Clinical Crossroads in TB Management

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A 35-year-old man, previously healthy, had productive cough and low-graded fever for 2 weeks. Crackles are heard at left upper lung field. Three consecutive sputum smears for AFB are negative.

1. Antibiotic, CXR in 2 weeks
2. Repeat AFB for 3 days
3. Chest CT scan
4. Tuberculin skin test
5. Start anti-TB drugs
A 60-year-old woman, previously healthy, presented with hemoptysis. She smoked 25 pack-years. Sputum smears were negative. Interferon gamma release assay was positive. Her symptoms did not improve after 2 months of HRZE, the CXR has no significant change.

1. Slow response of drug-sensitive TB
2. Drug-resistant TB
3. Lung cancer
4. Superimposed infection
5. Aspergilloma
A 40-year-old man, healthcare worker, presented with fever, cough, and weight loss for 1 month. Sputum smears were positive. His symptoms improved dramatically after 2 months of HRZE, but the smears still be positive.

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2. Drug-resistant TB
3. Paradoxical response
4. Drug reaction
5. Non-tuberculous mycobacterial infection
A 50-year-old man, livestock worker, presented with nonproductive cough, right cervical lymphadenopathy, and fever for 4 weeks. Sputum smears were positive. His symptoms did not improve with worsen CXR and the smears did not converted after 2 months of HRZE.

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2. Continue working with N-95 mask
3. Medical rest for 2 weeks
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A 65 year-old woman (BW 55 kg) was diagnosed to be smear-positive pulmonary TB treated with isoniazid 300 mg/d, rifampicin 600 mg/d, pyrazinamide 1,500 mg/d, and ethambutol 800 mg/d once daily before bedtime. At 1 week, his symptoms are improved, but nausea-vomiting is noted for 2 hours after taking the drugs with no additional abnormality.

1. Split the drugs into 3 times after meal
2. Reassure, antiemetic, taking just after supper
3. Discontinue all drugs until the symptoms subside
4. Discontinue isoniazid, rifampicin, and pyrazinamide
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A 65 year-old woman (BW 55 kg) was diagnosed to be smear-positive pulmonary TB, developed GI irritation from anti-TB drugs (H300, R600, Z1,500, E800). She further has fatigue and malaise.

LFT: Total/direct bilirubin 3.2/1.7 mg/dL, SGOT/SGPT 225/180 U/L (<40), alkaline phos. 200 U/L (<115)

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A 25-year-old woman, 16-week pregnancy, developed smear-positive pulmonary TB, and voluntary counselling test for HIV was positive. She interrupted treatment after improving from 8 weeks of HRZE. Three months later, the symptoms recurred along with positive smears.

1. Repeat previous regimen
2. Start standardized retreatment regimen (SHRZE)
3. Start empirical expanded regimen (SHRZE-Ofx)
4. Start standardized MDR-TB regimen (SZE-Ofx-PAS)
5. Start empirical MDR-TB regimen (Am-Ofx-Cs-Eto-PAS)
A 60-year-old man, previously healthy referred for treatment of MDR-TB. He received Category II treatment for 4 months with 5-kg weight gain and scanty cough. His CXR was markedly improved with few residual scarring, but smears were persistently positive. Initial DST revealed MDR-TB.

1. Discordance between in vitro DST and in vivo response
2. True MDR-TB
3. Specimen mislabeling
4. Laboratory cross contamination
5. Sampling variation
A 35-year-old man was diagnosed as smear-positive pulmonary TB last 2 years. He complete the standardized short course chemotherapy (SSCC) and was announced cure with residual scar in his CXR. One year later, he had blood-streak sputum for 1 week. Unremarkable change is noted in his present CXR. Sputum for AFB are are negative.

1. Infected bronchiectasis
2. Relapsed TB from drug sensitive strain
3. Relapsed TB from drug resistant strain
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5. Mycetoma
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What should we do when encounter smear-negative pulmonary TB

- Start anti-TB drugs if CXR reveal new cavity or adenopathy or effusion, miliary infiltrates
- Bronchoscopy ± CT scan if no suggestive CXR and harbor risk of lung cancer
- Otherwise, follow-up clinical symptoms and radiological findings every 3 months for 2 years

Consider risk for transmission and side effect of anti-TB drugs
A 40-year-old man, healthcare worker, presented with fever, cough, and weight loss for 1 month. Sputum smears were positive. His symptoms improved dramatically after 2 months of HRZE, but the smears still be positive.

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Conversion Rate after Treatment

- 53 patients, non-HIV, drug-sensitive TB
- Female 23, DM 4, cavity 31, extensive disease 14

<table>
<thead>
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<th></th>
<th>8 weeks</th>
<th>16 weeks</th>
<th>24 weeks</th>
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<td>58.5</td>
<td>88.7</td>
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<tr>
<td>PCR</td>
<td>47.1</td>
<td>79.2</td>
<td>92.5</td>
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Slow conversion in cavitary and extensive diseases

Slow Responder

• High mycobacterial load, usually encounter in cavitary disease
• Symptoms must be improved except for residual cough, CXR may improve or have no significant change
• Extend the extensive phase for one more month (both Cat I & II) and then maintain the same continuation phase
• In those with persistent positive cultures after 2 months, extension of continuation phase treatment for another 3 months can decrease relapse
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Non-tuberculous Mycobacteria (NTM)

- Environmental mycobacteria: soil, water
- Low grade pathogen, no animal-to-human or human-to-human transmission, preponderance in those with HIV co-infection
- Common extrapulmonary involvement: lymph node, skin and soft tissue, bone and joint
- Not dramatic response to medication, difficult to cure, and easy to relapse
- Usually response to: rifampicin, ethambutol, clarithromycin, quinolones, sulphonamides, doxycycline, streptomycin, amikacin, cefoxitin, imipenam
Diagnosis of NTM Lung Disease

• Pulmonary symptoms, nodular or cavitary opacities on CXR, or multifocal bronchiectasis with multiple small nodules
• Exclude other diagnoses
• One of microbiology criteria
  • Two separated positive sputum cultures
  • One positive bronchial washings or bronchoalveolar lavage culture
  • Compatible histology from lung biopsy plus positive culture (tissue, sputum, bronchial specimen)
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When will be safe for TB patient to resume social activity?

- **Condition**
  - Patient: no or scanty cough, sputum conversion or markedly decrease
  - Environment: proper ventilation and sun light
  - Surrounding people: children, aging or immunocompromised persons
- After treatment for 2 weeks, usually safe for resuming daily activity or elective surgery
- Elective surgery or long travel public service should be postponed until sputum conversion
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Risk factors for Anti-TB drugs Induced Hepatitis

1. Advanced age
2. Alcoholism
3. Previous significant liver abnormalitis
4. HBV, HCV, HIV infection
5. Malnourish
**Recommendation**

- Inform the patients before prescription
- Avoid alcohol and hepatotoxic agents
- Baseline LFT for those harbor risk
- Normal or near normal: repeat if symptomatic or every 2-4 weeks during the first 8 weeks
- Abnormal: close observe, repeat if symptomatic or twice weekly during the first 2 weeks and then every 2-4 weeks during the next 6 weeks
- Always aware for viral and alcoholic hepatitis
Recommendation

- Close follow-up in case suspected of TB hepatitis (infiltrative pattern of LFT)

- Criteria for diagnosis
  - Elevation of liver enzymes > 3 times with symptoms
  - Elevation of liver enzymes > 5 times without symptoms

- If develop hepatitis, weigh between disease severity and degree of liver impairment, consider to only discontinue or supplement other less hepatotoxic agents (ethambutol, quinolones, aminoglycosides)

- Isolate hyperbilirubinemia or cholestasis may resulted from rifampicin
Recommendation

- When symptoms subside and enzymes < 2 times with total bilirubin < 1.5 mg/dL, drug challenging
  - R: 150 → 300 → 450 mg/d, wait for 3 d
  - H: 100 → 200 → 300 mg/d, wait for 3 d
  - Z: 250 → 500 → 1,000 mg/d
- Add E when completely challenge and recount as first treatment day
- Alternative regimen
  - 6 RZE
  - 2 SHRE / 6 HR
  - 2 HRE / 7 HR
  - 2 HZE / 10 HE
  - 2 SH(O)E/ 16 H(O)E
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Paradoxical Response

- Abnormal expansion of previous lesions or appearance of new lesions after clinical response to anti-TB treatment for weeks or months
- Commonly encountered: lymphadenopathy, cranial tuberculoma, pleuritis
- Hypothesis: recovery of T cell function after treatment and antigen loading from destructed bacilli
- Well recognized in those with HIV co-infection treated with highly active anti-retroviral drugs (immune restoration syndrome)
Paradoxical Response

Baseline

Two weeks later
A 25-year-old woman, 16-week pregnancy, developed smear-positive pulmonary TB, and voluntary counselling test for HIV was positive. She interrupted treatment after improving for 8 weeks of HRZE. Three months later, the symptoms recurred along with positive smears.

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1. Discordance between in vitro DST and in vivo response
2. True MDR-TB
3. Specimen mislabeling
4. Laboratory cross contamination
5. Sampling variation
Categorization for Retreatment

- **Relapse**: previously complete or cure
- **Default**: interrupt for > 2 months after treated for > 1 months
- **Failure**:
  - Initial smear+ : persistent at 5 months, clinical and radiological not improved
  - Initial smear- : converted to positive at 2 months, clinical and radiological not improved, culture proven
Standardized Retreatment Regimen

• Smear-positive cases, drug susceptibility testing (DST) if available
• Category II (2 SHRZE + 1 HRZE + 5 HRE) for all (failure, default, relapse)
• Overall success rate is 60 % (80 % for relapse-default, 0-40 % for failure)
• Consideration
  • Prevalence of MDR-TB
  • Availability of laboratory for DST
  • System for containment
Managing Retreatment Cases

- **Relapse**
  - Category I if complete or cure under DOT
  - Category II if not

- **Default:** Category II

- **Failure:** Category IV
  - Standardized
  - Standardized + individualized
  - Empirical + individualized

More aggressive in those impaired immunity, poor respiratory reserved, life-threatening
Treatment after an Interruption

- Continue regimen if missed < 20% desired dose, restart if not
  - < 12 days in intensive phase
  - < 24 days in continuation phase
- Defaulter after complete 4 months, can be observed if asymptomatic, no or minimal abnormality in CXR, and negative smears
Definition of Drug Resistant TB

- Mono-resistance: infecting isolates of *M. tuberculosis* are confirmed to be resistant in vitro to one first-line antituberculosis drug
- Poly-resistance: resists to more than one first-line
- Multidrug-resistance: resists to at least isoniazid and rifampicin
- Drug resistance in those never received treatment or previously treated
## Prevalence of DR-TB in Thailand

<table>
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<tr>
<th>Year</th>
<th>Area</th>
<th>No.</th>
<th>Type</th>
<th>H</th>
<th>R</th>
<th>E</th>
<th>S</th>
<th>MDR-TB</th>
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<tr>
<td>1998</td>
<td>46 provinces</td>
<td>1,137</td>
<td>Initial</td>
<td>12.3</td>
<td>5.6</td>
<td>7.2</td>
<td>11.6</td>
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<td>1998</td>
<td>Chiang Rai</td>
<td>1,077</td>
<td>Initial</td>
<td>13.2</td>
<td>10.8</td>
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<td>1998</td>
<td>Chiang Rai</td>
<td></td>
<td>Acquired</td>
<td>44.4</td>
<td>42.4</td>
<td>19.2</td>
<td>37.7</td>
<td>33.8</td>
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</table>
Previously Treated TB Patients

• Probability of any resistance was over 4-fold higher and 10-fold for MDR-TB
• In some countries, re-treatment cases accounted for more than 20% of sputum smear-positive cases
• Globally, one third of MDR-TB cases had resistance to all 4 first-line drugs
• MDR-TB patients often live for several years before succumbing to the disease
Regimen Design

- At least 4 drugs which either certain or almost certain effectiveness
- Once-a-day dosing except for Eto, Cs, PAS, at least 6 days a week
- An injectable agent is used for a minimum of 6 months and remains persistent negative S or C
- Minimum duration of 18 months beyond culture conversion, under DOT
- Pyrazinamide can be used for the entire treatment

WHO. Guidelines for the programmatic management of drug-resistant tuberculosis, 2006
Extremely Drug Resistant TB

*Mycobacterium tuberculosis* that is resistant in vitro to at least isoniazid and rifampicin among first-line drugs, and at least three or more of the six main classes of second-line drugs (SLD)

- Aminoglycosides
- Polypeptides
- Fluoroquinolones
- Thioamides
- Cycloserine
- Para-aminosalicylic acid


Concerning in the Evaluation of DR-TB

- Wrong diagnosis
- Laboratory error
  - Sample mislabeling
  - Cross contamination
  - Technical assurance
- Discordance result
- Slow response
- Initial NTM infection or superimposed colonization
- Paradoxical response
A 35-year-old man was diagnosed as smear-positive pulmonary TB last 2 years. He completed the standardized short course chemotherapy (SSCC) and was announced cured with residual scar in his CXR. One year later, he had blood-streak sputum for 1 week. Unremarkable change is noted in his present CXR. Sputum for AFB are negative.

1. Infected bronchiectasis
2. Relapsed TB from drug sensitive strain
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5. Mycetoma
Causes of Hemoptysis after Cured TB

- Relapse TB
- Infected bronchiecstasis
- Mycetoma (aspergilloma)
- Scar tumor
- Rasmussen’s aneurysm
Management

- Repeat consecutive sputum smears
- Treatment as infected bronchiectasis, avoid quinolones
- Alert for lung cancer in those harbored risk
- In case with suggestive radiographic findings for mycetoma, request for aspergillus precipitin or sputum fungal cultures