Tuberculosis, Diabetes, Serum Drug levels

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No disclosures

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

The New England Journal of Medicine

The Association of Diabetes and Tuberculosis

(a) The development of pulmonary tuberculosis in juvenile diabetes occurred more than ten times as frequently in normo-diabetic American white and high school children.

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

(c) The incidence of pulmonary tuberculosis in adult diabetics is increasing despite the general decrease of tuberculosis mortality with consequent reduction of contacts in the community.
No “special insidiousness” of presentation
No difference in location of disease or lung cavitation

<table>
<thead>
<tr>
<th>Study</th>
<th>Race</th>
<th>Study location</th>
<th>Pulmonary (n)</th>
<th>Lower lung zone (n)</th>
<th>Other lung zone (n)</th>
<th>Micro AFBs (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dooley et al.</td>
<td>Black</td>
<td>Virginia</td>
<td>250</td>
<td>100</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Austrian et al.</td>
<td>White</td>
<td>California</td>
<td>100</td>
<td>100</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Berrios et al.</td>
<td>White</td>
<td>Texas</td>
<td>100</td>
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</tr>
<tr>
<td>Restrepo et al.</td>
<td>White</td>
<td>Mexico</td>
<td>100</td>
<td>100</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

Attributable risk of TB from Diabetes > HIV in Texas/Mexico border

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>RR (95% CI)</th>
<th>AA (n)</th>
<th>AC (n)</th>
<th>IB (95% CI)</th>
<th>LC (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-49</td>
<td>2.0 (1.6-2.4)</td>
<td>60</td>
<td>40</td>
<td>1.0 (0.8-1.2)</td>
<td>30</td>
</tr>
<tr>
<td>50-64</td>
<td>1.5 (1.2-1.9)</td>
<td>60</td>
<td>40</td>
<td>1.0 (0.8-1.2)</td>
<td>30</td>
</tr>
<tr>
<td>65-74</td>
<td>1.0 (0.8-1.2)</td>
<td>60</td>
<td>40</td>
<td>1.0 (0.8-1.2)</td>
<td>30</td>
</tr>
<tr>
<td>75+</td>
<td>0.5 (0.3-0.7)</td>
<td>60</td>
<td>40</td>
<td>1.0 (0.8-1.2)</td>
<td>30</td>
</tr>
</tbody>
</table>

Restrepo et al. - BJR WHO 2011

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


<table>
<thead>
<tr>
<th>Year</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>505</td>
<td>510</td>
<td>515</td>
<td>520</td>
<td>525</td>
<td>530</td>
<td>535</td>
<td>540</td>
<td>545</td>
</tr>
<tr>
<td>Deaths</td>
<td>70</td>
<td>75</td>
<td>80</td>
<td>85</td>
<td>90</td>
<td>95</td>
<td>100</td>
<td>105</td>
<td>110</td>
</tr>
<tr>
<td>Rate</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>13</td>
<td>14</td>
<td>15</td>
<td>16</td>
<td>17</td>
<td>18</td>
</tr>
</tbody>
</table>
Screening for diabetes in new TB patients can be highly effective (India)

<table>
<thead>
<tr>
<th>Type of TB</th>
<th>Number of patients with DM tested</th>
<th>Number of patients with diabetes known</th>
<th>Number of patients with diabetes newly diagnosed</th>
<th>Sensitivity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New sputum</td>
<td>507</td>
<td>57</td>
<td>73</td>
<td>69%</td>
</tr>
<tr>
<td>End stage</td>
<td>32</td>
<td>4</td>
<td>7</td>
<td>96%</td>
</tr>
<tr>
<td>New extra-pulmonary</td>
<td>128</td>
<td>15</td>
<td>21</td>
<td>59%</td>
</tr>
<tr>
<td>Miliary</td>
<td>26</td>
<td>14</td>
<td>8</td>
<td>49%</td>
</tr>
<tr>
<td>Patients who failed</td>
<td>18</td>
<td>7</td>
<td>2</td>
<td>22%</td>
</tr>
<tr>
<td>Initial (\uparrow) deficit</td>
<td>26</td>
<td>3</td>
<td>7</td>
<td>14%</td>
</tr>
</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

Based on studies like this,

The national TB guidelines in India have changed to recommend screening for diabetes in all new TB cases

In the USA
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.

Outcomes during treatment for TB

Most do well (>90%)

Some don’t

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Case-DM</th>
<th>Case-DM/TB</th>
<th>Adj. (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male/fem</td>
<td>31/89</td>
<td>68/93</td>
<td>1.31, 1.07-1.61</td>
</tr>
<tr>
<td>Age &lt;60/60+</td>
<td>32/88</td>
<td>69/93</td>
<td>1.11, 1.02-1.27</td>
</tr>
<tr>
<td>Tuberculin test</td>
<td>positive</td>
<td>17/18</td>
<td>64/106</td>
</tr>
<tr>
<td>Culture result</td>
<td>positive</td>
<td>21/18</td>
<td>66/101</td>
</tr>
<tr>
<td>CD4&lt;200/mm³</td>
<td>32/88</td>
<td>69/93</td>
<td>1.34, 1.05-1.72</td>
</tr>
<tr>
<td>Time to sputum</td>
<td>positive</td>
<td>18/19</td>
<td>66/101</td>
</tr>
</tbody>
</table>

-14.8% prevalence of undiagnosed DM in new TB patients:
-1.0% prevalence of DM in new TB patients

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, $p=0.09$)

### All cause mortality increased in diabetics during TB treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Mortality by %</th>
<th>Difference</th>
<th>CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker, 2002 (R) USA</td>
<td>10/139 (7.3%)</td>
<td>4.85 (0.37, 7.63)</td>
<td></td>
</tr>
<tr>
<td>Dooley, 2008 (R) USA</td>
<td>11/116 (9.5%)</td>
<td>6.76 (0.77, 12.92)</td>
<td></td>
</tr>
<tr>
<td>Dooley, 2009 (R) USA</td>
<td>11/118 (9.2%)</td>
<td>6.80 (0.77, 12.82)</td>
<td></td>
</tr>
<tr>
<td>Wald, 2009 (R) Tanzania (26/345 (7.6%))</td>
<td>5.60 (0.37, 15.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td>4.66 (0.98, 9.11)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Weights are inverse-variance.


### Slower culture conversion in diabetics (without cavitary disease)

>20% of diabetics with non-cavitary pulmonary TB remain sputum positive at 3 months of treatment

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

Host factors:
- HIV
- Diabetes
- Malnutrition
- Silicosis

M. tuberculosis strain:
- Drug resistance
- Virulence?

Low plasma drug levels?
- Start TB treatment
- Delayed culture conversion
- Death
- Acquired drug resistance
- Relapse

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

Outcomes during treatment for Tb

Most do well (>90%)

Some don't
- Death < "slow response" = persistent symptoms/smear+

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

P = NS

~40% of diabetics

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

- 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
Majority of slow responders had low C\textsubscript{2hr} levels of INH and rifampin

<table>
<thead>
<tr>
<th>Drug</th>
<th>% within target</th>
<th>% below target</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>59%</td>
<td>41%</td>
</tr>
<tr>
<td>RMP</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>LHN</td>
<td>31%</td>
<td>69%</td>
</tr>
<tr>
<td>PZA</td>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

Heysell et al., Emerg Infect Dis, 2010

Drug levels usually correct after first dose adjustment

INH daily

- 300 mg
- 450 mg
- 600 mg

INH biweekly

- 300 mg
- 450 mg
- 600 mg

RMP daily

- 150 mg
- 300 mg
- 450 mg

RMP biweekly

- 150 mg
- 300 mg
- 450 mg

spans C\textsubscript{\text{2hr}} expected range

Heysell et al., Emerg Infect Dis, 2010

Determinants of anti-TB drug pharmacokinetics:

1. mg/kg dosing (weight categories, poor availability of drug in fixed-dose combinations in some settings)
2. Adherence
3. Drug interactions
4. Gastroenteritis
5. Malabsorption
6. Poor solubility
7. Host genetics
   - Genetic polymorphism of gut xenobiotic transport
   - Metabolism
8. Age
9. Gender

Heysell et al., Clin Res Reg Affairs 2008
Rifampin exposure significantly reduced in diabetics from Indonesia

![Graph showing rifampin exposure over time]


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 randomized to RIF 10, 20, 25, 30, 35 mg/kg

PK testing

Drop in culture

Mean Cmax 10 mg/kg → 7.4 mg/L; 30 mg/kg → 33.1 mg/L

Adverse events: mostly grade 1 (Boeree et al. CROI 2013)

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)
Instead of only self-report and prior DM diagnoses, we now recommend checking HbA1C on all >6.5: education/resource packet, referral <6.5: education/resource packet.

### Implementation of early TDM in diabetics was operationally feasible

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diabetes (early TDM) N=21</th>
<th>Slow response (standard TDM) N=14</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years ±SD</td>
<td>57 ±17</td>
<td>46 ±12</td>
<td>0.045</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>15 (71)</td>
<td>11 (79)</td>
<td>0.69</td>
</tr>
<tr>
<td>Prior episode of TB, n (%)</td>
<td>0</td>
<td>2 (14)</td>
<td>0.17</td>
</tr>
<tr>
<td>Pulmonary TB only, n (%)</td>
<td>17 (81)</td>
<td>8 (57)</td>
<td>0.95</td>
</tr>
<tr>
<td>Foreign born (N with confirmed status)</td>
<td>15 (79)</td>
<td>12 (92)</td>
<td>0.63</td>
</tr>
<tr>
<td>HIV infected (N with confirmed status)</td>
<td>0</td>
<td>1 (11)</td>
<td>0.43</td>
</tr>
<tr>
<td>Insulin dependence, n (%)</td>
<td>10 (48)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Days to TDM from treatment initiation, median days (IQR)</td>
<td>2 (1-7)</td>
<td>88 ±54</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Heysell et al. NTCA 2013

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

- Of the 21 diabetics, 16 (76%) had a C2hr 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

A proper target population

- 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/RIF 900, while keeping to a 6 month total duration.

No major toxicities reported

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

Better than expected norms for diabetes/TB

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

May limit the need for prolonged treatment and program resources

Heysell et al. NTCA 2013
Acknowledgments

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  — Scott Heysell, Tania Thomas, Dorothy Bunyan, Suzanne Stroup

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  — Jane Moore, Suzanne Keller, Debbie Staley, Denise Dodge

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