Tuberculosis, Diabetes, Serum Drug levels
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University of Virginia
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No disclosures

Case
• 72 yo male DM, ESRD on hemodialysis MWF, former farmer, embalmer, and pipe smoker, cavitary upper lobe lesion (PET CT)
• Bronch 3+ AFB positive
• Treatment regimen?

Case
• 1.5 months
• Doing OK
• Sensitivities “low level” INH resistant in MGIT
• Serum drug levels for Rifampin
• Rifampin level 1.98 ug/ml (8-24)
• What would you do?

Case
• Rif 900qd, Moxi 400qd, PZA and EMB 3x week after HD
• 2.5 months
• Doing OK
• Still 3+ smear positive
• Cultures still positive
• What would you do?
• Re-send DST: same susceptibilities
• Re-send drug levels: RIF 16, Mox 2, PZA 18, Emb 3

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Overview
Diabetes increases the risk of progression to active TB disease (odds 2.4-8.3 compared to non-diabetics) and likely higher for poorly controlled diabetics
Diabetes/TB prevalence will increase globally
When a diabetic has TB, treatment outcomes are worse (compared to non-diabetics w TB)
Drug concentrations are suboptimal for most DM/TB patients
(a) The development of pulmonary tuberculosis in juvenile diabetes occurred more than ten times as frequently as among non-diabetic Massachusetts grade and high school children.

(b) Pulmonary tuberculosis developed in 8 per cent of diabetic patients within three years of recovery from coma.

Diabetes is the leading identified risk factor for TB in Virginia (10-15%)


<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>All Cases</td>
<td>272</td>
<td>284</td>
<td>281</td>
<td>225</td>
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<tr>
<td>IDU</td>
<td>53</td>
<td>54</td>
<td>56</td>
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<td>Non-IDU</td>
<td>219</td>
<td>230</td>
<td>225</td>
<td>175</td>
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</tbody>
</table>

Overall, number of TB patients needed to screen (with HbA1c) in order to detect one new case of diabetes was just 4.

Balakrishnan et al. PLoS ONE 2012

Overview

Diabetes increases the risk of progression to active TB disease (odds 2.4-8.3 compared to non-diabetics) and likely higher for poorly controlled diabetics

Diabetes/TB prevalence will increase globally

When a diabetic has TB, treatment outcomes are worse (compared to non-diabetics w TB)

Drug concentrations are suboptimal for most DM/TB patients
**No special presentation**

No difference in location of disease or lung cavitation

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Location</th>
<th>Participating</th>
<th>Lower lung more commonly involved?</th>
<th>More cavitation?</th>
<th>More diffuse involvement?</th>
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<tbody>
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<td>1993</td>
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<tr>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>1993</td>
<td>South Africa</td>
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<td>Yes</td>
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<tr>
<td>1993</td>
<td>Taiwan</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>1993</td>
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<tr>
<td>1993</td>
<td>All Stark et al.</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>


- In Maryland, odds of death were 6.5 times higher (p=0.039) for diabetics than non-diabetics with TB, even adjusting for HIV, age, weight, and foreign birth

- Time to sputum culture conversion was longer (49 days for diabetics vs 39 days for non-diabetics, p=0.09)

Diabetics in Indonesia more likely to be culture-positive at 6 months of treatment (22%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>No. (%) of patients with TB</th>
<th>No. (%) of patients without DM</th>
<th>Significance</th>
</tr>
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<tbody>
<tr>
<td>Alisjahbana et al.</td>
<td>2007</td>
<td>Indonesia</td>
<td>62/342 (18.1%)</td>
<td>22/152 (14.8%)</td>
<td>p=0.03</td>
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</table>

- 14.8% prevalence of undiagnosed DM in new TB patients

All cause mortality increased in diabetics during TB treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Population with DM</th>
<th>Population without DM</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker et al.</td>
<td>2011</td>
<td>USA</td>
<td>67/127 (52.8%)</td>
<td>3/9 (33.3%)</td>
<td>7.36 (95% CI: 1.95-28.4)</td>
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</table>

Worse outcomes.....What can we do about it?

TB disease:
- Extrapolmonary TB
- Extensive lung cavities
- Delayed presentation to care

Host factors:
- HIV
- Diabetes
- Malnutrition
- Silicosis

M. tuberculosis strain:
- Drug resistance
- Virulence

Start TB treatment → Delayed culture conversion → Death

Low plasma drug levels? → Acquired drug resistance

Relapse

Death

Many potential factors
- Extensive disease
- Drug resistance
- HIV
- Other comorbidities/smoking
- Low drug levels
- Diabetes

Summary
- Host are not as important as atypical presentations
- Drug levels are not what is important
Outcomes during treatment for Tb

Most do well (>90%)

Some don’t

Death < delayed cx conversion < “slow response” = persistent symptoms/smear+

Some patients don’t respond to treatment.

Many potential factors

- Extensive disease
- Drug resistance
- HIV
- Other comorbidities
  - Low drug levels
  - Diabetes

... P = NS

We have been routinely checking serum anti-TB drug concentrations in “slow responders” since ~2007 (thanks to some add’l funding)

- 14% of all Tb patients, defined as no improvement in sx or persistent smear +

- Diabetics were 6.3 times more likely to be slow responders (p<0.001) adjusted for age, gender, foreign birth, prior TB episodes, cavitary disease, HIV, alcohol and tobacco use.

- ~40% of diabetics

Among slow responders, diabetics had significantly lower serum rifampin levels (estimated peak C_{2h})


Majority of slow responders had low C_{2h} levels of INH and rifampin

Drug levels usually correct after first dose adjustment

82% had low levels to one of INH or RMP, hard to predict which one

Njiland et al. Emerg Infect Dis 2010

Low rifampin levels is not new

Rifampin exposure significantly reduced in diabetics from Indonesia

Low drug levels matter, at least in vitro

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean drug C_{2h} ± SD (μg/mL)</th>
<th>TDA ≤ 2.0</th>
<th>TDA &gt; 2.0</th>
<th>P value (t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>2.34 ± 1.2</td>
<td>2.56 ± 1.2</td>
<td>4.65 ± 3.2</td>
<td>0.05</td>
</tr>
<tr>
<td>Rifampin</td>
<td>0.92 ± 0.1</td>
<td>1.68 ± 0.93</td>
<td>0.03</td>
<td></td>
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<tr>
<td>Ethambutol</td>
<td>0.03 ± 0.07</td>
<td>6.65 ± 3.2</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>20.3 ± 7.5</td>
<td>28.0 ± 10.7</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

What is the right* dose of rifampin?

*In 1971 the dose of 10 mg/kg was arbitrarily chosen without a maximum tolerated dose study.

N= 68, smear positive PTB randomized to RIF 10, 20, 25, 30, 35 mg/kg

Adverse events: mostly grade 1

· Drop in culture was dose-related with most killing seen in 35 mg/kg group

· Mean $C_{\text{max}}$: 10 mg/kg $\rightarrow$ 7.4 mg/L; 30 mg/kg $\rightarrow$ 33.1 mg/L

It would not surprise me if eventually we use 900mg RIF routinely, or in high risk pts……..

In 2011, an initiative was started to measure isoniazid and rifampin levels (these 2 drugs only, PZA usually fine, EMB usually dropped) in all diabetics at 2 weeks of TB therapy (instead of waiting for ~40% to be slow responders)

The Virginia Algorithm


In TB Diabetes, if these early levels are low...

• Single incremental increases without rechecking
  – Easy, practical, generally increases the levels, patients are doing well at this point so we don’t go for broke

Early TDM in diabetics corrected low drug concentrations in the majority and may limit slow response

As expected many had low levels

• Of the 21 diabetics, 16 (76%) had a $C_{\text{max}}$ value below the expected range for isoniazid (mean 2.1±1.5 µg/ml; expected 3-5), rifampin (mean 6.6±4.3 µg/ml; expected 8-24) or both

Levels generally correct with single incremental increase

• 15 patients had follow-up concentrations after dose adjustment, all increased and 12 to the expected range (including all for rifampin).
  – In practice, what our algorithm does is shunt most diabetics to at least 3x weekly therapy during continuation phase, with INH 900/RIF 900, while keeping to a 6 month total duration
  – Patients do well, better than expected norms for TB

• 88% of diabetics with early TDM and pulmonary TB had sputum culture conversion <2 mos.

May limit the need for prolonged treatment and program resources

• Total statewide burden of slow response decreased from 1.6 patients/mo (40% diabetic) to 1.2 patients/mo (12.5% diabetic)

Acknowledgments

• UVA
  – Scott Heysell, Tania Thomas, Suzanne Stroup

• VDH
  – Jane Moore, Suzanne Keller, Debbie Staley, Denise Dodge

• Virginia TB Foundation
Key Messages for TB & Diabetes

Using this Flip Chart

- The flip chart is a patient centered tool, which promotes a health care worker to listen, respond and offer information to the patient's needs. This process promotes the development of the patient health care worker relationship.
- The topics are organized according to the standard TB and diabetes management plans. This supports patient monitoring and control for TB and diabetes control activities.
- Prompts for the health care worker are provided on each page of the flip chart to guide conversation. The prompts have a core question on each page to get the patient involved in TB and diabetes care and reinforce positive health behaviors.
- When using the flip chart hold the picture straight so people can see it clearly. The content is designed to be accessible for people who have visual impairments. Inserting the content in the patient’s own words is helpful to encourage discussion.
- Allow time for the patient to respond. This summarizes the key points and adds new.

About this Resource

TB outreach workers (ODW) and nurses have an opportunity to promote education and key messages to people over an extended time, during directly observed therapy (DOT). This resource was developed to support ODWs and nurses as they provide education to individual and community groups, 34 individuals and families. People diagnosed with TB should be checked for diabetes because having diabetes can affect the treatment and management of TB.

Educating Patients

This flip chart is designed to:
- Complement and reinforce TB education given at the time of TB diagnosis.
- Promote a patient centered approach to TB and diabetes education.

Conducting the TB and Diabetes Education Session

- Since TB and diabetes can cause great stress or worry, some educational information is provided rather than requiring home transitions.
- Give the flip chart to the patient and be ready to answer questions. For example, if it is unlikely that the patient will remember everything and/or may be left with the question, it is helpful to give the patient updates and bring the answer back for the patient.
- Avoid overwhelming patients with information or complex terms. Use clear, simple language and avoid medical jargon.
- This chart can be a resource for patients who may be newly diagnosed with TB and may feel their health is at risk. Education that TB is spread through:

Week 1

Help stop the spread of TB
How can you help stop the spread of TB?

This flip chart was adopted from the Australian Respiratory Council flip chart, "Key Messages for TB & Diabetes".