Proposed Recommendation for the Treatment of Culture-Negative Pulmonary Tuberculosis

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Background

• ATS/CDC recommends at least 6 months of treatment (Tx) for pan-sensitive pulmonary TB (6–month Tx: 2HRZE, 4HR).¹

• For sputum culture-negative pulmonary TB, ATS/CDC allows shortening continuous phase to 2 months (4-month Tx, 2HRZE, 2HR).

• However, the guideline does not specify eligibility criteria for the 4-month Tx.
Background

• A previous review of TB cases in Maryland identified several patients with co-morbidities (e.g. diabetes), lung cavitation, or extrapulmonary disease who received the 4-month Tx.

• These patients may be at higher risk for relapse when given shortened regimen.

• Therefore, establishing eligibility criteria for a 4 month Tx will be helpful for TB providers.
Purpose

• Conduct review of “new” patients who received less than 6 months of Tx, and for TB relapse (recurrence) in all patients in this group.

• Conduct a literature review to develop eligibility criteria for use of 4-month Tx regimen for sputum culture-negative pulmonary TB disease in Maryland.
Review of TB cases in Maryland (2010-2013)

Less than 6-month Tx (N=19)

Culture negative (N=17)
- Pleural TB (N=1) Tx 3.9 months
- Pulmonary TB (N=16) Median 4.1 months range, 3.8-5.4 months

Culture not done (N=2)
- Children (N=1) Tx 5.8 months
- Pleural TB* (N=1) Tx 1.1 months

* This Pt was diagnosed with pleural TB in Nepal but no culture was done initially. Pt reported 4 months of Tx in Nepal and received only 1.1 months of Tx in the US
Characteristics of culture-negative pulmonary TB

• **9 of 16 had \( \geq 1 \) factor listed below**
  
  – Less than 2 months of PZA = 2
  – \(<80\%\) directly observed therapy (DOT) = 3 (45, 70, and 76%)
  – Diabetes mellitus = 0
  – Cavity = 2
  – Bilateral pulmonary lesions = 4
  – Malignancy = 2 (Parotid cancer and melanoma)
Relapse

• No relapse was identified based on the national database among 69 patients who received less than 6 months of Tx between 2008 and 2013.
Current evidence on 4-month regimen for culture-negative pulmonary TB
# Efficacy of 4-month regimen for culture-negative pulmonary TB

<table>
<thead>
<tr>
<th>Design</th>
<th>N</th>
<th>Treatment</th>
<th>Relapse rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT²</td>
<td>195</td>
<td>2HRZ/2HR (daily) or 2HR (3x/wks)</td>
<td>Daily 0/99 3x/wks 1.0% (1/96)</td>
</tr>
<tr>
<td>RCT³</td>
<td>325</td>
<td>4HRZS (3x/wks)</td>
<td>1% (4/325)</td>
</tr>
<tr>
<td>Prospective⁴</td>
<td>414</td>
<td>1HR (daily)/3HR (2x/wks)</td>
<td>1.2% (5/414)</td>
</tr>
<tr>
<td>Retrospective⁵</td>
<td>377</td>
<td>4HRZS (3x/wks)</td>
<td>2.7% (10/377)</td>
</tr>
</tbody>
</table>

RCT: Randomized control trial  
H: Isoniazid, R: Rifampicin, Z: Pyrazinamide, S: streptomycin
Limitation of the studies

• Limited information on co-morbidities, such as diabetes and malignancy.
• Small number of patients with lung cavitation or extensive pulmonary lesions.
• 2 RCTs excluded children <15 years and 2 other studies included only a few.
Our recommended exclusion criteria for 4-month regimen for sputum culture-negative pulmonary TB
Exclusion criteria

1. HIV infection
2. Children <15 years of age
3. Extrapulmonary tuberculosis
4. Diabetes mellitus
5. End-stage renal disease (ESRD)
6. Malignancy
7. Receiving immunosuppressive therapy
8. Lung cavitation
9. Extensive pulmonary lesions
10. Anti-TB treatment initiated before sample collection
11. Known exposure to fluoroquinolones (FQs) or other antibiotics active against TB for 7 days or more within one month, or any exposure within one week prior to specimen collection for culture
1. HIV infection; 2. Children; 3. Extrapulmonary TB

- These criteria are already defined in the current guidelines.\(^1\)

- Negative cultures are common in childhood TB and extrapulmonary TB. Nevertheless, at least 6 months of Tx is recommended.\(^6,7\)

• These co-morbidities impair cellular immunity.
• Several studies suggested higher risk for relapse associated with diabetes.\(^7\)
• End-stage renal disease, malignancy, and immunosuppressants are associated with an increased risk of active TB.\(^8\)-\(^{13}\)

Previous studies on 4-month Tx included only a few cases with these co-morbidities.
8. Lung Cavitation,
9. Extensive pulmonary lesions

• The increased risk for relapse due to lung cavitation and extensive pulmonary lesion.

• Cavitation
  – 3-fold higher risk of relapse. (RCT by Benator et al, 2002)\textsuperscript{14}

• Extensive pulmonary lesions
  – Lesions beyond one lobe was associated with 3-fold higher risk for relapse. (RCT by Tam et al, 2002)\textsuperscript{15}

Little data on the 4-month regimen in patients with cavitation or extensive pulmonary lesions.
10.-11. Anti-TB Tx initiated or exposure to FQs prior to specimen collection

• Sputum samples should be obtained before initiating anti-TB Tx because it can lead to negative cultures that would otherwise have been positive ("false-negative" cultures).

• Exposure to FQs may also lead to false-negative cultures.
  – Previous studies suggested delayed diagnosis of TB due to FQ exposure.\textsuperscript{16}
  – One study suggested FQs can mask active TB.\textsuperscript{17}
Limitation

• Almost no information is available on the efficacy of 4-month Tx for patients with co-morbidities.

• Our exclusion criteria are based on the limited data available and thus tried to define the safest approach possible.
Policy and practice implications

• The eligibility for 4-month Tx for culture-negative TB regimen is not clearly defined in the current guidelines. Guidance is needed to prevent inadequate treatment.

• Therefore we developed a working list of exclusion criteria for Maryland patients.

• Other states might be interested in adopting these criteria.

→Poster will be presented at the National TB Controllers Conference in Atlanta in June.
Acknowledgements

• The Center for TB control and Prevention, DHMH
  – Wendy Cronin
  – Lisa Paulos
  – Andrea Palmer
  – Maureen Donovan
  – Nancy Baruch

• The Johns Hopkins Medicine
  – Jonathan Golub
  – Kelly Dooley
  – Eric Lee Nuermberger
References


