

RENAL FAILURE AND ACTIVE
TUBERCULOSIS IN A HIGH
INCIDENCE UK CITY

Latent TB and immunosuppression

- Over a lifetime a healthy individual with TB has approximately 1 in 10 chance of developing active TB.
- This risk is greatly increased with certain co-morbidities or forms of immunosuppression.
- E.g. anti-TNF therapies
 - ▣ Incidence increased 2-3 fold.
 - ▣ The UK MHRA recommends all patients in whom treatment with an agent is being considered are screened and treated for latent TB

TB and renal disease

- Renal disease is associated with increased risk of active TB.
 - ▣ Haemodialysis. <10-25x healthy individual (varies with cohort).
 - ▣ AKI requiring short spells of dialysis and those with CKD not requiring it have increased rates.
- All ethnicities but most apparent in those who are both at risk of TB and with high prevalence of CKD.
 - ▣ CKD, dialysis and following transplantation.
 - ▣ Particularly high in those in the UK <5 years
 - ▣ Africa, Asian, S American, or Eastern European
- In most cases thought to be result of reactivation.

Why are renal patients at high risk?

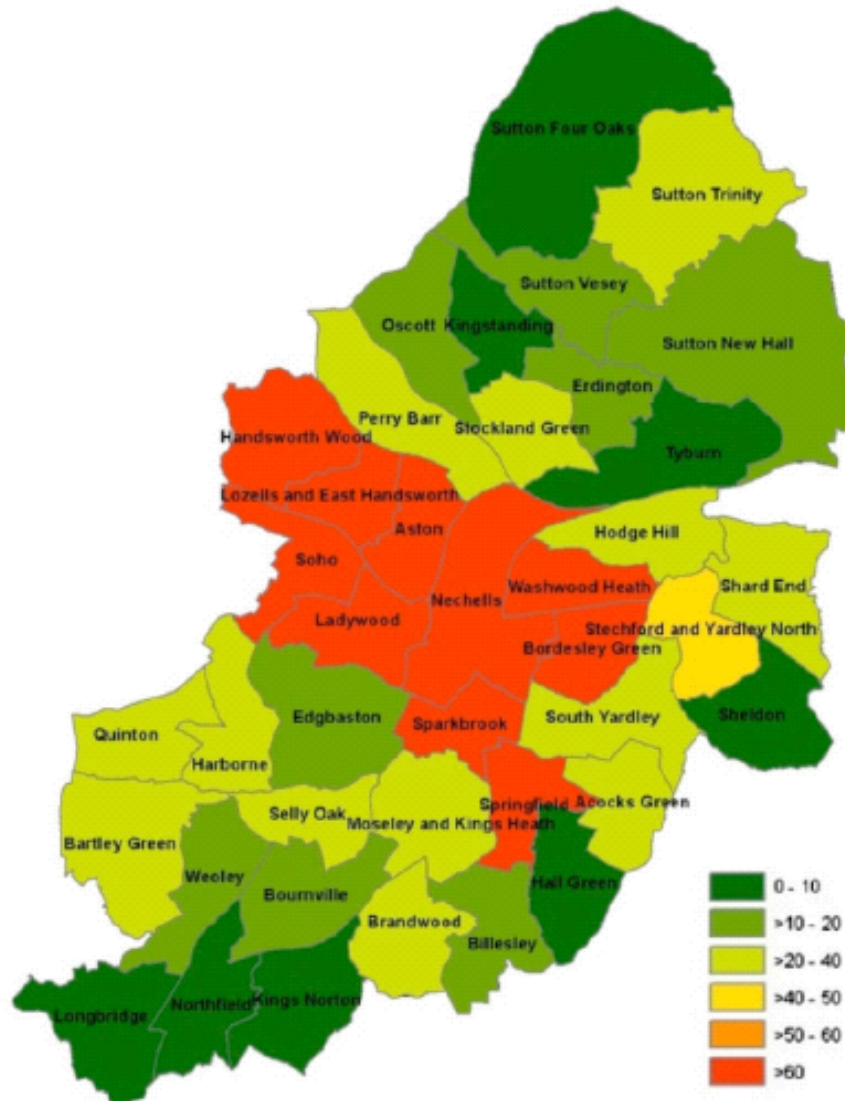
- Uraemia
 - Lymphopenia
 - Delayed T-cell hypersensitivity and mitogen response
 - Depressed monocytes phagocytic activity
 - Possible alterations in mucocilliary clearance
- Immunosuppressive therapies
- Iron – an important bacterial co-factor



In Birmingham

- Our demographics
 - ▣ 24% of the city born overseas, most India/Pakistan (ONS 2011)
 - ▣ TB rate 29 cases/100,000/y – England overall 10.2/100,000/y
- Current practice in Birmingham
 - ▣ HEFT: patients with CKD and entering dialysis are not routinely screened for latent TB.
 - ▣ QE: patients undergoing renal transplantation are given isoniazid prophylaxis regardless of risk.
- Question: Given our patient demographic and TB incidence is routine screening and treatment for latent TB among all patients with advanced CKD or entering dialysis justified?

Birmingham, rates 2013 per 100,000



What is the incidence of active TB?

- A retrospective analysis collaborating with Dept of Primary Care at UoB.
- Dept of Renal Medicine patient information system cross-referenced with the HoEFT TB register.
 - ▣ All patients seen by Renal Medicine between 1/1/2005 and 1/10/2016 with the exception of those with prior TB.
 - ▣ Patients were followed up until they either developed TB, died, transferred out of the unit, or reached 1/10/16.
 - ▣ CKD stage was taken from single eGFR or evidence of dialysis.

Demographics

- 8767 patients representing 53,833 patient years.
- Median age at entry 66, 71% white, 18% Asian/Asian British.
- By the end of follow up:
 - 24% were CKD<3
 - 45% were CKD 4/5
 - 31% were on RRT.
- 68 cases of active TB over the study period.

TB patients renal disease

	Number
Immunosuppression	
None	52
Immunosuppressive drugs	11
HIV	2
Not known	3
Renal diagnosis	
Diabetes	15
Glomerulonephritis	8
Hypertension	16
HIV nephropathy	1
Other	14
Unknown	14

Demographic and clinical factors associated with incident TB

	Incident TB	No incident TB	significance*
Renal patients (%)	68 (0.8%)	8699 (99.2%)	
Mean age at entry (SD)	55.0 (16.0)	62.5 (18.7)	p<0.001
Mean age at exit (SD)	60.2 (17.2)	66.3 (18.0)	p=0.003
Male (%)	36 (53%)	4883 (56%)	p=0.597
Ethnicity (%)			p<0.001
White	7 (10.3%)	6260 (72.0%)	
Asian/Asian British	53 (77.9%)	1556 (17.9%)	
Black/Black British	7 (10.3%)	446 (5.1%)	
Other Ethnic Groups	0 (0.0%)	116 (1.3%)	
Deaths (%)	16 (23.5%)	3218 (37.0)	p=0.022
Mean age at death in years (SD)	67.4 (16.1)	74.9 (12.7)	p=0.003
IV iron treatment (%)	23 (33.8%)	1764 (20.3%)	p=0.006
Diabetes at exit (%)	23 (33.8%)	2237 (25.7%)	p=0.128

Comparison of renal cohort patients with and without incident TB

Does iron influence incidence?

- Iron is an important co-factor for many bacteria.
- Iron supplementation may be associated with increased incidence of infection in developing settings.
- It is important for TB growth within macrophages
 - ▣ Macrophages ingest old RBC and accumulate iron
 - ▣ This is then returned to marrow for erythroid precursors
- Adding iron experimentally increases TB growth, chelating it limits growth.
- Low and high plasma ferritin associated with increased risk of treat failure
- High hepcidin and ferritin associated with risk of developing TB after household contact (Gambia)

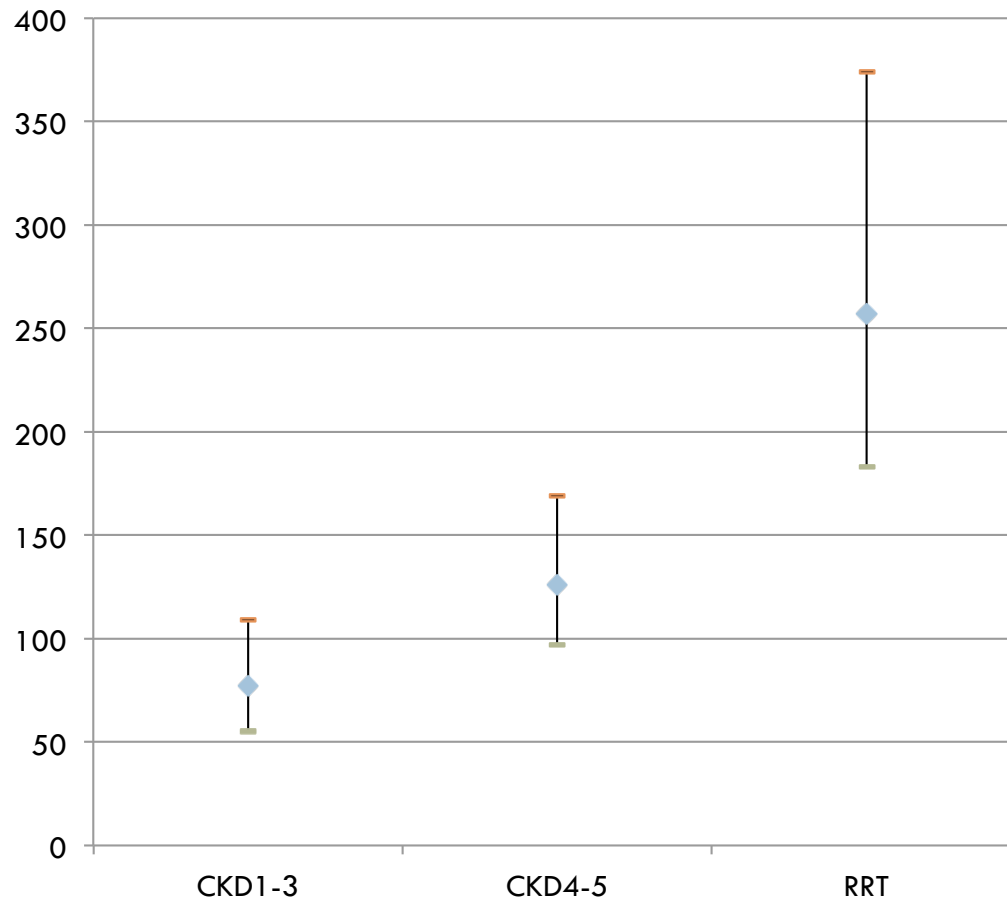
TB cases

	Number
TB site	
Pulmonary	33
Pleural	1
Abdominal	3
Intrathoracic LN	11
Extrathoracic LN	1
Miliary	4
Spinal	3
Other (joint, pericardial, urinary, unknown)	12
Diagnostics	
Smear positive (n culture positive)	22 (19)
Smear negative (n culture positive)	31 (1)
Histology (n culture positive)	8 (3)
Drug sensitivity (from 23 culture positive)	
Fully sensitive	21
INH mono-resistant	1
RIF resistant or MDR	1
Treatment duration	
6 months	40
7-9 months	7
10-12 months	9
13-24 months	3
Not treated	1
Unknown	7

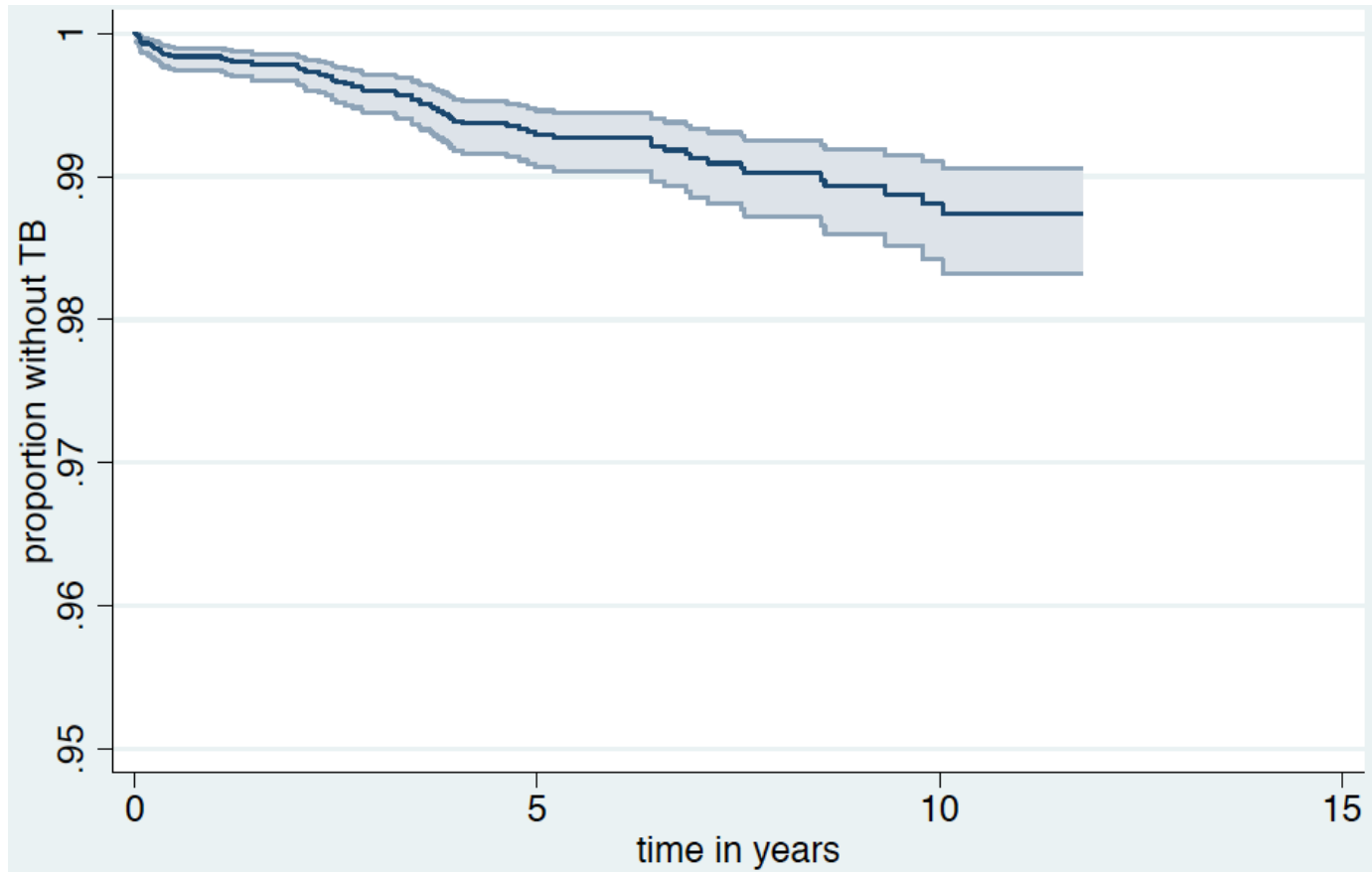
TB cases

- Deaths
 - ▣ 8 of the 16 recorded deaths among TB patients occurred within 2 years of starting treatment
 - ▣ 2 of these were directly attributable to TB, the remainder due to unrelated CV or respiratory disease.
- Molecular epidemiology
 - ▣ MIRU-VNTR genotyping was available for 20 of 23 culture positive specimens. 12 of those had WGS data.
 - ▣ Ruled out relation between all but two cases (same VNTR and no WGS data) – but these had no epidemiological link.
 - ▣ 4 of the 20 cases were identified by WGS as part of larger UK TB clusters.

TB incidence / 100,000 person years



TB-free survival among renal cohort patients with CKD 4/5 or receiving renal replacement therapy.



Time starts from earliest of CKD 4/5, dialysis or first seen in clinic with CKD 4/5/dialysis

Should we test routinely?

- BTS recommendations
 - ▣ All patients with CKD at risk of TB should have a history of prior TB or contact sought, clinical examination, CXR and “if appropriate” an IGRA
 - ▣ “Routine assessment of patients with CKD or on dialysis with skin test or IGRA is not recommended. Renal physicians may wish to assess individual patients at high risk of latent TB with an IGRA and discuss results with chest/ID”
 - ▣ Patients **awaiting transplantation** may be assessed with an IGRA – “an individual risk assessment can be made”. “In general all black African and Asian patients born outside the UK should be screened”
- WHO recommendations
 - ▣ Test all patients receiving dialysis

BTS, Thorax 2010;65:559

Getahum, Eur Respir J. 2015 46(6):1563–76

Testing for latent disease in CKD

- 50% of patients with CKD have reduced responsiveness to PPD skin testing – ie. A negative test is not useful.
- The performance of IGRA tests is variable but as specific and more sensitive than TST – less failures and repeats.
- T-SPOT performs better than QFT in dialysis patients in most series, e.g. in Korea:
 - ▣ Lower frequency of indeterminate results (4.8% vs 12.6%)
 - ▣ Higher positivity (60.4% vs 45.9%)
- There is a degree of conversion/reversion in serial testing
 - ▣ IGRA reversion in 16% and 29.8%
 - ▣ IGRA conversion 20 and 26.8%

What is the practice in UK renal units?

- 2011 survey of UK transplant units to assess whether practice mirrored the BTS guidance.
 - ▣ 16/19 performed “clinical risk assessment” for TB (e.g. country of origin).
 - ▣ 4/19 performed IGRA as part of patient evaluation
- 2015 survey of wider UK renal units (45 responses).
 - ▣ 70% did not routinely screen CKD4/5 and transplant patients.
 - ▣ 37% screened people born in high-incidence country.

Conclusion

- If the logic applied to anti-TNF therapy is followed the case for routine testing of all patients at CKD 4/5 or receiving dialysis is clear.
 - ▣ The risk increase appears to be much higher than with anti-TNF.
 - ▣ The cost is likely to be outweighed by the saving with an anticipated reduction in expensive contact tracing exercises.
- To consider:
 - ▣ Reliability of IGRA in this cohort. T-Spot seems to be fairly good.
 - ▣ Incidence of INH-induced hepatitis - around 2.4% for the average patient in our cohort.
 - ▣ Who to test – this data would imply at minimum, those of Asian/Asian British or Black/Black British ethnicity at CKD 4/5 or receiving dialysis.
 - ▣ But perhaps all CKD4/5 and RRT, cf. anti-TNF patients?

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