Reply to Muñoz and Santin

To the Editor—We thank Muñoz and Santin for their interest in our review [1, 2]. We agree that in the study by Theodoropoulos et al, the authors’ inclusion of only a subset of the subjects with negative QuantiFERON-TB Gold or QuantiFERON-TB Gold In-Tube results results in a reported frequency of indeterminate results that is inflated [3]. The actual proportion of liver transplant candidates with indeterminate interferon-γ release assay (IGRA) results in the Theodoropoulos study was 19.6% (134 of 685 IGRA results performed; M.G. Ison, personal communication). However, it remains true that liver transplant candidates were at significantly higher risk for an indeterminate IGRA result compared to other solid organ transplant (SOT) candidates (in the sample, 41% of liver transplant candidates vs 11% of kidney transplant candidates). Interestingly, of 3 subjects in the Theodoropoulos study who developed active tuberculosis (see Table 1 of [1]) and had an IGRA, only 1 individual had a positive IGRA result (sensitivity for prediction of active tuberculosis, 33% [95% confidence interval, 5%–88%]) [3].

Muñoz and Santin assert that IGRA results perform better than the tuberculin skin test (TST) in SOT candidates [4]. In our review, we point out that a positive IGRA result may have a greater association with tuberculosis risk factors than a positive TST result, suggesting improved accuracy in the diagnosis of latent tuberculosis [2]. However, there are inadequate data to state that IGRA results perform better than TSTs in SOT candidates and recipients [5]. For example, in the study cited by Muñoz and Santin, the outcome was concordance and discordance between TST and QuantiFERON-TB Gold In-Tube results, not development of active tuberculosis [4]. A number of longitudinal studies have demonstrated the poor agreement between TSTs and IGRA results by evaluating test ability to predict active tuberculosis [6]. Although tuberculosis rates were slightly higher (though not significantly) in discordant pairs when IGRA was positive compared to pairs where TST was positive, it is important to note that active tuberculosis developed in subjects who had TST-positive but IGRA-negative results.

Muñoz and Santin state that increasing test sensitivity (eg, through the use of 2-step TST testing) is a strategy that will lead to overtreatment as opposed to relying solely on IGRA results. Developing
a test and establishing cutoff values involves trade-offs between sensitivity and specificity. In a situation where the pretest probability of a disease is low, then a higher specificity is desirable. On the other hand, if the risk for not diagnosing a disease is high, then sensitivity may be the more important measure. Guidelines recommend that testing with both a TST and an IGRA may be considered when the initial test is negative and the risk for infection, progression, or poor outcome is increased [7]. In lieu of a 2-step process using the TST, we suggest a role for dual testing. As in other immunocompromised situations, the use of dual testing may maximize opportunities for diagnosing and treating latent tuberculosis in SOT candidates [2]. It would seem prudent in vulnerable populations to use the available tests to increase sensitivity in pursuit of preventing a disease that is associated with substantial morbidity and mortality.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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David J. Horne,1 Masahiro Narita,1,3,4 Christopher L. Spitters,2,3,4 and Ajit P. Limaye2
1Division of Pulmonary and Critical Care Medicine, 2Division of Allergy and Infectious Diseases, and 3Department of Medicine, University of Washington, Seattle; and 4Tuberculosis Control Program, Public Health–Seattle & King County, Washington

References


Correspondence: Ajit P. Limaye, MD, University of Washington, Division of Allergy and Infectious Diseases, Box 356174, 1959 NE Pacific St, Seattle, WA 98195-6174 (alimaye@medicine.washington.edu).

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