Poor performance of paired tests of latent tuberculosis in highly immune-compromised individuals exposed to multidrug-resistant tuberculosis: time for new diagnostic markers

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To the Editor:

Australia has one of the lowest incidence rates for tuberculosis (TB) in the world at <6 per 100 000 population [1]. The necessity to clarify diagnostic and management strategies for TB in vulnerable populations is heightened by an increasingly multicultural immigrant population from high TB prevalence locations and growing numbers of individuals exposed to immune suppressing and modulating therapies.

Immune suppression impacts the accuracy of diagnosis of latent TB (LTBI) and increases vulnerability of progression to active TB (ATB) in those infected. The current diagnostic tests for LTBI rely on intact T-cell functions.

Infection with *Mycobacterium tuberculosis* is a particular threat for solid organ transplant (SOT) recipients due to the effects on T-cell functions of agents used to prevent rejection [2]. We present the results of a case study that demonstrates the poor performance of these tests in immunosuppressed SOT recipients and highlights the urgent need for more accurate biomarkers that are independent of T-cell functions.

A middle-aged renal transplant recipient from a high TB risk country of birth (COB) was diagnosed with disseminated multidrug-resistant (MDR)-TB that included sputum 3+ smear positive pulmonary disease. This was diagnosed 6 months post-transplantation, with an estimated infectious period of 3 months prior to confirmation of the TB diagnosis. This individual had no clear history of TB exposure, nor risk factors for MDR-TB, but had an indeterminate interferon γ release assay (IGRA) during pre-transplant screening. No TB preventive therapy (TPT) was given despite the absence of contraindications to treatment. There was no evidence of transmission of TB from the organ donor. The index case's transplant was managed with prednisone, tacrolimus and mycophenolate, and TB treatment was initiated with a World Health Organization (WHO) endorsed long-course MDR regimen.

The threshold for screening of contacts was low given their vulnerability (majority were SOT recipients) and the MDR isolate. 530 contacts were screened (all >3 months after likely contact with the index case) with paired tuberculin skin test (TST) and IGRA testing (using the QuantiFERON-TB Gold in tube). This included seven healthy "household contacts" with the remainder (n=523) "casual contacts" (cumulative exposure <8 h), most often brief and in outpatient clinic settings [2, 3]. The outpatient waiting rooms had adequate ventilation and space to minimise close contact with a symptomatic patient. Utilising both tests for diagnosis of LTBI in highly immune-suppressed contacts was consistent with available guidelines [4, 5].

442 (83.4%) contacts were SOT recipients (renal n=387; liver n=55), 57 had chronic kidney disease (CKD), seven were immune-suppressed for other conditions and 24 were healthy contacts. 79 (14.9%) were from high TB risk COBs (defined as incidence >40 per 100 000 population) [6].

A TST was deemed positive with ⩾5 mm of induration and the IGRA scored as "positive", "negative" or "indeterminate" using the standard manufacturer's definition [7].

Shareable abstract (@ERSpublications)
Guideline-based recommendations for diagnosis of latent TB in highly immune suppressed populations are difficult to interpret and poorly characterised. More accurate biomarkers independent of T-cell functions are urgently required. https://bit.ly/41P8vTa

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The paired results are outlined in table 1. A positive result on either test was deemed consistent with LTBI [4, 5].

Analysis of the paired tests revealed very poor agreement with a Cohen's κ estimate (calculated excluding indeterminate IGRA results) of 0.08 (95% CI: 0.0–0.17) (table 1). A multivariate analysis revealed an increased odds of a positive TST (OR 2.4, 95% CI 1.4–4.7) associated with BCG vaccination, but reduced odds in the presence of immune suppression (OR 0.1, 95% CI: 0.1–0.3) and higher CKD stage (CKD stage >3 OR of 0.3 (95% CI: 0.0–0.3) compared to CKD stage 1).

A high-risk COB was seen in 78.6% (11 out of 14) with a positive IGRA (compared to 25.3% with a positive TST). Increased odds of concordant paired TST/IGRA were predicted by immune suppression (OR 4.5, 95% CI 2.1–9.9), but no associations of a positive result on either test with specific immune suppressive agents, or time since transplant, were demonstrated.

The overall rate of indeterminate IGRA due to inadequate control (mitogen) response was 3.2% with this group demonstrating a higher neutrophil/lymphocyte ratio compared to other IGRA results (p=0.001).

All positive cases were offered management including TPT or clinical/radiological surveillance for a minimum of 24 months. 16 contacts elected to receive TPT with moxifloxacin for 6 months (based on susceptibility of the index case isolate). No significant interactions or toxicity were observed in those who received TPT. The majority of those who declined TPT did so based on perceptions of low risk, and concerns regarding the risks of TPT. Physician bias may have influenced this decision in some cases.

At >36 months of follow-up no cases of ATB related to exposure to the index case have been identified.

While this study provides reassurance regarding the risk of transmission in high-risk contacts with casual contact, it demonstrates the limitations of the current diagnostic tests for LTBI both in pre-transplant screening, and for screening contacts as recommended in local and international guidelines [4, 5]. Previous studies have demonstrated inaccuracies and poor predictive values (PV) with immune suppression for both tests, with pooled data suggesting IGRA has a superior (but still modest) positive PV (4.5%) when compared to TST (2.3%) [8]. The negative PV for both tests are difficult to define in immune suppressed populations given the greater propensity for false negative results, although IGRA is thought to be superior in this setting [9].

Agreement between these tests is variable even in immune competent populations [10] and varies with the chosen cut-point for a positive TST [11]. The poor agreement demonstrated in this study calls into question recommendations to use paired testing in this setting given the higher rates of positive TST when compared to IGRA but with a suggestion that immune suppression reduces the sensitivity of both tests [4, 5]. The propensity for an indeterminate IGRA result with immune compromise further compounds this, as the PV of this result for progression to active infection is unknown. In our cohort only a high neutrophil/lymphocyte ratio predicted an indeterminate IGRA result [12]. The T-spot Tb assay may have performed better than the QuantiFERON-TB assay in this setting [13], although it is unclear how this would have influenced results. This commercially available assay was not available for use in this case, and is not routinely used in most Australian jurisdictions. Alternative biomarkers for LTBI diagnosis have been evaluated, including those that rely on immune profiling with T-cell targets [14] that may also be affected by T-cell dysfunction. Whole blood transcriptomic tests (mRNA signatures) have shown promise, although to this point the predictive value has been hampered by interactions with other non-mycobacterial infections [15], and their utility in highly immune-compromised is unknown.

TABLE 1 Cross table of tuberculin skin test (TST) and interferon γ release assay (IGRA) results (paired tests)[#]

	IGRA negative	IGRA positive	IGRA indeterminate	Total
TST negative	433 (94.5)	9 (2.0)	16 (3.5)	458 (86.4)
TST positive	66 (92)	5 (7.0)	1 (1.4)	72 (13.5)
Total	499 (94.1)	14 (2.6)	17 (3.2)	530 (100)

Data are presented as n (%). [#]: observed level of agreement (excluding indeterminates) 84.9%; Cohen's kappa estimate 0.08 (95% CI: 0.0–0.17).

No cases of ATB occurred during 3 years of follow-up, a period during which progression to ATB would be likely to have occurred in those infected [1]. This most likely reflects the relatively low risk of transmission in most contacts given minimal contact, and the association of positive results with other risks of prior exposure (including COB). Effective targeting of TPT for those at highest clinical risk was a potential influence, although this is impossible to define with certainty.

There are several limitations of this study. It is an observational study with data collected in a clinical context. Low numbers of positive and indeterminate IGRA results made more detailed analysis (particularly logistic regression and κ statistic estimate) difficult to perform with confidence. The strengths of this study are, however, that it was performed in a real world, clinical context and included a large proportion of highly immune suppressed subjects that had paired testing with the TST and IGRA, providing a unique analysis.

In summary, this case study highlights the limitations of the current tests for diagnosis of LTBI in highly immune suppressed individuals. It seems likely that the low threshold for screening of this vulnerable cohort due to the public health imperative and fear of MDR-TB transmission resulted in the recommendations for screening being exceeded. From an infection control aspect this approach was effective in preventing the development of active disease in contacts. While it provides a degree of reassurance regarding true transmission risk in those with likely limited exposure to a highly infectious case, it also indicates the importance of defining new diagnostic tests that are independent of T-cell functions in these individuals.

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