Treating TB – What Happened? All the Patients Have Challenging Co-Morbid Conditions Now!

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UT Health Northeast, Tyler, Texas
Objectives

• Review current epidemiology of TB

• Discuss current epidemiology of some of the co-morbid conditions affecting TB treatment in Four Corners Region

• Identify considerations for treatment in a patient diagnosed with TB and a co-morbidity (diabetes, persons receiving TNF alpha inhibitors, chronic kidney disease, and HCV)
TB Leading Infectious Disease Cause of Death Globally
FIG. 3.3
Estimated TB incidence in 2016, for countries with at least 100 000 incident cases
Tuberculosis in the United States

- TB reported in all 50 states
- Total of 9,272
  - Rate of 2.9/100,000
  - 3.6% decrease from 2015
- 14% recent transmission
- 470 TB attributed deaths in 2015
TB Case Rates by Race/Ethnicity, *  
United States, 2003–2016†

* All races are non-Hispanic; multiple race indicates two or more races reported for a person, but does not include persons of Hispanic/Latino origin.
† As of June 21, 2017.
Tuberculosis in the 4 Corners Area
Not That Much To Talk About
# Tuberculosis Case and Case Rates per 100,000 Population: Reporting 2016 & 2015

<table>
<thead>
<tr>
<th>Reporting Area</th>
<th>Cases</th>
<th>Case rates</th>
<th>Rank according to rate</th>
<th>Population estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2016</td>
<td>2015</td>
<td>2016</td>
<td>2015</td>
</tr>
<tr>
<td>Arizona</td>
<td>188</td>
<td>198</td>
<td>2.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Colorado</td>
<td>64</td>
<td>73</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td>New Mexico</td>
<td>39</td>
<td>47</td>
<td>1.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Utah</td>
<td>20</td>
<td>37</td>
<td>0.7</td>
<td>1.2</td>
</tr>
</tbody>
</table>


# Population Distribution by Race/Ethnicity

**Timeframe:** 2016

<table>
<thead>
<tr>
<th>Location</th>
<th>White</th>
<th>Black</th>
<th>Hispanic</th>
<th>Asian</th>
<th>American Indian/Alaska Native</th>
<th>Native Hawaiian/Other Pacific Islander</th>
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</thead>
<tbody>
<tr>
<td>Arizona</td>
<td>54%</td>
<td>4%</td>
<td>34%</td>
<td>3%</td>
<td>2%</td>
<td>N/A</td>
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<tr>
<td>Colorado</td>
<td>70%</td>
<td>4%</td>
<td>19%</td>
<td>4%</td>
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<td>N/A</td>
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<tr>
<td>New Mexico</td>
<td>37%</td>
<td>2%</td>
<td>46%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Utah</td>
<td>79%</td>
<td>1%</td>
<td>14%</td>
<td>2%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Percentage of Non-U.S.–Born Persons Among TB Cases, United States, * 2006 and 2016

*As of June 21, 2017.

DC, District of Columbia; NYC, New York City (excluded from New York state)
TB Co-Morbidities in U.S. 2016

- Among persons reported with TB in 2016, a total of 454 (5.6%) of TB cases with test result information) were co-infected with human immunodeficiency virus (HIV).

- Diabetes mellitus continues to be an important clinical risk factor for TB disease. In 2016, a total of 1,524 (16.4%) persons reported with TB also had diabetes.
TB Risk Factors

Of persons diagnosed with TB in 2016:

- 16.4% reported having diabetes
- 10.0% reported excessive alcohol use*
- 6.8% reported using non-injectable drugs (1.3% reported using injecting drugs) [8.1%]*
- 5.6% were co-infected with HIV (of TB cases with HIV test results reported)
- 4.9% reported being homeless in the past year
- 4.0% were residents of correctional settings at time of diagnosis
<table>
<thead>
<tr>
<th>Reporting area</th>
<th>United States</th>
<th>Arizona</th>
<th>Colorado</th>
<th>New Mexico</th>
<th>Utah</th>
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<tbody>
<tr>
<td>Total</td>
<td>9,272</td>
<td>188</td>
<td>64</td>
<td>39</td>
<td>20</td>
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<tr>
<td>MDR patient contact #</td>
<td>9</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>MDR patient contact %</td>
<td>0.1</td>
<td>0.5</td>
<td>0</td>
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<td>1</td>
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<tr>
<td>Missed Contact %</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Infectino TB patient contact #</td>
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<td>2</td>
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<tr>
<td>Infectino TB patient contact %</td>
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<td>2.1</td>
<td>3.1</td>
<td>7.7</td>
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<tr>
<td>Incomplete LTBI therapy #</td>
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<td>1</td>
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<tr>
<td>Incomplete LTBI therapy %</td>
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<td>2.1</td>
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<tr>
<td>Diabetes mellitus #</td>
<td>1,524</td>
<td>39</td>
<td>20</td>
<td>7</td>
<td>7</td>
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<tr>
<td>Diabetes mellitus %</td>
<td>16.4</td>
<td>20.7</td>
<td>31.3</td>
<td>17.9</td>
<td>35</td>
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<tr>
<td>Renal disease #</td>
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<td>4</td>
<td>6</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Renal disease %</td>
<td>2.3</td>
<td>2.1</td>
<td>9.4</td>
<td>7.7</td>
<td>0</td>
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<td>TNF-α inhibitors #</td>
<td>56</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>TNF-α inhibitors %</td>
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<td>0.5</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Post-organ transplantation #</td>
<td>53</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Post-organ transplantation %</td>
<td>0.6</td>
<td>0.5</td>
<td>1.6</td>
<td>5.1</td>
<td>0</td>
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<tr>
<td>Immunosuppression #</td>
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<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Immunosuppression %</td>
<td>4.4</td>
<td>1.6</td>
<td>3.1</td>
<td>2.6</td>
<td>0</td>
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<tr>
<td>Other #</td>
<td>2,155</td>
<td>28</td>
<td>3</td>
<td>12</td>
<td>1</td>
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<tr>
<td>Other %</td>
<td>23.2</td>
<td>14.9</td>
<td>4.7</td>
<td>30.8</td>
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<tr>
<td>None #</td>
<td>4,101</td>
<td>121</td>
<td>35</td>
<td>16</td>
<td>10</td>
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<tr>
<td>None %</td>
<td>44.2</td>
<td>64.4</td>
<td>54.7</td>
<td>41</td>
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<tr>
<td>Missing #</td>
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<td>0</td>
<td>0</td>
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<td>6.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Diabetes In Four Corner States

- Percent of population with diabetes
  - Utah: 7.4%
  - New Mexico: 10.7%
  - Colorado: 7.4%
  - Arizona: 10.8%
TB Complicated by HCV Infection

• Treatment of patients with HCV depends on degree of liver inflammation
  – Many patient may tolerate standard RIPE regimen
  – Those with evidence of baseline abnormal liver enzymes or low platelets may not tolerate PZA
    • If PZA used watch LFTs every one to two weeks initially
    • Some may tolerate rifampin and INH
    • Some may only tolerate rifampin or others only rifabutin
    • Some may need a completely “liver friendly” regimen
      – These are essentially MDR patients
Map 4.1. 2015 State Acute Hepatitis C Incidence Compared to Healthy People 2020 National Goal*

- Green: At or below national goal
- Light blue: Above national goal
- Dark blue: More than twice national goal
- Gray: Data unavailable

Source: CDC, National Notifiable Diseases Surveillance System (NNDS)

*National goal: 0.25 cases/100,000 population
Viral Hepatitis Surveillance - 2015

- New HCV cases increased 2.9 fold from 2010 to 2015
  - No longer just a disease of those 45-65+ years old

- 3.5 million persons infected with HCV

- Increase primarily due to increase in injecting drug use
  - Young, white, non-urban
Treatment of HCV During TB Therapy Means Treating Without a Rifamycin – Possible But Hard

• Most regimens for HCV are based on sofosbuvir
  – Both rifampin and rifabutin markedly decrease drug levels of sofosbuvir significantly decreasing efficacy of HCV treatment

• Patients with Genotype 4 also can be treated with regimen of paritaprevir-ritonavir-ombitasvir plus ribavirin
  – Rifampin significantly decreases serum level of ritonavir
  – Ritonavir markedly increases serum level of rifabutin
Treatment of HCV Means Treating MTB Without a Rifamycin – Possible But Not Desirable

- If it is possible to design an adequate liver-friendly regimen that patient can tolerate; best to treat TB first

- If patient is already on or needs HCV treatment:
  - Non rifamycin regimen – essentially treating MDR
  - Regimen may be long, difficult
    - Moxifloxacin, Cycloserine (watch kidney fx), EMB, Linezolid
  - Can consider adding a Rifamycin after HCV treatment
  - Likely need to avoid INH and PZA
TB in Patients on TNF-alpha Inhibitors

- Increased risk of reactivation

- Increased risk of disseminated, fulminant or extrapulmonary
  - Think TB if fever, night sweats weight loss etc.

- Stop TNF-alpha inhibitor if TB suspected or diagnosed.
<table>
<thead>
<tr>
<th>Biologic</th>
<th>FDA-approved indications (as of 1 November 2016)(^a)</th>
<th>RR of TB compared to that in the general population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>AS, JIA, RA, Ps, PsA, Crohn’s, UC</td>
<td>29.3 (95% CI, 20.3–42.4) (^3) based on SIR (standardized for age and sex)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>AS, RA, Ps, PsA, Crohn’s, UC</td>
<td>18.6 (95% CI, 13.4–25.8) (^3) based on SIR (standardized for age and sex)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>AS, JIA, RA, Ps, PsA</td>
<td>1.8 (95% CI, 0.7–4.3) (^3) based on SIR (standardized for age and sex) 3.5</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>AS, RA, PsA, Crohn’s</td>
<td>No definite increase in RR in pooled data from RCTs (^4)</td>
</tr>
<tr>
<td>Golimumab</td>
<td>AS, RA, PsA, UC</td>
<td>No definite increase in RR in pooled data from RCTs (^5)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Chronic lymphocytic leukemia, non-Hodgkin lymphomas, granulomatosis with polyangitis, microscopic polyangitis, RA</td>
<td>No definite increase in RR in pooled data from RCTs (^6)</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>JIA, RA</td>
<td>No definite increase in RR in pooled data from RCTs (^7)</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>UC, Crohn’s</td>
<td>No definite increase in RR from drug safety data (^8)</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Ps, PsA, Crohn’s</td>
<td>No definite increase in RR from drug safety data (^9)</td>
</tr>
<tr>
<td>Abatacept</td>
<td>JIA, RA</td>
<td>First choice in patients with PsA at high infection and TB risk (^10)</td>
</tr>
</tbody>
</table>

\(^a\) AS, ankylosing spondylitis; Crohn’s, Crohn’s disease; JIA, juvenile idiopathic arthritis; Ps, plaque psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCTs, randomized controlled trials; UC, ulcerative colitis.
Screening for TB in Persons Taking TNF alpha blockers

• Initial screen prior to starting RX most important

• Optimal screening strategy unclear
  – TST or IGRA versus both plus symptom screen, history
  – Both the TST and IGRA less sensitive due to underlying disease and therapy for that disease

• Screen again if exposed to TB

• Evaluate for TB if symptoms
<table>
<thead>
<tr>
<th>Agency and/or country or region, year</th>
<th>LTBI screening tests</th>
<th>LTBI treatment regimen (duration in months, medication)</th>
<th>Anti-TNF-α starting delay</th>
<th>Repeat testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers for Disease Control and Prevention, United States, 2004 and 2010 (update)</td>
<td>TST or IGRA, combined use of TST and IGRA supported; Positive TST: ≥5 mm</td>
<td>9H</td>
<td>No definite recommendation, completion of LTBI treatment before anti-TNF-α therapy, if possible</td>
<td>Only in individuals at increased risk for TB infection</td>
</tr>
<tr>
<td>American College of Rheumatology, United States</td>
<td>TST or IGRA</td>
<td>Not specified</td>
<td>1 mo</td>
<td>Annually in individuals with risk factor for future or ongoing TB exposure</td>
</tr>
<tr>
<td>Canada, 2013</td>
<td>TST or IGRA, combined (sequential) use of TST and IGRA supported</td>
<td>9H</td>
<td>No recommendation</td>
<td>Only in individuals at increased risk for TB infection</td>
</tr>
<tr>
<td>British Thoracic Society, United Kingdom, 2005</td>
<td>Use of risk stratification tables (and chest X ray) for patients on IST. TST performed only in patients not on IST (positive TST is &gt;15 mm in BCG-vaccinated patients and &gt;5 mm in non-BCG-vaccinated patients)</td>
<td>6H</td>
<td>≥2 mo</td>
<td>Delay until completed LTBI treatment if abnormal chest X ray, history of TB</td>
</tr>
<tr>
<td>France, 2003</td>
<td>TST only; Positive TST: ≥10 mm</td>
<td>2RZ, 3RH, 9H</td>
<td>≥3 wks</td>
<td>Not specified</td>
</tr>
<tr>
<td>Switzerland, 2007</td>
<td>IGRA only</td>
<td>9H</td>
<td>1 mo</td>
<td>Not specified</td>
</tr>
<tr>
<td>TBNET International consensus, Europe</td>
<td>TST or IGRA. TST performed only in patients without BCG. Positive TST: ≥10 mm</td>
<td>9–12H, 3RH</td>
<td>4 wks</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

*R, rifampin; H, isoniazid; Z, pyrazinamide; IST, immunosuppressive therapy.
TB in Patient on a TNF-alpha Inhibitor

• Stop TNF-alpha inhibitor if TB suspected or diagnosed.

• TNF-alpha inhibitor can be restarted safely in most
  – Timing not clear
    • Once patient on treatment, drug susceptibility known and clinical improvement.

• Consider 9 month treatment course in most
TB and Chronic Kidney Disease

- Systematic review
- CKD linked to conditions known to increase the risk of active TB.
  - DM is most common cause of CKD globally
- Dialysis patients had 3.62 fold increase in TB rate
- Risk in renal transplants 20.10

— Al-Efraok, K et al Int J Tuberc Lungs Dis 19(12):1493-1499 2015
People with diabetes should get tested for tuberculosis (TB) infection.

Without treatment, the risk of developing TB disease once infected is 3 times higher for diabetics.

www.cdc.gov/tb
WHO:

- Diabetes rises fourfold over last quarter-century

WHO reported:

- 8.5% of the world population had DM two years ago, up from 108 million, or 4.7%, in 1980.

- Blamed the growing consumption of food and beverages high in sugar.

- DM grew around the world, but increased most in Africa, the Middle East and Asia.
Global Rising Tide of Diabetes
Global Rising Tide of Diabetes

Millions of Cases in 2000 and Projected Cases for 2030

- India: 79.4 million cases in 2000, 150% increase to 2030
- China: 42.3 million cases in 2000, 104% increase to 2030
- Southeast Asia: 22.3 million cases in 2000, 161% increase to 2030
Growing Diabetic Epidemic Will Have a Significant Impact on TB Control
RESEARCH ARTICLE

Prevalence and associated factors of tuberculosis and diabetes mellitus comorbidity: A systematic review

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Prevalence of Diabetes Among TB Patients by Region

North America 23.6%
South America 11.1%
Asia 17%
Africa 6.7%
Europe 5.9%
Oceania 23.2%

(IQR 12.8%-39.0%). Three (3.8%) studies conducted in South America indicated prevalence rates ranging from 6.1% in Brazil to 14% in Guyana [98,101]. This amounted to an overall median prevalence of 11.1% (IQR 6.1%-14.0%). There was only one study from Europe that showed a prevalence rate of 5.9% (Fig 2).

Fig 2. Map showing median prevalence of DM among TB patients by region. (NB: There is only one study reported in Europe). IQR: Interquartile range (Source of the map: https://www.flickr.com/photos/blatantworld/5052373414#. Accessed March 20/2017).

https://doi.org/10.1371/journal.pone.0175925.g002
About 95% of TB and 75% of DM cases live in low and middle income countries.

Prevalence of TB in Diabetics
Global 4.1%

Fig 3. Map showing median prevalence of TB among DM patients by region. (NB: North America and Europe each reported only one study). IQR: Interquartile range (Source of the map: http://www.sawyoo.com/postpic/2015/02/what-are-the-7-seven-continents_118851.png. Accessed March 20/2017).

https://doi.org/10.1371/journal.pone.0175925.g003
Prevalence of DM and Pre-diabetes and Associated Risk Factors in India

• Nationwide study in 2011 reported prevalence of diabetes & pre-diabetes **10.4% and 8.3% in general population** of Tamil Nadu, South India

• **5 TB units** in state studied adults treated by DOT in 2011
  – Evaluated for history of DM, BMI, 2 hour Glucose tolerance test, FBS, postprandial glucose and HBA1C

• **25.3%** had diabetes, **24.5%** pre-diabetes
  – Diabetics: higher BMI (19.3 vs 18.4), AFB+ (55.* vs 42.5%), older (49.3 vs 35.6 years)  

Viswanathan et al., PLoS one July 2012
MULTIMORBIDITY

Why India should worry about a coepidemic of diabetes and tuberculosis

More collaboration may be needed between largely private sector diabetes care and the public tuberculosis control programme, finds Talha Burki

Talha Burki journalist, London, UK

Diabetes is fuelling the spread of tuberculosis warns a report published in October 2014 from the International Union Against Tuberculosis and Lung Disease and the World Diabetes Foundation. The report warns of a “looming co-epidemic,” which could have catastrophic consequences for healthcare systems in affected countries. With the world’s highest burden of tuberculosis—an estimated 65 million cases—India is especially vulnerable.

A coepidemic threatens to set back recent gains in tuberculosis control. According to WHO, India’s tuberculosis prevalence dropped from 217/100 000 population in 1990 to around 171/100 000 population in 2013, the most recent year for which records are available. But patients with tuberculosis and diabetes are already thought to outnumber those conxected with tuberculosis and HIV. In India, tuberculosis rates are around 650-900/100 000 in people with diabetes. Moreover, only 40-50% of people with diabetes in India are thought to have been identified, and only half of patients with diabetes (something similar may happen in gestational diabetes). Certainly, it makes it trickier to treat existing diabetes.
WHY Am I TALKING ABOUT TB AND Diabetes in India?

-- BECAUSE WE KNOW TB CAN TRAVEL
Increased risk of latent tuberculous infection among persons with pre-diabetes and diabetes mellitus

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*School of Medicine, Emory University, Atlanta, †Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, ‡DeKalb County Board of Health, Decatur, §Departments of Epidemiology and Global Health, Emory Rollins School of Public Health, Atlanta, †Division of Epidemiology and Biostatistics, Georgia State University, School of Public Health, Atlanta, Georgia, USA

SUMMARY

SETTING: Although diabetes mellitus (DM) is an established risk factor for active tuberculosis (TB) disease, little is known about the association between pre-DM, DM, and latent tuberculous infection (LTBI).

OBJECTIVE: To estimate the association between DM and LTBI.

DESIGN: We conducted a cross-sectional study among recently arrived refugees seen at a health clinic in Atlanta, GA, USA, between 2013 and 2014. Patients were screened for DM using glycated-hemoglobin (HbA1c), and for LTBI using the QuantiFERON®-TB (QFT) test. HbA1c and QFT results, demographic information, and medical history were abstracted from patient charts.

RESULTS: Among 702 included patients, 681 (97.0%) had HbA1c and QFT results. Overall, 54 (7.8%) patients had DM and 235 (33.8%) had pre-DM. LTBI was prevalent in 31.3% of the refugees. LTBI prevalence was significantly higher (P < 0.01) among patients with DM (43.4%) and pre-DM (39.1%) than in those without DM (25.9%). Refugees with DM (adjusted OR [aOR] 2.3, 95%CI 1.2–4.5) and pre-DM (aOR 1.7, 95%CI 1.1–2.4) were more likely to have LTBI than those without DM.

CONCLUSION: Refugees with DM or pre-DM from high TB burden countries were more likely to have LTBI than those without DM. Dysglycemia may impair the immune defenses involved in preventing Mycobacterium tuberculosis infection.

KEY WORDS: hemoglobin A1c; QuantiFERON test; refugee; vitamin D
Does Diabetes or Pre-Diabetes Increase Risk of LTBI - A Look at LTBI in Refugees in an Atlanta Clinic

- Presumption that DM increases risk of LTBI –
  - Two small studies suggested more LTBI in diabetics

- Study of newly arrived refugees evaluated prevalence of DM with HBA1C;
  - DM ≥ 6.5%, pre-DM 5.7-6.4%, no DM < 5.7%

- 681 patients with both HBA1C and QFT results
  - 54 DM, 235 pre-DM,

  Int J TB and Lung Disease; Hensel 2016
Does Diabetes or Pre-Diabetes Increase Risk of LTBI?

- LTBI found in 31% of refugees overall

- LTBI significantly more common in patients with DM
  - DM (43.4%)
  - Pre-DM (39.1%)
  - No DM (25.9%)
Pre-Diabetes Associated with Increased Risk of LTBI and TB

- Significant alterations of immune response in LTBI noted with compromised CD4+ and CD8+ cells

  – Kumar PLOS ONE May 30 2017
Approach to LTBI in Diabetics

• Due to the increased risk for progression to active TB disease, the following should be done:

  – Diabetics who are *at risk for TB exposure* should be screened for TB with an IGRA or TST

  – The risk of progression to TB disease should be communicated to community physicians caring for diabetics

  – In U.S. recommendation to screen those at risk of TB and if present treat

  – WHO does not recommend unless other risk factors
WHO LTBI Guidelines 2014

- Recommended against treatment of LTBI in: diabetics, people with harmful alcohol use, tobacco smokers and underweight people unless they are already included in prior risk group recommended for treatment.
  
  – (Conditional recommendation, very low quality of evidence)
TB in Diabetics Often Challenging to Treat

- Patients sicker, most advanced disease, more infectious
- Outcomes are not as good.
Prevalence of dysglycemia and clinical presentation of pulmonary tuberculosis in Western India

The International Journal of Tuberculosis and Lung Disease

Table 4  Diabetes as a risk factor for severe TB disease* using multinomial logistic regression analyses

<table>
<thead>
<tr>
<th>TB disease markers</th>
<th>Univariable analysis</th>
<th>Multivariable analysis†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RRR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>TB symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4</td>
<td>Reference</td>
<td>—</td>
</tr>
<tr>
<td>≥ 4</td>
<td>1.49 (0.81–2.76)</td>
<td>0.20</td>
</tr>
<tr>
<td>DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4</td>
<td>Reference</td>
<td>—</td>
</tr>
<tr>
<td>≥ 4</td>
<td>1.89 (0.82–4.36)</td>
<td>0.13</td>
</tr>
<tr>
<td>Cavitory TB disease or ≥ 1 lobe affected or miliary infiltrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>Reference</td>
<td>—</td>
</tr>
<tr>
<td>Present</td>
<td>1.34 (0.65–2.79)</td>
<td>0.43</td>
</tr>
<tr>
<td>DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>Reference</td>
<td>—</td>
</tr>
<tr>
<td>Present</td>
<td>1.29 (0.55–3.04)</td>
<td>0.56</td>
</tr>
<tr>
<td>Smear grade &gt;1+ or TTD &lt;9 days</td>
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<td></td>
</tr>
<tr>
<td>Pre-DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Reference</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>1.24 (0.84–1.85)</td>
<td>0.28</td>
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<tr>
<td>DM</td>
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<td>No</td>
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<td>—</td>
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<tr>
<td>Yes</td>
<td>3.12 (1.62–6.04)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* Giving one point to each major TB-related symptom (cough, fever, weight loss, night sweats, anorexia, hemoptysis and malaise), TB disease was classified as severe (≥4) and non-severe TB (<3). Radiologic findings of cavitory lung lesions and/or involvement of ≥ 1 lung lobe, and microbiologic findings of ≥ 1+ spumt AFB and/or shorter TTD in culture was classified as severe TB disease. Shorter TTD by culture was defined as less than the median number of days required for MGT culture.

* Adjusted for age, sex, religion, education, body mass index and anemia.

TB = tuberculosis; RRR = relative risk reduction; CI = confidence interval; DM =diabetes mellitus; AFB = acid-fast bacilli; TTD = time to TB detection; MGT = Mycobacterial Growth Indicator Tube.
Association of DM and TB Impact on TB Outcomes

• Prospective study Southern Mexico 1995-2010
  – Prevalence of DM among 1262 patients 29.63%

• Presentation: More severe clinical manifestation
  – Cavities aOR 1.82

Jimenez-Corona et al; Thorax Vol 68; 2013
Diabetes and TB Treatment Outcomes

Sputum conversion ≥ 60 days
- 45.86 vs. 37.22 days $P = 0.014$; OR 1.51

• Failure 4.68% vs. 2.24%; OR 2.93

• Death during treatment similar

• Death from other causes was more common in diabetics

Jimenez-Corona et al; Thorax Vol 68; 2013
Diabetes and TB Treatment Outcomes

- Recurrent disease **11.6% vs. 8.14%**; OR **1.76**
  - Diabetic patients were more likely to have new isolate of TB (by genotype)
  - Identical strains in 1st and 2nd samples **80.77% vs. 89.47%**; OR **1.8**

- Retreated diabetics more likely to have INH and rifampin resistant isolate

  Jimenez-Corona et al; Thorax Vol 68; 2013
Impact of Diabetes on Tuberculosis Treatment Outcomes

• A Systematic Review of 33 studies:

  » Baker et al. Bio Med Central, Medicine, 2011
### Table 1: Characteristics of included studies for the association between DM and TB outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Country</th>
<th>Type of TB</th>
<th>Population with DM</th>
<th>Duration of Culture Conversion 2-3 months</th>
<th>Failure &amp; Death</th>
<th>Death (4 studies death)</th>
<th>Relapse</th>
<th>Adjusted Variables for Death Outcome</th>
<th>DR Recurrence</th>
<th>DM Definition</th>
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<tbody>
<tr>
<td>Alisjahbana [11]</td>
<td>Prospective cohort</td>
<td>Indonesia</td>
<td>Pulmonary TB</td>
<td>634</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>2 measurements of FBG &gt; 12 mg/dL</td>
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<td>Medical records</td>
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<tr>
<td>Ambrosetti [28]</td>
<td>Prospective cohort</td>
<td>Italy</td>
<td>Undifferentiated TB</td>
<td>778</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>Medical records</td>
<td></td>
<td></td>
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<td>Ambrosetti [29]</td>
<td>Prospective cohort</td>
<td>Italy</td>
<td>Undifferentiated TB</td>
<td>838</td>
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<td>Medical records</td>
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<td>Ambrosetti [30]</td>
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<td>Anunnatsiri [31]</td>
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<td>Thailand</td>
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<td>Banu Rekha [32]</td>
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<td>India</td>
<td>Pulmonary TB</td>
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<td>Medical records, FBG</td>
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<td>Bashir [33]</td>
<td>Retrospective case-control</td>
<td>USA</td>
<td>Undifferentiated TB</td>
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<td>Medical records, FBG</td>
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<td></td>
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<td>Blanco [34]</td>
<td>Retrospective cohort</td>
<td>Canary Islands</td>
<td>Pulmonary TB</td>
<td>98</td>
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<td>Medical records, FBG</td>
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<td>Cents [35]</td>
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<td>Undifferentiated TB</td>
<td>1,162</td>
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<td>Chiang [37]</td>
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<td>Taiwan</td>
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<td>Dooley [12]</td>
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<td>Undifferentiated TB</td>
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<td>Medical records, non-FBG &gt; 200 mg/dL, DM medications</td>
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<td>Fielder [38]</td>
<td>Retrospective cohort</td>
<td>USA</td>
<td>Pulmonary TB</td>
<td>174</td>
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<td>Medical records</td>
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<td>Fisher-Hoch [39]</td>
<td>Retrospective cohort</td>
<td>Mexico &amp; USA</td>
<td>Pulmonary TB</td>
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<td>Medical records</td>
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<td>Harai [41]</td>
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<td>Japan</td>
<td>Pulmonary TB</td>
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<td>√</td>
<td>√</td>
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<tr>
<td>Hasibi [42]</td>
<td>Retrospective cohort</td>
<td>Iran</td>
<td>Disseminated TB</td>
<td>50</td>
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<td>√</td>
<td>√</td>
<td>√</td>
<td>Medical records</td>
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<td>Ito [43]</td>
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<td>√</td>
<td>√</td>
<td>Medical records</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kita [44]</td>
<td>Retrospective cohort</td>
<td>Japan</td>
<td>Pulmonary TB</td>
<td>520</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>Medical records</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Relative Risk (DM):**
- Failure & Death: 1.69
- Death (4 studies death): 4.95
- Relapse: 3.89

Baker, BMC Medicine 2011
TB and Diabetes - Clinical Presentation

- Around 20% of the 85-95 active TB cases each year in San Antonio TB Clinic are diabetics
  - More likely to have higher BMI
  - Nearly all have poor diabetic control
  - Often have had > 2 medical evaluations that did not diagnose TB
  - Most have not had routine screening for TB risk factors or testing for TB
October 10, 2015

40 yr old DM with HBA1C 9.3%
2 ½ mo history of cough, night sweats, weight loss
DX as CAP; treated with levaquin
Increased symptoms, returned to ER
Treated with Levaquin/Vancomycin
BAL showed AFB +
RIPE started 10/29/15
First negative culture 1/4/2016
Effect of DM Control status on Treatment Response in Pulmonary TB: A Prospective Study

• Multicenter (10) prospective study: 9/2012-9/2014 in South Korea
  – 661 patients with pulmonary TB
  • 157 (23%) were diabetic with good control
    – 68.8% poor control HbA1C >7.0%

Yoon YS, Thorax 2017
Effect of DM Control status on Treatment Response in Pulmonary TB: A Prospective Study

• Uncontrolled diabetic group had more symptoms, more + sputum smears, and more cavities

• Uncontrolled diabetics more likely to have + culture after 2 months, and either treatment failure or death

• Those with controlled diabetes had similar responses to non-diabetics.

Yoon YS, Thorax 2017
Should Treatment of Diabetics with TB be Different?

• No data to make comprehensive recommendations on diabetics
  – But we should treat aggressively and monitor carefully

• Case by case decision:
  – Intensity of dosing, most if not all should have daily dosing
  – Duration of therapy
  – Monitoring during treatment
    • Drug levels if slow to convert
ADJUNCTIVE AND HOST DIRECTED THERAPY
Metformin as adjunct antituberculosis therapy

Amit Singhal,1* Liu Jie,1† Pavanish Kumar,1† Gan Suay Hong,2 Melvin Khee-Shing Leow,3,4 Bhairav Paleja,1 Liana Tsenva,5,6 Natalia Kreipina,5 Jinmiao Chen,1 Francesca Zolezzi,1 Barry Kreiswirth,5 Michael Poidinger,1,7 Cynthia Chee,2 Gilla Kaplan,5,8 Yee Tang Wang,2 Gennaro De Libero1,9*

The global burden of tuberculosis (TB) morbidity and mortality remains immense. A potential new approach to TB therapy is to augment protective host immune responses. We report that the antidiabetic drug metformin (MET) reduces the intracellular growth of Mycobacterium tuberculosis (Mt) in an AMPK (adenosine monophosphate–activated protein kinase)–dependent manner. MET controls the growth of drug-resistant Mt strains, increases production of mitochondrial reactive oxygen species, and facilitates phagosome–lysosome fusion. In Mt-infected mice, use of MET ameliorated lung pathology, reduced chronic inflammation, and enhanced the specific immune response and the efficacy of conventional TB drugs. Moreover, in two separate human cohorts, MET treatment was associated with improved control of Mt infection and decreased disease severity. Collectively, these data indicate that MET is a promising candidate host-adjunctive therapy for improving the effective treatment of TB.
Metformin as an Adjunctive Therapy for MTB

- Metformin restricts mycobacterial growth by inducing mitochondrial reactive oxygen species (ROS) production
- Metformin enhances the efficacy of conventional anti-TB drugs.
- Metformin reduces TB-induced tissue pathology and enhances immune response.
- Metformin reduces inflammatory response
Association of Vitamin D and MTB

• Vitamin D deficiency is associated with:
  – Increased risk of active TB and
  – Increased risk of progression from LTBI to active TB disease

• Noted association between DM and LTBI in those with low Vitamin D levels
  – Median 25OHD plasma level among patients with DM was significantly lower than in those without DM
Increased risk of latent tuberculous infection among persons with pre-diabetes and diabetes mellitus

R. L. Hensel,* R. R. Kempker,*† J. Tapia,† A. Oladele,‡ H. M. Blumberg,*†§ M. J. Magee†

*School of Medicine, Emory University, Atlanta, †Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, ‡DeKalb County Board of Health, Decatur, §Departments of Epidemiology and Global Health, Emory Rollins School of Public Health, Atlanta, ††Division of Epidemiology and Biostatistics, Georgia State University, School of Public Health, Atlanta, Georgia, USA

Table 5 Interaction between DM status with vitamin D level and odds of latent tuberculous infection, DeKalb County Refugee Clinic, Atlanta, GA, USA

<table>
<thead>
<tr>
<th>Vitamin D level</th>
<th>DM status</th>
<th>OR (95%CI)</th>
<th>aOR (95%CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥20 ng/ml</td>
<td>No DM</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Pre-DM</td>
<td>1.35 (0.86–2.10)</td>
<td>1.24 (0.77–2.00)</td>
</tr>
<tr>
<td></td>
<td>DM</td>
<td>1.14 (0.49–2.68)†</td>
<td>1.22 (0.29–2.54)</td>
</tr>
<tr>
<td>&lt;20 ng/ml</td>
<td>No DM</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Pre-DM</td>
<td>2.89 (1.64–5.10)‡</td>
<td>2.63 (1.45–4.74)</td>
</tr>
<tr>
<td></td>
<td>DM</td>
<td>4.79 (2.05–11.21)‡</td>
<td>4.44 (1.75–11.24)</td>
</tr>
</tbody>
</table>

* Multivariable model adjusted for age, sex, body mass index, TB incidence in country of origin, and smoking status.
† Breslow-day test for homogeneity statistically significant, \( P < 0.05 \).
DM = diabetes mellitus; OR = odds ratio; CI = confidence interval; aOR = adjusted OR.
Nutritional supplements for people being treated for active tuberculosis (Review)

Grobler L, Nagpal S, Sudarsanam TD, Sinclair D

Grobler L, Nagpal S, Sudarsanam TD, Sinclair D.
Nutritional supplements for people being treated for active tuberculosis.
DOI: 10.1002/14651858.CD006086.pub4.

www.cochranelibrary.com
Although supplementation of Vitamin D improves plasma levels this has not been shown to have clinically important benefits.

Despite multiple studies of vitamin D supplementation in different doses, statistically significant benefits on sputum conversion have not been demonstrated.

**Author’s Conclusions:** Food or energy supplements may improve weight gain during recovery from TB in some settings but there is currently no evidence that they improve TB treatment outcomes.
End of the Road for Adjunctive Vitamin D Therapy for Pulmonary Tuberculosis?

Ibrahim Abubakar*, Frank Kloprogge
University College London Institute for Global Health
*correspondence: i.abubakar@ucl.ac.uk

Adjunctive and host directed therapies are increasingly recognised as an important target in the quest for novel effective antituberculous therapy. (1) The global increase in drug resistance to antibiotics suggests that effective adjunctive medications may provide an alternative avenue to treat infections. Vitamin D supplementation has been hypothesized as a potential adjunctive agent for the treatment of tuberculosis and evaluated in several trials. (2) Ganmaa and colleagues (2) evaluated the effectiveness of adjunctive vitamin D on sputum culture conversion and assessed the influence of key vitamin D pathway single nucleotide polymorphisms (SNPs) on sputum culture conversion concluding that there is no evidence that vitamin D supplementation improved outcomes.
Adjunctive and Host Directed Therapy

NOT THERE YET!
Optimize Drug Exposure – Get The Dose Right
Slow Response To TB Treatment

- Retrospective study of slow responders (42/311) ≥ 30 days of treatment

- Slow response ≥ 2 of following:
  - Smear still positive
  - Symptoms present and not improved
  - CXR shows no improvement

- All had serum therapeutic drug level done
  - Low INH 23/39 (39%)
  - Low rifampin 22/42 (52%)
  - Low INH and rifampin 13/39 (33%)

Heysel, EID October 2010
Slow Response to Treatment

- Diabetes was only independent predictor of low rifampin level:
  - 5.8 times greater risk, $p = 0.01$

- Only independent significant predictor of slow response was diabetes:
  - 6.9 OR, $p < 0.001$

- 90% of those with low initial rifampin level were therapeutic with increase dose from 600 to 900 mg
  - No associated toxicity
  - Good treatment outcomes

Heysel, EID October 2010
Benefit of early therapeutic serum drug level monitoring.

Table 3 Sputum culture conversion in adults with pulmonary tuberculosis matched 2:1 non-diabetes to diabetes for age, gender, sputum smear result and chest x-ray findings

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>non DM</td>
<td>DM</td>
</tr>
<tr>
<td></td>
<td>N = 60</td>
<td>N = 30</td>
</tr>
<tr>
<td>Time to culture conversion (days, mean ± SD)</td>
<td>57 ± 35</td>
<td>61 ± 32</td>
</tr>
<tr>
<td>2 months culture conversion, No. (%)</td>
<td>34 (57)</td>
<td>15 (50)</td>
</tr>
</tbody>
</table>
Take Home

We are Dosing Rifampin (Our Very Best Drug) Too Low!

INH 3-5
Rifampin 8-24

Fig. 2 C_{TIV} results for early therapeutic drug monitoring among diabetes patients in the post-intervention group. Boxes= interquartile ranges with median line, whiskers= minimum and maximum values, and one circle (for isoniazid) is a statistical outlier. Brackets represent the expected range for the Cmax; isoniazid 3-5 µg/ml and rifampin 8-24 µg/ml
Anti-TB Drug Concentrations in TB Patients with and without Diabetes

- Three times/week treatment – peak level 2 hours
  - INH 600 mg
  - Rifampin 450 mg if < 60 kg, for ≥ 60 mg then 600 mg
  - PZA 1500 mg

- Median INH (6.6 vs 7.8) & PZA (31 vs 34.1) significantly lower in diabetics

- INH, RIFAMPIN and PZA influenced by age and dose
  - INH and PZA by DM
  - RIFAMPIN by alcohol use

- Rifampin peak < 8 in: 92% TB DM and 91% TB without diabetes

Kumar AKH, Eur J Clinical Pharmacol, 2017 Chennai India
Fig. 1 Two-hour drug concentrations in TB patients with and without diabetes mellitus. The \textit{central line} of the box plot denotes median and the \textit{lower} and \textit{upper lines} denote 25 and 75 percentiles. The \textit{vertical bars} denote minimum and maximum values. \textit{RMP} rifampicin, \textit{INH} isoniazid, \textit{PZA} pyrazinamide
How About Good Case Management?

For Diabetes

For Tuberculosis
Does Enhanced DM Management Reduce Risk and Improve the Outcome of TB?


• Pay-for-Performance (p4p) plan in Taiwan
  – Case management plan for diabetics with package of services
    • Reimburses regular health care services (also for others)
    • Diabetic education
    • Initial, comprehensive F/U visits and annual evaluation visit
    • HbA1c and fasting glucose quarterly, BP, cholesterol checked
    • Medications for DM, BP and hyperlipidemia
Does Enhanced DM Management Reduce Risk and Improve the Outcome of TB?


- Evaluated 79,471 DM-p4p versus 100,000 DM-non-p4p and 100,000 non-diabetics from 2008-2009 NHI database
  - Evaluated newly diagnosed incident TB
  - Evaluated TB treatment outcomes 2008-2009
Does Enhanced DM Management Reduce Risk and Improve the Outcome of TB?


- Cummulative TB incidence DM-non-p4p higher than among DM-p4p
  - 259.9/100,000 DM-non-p4p
  - 137.5/100,000 DM-p4p
  - 74.1/100,000 non-DM
- DM-non-p4p significantly higher risk TB vs non-DM but DM-p4p did not have significantly higher risk TB vs non-DM
- Treatment success better for DM-p4p
  - DM-non-p4p 68.9% DM-p4p 75.6% non-DM 73.6%
Table 3 1-year, 2-year and 3-year cumulative incidence rates of TB per 100,000 population in a random sample of DM-p4p, DM-non-p4p and non-DM patients, from the 2008–2009 NHI database*

<table>
<thead>
<tr>
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<th>Number at risk</th>
<th>Cumulative number</th>
<th>Cumulative incidence</th>
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<tbody>
<tr>
<td><strong>DM-p4p</strong></td>
<td></td>
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</tr>
<tr>
<td>Total</td>
<td>79,471</td>
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</tr>
<tr>
<td>2008 cohort</td>
<td>46,226</td>
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</tr>
<tr>
<td>1-year</td>
<td></td>
<td>63</td>
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<td>2-year</td>
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<td>130</td>
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<td>3-year</td>
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<td>441</td>
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<td>2-year</td>
<td></td>
<td>85</td>
<td>256</td>
</tr>
<tr>
<td><strong>DM-non-p4p</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>100,000</td>
<td>85,810</td>
<td>239</td>
</tr>
<tr>
<td>2008 cohort</td>
<td></td>
<td>130</td>
<td>281</td>
</tr>
<tr>
<td>1-year</td>
<td></td>
<td>204</td>
<td>441</td>
</tr>
<tr>
<td>2-year</td>
<td></td>
<td>603</td>
<td>703</td>
</tr>
<tr>
<td><strong>Non-DM</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>100,000</td>
<td>48,334</td>
<td>66</td>
</tr>
<tr>
<td>2008 cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td></td>
<td>33</td>
<td>66</td>
</tr>
<tr>
<td>2-year</td>
<td></td>
<td>61</td>
<td>126</td>
</tr>
<tr>
<td>3-year</td>
<td></td>
<td>95</td>
<td>197</td>
</tr>
<tr>
<td>2009 cohort</td>
<td></td>
<td>51,666</td>
<td>49</td>
</tr>
<tr>
<td>1-year</td>
<td></td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>2-year</td>
<td></td>
<td>85</td>
<td>165</td>
</tr>
</tbody>
</table>


DM = diabetes mellitus, TB = tuberculosis; NHI = National Health Insurance.

Table 5 Factors associated with the outcome of TB among 766 incident TB cases that occurred in 2008–2009 in a sample of 279,471 patients from the 2008–2009 NHI database

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Success</th>
<th>Died</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (row %)</td>
<td>766</td>
<td>544 (71.0)</td>
<td>141 (18.4)</td>
<td>81 (10.6)</td>
</tr>
<tr>
<td>DM status*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM-p4p</td>
<td>164</td>
<td>124 (75.6)</td>
<td>21 (12.8)</td>
<td>19 (11.6)</td>
</tr>
<tr>
<td>DM-non-p4p</td>
<td>492</td>
<td>339 (68.9)</td>
<td>99 (20.1)</td>
<td>54 (11.0)</td>
</tr>
<tr>
<td>Non-DM</td>
<td>110</td>
<td>81 (73.6)</td>
<td>21 (19.1)</td>
<td>8 (7.3)</td>
</tr>
</tbody>
</table>
What Else Can We Offer in TB Clinics?

- Include glucose or HB A1C on blood work.
- Educate on need to follow a healthy eating plan.
- Encourage physical activity for 30 to 60 minutes/day.
- Stress the importance of taking medicines as directed.
- Encourage patients to quit smoking.
- Refer for regular physician visits
- Educate on need for daily foot check for cuts, blisters, sores, swelling, redness, or sore toenails.
TB and Diabetes - Treatment Issues

• Diabetics have an increased risk of hepatotoxicity
  – Multiple medications
  – Fatty liver
  – Some Hepatitis B or C positive

• Baseline and monthly liver enzymes

• Educate regarding risk of liver toxicity, symptoms to watch for, and what to do should these occur
TB and Diabetes - Treatment Issues

• Gastroparesis
  – Vomiting and slow emptying could prevent good drug levels

• Diabetic neuropathy at baseline complicates therapy due to risk of INH-related neuropathy
  – Baseline assessment of neuropathy
  – Vitamin B 6 to all diabetics on INH or ethionamide

• Renal insufficiency is associated with diabetes, especially long standing or poorly controlled DM
  – Adjust dose and dosing interval of EMB & PZA (Cr Cl < 30)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Change in frequency?</th>
<th>Recommended dose and frequency for patients with creatinine clearance &lt;30 ml/min or for patients receiving hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>No change</td>
<td>300 mg once daily, or 900 mg three times per week</td>
</tr>
<tr>
<td>Rifampin</td>
<td>No change</td>
<td>600 mg once daily, or 600 mg three times per week</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Yes</td>
<td>25–35 mg/kg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Yes</td>
<td>15–25 mg/kg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Yes</td>
<td>750–1,000 mg per dose three times per week (not daily)</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Yes</td>
<td>250 mg once daily, or 500 mg/dose three times per week*</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>No change</td>
<td>250-500 mg/dose daily</td>
</tr>
<tr>
<td>p-Aminosalicylic acid</td>
<td>No change</td>
<td>4 g/dose, twice daily</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Yes</td>
<td>12–15 mg/kg per dose two or three times per week (not daily)</td>
</tr>
</tbody>
</table>
I Don’t Think I Answered My Question

TREATING TB – WHAT HAPPENED?
ALL THE PATIENTS HAVE CHALLENGING CO-MORBID CONDITIONS NOW!