Tuberculosis and Diabetes

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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
No “special insidiousness” of presentation

No difference in location of disease or lung cavitation

No “special insidiousness” of signs and symptoms in the “tuberculous diabetic”

TB more frequent in those with poor diabetes control

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.

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

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.

<table>
<thead>
<tr>
<th>Year</th>
<th>Study Location</th>
<th>Participants (n)</th>
<th>Lower Lung More Commonly Involved</th>
<th>More Cavitory Lesions?</th>
<th>More Diffuse Involvement?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>With Diabetes</td>
<td>Without Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1974</td>
<td>USA</td>
<td>20</td>
<td>182</td>
<td>Yes</td>
<td>--</td>
</tr>
<tr>
<td>1980</td>
<td>South Africa</td>
<td>9</td>
<td>417</td>
<td>Yes</td>
<td>--</td>
</tr>
<tr>
<td>1992</td>
<td>Japan</td>
<td>311</td>
<td>71</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>1992</td>
<td>USA</td>
<td>20</td>
<td>20</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>1994</td>
<td>Turkey</td>
<td>37</td>
<td>37</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>1996</td>
<td>Cameroon</td>
<td>--</td>
<td>273</td>
<td>Yes</td>
<td>--</td>
</tr>
<tr>
<td>1997</td>
<td>Saudi Arabia</td>
<td>28</td>
<td>38</td>
<td>No</td>
<td>--</td>
</tr>
<tr>
<td>2001</td>
<td>Turkey</td>
<td>92</td>
<td>92</td>
<td>No5</td>
<td>No5</td>
</tr>
<tr>
<td>2000-01</td>
<td>Mexico</td>
<td>162</td>
<td>130</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2002</td>
<td>Saudi Arabia</td>
<td>187</td>
<td>306</td>
<td>Yes</td>
<td>--</td>
</tr>
<tr>
<td>2005</td>
<td>Taiwan</td>
<td>99</td>
<td>562</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2008</td>
<td>Taiwan</td>
<td>74</td>
<td>143</td>
<td>Yes</td>
<td>--</td>
</tr>
<tr>
<td>2009</td>
<td>Saudi Arabia</td>
<td>57</td>
<td>78</td>
<td>--</td>
<td>No</td>
</tr>
</tbody>
</table>

Dooley et al. Lancet ID 2009
### Attributable risk of TB from Diabetes > HIV in Texas/Mexico border

**Diabetes**
- NB suspects ≥ 20 years of age (n = 333)
- Participants excluded due to missing data:
  - TB ruled out (n = 41)
  - MOTT (n = 14)
  - Missing data required for TB or inconclusive TB diagnosis (n = 41)
  - Missing information required for diabetes classification (n = 6)

**Total TB cases for analysis (n = 233)**
- South Texas (n = 61), North-eastern Mexico (n = 172)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Diabetes</th>
<th>HIV Infection</th>
<th>AR(population) (%)</th>
<th>RR (95% CI)</th>
<th>AR(population) (%)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Texas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20+ (n=61)</td>
<td>2.7 (1.0-4.4)</td>
<td>63</td>
<td>26</td>
<td>17.8 (6.5-9.0)</td>
<td>94</td>
<td>5</td>
</tr>
<tr>
<td>20-34 (n=20)</td>
<td>0.9 (0.1-6.0)</td>
<td>-9</td>
<td>1</td>
<td>34.4 (8.0-147.7)</td>
<td>97</td>
<td>6</td>
</tr>
<tr>
<td>35-64 (n=32)</td>
<td>5.1 (2.5-10.2)</td>
<td>80</td>
<td>48</td>
<td>12.2 (2.9-50.9)</td>
<td>92</td>
<td>5</td>
</tr>
<tr>
<td>65+ (n=9)</td>
<td>1.7 (0.5-5.8)</td>
<td>41</td>
<td>22</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>NE Mexico (n=172)</td>
<td>3.1 (2.3-4.2)</td>
<td>68</td>
<td>24</td>
<td>16.0 (7.5-34.0)</td>
<td>94</td>
<td>3</td>
</tr>
</tbody>
</table>

Restrepo et al. *Bull WHO* 2011

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


**Table 15. Tuberculosis Cases by Selected Risk Factors: Virginia, 2008-2012**

<table>
<thead>
<tr>
<th>Occupation</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td><strong>Total Cases</strong></td>
<td>292</td>
<td>273</td>
<td>268</td>
<td>221</td>
<td>235</td>
<td></td>
</tr>
<tr>
<td><strong>Type of Residence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long Term Care</td>
<td>5</td>
<td>1.7</td>
<td>5</td>
<td>1.7</td>
<td>5</td>
<td>1.7</td>
</tr>
<tr>
<td>Prison/Jail</td>
<td>7</td>
<td>2.4</td>
<td>7</td>
<td>2.4</td>
<td>8</td>
<td>3.6</td>
</tr>
<tr>
<td>Homeless</td>
<td>4</td>
<td>1.4</td>
<td>5</td>
<td>1.8</td>
<td>6</td>
<td>2.6</td>
</tr>
<tr>
<td>Co-Morbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>40</td>
<td>13.7</td>
<td>37</td>
<td>13.6</td>
<td>37</td>
<td>13.6</td>
</tr>
<tr>
<td><strong>Substance Use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>19</td>
<td>6.5</td>
<td>21</td>
<td>7.7</td>
<td>23</td>
<td>8.6</td>
</tr>
<tr>
<td>IDU</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Non-IDU</td>
<td>6</td>
<td>2.1</td>
<td>6</td>
<td>2.2</td>
<td>4</td>
<td>1.5</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 TB patients whose DM status was ascertained (a)</th>
<th>Number with previously known DM (b)</th>
<th>Number of DM newly diagnosed (c)</th>
<th>Additional Yield (c/(b+c)*100)</th>
<th>Number needed to screen (NNS) (a−b)/c</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Smear Positive Pulmonary TB</td>
<td>307</td>
<td>87</td>
<td>70</td>
<td>45%</td>
<td>3.1</td>
</tr>
<tr>
<td>New Smear Negative Pulmonary TB</td>
<td>37</td>
<td>4</td>
<td>7</td>
<td>64%</td>
<td>4.7</td>
</tr>
<tr>
<td>New Extra-pulmonary TB</td>
<td>128</td>
<td>15</td>
<td>21</td>
<td>58%</td>
<td>5.3</td>
</tr>
<tr>
<td>Relapse</td>
<td>35</td>
<td>12</td>
<td>8</td>
<td>40%</td>
<td>3.3</td>
</tr>
<tr>
<td>Treatment after Failure</td>
<td>19</td>
<td>7</td>
<td>2</td>
<td>22%</td>
<td>6.0</td>
</tr>
<tr>
<td>Treatment after Default</td>
<td>26</td>
<td>3</td>
<td>7</td>
<td>70%</td>
<td>3.3</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.

Based on studies like this,

**The national TB guidelines in India have changed to recommend screening for diabetes in all new TB cases**
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
- Low drug levels
- Diabetes

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

Table 1. Treatment response and outcome of patients with tuberculosis (TB) with and without diabetes mellitus (DM).

<table>
<thead>
<tr>
<th>Period, variable</th>
<th>No. (%) of patients with TB</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With DM (n = 94)</td>
<td>Without DM (n = 56)</td>
<td>Crude OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td>Intensive phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFB negative</td>
<td>67 (71.3)</td>
<td>455 (80.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFB positive</td>
<td>17 (18.1)</td>
<td>64 (11.6)</td>
<td>2.14 (1.17-3.5)</td>
<td>1.00 (0.82-4.42)</td>
</tr>
<tr>
<td>No sputum sample available, hospital transfer, and or study default</td>
<td>8 (8.6)</td>
<td>31 (5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2 (2.1)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture result positive for Mycobacterium tuberculosis</td>
<td>7/41 (17.1)</td>
<td>69/372 (18.3)</td>
<td>0.92 (0.59-2.16)</td>
<td>0.90 (0.30-2.68)</td>
</tr>
<tr>
<td>End of treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFB negative</td>
<td>70 (74.5)</td>
<td>435 (80.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFB positive</td>
<td>3 (3.4)</td>
<td>17 (3.1)</td>
<td>1.46 (0.48-4.7)</td>
<td>1.05 (0.35-3.62)</td>
</tr>
<tr>
<td>No sputum sample available, hospital transfer, and or study default</td>
<td>18 (19.1)</td>
<td>88 (16.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2 (2.1)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture result positive for M. tuberculosis</td>
<td>6/27 (22.2)</td>
<td>22/333 (6.6)</td>
<td>2.69 (1.01-7.14)</td>
<td>7.65 (1.89-30.96)</td>
</tr>
</tbody>
</table>

**NOTE:** The intensive phase was the first 2 months of treatment, and end of treatment was at 6 months. AFB, acid-fast bacilli.

- **14.8% prevalence of undiagnosed DM in new TB patients**
- **TB-DM had greater symptoms at time of diagnosis**  

- 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

  ![5% of deaths were not TB related]

  *½ of deaths were not TB related*

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


9/25/2013
All cause mortality increased in diabetics during TB treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Population with DM Deaths/Total</th>
<th>Population without DM Deaths/Total</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fielder, 2002 [38] USA</td>
<td>13/22 (59%) 20/152 (19%)</td>
<td></td>
<td>3.80 (1.42, 10.16)</td>
<td></td>
</tr>
<tr>
<td>Oursley, 2002 [40] USA</td>
<td>8/18 (44%) 14/108 (13%)</td>
<td></td>
<td>6.70 (1.57, 26.92)</td>
<td></td>
</tr>
<tr>
<td>Dooley, 2009 [12] USA</td>
<td>6/42 (14%) 20/255 (8%)</td>
<td></td>
<td>0.50 (1.11, 36.20)</td>
<td></td>
</tr>
<tr>
<td>Wang, 2009 [36] Taiwan/1974 (18%) 11/143 (8%)</td>
<td></td>
<td></td>
<td>5.20 (1.77, 15.25)</td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td></td>
<td></td>
<td></td>
<td>4.95 (2.09, 9.09)</td>
</tr>
</tbody>
</table>

Heterogeneity $I^2$ calculated = 0% (3, 85)
Weights are from random effects analysis

Baker et al. BMC Med 2011

Slower culture conversion in diabetics (without cavitary disease)

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


9/25/2013
Worse outcomes.....What can we do about it?

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
Acquired drug resistance
Death
Relapse

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

9/25/2013
• 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\textsubscript{2h}).

  Heysell et al. *Emerg Infect Dis* 2010

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low</th>
<th>Within Target</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>59%</td>
<td>41%</td>
<td></td>
</tr>
<tr>
<td>RMP</td>
<td>52%</td>
<td>46%</td>
<td>2%</td>
</tr>
<tr>
<td>EMB</td>
<td>31%</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>PZA</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Drug levels usually correct after first dose adjustment

[Graph showing drug levels over time]

\[ \text{spans } C_{\text{thres}}, \text{ expected range} \]

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

(AUC$_{0-6\text{h}}$), $C_{\text{max}}$ and overall *rifampin exposure was 53% lower in diabetics* with TB compared to non-diabetics in continuation phase, with some linkage to high body wt.

Nijland et al. *Clin Infect Dis* 2006

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**Low drug levels matter, at least in vitro**

**TABLE 2.** TB drug activity (TDA) values and $C_{\text{max}}$ drug levels at 14 days of TB treatment for Tanzanian patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mean drug $C_{\text{max}}$ ± SD (µg/ml)</th>
<th>TDA ≤ 2.0 (n = 9)</th>
<th>TDA &gt; 2.0 (n = 7)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>1.31 ± 1.2</td>
<td>2.56 ± 1.2</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td><strong>0.77 ± 1.3</strong></td>
<td>4.65 ± 3.2</td>
<td><strong>0.005</strong></td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>0.83 ± 0.37</td>
<td>1.68 ± 0.93</td>
<td><strong>0.03</strong></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>20.3 ± 7.3</td>
<td>28.0 ± 10.7</td>
<td><strong>0.11</strong></td>
<td></td>
</tr>
</tbody>
</table>

Among subjects with the lowest TDA (≤1.5), only 2 (40%) were cured at 6 months compared to 10 (91%) with the higher TDA values ($p=0.06$)

What is the right* dose of rifampin?

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

- 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

Adverse events: mostly grade 1

It would not surprise me if eventually we use 900mg RIF routinely........

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

• Of the 21 diabetics, 16 (76%) had a \( C_{\text{anh}} \) 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 900/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

• UVA
  – Scott Heysell, Tania Thomas, Dorothy Bunyan, Suzanne Stroup

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

• Virginia TB Foundation
Improving TB-DM Care
in the Pacific:
Can we make a difference?

Southeastern National TB Center
TB-DM Webinar, Sept 25, 2013

R. Brostrom, MD-MSPH
Regional TB Medical Officer, CDC-DTBE
Hawaii TB Control Branch Chief
CDR USPHS

Improving TB-DM Care

• Quick Update of TB-DM Link
• Epidemiology of TB-DM in US
• Pacific Standards
• Pacific Plan
• Summary - Questions
Pacific Dietary Change after 1944

Global Rising Tide of Diabetes

Millions of Cases in 2000 and Projected Cases for 2030

Webinar: TB & Diabetes
Southeastern National TB Center
TB cases with DM

- India
- Mexico
- Pacific Islander

Percent Adult TB Patients with Diabetes

A1c > 7
No DM
A1c < 7
DM


Webinar: TB & Diabetes
Southeastern National TB Center
Webinar: TB & Diabetes
Southeastern National TB Center

TB-DM Outcomes: Relapse

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Population with DM Relapsed</th>
<th>Population without DM Relapsed</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wada, 2000 [54]</td>
<td>Japan</td>
<td>7/61 (11%)</td>
<td>4/294 (1%)</td>
<td>8.15 (2.46, 26.97)</td>
</tr>
<tr>
<td>Msoyaa, 2003 [47]</td>
<td>Congo</td>
<td>6/17 (35%)</td>
<td>9/77 (12%)</td>
<td>3.02 (1.24, 7.35)</td>
</tr>
<tr>
<td>Singla, 2006 [50]</td>
<td>Saudi Arabia</td>
<td>2/130 (2%)</td>
<td>3/367 (1%)</td>
<td>1.88 (0.32, 11.14)</td>
</tr>
<tr>
<td>Malek, 2009 [48]</td>
<td>Tunisia</td>
<td>4/55 (7%)</td>
<td>1/82 (1%)</td>
<td>6.96 (0.68, 51.95)</td>
</tr>
<tr>
<td>Zhang, 2009 [57]</td>
<td>China</td>
<td>33/165 (20%)</td>
<td>9/1170 (0%)</td>
<td>1.90 (1.37, 7.66)</td>
</tr>
</tbody>
</table>

Summary
Heterogeneity I-squared = 0% (0.79)
Weights are from random effects analysis

3.89

TB-DM Outcomes: Death during TB Tx

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Population with DM Death/ Total</th>
<th>Population without DM Death/ Total</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felder, 2002 [58]</td>
<td>USA</td>
<td>13/22 (59%)</td>
<td>29/152 (19%)</td>
<td>3.80 (1.42, 10.16)</td>
</tr>
<tr>
<td>Duski, 2002 [48]</td>
<td>USA</td>
<td>8/18 (44%)</td>
<td>14/109 (13%)</td>
<td>6.70 (1.57, 28.52)</td>
</tr>
<tr>
<td>Dooley, 2009 [52]</td>
<td>USA</td>
<td>6/42 (14%)</td>
<td>20/255 (8%)</td>
<td>6.50 (1.11, 30.20)</td>
</tr>
<tr>
<td>Wang, 2009 [56]</td>
<td>Taiwan</td>
<td>13/74 (18%)</td>
<td>11/143 (8%)</td>
<td>5.20 (1.77, 15.25)</td>
</tr>
</tbody>
</table>

Summary
Heterogeneity I-squared = 0% (0.86)
Weights are from random effects analysis

4.95

9/25/2013
TB-DM Teaching Points

- **2x** risk of remaining culture positive
- **3x** risk of progression to active TB
- **4x** risk of relapse after standard tx
- **5x** risk of death during TB treatment


Improving TB-DM Care

- Quick Update of TB-DM Link
- **Epidemiology of TB-DM in US**
- Pacific Standards
- Pacific Plan
- Summary - Questions
Rising Diabetes Rates in the US

TB Risk Factors in the US - 2011

- Diabetes Mellitus
- Contact of Infectious TB
- Immuno-suppression
- Incomplete LTBI Tx
- End-Stage Renal Disease
- Missed Contact
- Post-Transplant
- TNF-Alpha Antagonist Tx
- Contact of MDR TB

Contact of MDR TB
TNF-Alpha Antagonist Tx
Post-Transplant
Missed Contact
End-Stage Renal Disease
Incomplete LTBI Tx
Immunosuppression
TB - Contact of Infectious
Diabetes Mellitus
Improving TB-DM Care

- Quick Update of TB-DM Link
- Epidemiology of TB-DM in US
- Pacific Standards
- Pacific Plan
- Summary - Questions
US Pacific Region for TB Control

Screening for DM in persons with TB

**Standard 1**  Every person with TB over the age of 18 should be screened for DM

1.1 The diagnosis of DM may be made using one of the following criteria:
- Fasting plasma glucose ≥ 126 mg/dl
- Random plasma glucose ≥ 200 mg/dl
- Hemoglobin A1C ≥ 6.5%

1.2 Abnormal glucose values should be verified in patients who have no symptoms of DM.

1.3 Rifampin can elevate blood glucose in TB patients. Glucose testing should be repeated after 2-4 weeks of TB treatment, or if symptoms of hyperglycemia develop during TB treatment.
Polling Question #1

When a new smear positive adult TB case is referred to your clinic for the first time, do you:

1. Ask them if they have diabetes?
2. Ask and send them for diabetes testing?
3. Ask and test them in clinic for diabetes?
4. We don’t usually ask about diabetes.
Screening for TB in persons with DM

Standard 2  Every person with DM should be screened for active TB disease and latent TB infection

2.1 A test for TB infection should be done at the time of DM diagnosis.

2.2 Screening should be repeated as often as local TB epidemiology warrants.

Standard 3  Persons with DM and TB infection should be encouraged to take preventive therapy

3.1 If INH is used for prevention, give B6 to help prevent INH induced neuropathy (10 – 25 mg/day).*

3.2 Monitor for adherence and side effects of preventive treatment.

* Targeted tuberculin testing and treatment of latent TB infection, MMWR 2000;49.

Standard 4  Persons with DM and TB disease should be referred to the local TB Program for TB management

Best Practices: RMI Community Clinic

Program Collaboration

In 2010, the KAHC adopted and started implementing the USAPI Standards for the Management of Tuberculosis and Diabetes. In this guideline – standards were set for DM screening in persons with active TB; screening for TB in persons with DM; treating TB in persons with DM; and managing DM in persons with active TB.

To improve implementation of the USAPI clinical guidelines – KAHC have set the following measures to accomplish the collaborative initiatives:
Webinar: TB & Diabetes
Southeastern National TB Center

**TB Screening in Diabetes Clinic: Finding TB**

- Ebeye DM Clinic Rate
- Ebeye Island
- RMI NTP Rate
- Global TB Rate
- US TB Rate

**TB Screening in Diabetes Clinic: Results**

Tuberculosis Case Finding Among Persons with Diabetes in Ebeye Island:
April 2010 to March 2012 (n=219)

Rate of Active Tuberculosis per 100,000

Age of Person with Diabetes at time of TB Screening

9/25/2013
Treating TB in persons with DM

**Standard 5**  Clinicians may need to adjust TB treatment in persons with DM

5.1 Make sure that TB medications are properly dosed.
   Check creatinine for diabetic nephropathy, and if present, adjust the frequency of PZA and EMB according to ATS-CDC guidelines.*
   Administer B6 to prevent neuropathy (10 – 25 mg/day).

5.2 Observe closely for TB treatment failure in persons with DM.
   Be aware of poor absorption of some TB meds in DM.
   Some programs follow INH or RIF levels in persons with DM.
   Manage the many interactions between TB and DM meds.

5.3 “Assure the Cure”
   Consider extending treatment to 9 months for persons with DM, esp. patients with cavitary disease or delayed sputum clearance.*
   Upon completion of therapy, obtain sputum for smear and culture.
   Evaluate patients at one year after treatment for evidence of relapse.

* : Treatment of Tuberculosis, American Thoracic Society, CDC, and ISD, MMWR 2003;52

Managing DM in persons with TB

**Standard 6**  Use TB clinic visits to help the patient manage their DM

6.1 There should be a glucometer in every TB clinic for monitoring blood glucose.

6.2 TB patients with DM should have their glucose checked at least weekly for the first 4 weeks, less frequently if diabetes is controlled.
   Monthly glucose testing during treatment is recommended.

6.3 All clinic staff should reinforce DM lifestyle changes at TB clinic visits.

6.4 If available, refer persons with DM to the Diabetes Clinic for long-term diabetes care. Ensure the DM clinician is aware of TB diagnosis and TB medications.

**Standard 7**  Use DOT visits to help the patient manage their DM

7.1 DOT workers should encourage lifestyle changes at every patient encounter.
   DOT workers should use standardized diabetes educational materials.*
   Dietary changes and physical activity are most important.

7.2 Consider delivering DM meds with TB meds via DOT for persons with poorly-controlled DM who have suspected non-adherence to diabetic medications.

Best Practices: TB-DM Educational Tool (PITCA - Australian Respiratory Council)

• Standardized approach
• DOT-based education
• Weekly topics: TB and DM
  • Simplified and focused
• “Brief Intervention”
  • 5 min or less
  • Repeated messages

Key Messages for TB & Diabetes
“Diabetes? It’s not my job!”

Exercises at Battle Creek Sanitarium, Michigan, 1911

TB-DM Nurses Training: Yes We Can!

- Ask about DM at monthly case conference and quarterly cohort review (Aug, 2010)
- Improve TB-DM Surveillance with A1C for every adult case on entry to TB Program (Dec, 2010)
- Expand A1C to q 3 months while tx (June, 2012)
- Initiate TB Clinic Glucometry Training (Oct, 2012)
- Begin TB Clinic A1C Training (Feb, 2013)
- Started TB Clinic Diabetes Education Training
  - 2 Afternoon sessions 3/13, 4/13
  - Community Clinic partnership
TB-DM Nurses Education

DM Education Quotes from TB Patients:

“Can I come back to clinic tomorrow to talk some more?”

“What about my kids, can they catch my diabetes?

“What can I eat at McDonalds that’s OK for me?”

“I thank God for you.”
Polling Question #2
You begin DM screening and find that 20% of your adult cases have diabetes. How many of these interventions are realistic for your program?

1. Referring them to primary care.
2. Providing ongoing DM testing in clinic.
4. Providing DM education with DOT.
5. Delivering DM medications with DOT.

Hawaii TB-DM Study

- Measure A1C on all adult TB Cases
  - If DM, then measure A1C at 3 months

- Integrate Standard 6 and Standard 7 into care
  - Glucose testing at each visit
  - A1C Testing every 3 months
  - Refer to DM Center for Care
  - TB-DM Patient Education in Clinic
  - TB-DM Patient Education during DOT
Hawaii TB-DM Study

Clinical Disease vs. Lifestyle Disease

**130 encounters in 6 months**
May be the patient’s best opportunity to be motivated for lifestyle changes

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TB-DM Integration

*Improve Patient Care During TB Tx*

- **Regional Partners** (CITC, SPC)
- **Local and External Diabetes Programs**
- **Local Private and Public Partners** (Clinics)

**NGO’s** (Australian Respiratory Council)

**External Public Partners** (WHO, CDC)

**Improve Life-Long Diabetes Control**

**Improve TB Outcomes**

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Webinar: TB & Diabetes
Southeastern National TB Center

9/25/2013
Collaborative framework for care and control of tuberculosis and diabetes

Pacific Regional Standards for the Management of TB and DM:
http://www.currytbcenter.ucsf.edu/international/TBDM_poster_pressquality.pdf

Key Messages for TB and DM (flipchart):

Acknowledgments
• US Centers for Disease Control and Prevention
• WPRO, World Health Organization
• International Union Against TB and Lung Diseases
• Curry International TB Center
• Secretariat for the Pacific Community
• Australian Respiratory Council
• CNMI Public Health Department
• Pacific Islands Health Officers Association
• Pacific Islands TB Controllers Association