An age-old problem in elderly

Dr. MF Cheng, TKOH
Supervisor : Dr. MK Cheng
The case

• LCM, M90
• Chiuchow dialect
• Walked with stick
• IADL 5
• Living with son’s family
Past medical history

- HT
- DM, HbA1c 7.1
- LUTS pending KWH/Uro
- FU in GOPD
Medications

- Diamicron 40mg bd
- Metformin 750mg bd
- Adalat Retard 20mg bd
- Hytrin 5mg nocte
- Zestril 10mg daily
- Betaloc 25mg bd
Chief complaints

- Decreased appetite
- Cough for 2 months, mucoid sputum
- Weight loss (subjective)
- No fever
- No haemoptysis
- No night sweating
- No bone pain
- No pTB history
- No contact or recent travel history
- Occasionally non-specific dizziness
• No LOC
• BO habit normal, yellow stool
• No chest pain or palpitations
• No fall
Physical examination at GOPD

- Bwt 46kg, BH 1.65m
- GCS 15/15
- BP 123/88
- P 62
- Temp 36.2
- Euvolaemic
- Cardiovascular N
- Abdominal N
- Power full, reflex N
- CNs N
- Routine blood taken at GOPD
- HypoNa 122
- K 3.6
- Ur/Cr 6.2/90
- LFT N
• Cortisol 567
• TSH N
• Serum Osm 264
• Urine Osm 401
• Spot urine Na 79
Common causes of SIADH

- Head injury
- SAH
- Meningitis
- Ca lung
- Pneumonia
- Lung abscess
- GBS
- Drugs, ciprofloxacin, chlorpropamide, carbamazepine, SSRI, MDMA, amitriptyline, etc
- Hypothyroid
Miliary pattern on CXR

- Miliary TB
- Histoplasmosis
- Sarcoidosis
- Pneumoconiosis
- Bronchoalveolar carcinoma
- Pulmonary siderosis
- Primary or Secondary Ca

• Sputum routine culture > MOF
• Sputum AFB smear 2+
• Sputum cytology –ve
• Early morning urine AFB -ve
Progress

- Started HRZO on 16.3.2013
- Isoniazid 300mg qd / Rifampicin 450mg qd / pyrazinamide 1250mg qd
- Then transferred to HHH
- Incidental finding of HBsAg +ve, e-ve, HBV DNA 293IU
- Anti-HCV / Anti-HIV -ve
• ALT 10 >>> 49 23.3.2013 (7 days after anti-TB Rx)
• ALT 49 >>> 280 (27.3.2013)
• Bili / ALP / INR normal

• HRZO (16.3.2013 – 22.3.2013)
• HRZ  (23.3.2013 – 23.3.2013) ALT 280 (27.3.2013)
• MO   (24.3.2013 – 2.4.2013) ALT 28 on 2.4.2013
• RMO  (3.4.2013 – 6.4.2013) ALT 24
• HRO   (7.4.2013 - )
pTB in elderly
Discussion points

• Prevalence of elderly TB
• Characteristics of the elderly patients
• Diagnostic methods
• DM and TB
• Hepatitis B and TB
• Hepatotoxicity
I - Prevalence

- TB is a notifiable disease in Hong Kong since 1939
- Mycobacterium tuberculosis infection remains a major cause of global mortality and morbidity and the resulting disease
- Estimated 1.7 million deaths in 2009
- Estimated 2 billion infected, but asymptomatic – latent TB
- Lifetime risk of such latent TB individuals to have active, symptomatic disease = 10%
- Defects in cellular immunity can increase the risk substantially, esp HIV
- HIV + TB 0.38 million deaths in 2009

Update on tuberculosis: TB in the early 21st century
Eur Respir Rev 2011, 20:120, 71-84
• It has been estimated that approximately 90% of the cases with tuberculosis in the older age group are the result of reactivation of a primary infection

Reactivation of tuberculosis: A problem of aging
Some studies of Hong Kong elderly

• The number of patients aged 65+ with TB rose from 15.3% to 36.9% of total annual notifications, from 1985 to 1999
  (1158 to 2788)  
  Tuberculosis in Older people: A Retrospective and Comparative Study from Hong Kong
  JAGS 50:1219-1226, 2002

• Total number of notified TB in HK is decreasing
  
  Centre for Health Protection, Department of Health, HKSAR

• The increasing proportion of TB patients aged > 65 also seen in Japan (60% in 2011), (30% > 80yo)
  
  Tuberculosis Annual report 2011 – Childhood and elderly tuberculosis
  Tuberculosis 88:7 2013 Jul pg 611-6
<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Vietnam Ref</th>
<th>Chin Immi</th>
<th>Noti Rate</th>
<th>Deaths</th>
<th>Death Rate (per 100000 pop)</th>
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<td>2006</td>
<td>5766</td>
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<td>58</td>
<td>84.1</td>
<td>294</td>
<td>4.3</td>
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<td>2007</td>
<td>5463</td>
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<td>79.0</td>
<td>231</td>
<td>3.3</td>
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<td>81.0</td>
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<td>3.3</td>
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<td>2009</td>
<td>5193</td>
<td>0</td>
<td>68</td>
<td>74.5</td>
<td>204</td>
<td>2.9</td>
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<td>2010</td>
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<td>80</td>
<td>72.5</td>
<td>191</td>
<td>2.7</td>
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<tr>
<td>2011</td>
<td>4794</td>
<td>0</td>
<td>81</td>
<td>67.8</td>
<td>187</td>
<td>2.6</td>
</tr>
<tr>
<td>2012**</td>
<td>4969</td>
<td>0</td>
<td>104</td>
<td>69.5</td>
<td>199</td>
<td>2.8</td>
</tr>
</tbody>
</table>
Elderly home

- HK study published in 1996
- 16/62 nursing homes chosen
- N = 587
- Mantoux test
- Overall weighted prevalence positive skin test was 43.8%
- Estimated prevalence of tuberculosis infection was between 1.2 and 1.9%
- However, **none** of the confirmed cases were smear positive

Tuberculosis among elderly Chinese in residential homes: Tuberculin reactivity and estimated prevalence
Gerontology 1996;42:155-162
The study

- TB prevalence higher in
- Men
- Age < 70
- No previous history of hospitalization
- Habit of eating their meals with other residents
II - Characteristics of elderly patients

- Immunity
- Clinical features
- Presentation
- Treatment outcomes
Immunity

• The capacity to control an infection with M tuberculosis is dependent on the generation of a robust antigen-specific CD4+ T-cell response and the production of Th1-associated cytokines IFN-gamma, IL-12 and TNF

  Immunology of tuberculosis

• Impaired generation of antigen-specific CD4+ T-cell immunity is observed (Mouse model)

  The influence of age on immunity to infection with Mycobacterium tuberculosis
  Immunological Reviews Vol. 205:229-243, 2005
Immunity

- Major component of the immune system affected by senescence is the T cell-mediated response
- Dermal reactivity to tuberculin must be evaluated with caution

Anergy in active pulmonary tuberculosis: a comparison between positive and negative reactors and an evaluation of 5TU and 250 skin test doses
Chest 1980;77:32-7

- False-negative tuberculin test result was partly explained by anergy
- Booster-effect – positive tuberculin skin test (reaction > 10mm) in comparison with the first skin test reaction
Immunity

• To ensure that a potentially false-negative result is recognized. Retest within 2/52
• For the potential booster effect, may warrant CXR
Clinical features

• Tuberculosis in older patients can present atypically
  The challenge and unique aspects of tuberculosis in older patients

• Approximately 75% of elderly patients with tuberculosis
disease manifest lung involvement
  Does aging modify pulmonary tuberculosis? A meta analytical review
  Chest 1999;116:961-7

• In a local study, 81.8% of the older subjects (>= 65) had
  pulmonary TB alone, in comparison with 76.0% of younger
  subjects (p = 0.035)
  Tuberculosis in Older People: A Retrospective and Comparative Study from Hong Kong
  JAGS 50:1219-1226, 2002
Clinical features, of the local study

- The remaining cases, extrapulmonary manifestation
- Pleural effusion (13.6% vs 9.7%)
- Extrathoracic lymphadenopathy (3.9% vs 13.6%)

Tuberculosis in Older People: A Retrospective and Comparative Study from Hong Kong
JAGS 50:1219-1226, 2002
## Presentation, local study

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Age≥65 (n=457)</th>
<th>Age&lt;65 (n=413)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>310(67.8%)</td>
<td>266(64.4%)</td>
<td>.286</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>80(17.5%)</td>
<td>88(21.3%)</td>
<td>.156</td>
</tr>
<tr>
<td>Chest pain</td>
<td>47(10.3%)</td>
<td>59(14.3%)</td>
<td>.072</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>111(24.3%)</td>
<td>37(9%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Fever</td>
<td>66(14.4%)</td>
<td>69(16.7%)</td>
<td>.357</td>
</tr>
<tr>
<td>Weight loss</td>
<td>107(23.4%)</td>
<td>74(17.9%)</td>
<td>.046</td>
</tr>
<tr>
<td>Sweating</td>
<td>26(5.7%)</td>
<td>33(8%)</td>
<td>.178</td>
</tr>
<tr>
<td>Malaise</td>
<td>76(16.6%)</td>
<td>21(5.1%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>18(3.9%)</td>
<td>56(13.6%)</td>
<td>&lt;.001</td>
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</table>
Presenting symptoms, Taiwan study

<table>
<thead>
<tr>
<th></th>
<th>Age ≥ 60 year (n = 83)</th>
<th>Age &lt; 60 year (n = 74)</th>
<th>OR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>74 (89.2)</td>
<td>68 (91.9)</td>
<td>0.725 (0.245–2.145)</td>
<td>0.561</td>
</tr>
<tr>
<td>Expectoration</td>
<td>54 (65.1)</td>
<td>58 (78.4)</td>
<td>0.514 (0.252–1.049)</td>
<td>0.065</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>9 (10.8)</td>
<td>15 (20.3)</td>
<td>0.478 (0.196–1.170)</td>
<td>0.101</td>
</tr>
<tr>
<td>Weight loss</td>
<td>26 (31.3)</td>
<td>26 (35.1)</td>
<td>0.842 (0.433–1.638)</td>
<td>0.613</td>
</tr>
<tr>
<td>Fever</td>
<td>26 (31.3)</td>
<td>17 (23.0)</td>
<td>1.529 (0.750–3.120)</td>
<td>0.241</td>
</tr>
<tr>
<td>Night sweats</td>
<td>7 (8.4)</td>
<td>4 (5.4)</td>
<td>1.612 (0.452–5.743)</td>
<td>0.458</td>
</tr>
<tr>
<td>Anorexia</td>
<td>21 (25.3)</td>
<td>13 (17.6)</td>
<td>1.589 (0.731–3.456)</td>
<td>0.240</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (10.8)</td>
<td>3 (4.1)</td>
<td>2.878 (0.749–11.065)</td>
<td>0.110</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>26 (31.3)</td>
<td>13 (17.6)</td>
<td>2.140 (1.004–4.565)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Data are presented as No. (%) unless otherwise indicated.
Radiological features, of the local study

<table>
<thead>
<tr>
<th>CXR finding</th>
<th>Age &gt;=65 (n=429)</th>
<th>Age &lt;65 (n=372)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Mod/extensive</td>
<td>274(63.9%)</td>
<td>138(37.1%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lower zone involvement</td>
<td>67(15.6%)</td>
<td>30(8.1%)</td>
<td>.001</td>
</tr>
<tr>
<td>Cavity</td>
<td>63(14.7%)</td>
<td>66(17.7%)</td>
<td>.240</td>
</tr>
<tr>
<td>Mass</td>
<td>43(10.0%)</td>
<td>43(11.6%)</td>
<td>.484</td>
</tr>
<tr>
<td>Acinar shadow</td>
<td>369(86.0%)</td>
<td>337(90.6%)</td>
<td>.046</td>
</tr>
<tr>
<td>Collapse</td>
<td>27(6.3%)</td>
<td>12(3.2%)</td>
<td>.065</td>
</tr>
<tr>
<td>Effusion</td>
<td>51(11.9%)</td>
<td>34(9.1%)</td>
<td>.208</td>
</tr>
<tr>
<td>Miliary</td>
<td>18(4.2%)</td>
<td>7(1.9%)</td>
<td>.060</td>
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Moderate: Radiographic extent greater than that of RUL
Extensive: Radiographic extent greater than that of one lung
## Radiological features, Taiwan study

<table>
<thead>
<tr>
<th></th>
<th>Age ≥ 60 year (n = 83)</th>
<th>Age &lt; 60 year (n = 74)</th>
<th>OR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right upper field</td>
<td>58 (69.9)</td>
<td>51 (68.9)</td>
<td>1.046 (0.530–2.065)</td>
<td>0.896</td>
</tr>
<tr>
<td>Right lower field</td>
<td>52 (62.7)</td>
<td>34 (45.9)</td>
<td>1.973 (1.043–3.734)</td>
<td>0.036</td>
</tr>
<tr>
<td>Left upper field</td>
<td>52 (62.7)</td>
<td>47 (63.5)</td>
<td>0.964 (0.503–1.845)</td>
<td>0.911</td>
</tr>
<tr>
<td>Left lower field</td>
<td>51 (61.4)</td>
<td>30 (40.5)</td>
<td>2.338 (1.231–4.437)</td>
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<tr>
<td>Normal</td>
<td>3 (3.6)</td>
<td>6 (8.1)</td>
<td>0.425 (0.102–1.764)</td>
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<tr>
<td>Nodule</td>
<td>39 (47.0)</td>
<td>34 (45.9)</td>
<td>1.043 (0.556–1.955)</td>
<td>0.896</td>
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<tr>
<td>Consolidation</td>
<td>66 (79.5)</td>
<td>56 (75.7)</td>
<td>1.248 (0.588–2.648)</td>
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<td>Infiltration</td>
<td>73 (88.0)</td>
<td>63 (85.1)</td>
<td>1.275 (0.508–3.199)</td>
<td>0.605</td>
</tr>
<tr>
<td>Cavity</td>
<td>19 (22.9)</td>
<td>37 (50.0)</td>
<td>0.297 (0.150–0.589)</td>
<td>&lt;0.001</td>
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<td>Atelectasis</td>
<td>12 (14.5)</td>
<td>5 (6.8)</td>
<td>2.332 (0.781–6.969)</td>
<td>0.121</td>
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<tr>
<td>Pleural effusion</td>
<td>19 (22.9)</td>
<td>7 (9.5)</td>
<td>2.842 (1.119–7.215)</td>
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aData are presented as No. (%) unless otherwise indicated
Complications, HK

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Age&gt;=65 (n=457)</th>
<th>Age&lt;65 (n=413)</th>
<th>P-value</th>
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<tr>
<td>Hepatic dysfunction</td>
<td>81(17.7%)</td>
<td>38(9.2%)</td>
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<td>Skin rash</td>
<td>60(13.1%)</td>
<td>55(13.3%)</td>
<td>.935</td>
</tr>
<tr>
<td>GI intolerance</td>
<td>54(11.8%)</td>
<td>40(9.7%)</td>
<td>.312</td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>14(3.1%)</td>
<td>13(3.1%)</td>
<td>.943</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>6(1.3%)</td>
<td>1(0.2%)</td>
<td>.127</td>
</tr>
<tr>
<td>CNS toxicity</td>
<td>3(0.7%)</td>
<td>1(0.2%)</td>
<td>.626</td>
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<tr>
<td>Hematological abn</td>
<td>2(0.4%)</td>
<td>2(0.5%)</td>
<td>.649</td>
</tr>
<tr>
<td>Ophthalmologic toxicity</td>
<td>13(2.8%)</td>
<td>7(1.7%)</td>
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## Treatment outcomes, HK

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Age $\geq$65, n=457, (%)</th>
<th>Age &lt;65, n=413, (%)</th>
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<tbody>
<tr>
<td>Cured</td>
<td>312(68.3)</td>
<td>351(85.0)</td>
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<tr>
<td>Treatment completed</td>
<td>19(4.2)</td>
<td>10(2.4)</td>
</tr>
<tr>
<td>Died</td>
<td>73(16.0)</td>
<td>4(1.0)</td>
</tr>
<tr>
<td>Treatment interrupted</td>
<td>23(5.0)</td>
<td>21(5.1)</td>
</tr>
<tr>
<td>Transferred out</td>
<td>6(1.3)</td>
<td>12(2.9)</td>
</tr>
<tr>
<td>Still on treatment</td>
<td>24(5.3)</td>
<td>15(3.6)</td>
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P < 0.005 except Treatment interrupted
### Table 5: Treatment outcomes after 1 year from the initiation of anti-TB treatment in elderly and young patients with pulmonary TB

<table>
<thead>
<tr>
<th></th>
<th>Age ≥ 60 year (n = 83)</th>
<th>Age &lt; 60 year (n = 74)</th>
<th>OR (95% CI)</th>
<th>p-Value</th>
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</thead>
<tbody>
<tr>
<td>Cure</td>
<td>21 (25.3)</td>
<td>24 (32.4)</td>
<td>0.706 (0.352–1.413)</td>
<td>0.324</td>
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<tr>
<td>Treatment completed</td>
<td>33 (39.8)</td>
<td>40 (54.1)</td>
<td>0.561 (0.298–1.058)</td>
<td>0.073</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Died</td>
<td>22 (26.5)</td>
<td>3 (4.1)</td>
<td>8.536 (2.436–29.907)</td>
<td>0.000</td>
</tr>
<tr>
<td>Default</td>
<td>2 (2.4)</td>
<td>4 (5.4)</td>
<td>0.432 (0.077–2.431)</td>
<td>0.422</td>
</tr>
<tr>
<td>Transfer out</td>
<td>4 (4.8)</td>
<td>1 (1.4)</td>
<td>3.696 (0.404–33.838)</td>
<td>0.371</td>
</tr>
<tr>
<td>Still on treatment</td>
<td>1 (1.2)</td>
<td>2 (2.7)</td>
<td>0.439 (0.039–4.943)</td>
<td>0.602</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%) unless otherwise indicated*
Patients with and without immunocompromising comorbidities, are they different?

- Comorbidity group N = 78
- Non-comorbidity group N = 104
- All pulmonary TB
- Age 65-90
- Common immunocompromising conditions:
  - DM, ESRF requiring dialysis, chronic hepatitis B or C, liver cirrhosis, malignancy, immunosuppressive therapy, malnutrition, HIV and AIDS

Treatment Response and Adverse Reactions in Older Tuberculosis Patients with Immunocompromising Comorbidities
• No significant differences in the rates of drug-related side effects between groups, which is consistent with an earlier study

Clinical features of immunocompromised and nonimmunocompromised patients with pulmonary tuberculosis
J Infect Chemother 2007;13:405-10
III – Diagnostic methods

• The gold standard of tuberculosis is the detection of *Mycobacterium tuberculosis*

• However, culture growth of *M. tuberculosis* may take two or more weeks on average
Diagnostic methods

• Imaging
• Microbiological
• Immunological
Radiological

• None of the radiological abnormalities seen in pulmonary tuberculosis are pathognomonic

• Primary tuberculosis – unilateral LN enlargement, parenchymal airspace consolidation, pleural effusion

• Reactivation tuberculosis – focal or patchy heterogeneous consolidation involving apical and posterior segments of the upper lobes and the superior segments of lower lobes, poorly defined nodules, linear opacities and cavitations

Pulmonary tuberculosis: up-to-date imaging and management
Radiological

- CXR is still most commonly used
- HRCT – more sensitive than CXR to identify early parenchymal lesions or mediastinal LN enlargement
- Active TB on CT – cavitations and parenchymal abnormalities and/or centrilobular nodules and tree-in-mud pattern

Pulmonary tuberculosis: up-to-date imaging and management
AJR Am. J. Roentgenol. 2008;191:834-44
 Radiological

• PET-CT as non-invasive method to monitor disease activity and responses to anti-TB chemotherapy
• In selected MDR and XDR TB

Usefulness of 18F-fluorodeoxyglucose positron emission tomography for diagnosing disease activity and monitoring therapeutic response in patients with pulmonary mycobacteriosis
Microbiological

• Currently 57% of global tuberculosis patients receive a bacteriological diagnosis
• Fluorescence microscopy of sputum more sensitive than ordinary light microscopy
• In order to increase sensitivity, 3 sputum specimens should be collected
### Microbiological

- **No sputum? Or, other samples**

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Amount</th>
<th>Application</th>
<th>Preservation/transport</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum</td>
<td>2–5 mL</td>
<td>A, B, C</td>
<td>Unprocessed</td>
<td>3× in the morning on an empty stomach</td>
</tr>
<tr>
<td>Induced sputum</td>
<td>2–5 mL</td>
<td>A, B, C</td>
<td>Unprocessed</td>
<td>Expectorotion following inhalation of 3% NaCl solution</td>
</tr>
<tr>
<td>Bronchial secretion or bronchoalveolar-lavage</td>
<td>2–5 mL</td>
<td>A, B, C, D</td>
<td>Unprocessed</td>
<td>BAL-ELISPOT should be performed on the day of sample collection</td>
</tr>
<tr>
<td>Gastric aspirate</td>
<td>&gt;2 mL</td>
<td>A, B, C</td>
<td>In 1–2 mL phosphate buffer</td>
<td>Only when sputum cannot be obtained and bronchoscopy (BAL) is not indicated</td>
</tr>
<tr>
<td>Biopsy, survival specimen (e.g., lymph nodes)</td>
<td>2 separate portions (1) and (2)</td>
<td>A, B, C, E</td>
<td>(1) In 0.9% NaCl for microbiological examination; (2) in formalin for histopathological examination</td>
<td>(1) Not in formalin</td>
</tr>
<tr>
<td>Pleural effusion, ascites</td>
<td>20 mL</td>
<td>A, B, C, D,</td>
<td>Unprocessed</td>
<td>ELISPOT should be performed on the day of sample collection</td>
</tr>
<tr>
<td>Cerebrospinal fluid</td>
<td>2–3 mL</td>
<td>A, B, C, D</td>
<td>Unprocessed</td>
<td>ELISPOT should be performed on the day of sample collection</td>
</tr>
<tr>
<td>Urine</td>
<td>30 mL</td>
<td>A, B, C</td>
<td>Unprocessed</td>
<td>– 3× – First specimen of urine in the morning – Fluid restriction the evening/night before</td>
</tr>
<tr>
<td>Stool</td>
<td>5–10 mL</td>
<td>A, B, C</td>
<td>Unprocessed</td>
<td>– 3× – Indicated only in immunosuppressed patients – Do not use EDTA blood</td>
</tr>
<tr>
<td>Blood</td>
<td>5–10 mL</td>
<td>A, B, C, D</td>
<td>Heperin- or lithium-citrate tubes</td>
<td>– Indicated only in immunosuppressed patients – Biopsy or aspirate for (1) not in EDTA or formalin</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>2 separate portions (1) and (2)</td>
<td>A, B, C, E</td>
<td>(1) In heparin- or lithium-citrate tubes; (2) air-dried smears and/or formalin preserved biopsies</td>
<td></td>
</tr>
</tbody>
</table>
Microbiological

• Liquid cultures are more rapid and sensitive than solid medium cultures
• Mean time to detection
• BACTEC MGIT960 12.9days
• BACTEC 460 15.0days
• Lowenstein Jensen solid medium 27days

Meta-analysis of BACTEC MGIT 960 and BACTEC 460 TB, with or without solid media, for detection of mycobacteria
Microbiological

• Novel diagnostic test using mycobacteriophages to identify *M. tuberculosis* from biological specimen
• Only 2 days of turnaround time
• High specificity (83-100%)
• But low sensitivity (21-88%)

Bacteriophage-based tests for the detection of *Mycobacterium tuberculosis* in clinical specimens: a systemic review and meta-analysis
BMC Infect. Dis. 2005;5:59
Microbiological

- M Tuberculosis-specific nucleic acid amplification
- Result available within one day
- Diagnostic accuracy is highly heterogeneous as amplification targets are not standardized
- Positive AFB smear sputum sensitivity > 95%
- Negative AFB smear sputum sensitivity not consistent, < 50% sensitivity according to one study

Bronchoalveolar lavage enzyme-linked immunospot for a rapid diagnosis of tuberculosis: a TBNET study
Immunological

- TST
- IGRA (Interferon-gamma release assays)
Immunological

- TST was developed by the Austrian paediatrician Clemens v. Pirquet as an allergic-test for the diagnosis

Diagnose der Tuberkulose im Kindesalter
Immunological

- TST reactions are measured 48-72 hours after antigen injection
- Overall sensitivity of TST for active tuberculosis is 77%
  
  Systemic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update

- Sensitivity dramatically impaired in elderly persons, in individuals with immunodeficiencies, being treated with steroids, or other immunosuppressive drugs, CRF, malnutrition, cancer, or overt form of tuberculosis
Immunological

- Specificity dependent on BCG vaccination status and immune status of the tested individual
- Cross-reactivity with positive reaction in exposure to NTM, M. bovis BCG vaccination
- TST induration reactions exceeding 15mm are likely related to tuberculosis or latent TB infection, irrespectively of BCG vaccination status

Influence of bacille Calmette-Guerin vaccination on size of tuberculin skin test reaction: to what size?
Immunological

- IGRA
- Related to antigens ESAT-6 and CFP-10
• QuantiFERON-Gold QFT-G
• Measuring IFN-gamma IU/mL

• T-SPOT.TB
• Counting the cells releasing IFN-gamma visualized as spots
Immunological

• Specificity of IGRA is high
• Sensitivity is rather variable between studies
• Unable to distinguish individuals with active tuberculosis from latent TB infection
Figure 1  Flow diagram for the diagnosis of tuberculosis in clinical practice. *NTM NAAT may be helpful, when available. # In accordance with WHO recommendations (WHO. Treatment of tuberculosis. Guidelines for national programmes. Geneva; 2003), clinical response to antibiotic therapy may be considered before further investigations; however, in countries of low TB incidence immediate further diagnosis with bronchoscopy can be indicated at this stage to better rule out other diseases. BAL, bronchoalveolar lavage; IGRA, interferon-γ release assay; MTB, *Mycobacterium tuberculosis;* NAAT, nucleic acid amplification test; NTM, non-tuberculous Mycobacteria; TB, tuberculosis; TBB, tubercle bacilli; TST, tuberculin skin test; WHO, World Health Organisation.
IV - DM & TB

- Risk ratio of tuberculosis in DM compared to non-DM was 3.47, in a South Korea study. Incidence of pulmonary tuberculosis among diabetics Tuber Lung Dis 1995;76:529-33

- A meta-analysis showed that diabetes increased the risk of tuberculosis infection regardless of background tuberculosis incidence or geographical region: DM+ve have an approximately 3-fold risk of developing active tuberculosis. Diabetes mellitus increase the risk of active tuberculosis: a systemic review of 13 observational studies PLoS Med 2008;5:e152
DM & TB

• The direct mechanism not clearly identified
• Reduced immunity may play a major role in increase in of tuberculosis in DM patients
• Reduced chemotaxis and oxidative killing potential

Infection and diabetes: the case for glucose control

• Hyperglycaemia is associated with a lower production of interferon-gamma and IL-12

Tuberculosis susceptibility of diabetic mice

• The level of IFN-gamma is negatively correlated with HbA1c level

The relation between diabetes mellitus and IFN-gamma, IL-12, and IL-10 productions by CD4+ alpha beta T cells and monocytes in patients with pulmonary tuberculosis
Kekkaku 1997;72:617-22
DM & TB

• Diabetic patients had more symptoms associated with tuberculosis infection than normal control on presentation
• Early microscopic negative conversion rate in diabetic patients was lower
• Higher treatment failure rate of 6-month’s medication

The effect of type 2 Diabetes mellitus on the presentation and treatment response of pulmonary tuberculosis

• Considering the association of tuberculosis and diabetes, screening for tuberculosis in those with diabetes should be considered, esp in the region with high tuberculosis incidence

Diabetes Mellitus and Tuberculosis
Diabetes Metab J 2013;37:249-251
DM & TB

• Diabetes is highly associated with mortality during the first 100 days of TB treatment (5-fold increased mortality among HIV uninfected DM patients)
  Diabetes is a strong predictor of mortality during tuberculosis treatment: a prospective Cohort study among tuberculosis patients from Mwanza, Tanzania
  Tropical Medicine and International Health Vol 18, No.7, pp822-829, Jul 2013

• No association of DM with fatality rate in another study
  Diabetes mellitus and tuberculosis: pattern of tuberculosis, two-month smear conversion and treatment outcomes in Guangzhou, China
  Tropical Medicine and International Health Vol 18, No.11, pp1379-1385, Nov 2013
V - Hepatitis B and TB treatment

• First line drugs for anti-TB Rx
• Isoniazid
• Rifampicin
• Pyrazinamide
• Streptomycin / Ethambutol
Hepatitis B and TB

- A study from South Korea
- Inactive HBsAg carrier
- HBsAg +ve
- HBeAg –ve
- HBV DNA < $10^5$ copies per ml

Inactive Hepatitis B surface antigen carrier state and hepatotoxicity during antituberculosis chemotherapy
Chest 2005;127:1304-1311
The study

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>HBsAg Carriers (n = 110)</th>
<th>Control Subjects (n = 97)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>44.0 ± 15.3</td>
<td>44.0 ± 15.8</td>
<td>0.982</td>
</tr>
<tr>
<td>Male sex</td>
<td>58 (53)</td>
<td>58 (60)</td>
<td>0.307</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21.5 ± 3.5</td>
<td>21.6 ± 2.9</td>
<td>0.876</td>
</tr>
<tr>
<td>Baseline AST, IU/L</td>
<td>21.2 ± 7.1</td>
<td>19.5 ± 7.0</td>
<td>0.084</td>
</tr>
<tr>
<td>Baseline ALT, IU/L</td>
<td>19.3 ± 8.3</td>
<td>17.7 ± 8.5</td>
<td>0.190</td>
</tr>
<tr>
<td>Baseline albumin, g/dL</td>
<td>4.0 ± 0.8</td>
<td>4.0 ± 0.6</td>
<td>0.627</td>
</tr>
<tr>
<td>Site of TB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary TB</td>
<td>63 (57)</td>
<td>60 (62)</td>
<td>0.311</td>
</tr>
<tr>
<td>Pulmonary and extrapulmonary TB</td>
<td>5 (5)</td>
<td>8 (8)</td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary TB</td>
<td>42 (38)</td>
<td>29 (30)</td>
<td></td>
</tr>
<tr>
<td>Initial treatment regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH, RIF, EMB, PZA</td>
<td>93 (85)</td>
<td>82 (85)</td>
<td>0.999</td>
</tr>
<tr>
<td>INH, RIF, EMB</td>
<td>17 (15)</td>
<td>15 (15)</td>
<td></td>
</tr>
</tbody>
</table>

*Values given as mean ± SD or No. (%), unless otherwise indicated. TB = tuberculosis; INH = isoniazid; RIF = rifampin; EMB = ethambutol; PZA = pyrazinamide.
The study

- Treatment
- 2HRZM + 4 HRM
- Hepatotoxicity defined as
  - AST/ALT > 120
  - 120-200 mild
  - 200-500 moderate
  - >500 severe
<table>
<thead>
<tr>
<th>Variables</th>
<th>HBsAg Carriers (n = 110)</th>
<th>Control Subjects (n = 97)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal liver function during treatment</td>
<td>38 (34)</td>
<td>19 (20)</td>
<td>0.016</td>
</tr>
<tr>
<td>Transient transaminase elevation</td>
<td>29 (26)</td>
<td>15 (16)</td>
<td>0.056</td>
</tr>
<tr>
<td>Drug-induced hepatotoxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0 (0)</td>
<td>4 (4)</td>
<td>0.230</td>
</tr>
<tr>
<td>Moderate</td>
<td>8 (7)</td>
<td>2 (2)</td>
<td>0.218</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*Values given as No. (%), unless otherwise indicated.
The study

- No significant differences observed with regard to
- Age
- Sex
- BMI
- Baseline AST/ALT
- Albumin Level
- Inclusion of PZA
The study

### Table 3—Factors Associated With Drug-Induced Hepatotoxicity During Antituberculosis Treatment*

<table>
<thead>
<tr>
<th>Factors</th>
<th>DIH Group (n = 13)</th>
<th>No DIH Group (n = 194)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 35 yr</td>
<td>8 (62)</td>
<td>133 (69)</td>
<td>0.599</td>
</tr>
<tr>
<td>Female sex</td>
<td>9 (69)</td>
<td>82 (42)</td>
<td>0.058</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.1 (18.1–30.2)</td>
<td>21.3 (14.7–31.6)</td>
<td>0.653</td>
</tr>
<tr>
<td>Baseline AST, IU/L</td>
<td>19 (10–38)</td>
<td>20 (2–40)</td>
<td>1.000</td>
</tr>
<tr>
<td>Baseline ALT, IU/L</td>
<td>13 (10–40)</td>
<td>16 (6–40)</td>
<td>0.121</td>
</tr>
<tr>
<td>Baseline albumin, g/dL</td>
<td>4.2 (3.2–8.3)</td>
<td>4.0 (1.1–7.2)</td>
<td>0.409</td>
</tr>
<tr>
<td>Initial treatment regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INH, RIF, EMB, PZA</td>
<td>12 (92)</td>
<td>163 (84)</td>
<td>0.697</td>
</tr>
<tr>
<td>INH, RIF, EMB</td>
<td>1 (8)</td>
<td>31 (16)</td>
<td></td>
</tr>
</tbody>
</table>

*Values given as No. (%) or median (range), unless otherwise indicated. DIH = drug-induced hepatitis. See Table 1 for abbreviations not used in the text.
Review of anti-tuberculosis drug-induced hepatotoxicity

- Isoniazid
- Rifampicin
- Pyrazinamide
- Are potentially hepatotoxic

- No hepatotoxicity has been described for ethambutol or streptomycin
<table>
<thead>
<tr>
<th>Grade</th>
<th>WHO definition of hepatotoxicity</th>
<th>ALT values</th>
<th>ULN values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (mild)</td>
<td>&lt;2.5 times ULN (ALT 51–125 U/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (mild)</td>
<td>2.5–5 times ULN (ALT 126–250 U/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 (moderate)</td>
<td>5–10 times ULN (ALT 251–500 U/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 (severe)</td>
<td>&gt;10 times ULN (ALT &gt; 500 U/L)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; ULN, upper limit of normal, i.e. 50 U/L.
• The incidence of ATDH during standard multidrug TB treatment has been variably reported as between 2% and 28%, depending on the investigators’ definition of hepatotoxicity and the population studied

  Antituberculosis drug-induced hepatotoxicity: Concise up-to-date review

• It was reported that pyrazinamide causes more hepatotoxicity than isoniazid or rifampicin

  Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis
  Am J Respir Crit Care Med.2003;167:1472-7
• Hepatic drug reactions usually occur in the first 2 months of treatment but may happen at any moment during the treatment period.
• Clinical, biochemical and histological features of ATDH are hard to distinguish from viral hepatitis
• Signs and symptoms
  • Jaundice
  • Abdominal pain
  • Nausea and vomiting
  • Malaise
Isoniazid

• Predominant metabolic pathway of isoniazid metabolism is acetylation by the hepatic enzyme NAT2
• Human acetylation rate is genetically determined
• But INH-induced liver injury is considered idiosyncratic

Drug-induced hepatotoxicity
Rifampicin

• The major pathway is desacetylation + separate hydrolysis
• May induce hepatocellular dysfunction early in the treatment, which resolves without discontinuing the drug
• Mechanism of toxicity is unknown and is unpredictable
• No toxic metabolite identified
• A potent inducer of the hepatic CYP450 system in the liver and intestine, thereby increasing metabolism of other compounds
Pyrazinamide

• Metabolized by xanthine oxidase
• Does not induce the enzymes responsible for its metabolism
• Mechanism of toxicity is unknown
Risk factors for hepatotoxicity

- > 60yo
- Female
- Low BMI
- Malnutrition
- Hepatitis B and C coinfection
- Alcoholism
• Dosing schedule (Daily vs thrice-weekly) TB treatment has little impact

  Standard anti-tuberculosis treatment and hepatotoxicity: do dosing schedules matter?
  Eur Respir J 2007;29:347-51

• It is important to note that asymptomatic transaminase elevations occur in 20% of patients treated with standard anti-TB regimens prior to treatment or immediately after the start of treatment. Usually these elevations resolve spontaneously.
Prophylaxis

- A small study from Iran N = 60, aged >= 60
- An open-label study
- Standard anti-TB Rx (HRZM) vs NAC + standard anti-TB Rx group
- Viral hepatitis, alcoholism, chronic kidney and lung diseases, abnormal pre-treatment liver functions level, HIV, hepatotoxic drug use, moribund state excluded
- NAC 600mg bd
- LFT taken at wk 1 and 2

Protective effect of N-acetylcysteine on antituberculosis drug-induced hepatotoxicity
Eur J Gastroenterol Hepatol 2010 Oct;22(10):1235-8
Table 1  Patient demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Mean age (years) ± SD</td>
<td>73.41 ± 6.72</td>
<td>74.46 ± 7.83</td>
</tr>
<tr>
<td>Sex ratio (male/female)</td>
<td>17/15</td>
<td>14/14</td>
</tr>
<tr>
<td>Mean weight (kg) ± SD</td>
<td>56.12 ± 9.97</td>
<td>54.16 ± 14.96</td>
</tr>
<tr>
<td>Origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iranian</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td>Non-Iranian</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2  Mean ± SD values of aspartate aminotransferase, alanine aminotransferase, and bilirubin levels in groups I and II

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>Group I (n=32)</th>
<th>Group II (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>27.47 ± 13.55</td>
<td>27.04 ± 16.24</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>22.84 ± 14.35</td>
<td>22.50 ± 18.57</td>
</tr>
<tr>
<td>Bilirubin total (mg/dl)</td>
<td>0.75 ± 0.39</td>
<td>0.68 ± 0.32</td>
</tr>
<tr>
<td>First week after treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>99.44 ± 150.11*</td>
<td>27.68 ± 13.79</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>65.78 ± 88.64*</td>
<td>20.96 ± 11.95</td>
</tr>
<tr>
<td>Bilirubin total (mg/dl)</td>
<td>1.13 ± 0.91**</td>
<td>0.61 ± 0.29</td>
</tr>
<tr>
<td>Second week after treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>57.22 ± 75.81*</td>
<td>27.32 ± 13.11</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>58.09 ± 86.18*</td>
<td>21.53 ± 9.56</td>
</tr>
<tr>
<td>Bilirubin total (mg/dl)</td>
<td>0.73 ± 0.40</td>
<td>0.58 ± 0.31</td>
</tr>
</tbody>
</table>

*P<0.05.  
**P<0.01.
Outcome of the case

• Normal LFT in 10.2013
• Good compliance to treatment according to GOPD notes
What should we tell patient’s family?

- TB can be treated
- A long process
- Drug compliance is important (Default rate 5%)
- No need for isolation after discharge
- Live together as usual
- Avoid TCM
- Infected individuals have low probability of developing into active disease
The end
Interrupted Rx

- Initial phase, cut off 14d
- > 14d, restart

- Continuation phase
- Completed 80% already, sputum smear –ve, ok
- < 80% completed + interruption < 3/12
- Culture –ve < completed Rx within 9/12
- Culture +ve < Restart with 4 drug Rx + sensitivity test
- < 80% completed + interruption > 3/12 + culture -ve
- 4 drug Rx restarted + total 9/12 Rx