

**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

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THE ASSOCIATION OF DIABETES AND TUBERCULOSIS*
Epidemiology, Pathology, Treatment and Prognosis
BY HOWARD F. HOOT, M.D.†

(a) The development of pulmonary tuberculosis in juvenile diabetics 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.

(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 signs and symptoms in the "tuberculous diabetic"

TB more frequent in those with poor diabetes control

Overview

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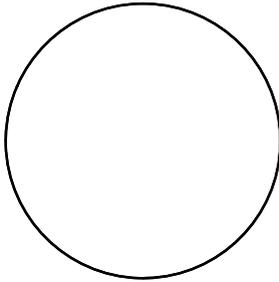
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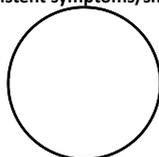
Drug concentrations are suboptimal for most DM/TB patients

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

Period, variable	No. (%) of patients with TB		Crude OR (95% CI)	Adjusted OR (95% CI)
	With DM (n = 84)	Without DM (n = 842)		
Intensive phase				
AFB negative*	67 (71.2)	466 (84.2)
AFB positive	17 (19.1)	64 (10.0)	2.14 (1.17-3.9)	1.90 (0.82-4.42)
No sputum sample available, hospital transfer, and/or study default	4 (4.8)	21 (3.7)
Death	2 (2.3)	0 (0)
Culture result positive for Mycobacterium tuberculosis	1/41 (1.7.1)	38/372 (10.3)	0.32 (0.09-2.16)	0.90 (0.30-2.08)
End of treatment				
AFB negative*	70 (74.5)	495 (80.6)
AFB positive	4 (4.8)	17 (3.1)	1.46 (0.48-4.47)	1.06 (0.17-6.60)
No sputum sample available, hospital transfer and/or study default	18 (19.1)	88 (16.3)
Death	2 (2.3)	0 (0)
Culture result positive for M. tuberculosis†	0/27 (0.2.2)	32/323 (9.6)	2.09 (1.01-7.14)	7.05 (1.09-20.95)

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

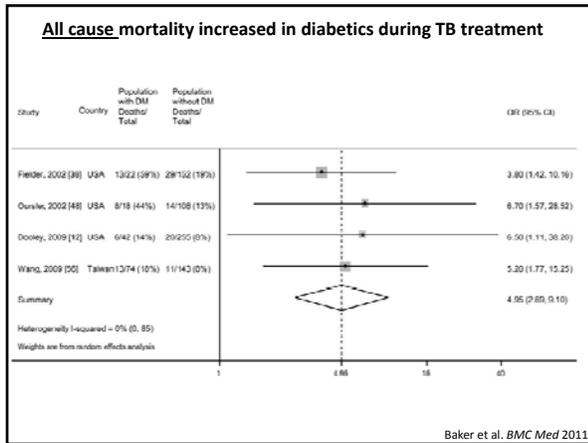
- 14.8% prevalence of undiagnosed DM in new TB patients
- TB-DM had greater symptoms at time of diagnosis

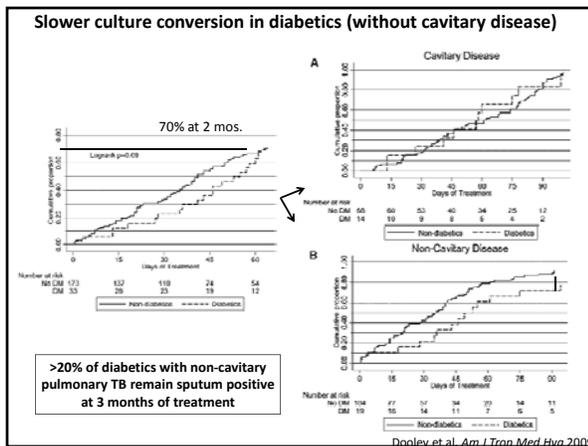
Alisjahbana et al. Clin Infect Dis 2007

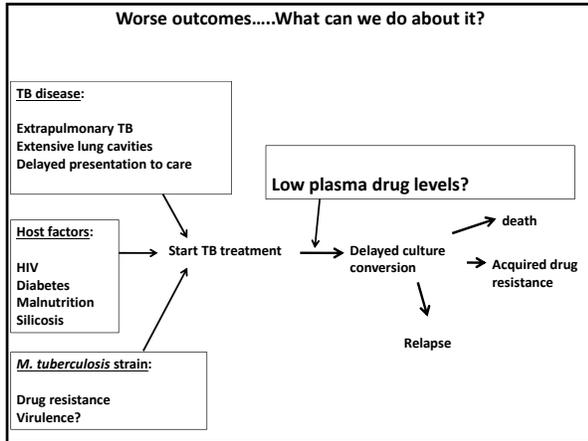


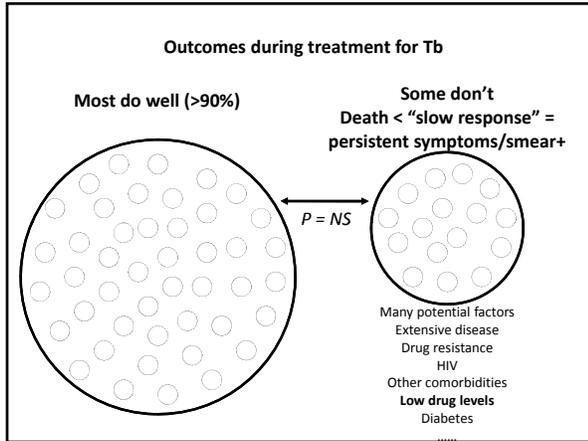
- In Maryland, odds of death were 6.5 times higher (p=0.039) for diabetics than non-diabetics with TB, even adjusting for HIV, age, weight, and foreign birth
- ★ ½ of deaths were not TB related
- Time to sputum culture conversion was longer (49 days for diabetics vs 39 days for non-diabetics, p=0.09)

Dooley et al. Am J Trop Med Hyg 2009





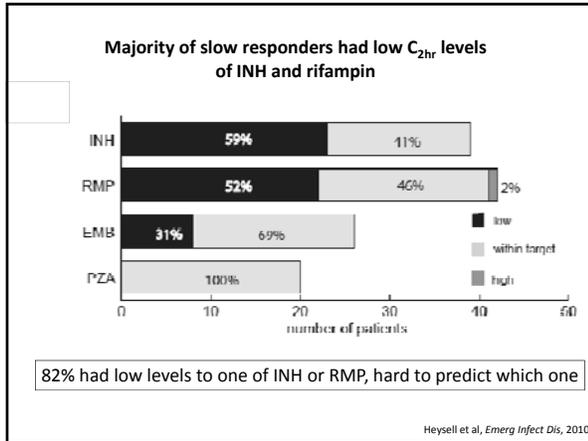


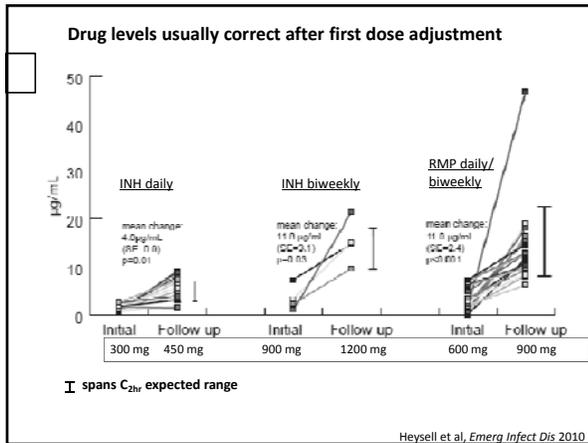


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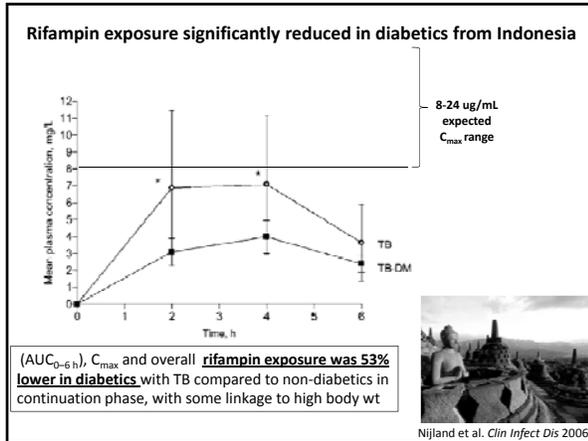
- We have been routinely checking serum anti-TB drug concentrations in "slow responders" since ~2007 (thanks to some add'l funding)
 - ~14% of all Tb patients, defined as no improvement in sx or persistent smear +
- Diabetics were **6.3 times more likely to be slow responders** ($p < 0.001$) adjusted 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})

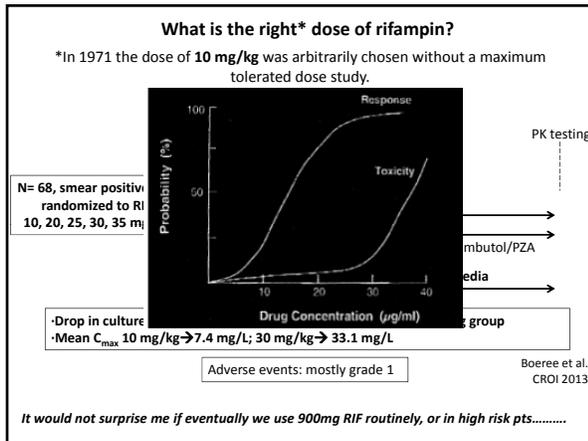
Heysell et al. Emerg Infect Dis 2010





- ### 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
 - HIV
 - Diabetes ?
 - Cystic Fibrosis
 6. Poor solubility¹
 7. Host genetics
 - Genetic polymorphism of gut xenobiotic transport
 - Metabolism
 8. Age
 9. Gender
-
1. Ashokraj et al. *Clin Res Reg Affairs* 2008





VIRGINIA

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)

Acknowledgments

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