>
<th>Imaging (CXR)</th>
<th>Sputum AFB</th>
<th>TB C/S</th>
<th>Remark</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Treatment</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-/pending</td>
<td>Further Investigation or treatment</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Further Investigation</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+/pending</td>
<td>Treatment</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>F/up Sputum TB C/S Lab error?(only scanty/one Sputum AFB positive)</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td></td>
<td>Further investigation &gt;&gt;treatment</td>
</tr>
</tbody>
</table>

Consider clinical urgency of treatment.
Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents

Recommendations for HIV-prevalent and resource-constrained settings

All patients suspected of having pulmonary tuberculosis

Sputum microscopy for AFB

Three negative smears

Broad-spectrum antimicrobials (excluding anti-tuberculosis drugs and fluoroquinolones)

No improvement

Improved

Repeat sputum microscopy

One or more positive smears

All smears negative

Chest radiograph and physician's judgement

Tuberculosis

No tuberculosis

Missed up to 54% of culture pos case.

(Sensitivity=38.1%, Specificity=74.5%)

(DTM Nguyen; Tuberculosis Research and Treatment; 2012)
Algorithm for the diagnosis of tuberculosis in HIV-negative patients
(International standards for tuberculosis care, 2006)

1. All patients suspected of having pulmonary tuberculosis
   - **SPUTUM TB C/S**
   - Sputum microscopy for AFB
   - **CXR**
     - Three negative smears
     - Broad-spectrum antimicrobials (excluding anti-tuberculosis drugs and fluoroquinolones)
       - No improvement
       - Improved
         - **SPUTUM TB C/S**
           - Repeat sputum microscopy
             - One or more positive smears
             - All smears negative
               - Chest radiograph and physician’s judgement
                 - Tuberculosis
                 - No tuberculosis
           - **NAAT if available**
             - CXR consistent with PTB
               - NO
                 - Further investigation
Trial of Antibiotic

• Not to use any antiTB drugs, both first line or second line.
  – Quinolone: very effective Secondline AntiTB!!!
  – Augmentin: WHO class 5 antiTB drug (uncertain antiTB activity)

**ONLY BE DONE AFTER 3 SMEARS ARE NEGATIVE**
Trial of Antibiotics

• 50% of Smear Neg-Culture Pos cases can response to antibiotic\(^1\).
  – Unrelated fluctuations in disease severity
  – Successful treatment of a superimposed bacterial infection.
• Unable to exclude non-pneumonia lung diseases.

Trial of TB drugs

• Not recommended.
• Poor specificity: bacteria infection response to rifampicin.
• antiTB drugs toxicity
• Delay in diagnosis of non-TB disease
• ATT drug resistance
Further Investigation

use all tools that you have to establish the diagnosis if possible.

1. CT Thorax/HRCT
2. BAL, Transbronchial lung biopsy, open lung biopsy.
3. FNAC, pleural biopsy. Etc
4. Use of Nucleic acid amplification tests.
5. Other tests deemed relevant.
• Can define the anatomical distribution better.

• Better in defining mass, cavity, consolidation, pattern of diffuse nodules (random, lymphatic, centrilobular), collapse, interstitial involvement.

**Table 4.** Diagnostic accuracy of HRCT findings, TB-PCR assay results, and QFT-G assay results in smear-negative TB

<table>
<thead>
<tr>
<th>Diagnostic method</th>
<th>Sensitivity(^1), %</th>
<th>Specificity(^1), %</th>
<th>PPV(^1), %</th>
<th>NPV(^1), %</th>
<th>LR(^+)(^1)</th>
<th>LR(^-)(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HRCT</td>
<td>80.0 (63.9–90.4)</td>
<td>70.5 (54.6–82.8)</td>
<td>71.1 (55.5–83.2)</td>
<td>79.5 (61.1–90.1)</td>
<td>2.71 (1.67–4.38)</td>
<td>0.26 (0.14–0.48)</td>
</tr>
<tr>
<td>TB-PCR</td>
<td>43.2 (27.5–60.4)</td>
<td>97.7 (86.2–99.9)</td>
<td>94.1 (69.2–99.7)</td>
<td>66.7 (53.6–77.7)</td>
<td>18.59 (2.59–133.59)</td>
<td>0.58 (0.44–0.77)</td>
</tr>
<tr>
<td>QFT-G</td>
<td>84.4 (66.5–94.1)</td>
<td>82.9 (67.4–92.3)</td>
<td>79.4 (61.6–90.7)</td>
<td>87.2 (71.8–95.2)</td>
<td>4.94 (2.48–9.86)</td>
<td>0.19 (0.08–0.43)</td>
</tr>
</tbody>
</table>

HM Lee, Respiration 2010;79:454
67 years old lady with cough for 4 months. Weight loss of 6Kg. Chronic smoker. Clinically crepitation noted at right upper zone.
Right upper lobe mass with Lymphangitis carcinomatosa
Bronchoscopy with Transbronchial lung biopsy:
Adenocarcinoma
NAAT in Smear Neg PTB

- Meta-analysis of commercially based NAAT for respiratory sample.
  - In smear Pos PTB: Sensitivity=96%, specificity=85%.
  - In smear Neg PTB: sensitivity=66% (50-80), specificity=98%, PPV=>95%.
  - False positive rate can be very high if careful attention to lab quality not observed. (Canadian TB Standard 6th ed)

<table>
<thead>
<tr>
<th>Test</th>
<th>NAA method</th>
<th>AFB+</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>AFB-</th>
<th>DOR</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplicor</td>
<td>PCR</td>
<td>117 (56 to 246)</td>
<td>0.96 (0.94 to 0.97)</td>
<td>0.83 (0.8 to 0.86)</td>
<td>77 (51 to 115)</td>
<td>0.61 (0.57 to 0.65)</td>
<td>0.97 (0.968 to 0.974)</td>
<td></td>
</tr>
<tr>
<td>Cobas Amplicor</td>
<td>PCR</td>
<td>99 (56 to 173)</td>
<td>0.96 (0.95 to 0.97)</td>
<td>0.74 (0.68 to 0.8)</td>
<td>220 (144 to 335)</td>
<td>0.64 (0.59 to 0.69)</td>
<td>0.993 (0.992 to 0.994)</td>
<td></td>
</tr>
<tr>
<td>BDP</td>
<td>SDA</td>
<td>181 (39 to 834)</td>
<td>0.98 (0.96 to 0.99)</td>
<td>0.89 (0.84 to 0.93)</td>
<td>96 (53 to 175)</td>
<td>0.71 (0.66 to 0.76)</td>
<td>0.97 (0.964 to 0.974)</td>
<td></td>
</tr>
<tr>
<td>E-MTD</td>
<td>TMA</td>
<td>314 (99 to 995)</td>
<td>0.97 (0.95 to 0.98)</td>
<td>0.96 (0.93 to 0.97)</td>
<td>157 (48 to 510)</td>
<td>0.76 (0.7 to 0.8)</td>
<td>0.97 (0.966 to 0.974)</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>LCR</td>
<td>42 (12 to 142)</td>
<td>0.96 (0.94 to 0.98)</td>
<td>0.71 (0.64 to 0.78)</td>
<td>71 (38 to 132)</td>
<td>0.57 (0.5 to 0.64)</td>
<td>0.98 (0.978 to 0.985)</td>
<td></td>
</tr>
</tbody>
</table>

PCR, polymerase chain reaction; SDA, strand displacement amplification; TMA, transcription mediated amplification; LCR, ligase chain reaction; DOR, diagnostic odds ratio.

*Random effect model.

S. Greco et al. Thorax 2006;61:783
NAAT for the detection of SNTB

• Xpert MTB/RIF assay:
  – Sensitivity 72.5% for Smear Neg-culture positive isolates.
  – Second Xpert: increase sensitivity by 12.6%
  – Third Xpert: increase sensitivity by 5.1%
  – Specificity=99.2%

Boehme CC. NEJM2010;363:1005
SNTB: GenoType MTBDRplus

- Cross sectional study, South Africa, Gold miners, 29%HIV, high prevalence of silicosis (Thibela TB cohort)

<table>
<thead>
<tr>
<th>MTBDRplus result</th>
<th>M. tuberculosis present</th>
<th>NTM only</th>
<th>Contaminated</th>
<th>Negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. tuberculosis present</td>
<td>256 (48.4)</td>
<td>4 (1.6)</td>
<td>11 (3.0)</td>
<td>9 (0.7)</td>
<td>280</td>
</tr>
<tr>
<td>No M. tuberculosis present</td>
<td>263 (49.7)</td>
<td>247 (98.4)</td>
<td>355 (96.2)</td>
<td>1,347 (99.0)</td>
<td>2,212</td>
</tr>
<tr>
<td>Indeterminate-final</td>
<td>10 (1.9)</td>
<td>0 (0)</td>
<td>3 (0.8)</td>
<td>5 (0.4)</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>529 (100)</td>
<td>251 (100)</td>
<td>369 (100)</td>
<td>1,361 (100)</td>
<td>2,510</td>
</tr>
</tbody>
</table>

* Percentages shown are those of the column total.

<table>
<thead>
<tr>
<th>Smear status</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>13.7%</td>
</tr>
<tr>
<td>Scanty</td>
<td>46.2%</td>
</tr>
<tr>
<td>1+</td>
<td>69.1%</td>
</tr>
<tr>
<td>2+</td>
<td>86.3%</td>
</tr>
<tr>
<td>3+</td>
<td>89.8%</td>
</tr>
</tbody>
</table>
# US CDC 2009 recommendation on commercial NAAT

<table>
<thead>
<tr>
<th>Smear</th>
<th>NAAT</th>
<th>Culture</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>pending</td>
<td>Treat as TB. Trace culture.</td>
</tr>
</tbody>
</table>
| -     | +    | pending | 1. Use Clinical judgment to decide on TB Treatment.  
2. Consider additional test.  
3. Can consider to send second NAAT (a person can be presumed to have TB if both NAAT positive, pending culture) |
| -     | -    | pending | 1. Use clinical judgment to decide on TB treatment (NAAT unable to exclude TB)  
2. Consider additional tests. |
| +     | -    | Pending | 1. Send amplification inhibitor test and repeat NAAT.  
2. If Inhibitor neg-Clinical judgment/additional test.  
3. if inhibitors neg + second NAAT -: presumed NTM  
4. If inhibitor positive(3-7%): NAAT is not a useful test. |
Case Study

- 65 years old gentlemen.
- Cough for 5 months, LOW 5Kg.
- Well
- Left supraclavicular LN, Hard
Summary

• Develop your clinical acuity.

• Read, ask.

• Use all tests available to diagnose TB
Nucleic acid amplification test and bronchoscopy improve the diagnostic accuracy of smear-negative tuberculosis.

**DESIGN:**
Bronchoscopy was performed among smear-negative PTB suspects to collect respiratory specimens to assess the efficacy and accuracy of the Amplified Mycobacterium Tuberculosis Direct (AMTD) test in the diagnosis of PTB.

**RESULTS:**
In 105 PTB suspects, 80 were finally excluded, of whom two were false-AMTD-positive. PTB (n = 25) was diagnosed in 10 patients culture-positive for Mycobacterium Tuberculosis (7/105 bronchial wash/bronchoalveolar lavage [BW/BAL] specimens, 6/315 expectorated sputum specimens [2 positive in 2 patients; 1 positive in 2 patients], and one with both), and in 15 patients with improvement after anti-tuberculosis treatment. Among the 25 PTB patients, 20 were AMTD-positive, of whom four were culture-positive. Three AMTD-negative patients were culture-positive. The sensitivity and specificity of AMTD were respectively 80.0% and 97.5%. The diagnostic yield was higher in respiratory specimens obtained at bronchoscopy and measured by AMTD than in conventional sputum or BW/BAL culture.

**CONCLUSION:**
NAA testing on specimens collected using bronchoscopy provides a highly efficient and reliable approach in the diagnosis of PTB in smear-negative PTB suspects.

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Bronchoalveolar Lavage Enzyme-linked Immunospot for a Rapid Diagnosis of Tuberculosis
A Tuberculosis Network European Trialsgroup Study

Methods: Subjects suspected of having active TB who were unable to produce sputum or with AFB-negative sputum smears were prospectively enrolled at Tuberculosis Network European Trialsgroup centers in Europe. ELISpot with early-secretory-antigenic-target-6 and culture-filtrate-protein-10 peptides was performed on peripheral blood mononuclear cells (PBMCs) and bronchoalveolar lavage mononuclear cells (BALMCs). M. tuberculosis-specific nucleic acid amplification (NAAT) was performed on bronchoalveolar lavage fluid. Measurements and Main Results: Seventy-one of 347 (20.4%) patients had active TB. Out of 276 patients who had an alternative diagnosis, 127 (46.0%) were considered to be latently infected with M. tuberculosis by a positive PBMC ELISpot result. The sensitivity and specificity of BALMC ELISpot for the diagnosis of active pulmonary TB were 91 and 80%, respectively. The BALMC ELISpot (diagnostic odds ratio [OR], 40.4) was superior to PBMC ELISpot (OR, 10.0), tuberculin skin test (OR, 7.8), and M. tuberculosis specific NAAT (OR, 12.4) to diagnose sputum AFB smear-negative TB. In contrast to PBMC ELISpot and tuberculin skin test, the BALMC ELISpot was not influenced by previous history of TB.

Conclusions: Bronchoalveolar lavage ELISpot is an important advancement to rapidly distinguish sputum AFB smear-negative TB from latent TB infection in routine clinical practice.
Fiberoptic bronchoscopy for the rapid diagnosis of smear-negative pulmonary tuberculosis

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Abstract

Background: This study was aimed to investigate the diagnostic value of fiberoptic bronchoscopy (FOB) with chest high-resolution computed tomography (HRCT) for the rapid diagnosis of active pulmonary tuberculosis (PTB) in patients suspected of PTB but found to have a negative sputum acid-fast bacilli (AFB) smear.

Methods: We evaluated the diagnostic accuracy of results from FOB and HRCT in 126 patients at Gangnam Severance Hospital (Seoul, Korea) who were suspected of having PTB.

Results: Of 126 patients who had negative sputum AFB smears but were suspected of having PTB, 54 patients were confirmed as having active PTB. Hemoptysis was negatively correlated with active PTB. Tree-in-bud appearance on HRCT was significantly associated with active PTB. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FOB alone was 75.9%, 97.2%, 95.3%, and 84.3%, respectively, for the rapid diagnosis of active PTB. The combination of FOB and HRCT improved the sensitivity to 96.3% and the NPV to 96.2%.

Conclusions: FOB is a useful tool in the rapid diagnosis of active PTB with a high sensitivity, specificity, PPV and NPV in sputum smear-negative PTB-suspected patients. HRCT improves the sensitivity of FOB when used in combination with FOB in sputum smear-negative patients suspected of having PTB.

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