Pulmonary TB
Clinical Diagnosis

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History – ‘back to basics’

- Symptoms
- Ethnicity/ age
- Recent arrival/ travel history
- Contact history
- BCG history
Table 1.2. Tuberculosis case reports by site of disease, UK, 2009

<table>
<thead>
<tr>
<th>Site of disease*</th>
<th>Number of cases</th>
<th>Percentage**</th>
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<tbody>
<tr>
<td>Pulmonary</td>
<td>4,851</td>
<td>54.1</td>
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<tr>
<td>Extra-thoracic lymph nodes</td>
<td>1,831</td>
<td>20.4</td>
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<tr>
<td>Intra-thoracic lymph nodes</td>
<td>810</td>
<td>9.0</td>
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<td>Other extra-pulmonary</td>
<td>694</td>
<td>7.7</td>
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<tr>
<td>Pleural</td>
<td>620</td>
<td>6.9</td>
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<td>Gastrointestinal</td>
<td>367</td>
<td>4.1</td>
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<tr>
<td>Bone – spine</td>
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<td>4.1</td>
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<tr>
<td>Cryptic/miliary</td>
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<tr>
<td>Bone – other</td>
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<td>2.0</td>
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<td>CNS – meningitis</td>
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<td>2.0</td>
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<tr>
<td>Genitourinary</td>
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<tr>
<td>CNS – other</td>
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<td>1.0</td>
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<td>Laryngeal</td>
<td>17</td>
<td>0.2</td>
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<tr>
<td>Unknown extra-pulmonary</td>
<td>13</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Clinical Manifestations:
Symptoms of pulmonary TB

- Cough – 80%
- Weight loss – 74%
- Malaise/lethargy 68%
- Night sweats 55%
- Haemoptysis 6-37%
- Fever (peaks evening) – Only 21-60%
- Dyspnoea – late – or effusion
- (None)

Length of history may be short
PTB 2003 - 2006 n=143

- Absent fever 37%
- Absent sweats 39%
- Absent weight loss 38%
- All three symptoms were absent in 25%

Factors associated:
- Drug-resistant TB (aOR 3.58, P = 0.004)
- Non-HIV vs HIV (aOR 4.03, P = 0.001)
- Female sex (aOR 3.15, P = 0.004)
Clinical Manifestations: Signs

- None
- Weight loss
- Usually few or none in chest
- Lymphadenopathy (esp ISC)
- Erythema nodosum (1ry)
- Uveitis (1ry)
- Phylectenular conjunctivitis (1ry)
- Lupus vulgaris
- Clubbing (chronic)
Clinical Diagnosis TB
Pulmonary Chest X-Ray Presentations

• Primary TB
  – Mediastinal lymphadenopathy
    • Normally unilateral
    • Only 15% Bilateral Hilar Lymphadenopathy
  – Pleural effusion
  – Lobar collapse/consolidation
    • Any segment
    • Anterior RUL/ medial RML commonest
  – Miliary

Pneumonic lesion with enlarged hilar nodes
- consider primary TB
Clinical Diagnosis TB

Pulmonary Chest X-Ray Presentations

- Post-Primary TB
  - Classical:
    - Apices
    - Apical and posterior segments
    - Soft ‘fluffy’ /nodular upper zone
    - Cavitation (10-30%)
  - Mid-zone disease (apex lower lobes)
  - Bronchopneumonia
  - Consolidation
  - (Pleural effusion)
  - Lymphadenopathy rare

Beware the immunocompromised confounder
‘Normal’ CXR’s

- SMH data – 13% ‘normal’ CXR’s with definite PTB

Normal chest radiography in pulmonary tuberculosis: implications for obtaining respiratory specimen cultures. Pepper T et al.

- Urban TB clinic - Nashville
- October 1992 - July 2003
- 601 study patients
- 53 (9%) had normal CXRs:
  - 31/138 (22%) were human immunodeficiency virus (HIV) infected
  - 22/463 (5%) were non-HIV-infected/unknown
Clinical Manifestations PTB
Role of CT

• Miliary
• Tree-in-bud
• Cavitation
• Lymphadenopathy
• Ruling out other diagnoses
• (Extrapulmonary sites)
Miliary TB

- 2-6% primary TB
- 2-25% choroidal tubercles
- Fever 90% (classically morning)
- Hepatomegaly 1/3-1/2
- Splenomegaly 15-30%
- Skin tests negative in 50% ?role of IGRA’s
- Anaemia 50%/ leukopenia 15%/lymphopenia 90%/leukaemoid reactions
- 1-3 mm nodules (millet seed)
  - Micronodules yellow-white
  - Caseation in alveolar walls and interlobular septa
Miliary TB ii

• HRCT
  – More sensitive (CXR only 59-69%)
  – fine nodules
  – Uniform distribution
  – Interlobular septal thickening/groundglass rare
  – Rare diffuse alveolar filling
  – Do not scar with calcification
• Diagnosis
  – Sputum only 50% positive culture
  – TBB 63% positive histology/smear
  – Lung/ liver/ spleen 80-90%
  – Kidney 60%
  – Bone Marrow 25-75%
  – Use CSF to define length of treatment (CSF disease in up to 20%)
  – Tuberculin test poor sensitivity

• Trial of treatment
  – Expect pyrexia to respond 7-10 days
  – Clinical improvement 4-6 weeks

Miliary TB iii
‘Tree in bud’

- Multiple linear branching structures
- Lobar or segmental
- ?Marker of activity
- Good marker of TB in association with cavitation/ nodular opacification
Intrapulmonary LN

• > 2cm
• Unilateral
• Paratracheal/hilar/subcarinal
• Hypodense central area
  – correlates to necrosis
• Rim enhancement
• Calcify later
TB Samples

- Sputum
- Induced sputum
- Bronchoscopy/BAL
- Gastric lavage
- Pleural aspirate/biopsy
- Biopsy CT guided/thoracoscopic
- Lymph node biopsy/aspirate
- Transbronchial needle aspiration
- Endobronchial Ultrasound Needle Aspiration
- Endoscopic Ultrasound Needle Aspiration
- Bone marrow biopsy
- Early morning urine
- Lumbar puncture
- Blood cultures
Samples: sites of collection; number of samples


US study compared cumulative proportion of +ve smears upon microscopy for direct vs concentrated sputum (all patients were subsequently *M. tuberculosis* culture +ve); 3 or more specimens were received:

<table>
<thead>
<tr>
<th>Sample</th>
<th>Direct (%)</th>
<th>Concentrated (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>57</td>
<td>74</td>
</tr>
<tr>
<td>1,2</td>
<td>76</td>
<td>83</td>
</tr>
<tr>
<td>1,2,3</td>
<td>81</td>
<td>91</td>
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</table>

The positive predictive value of positive sputum microscopy is 92% for spontaneously produced sputum, and 71% for both BAL and induced sputum. Microscopy on gastric washings has some utility in children, but a recent comparative study in children showed a single induced sputum (by hypertonic saline) to be superior to three gastric washings.
Sputum Practicalities

- Minimum 3 samples on consecutive days
- Sample first thing in morning
- Induced sputum
  - 3% Hypertonic saline
  - 20 minutes using ultrasonic nebuliser
  - Infection control issues
  - Better yield than gastric wash in children
  - 3 consecutive better yield than bronchoscopy?
Induced sputum and bronchoscopy in the diagnosis of pulmonary tuberculosis

T McWilliams, A U Wells, A C Harrison, S Lindstrom, R J Cameron, E Foskin

Background: Previous studies suggest that bronchoscopy and a single induced sputum sample are equally effective for diagnosing pulmonary tuberculosis.

Methods: In a prospective study of subjects with possibly active pulmonary tuberculosis, the diagnostic yield of three induced sputum tests was compared with that of bronchoscopy. Subjects either produced no sputum or (acid fast) smear negative sputum. Bronchoscopy was only performed if at least two induced sputum samples were smear negative.

Results: Of 129 subjects who completed all tests, 27 (21%) had smear negative and culture positive specimens, 14 (52%) on bronchoscopy and 26 (96%) on induced sputum (p<0.005). One patient was culture positive on bronchoscopy alone compared with 13 on induced sputum alone; 13 were culture positive on both tests. Induced sputum positivity was strikingly more prevalent when chest radiographic appearances showed any features of active tuberculosis (20/63, 32%) than when appearances suggested inactivity (1/44, 2%; p<0.005). Induced sputum costs were about one third those of bronchoscopy, and the ratio of costs of the two tests per case of tuberculosis diagnosed could be as much as 1:8.

Conclusions: In subjects investigated for possibly active or inactive tuberculosis who produce no sputum or have smear negative sputum, the most cost effective strategy is to perform three induced sputum tests without bronchoscopy. Induced sputum testing carries a high risk of nosocomial tuberculosis unless performed in respiratory isolation conditions. The cost benefits shown could be lost if risk management measures are not observed.
Figure 2. Proportion of subjects with cultures positive for Mycobacterium tuberculosis, by diagnostic technique, for 79 subjects with results for all 5 sputum samples obtained by induction with nebulized hypertonic saline (IS) and all 3 gastric washing (GW) specimens. Cumulative proportions are shown for the 5 IS samples, paired binomial probability test comparing diagnostic yield of all 5 IS samples versus 3 day 1 IS samples. Bronchoalveolar lavage (BAL) culture results were available for 19 subjects.

Pasvol et al. Clinical Infectious Diseases 44(11):1415–1420
Nucleic Acid Amplification

In respiratory samples:
• High specificity 95-100%
• Sensitivity 50-95%
• Most positive in smear positive cases
• Least positive in smear negative cases
NAA – NICE 2006

Indications:
1) rapid confirmation of a diagnosis in a sputum smear-positive person would alter care
OR
2) before conducting a large contact-tracing initiative
3) Rapid diagnostic tests for *M. tuberculosis* complex identification should be conducted on biopsy material only if:
   ● all the sample has been inappropriately placed in formalin, and
   ● AFB are visible on microscopy.

Non-respiratory TB
• Even if rapid diagnostic tests are negative (eg pleural fluid, CSF and urine) - Clinical signs and other laboratory findings consistent with TB meningitis should be Rx
• GeneXpert® System (Sunnyvale, CA), a single-use sample processing cartridge system with integrated multi-color real-time PCR capacity
• on-demand, near-patient PCR assay - novel six-color dye set to detect *M. tuberculosis* and identify rifampicin-resistance as a surrogate for MDR directly from patients' sputum in less than two hours
N=1462
India, Peru, Azerbaijan, S Africa

Specificity: 99.2%

Sensitivity for smear +ve: 98.2%

Sensitivity vs culture: 90%

Accuracy for MDR-TB: 98%

Directly from untreated sputum < 2 hrs
Bronchoscopy

- **In smear negative disease**
  - BAL +ve AFB in 34%
  - BAL culture +ve in 95%
  - Exclusive diagnosis in 46%

- **Endobronchial involvement**

- **Miliary disease**
  - consider transbronchial biopsy (73%) and brush (57%)

- **Excluding other causes of obstruction**

- **Infection control issues**

- **Safe**

- **Post bronchoscopy sample**
Post-bronchoscopy sputum: Improving the diagnostic yield in smear negative pulmonary TB

Peter M. George a,d, Meera Mehta a,d, Jaideep Dhariwal a, Aran Singanayagam a, Claire E. Raphael a, Mohammad Salmasi a, David W. Connell a, Philip Molyneaux a, Melissa Wickremasinghe a, Annette Jepson b, Onn Min Kon a,c,*

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Available online 15 August 2011
**Results:** Over the study period, 236 patients had microbiologically confirmed smear negative PTB of which 57 patients were eligible for the study. 15 patients (26.3%) were infected with HIV. 19 patients (33.3%) converted to AFB sputum smear positivity post-bronchoscopy and 5 patients (8.8%) were exclusively AFB sputum smear positive on PBS microscopy. *Mycobacterium tuberculosis* was cultured from the PBS of 43 patients (75.4%) and of these, 4 (7.0%) were exclusively PBS culture positive.
Gastric Wash

- Bronchial secretions swallowed
- First thing in am – 50 ml aspirated
- Normally 2 consecutive samples suffice
- Process within 4 hours
- Paediatrics
- Best yield 2 GW in combination with BAL
- Induced sputum x 1 may be superior to 3 GW in paediatrics
Bronchoscopy vs Induced Sputum?

- Current data – probably equivalent in high probability PTB
- No good head to head studies
- Bronchoscopy
  - if significant differential diagnosis
  - Directed to limited lesions
  - Combine FNA/TBBx/EBUS
- Pragmatics/ infection control
Intrathoracic Lymph Nodes TB
Commonest sites

• R paratracheal 42%
• R main bronchial 17%
• R hilar 12%
• Subcarinal 8%
• L paratracheal 8%
• L hilar 5%
• Anterior mediastinal 3%
• AoPulm window 3%

Chest 2004;126:259-267
Transbronchial Needle Aspiration for TB

- most frequently for subcarinal / paratracheal nodes
- Adequate specimens in approximately 90%
- Sensitivity 83%
- Specificity 100%
- Positive predictive value 100%
- Negative predictive value 38%

Application: provide a diagnosis in patients in whom there is little doubt about mediastinal involvement on CT
• Isolated mediastinal or hilar LN suspicious for TB
• 84 eligible patients (HIV-negative)
  – Histo/cytological
    63 (75%) cases
    histology - 48 patients [76%]; cytology - 9 patients [14%]
  – bacteriologic studies
    21 patients [33%]
    smear 8 patients/ culture 17 patients

• Immediately diagnostic in 59 patients (78%)
• Exclusively in 52 patients (68%)
• Self-limiting hemorrhage of < 30 mL volume - 77%
Harkin et al.


• HIV cases / Bellevue Hospital NY
• 44 procedures in 41 patients
• Adequate sampling - 80%
• Diagnostic - 23 of 44 (52%) procedures
• TBNA exclusive diagnosis - 13 of 41 (32%) patients
• 23 (52%) were performed in patients with mycobacterial disease - diagnosis in 20 of 23 (87%)
• Of positive TBNA
  – Sm +ve 11, culture in 14, histology in 15
• No complications
Endoscopic Ultrasound (EUS) Needle Aspiration

- Negligible risk of infection or bleeding
- Good for inf pulm ligament, subcarinal, and APW nodes
- Difficult to sample anterolateral to the trachea (2R, 2L, 4R and 4L)
- Sensitivity approximately 90% with NA
- 11/18 positive microbiology TB patients
- Needs experienced cytologist

BTS 2004– Fritscher Ravens
Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of extra-pulmonary tuberculosis

- Retrospective 6-year review single centre US
- 81 potential patients, 20 cases with EPTB diagnosed by EUS-FNA
- Necrotizing granulomas a 58% likelihood of TB vs. 14% for other cytologic findings (P < 0.0001)
- Necrosis also predictive, with a 44% likelihood of TB vs. 19% (P < 0.0225)
- Non-necrotizing granulomas were not predictive of TB and an alternative diagnosis was more likely, including sarcoidosis and cancer

Berzosa et al
Utility of endobronchial ultrasound-guided transbronchial needle aspiration in patients with tuberculous intrathoracic lymphadenopathy: a multicentre study

Neal Navani,1 Philip L Molyneaux,2 Ronan A Breen,3 David W Connell,2 Annette Jepson,4 Matthew Nankivell,5 James M Brown,1 Stephen Morris-Jones,6 Benjamin Ng,7 Melissa Wickremasinghe,2 Ajit Lalvani,2 Robert C Rintoul,7 George Santis,3 Onn Min Kon,2 Sam M Janes1

Thorax 2011
Methods

• Multicentre Study
  – SMH, UCL, GST, Papworth

• Patients' with Intrathoracic lymph node TB who underwent EBUS identified

• Exclusion criteria
  – BAL or Sputum Smear positive
  – Other peripheral nodes to sample
  – Must have completed and responded to TB treatment
Lymph Nodes

<table>
<thead>
<tr>
<th>Lymph node station*</th>
<th>Number of nodes sampled at EBUS-TBNA</th>
<th>Number of nodes from which pathological grades I–III were obtained</th>
<th>Number of nodes from which positive culture for tuberculosis was obtained</th>
</tr>
</thead>
<tbody>
<tr>
<td>2R</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>2L</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>4R</td>
<td>63</td>
<td>54</td>
<td>27</td>
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<td>4L</td>
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</tr>
<tr>
<td>11L</td>
<td>2</td>
<td>2</td>
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Results

- 156 cases over 4 sites
- Diagnostic procedure in 146 cases (94%)
- Pathology consistent with TB in 134 (86%)
- Microbiology consistent with TB in 82 (53%)
  - Smear 27 patients (17%)
  - Culture 74 (47%)
  - 8 patients (5%) were Isoniazid resistant
Results

156 patients with tuberculous intrathoracic lymphadenitis underwent EBUS-TBNA

Grade I—Granulomas with caseation (n=68)
  - Culture positive for M.tb (n=37)

Grade II—Granulomas without caseation (n=58)
  - Culture positive for M.tb (n=20)

Grade III—Non-granulomatous reaction with necrosis (n=8)
  - Culture positive for M.tb (n=5)

Grade IV—Lymphocytes only (n=19) and Grade V—Inadequate sample (n=3)
  - Culture negative (n=10)
    - Mediastinoscopy (n=4)
    - Clinical Follow-up (n=6)

All patients responded to anti-tuberculous therapy
How does EBUS compare?

• Endoscopic ultrasound guided fine needle aspiration (EUS-FNA)
  – Diagnostic yield 93%, Culture rate 21%
  – Doesn’t allow access to Rt. Paratracheal Nodes which were sampled in 47% of our patients

• Mediastinoscopy
  – Culture positive rate of 48%
  – 1-2% morbidity and General Anaesthetic
  – posterior sub-carinal and hilar nodes are inaccessible

• Bronchoscopy and Blind FNA?
  – 26% Culture rate (17/63)
Pleural TB

- Aspirate
  - Straw coloured
  - High protein (ratio > 0.5)
  - Low glucose
  - pH 7.2-7.4
  - Lymphocytic >50%

  - Raised ADA (>40IU sensitivity 96-100% specificity 89-97%)
  - Pleural interferon gamma > 138pg/ml sensitivity 90% and specificity 97%

  - Culture only positive in 23-67%
• Pleural Biopsy
  – Histology Granuloma - yield increases to 60% (?87% with 6 passes in experienced hands)
  – Culture (can increase microbiology yield to 80-90%)
  – Archival tissue can use NAA techniques (low sens/hi spec)
• Parenchymal involvement significant (18.9-78%)
  – Consider CT and BAL/induced sputum (50%)
• VATS
  – High sensitivity and specificity
PET

Standardised uptake value (SUV) corrected for body weight
>3-4 definite
<2 benign
IF as hot or hotter than liver then likely significant

‘False’ positives
TB/ sarcoidosis/ granulomatous disease/ fungi/ Wegener's

False negatives
bronchoalveolar or carcinoid or nodules < 6mm