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Interferon γ–Release Assays for Diagnosis of Latent Tuberculosis in Healthcare Workers in Low-Incidence Settings: Pros and Cons

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Guest:
Dr. Niaz Banaei is from the division of infectious diseases and geographic medicine and Medical Director of the Clinical Microbiology Laboratory at Stanford University.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

In well-resourced countries with a low incidence of tuberculosis, a major focus of TB control efforts is the detection and treatment of latent TB infection to prevent reactivation to active TB disease.

This approach is particularly relevant for healthcare workers. Interferon Gamma Release Assays are used to detect the release of interferon from T cells stimulated by tuberculosis specific antigens.

However, these tests differ in cost and complexity than the conventional tuberculin skin test.

The May 2014 issue of *Clinical Chemistry* includes a question and answer feature on the pros and cons of the use of the Interferon Gamma Release Assays.

In this article, five leaders in the field provide their opinion of this issue. One of those participants was Dr. Niaz Banaei of the Division of Infectious Diseases and Geographic Medicine, and Medical Director of the Clinical Microbiology Laboratory at Stanford University. He joins us today in this podcast.

Dr. Banaei, what are the advantages and disadvantages of using Interferon Gamma Release Assays compared to the tuberculin skin test for baseline screening?

Dr. Niaz Banaei: So, a number of studies have shown that both tests are equivalent in their accuracy. However, the Interferon Gamma Release Assays are more specific compared to tuberculin skin test in those populations that have received a BCG vaccine and the reason for that is that Interferon Gamma Release Assays use antigens that are absent from the BCG vaccine, so there is no cross reaction.

Another advantage of IGRAs is that they only require one visit and that's compared to two to four visits that may be required for tuberculin skin test.

IGRAs have some disadvantages over the tuberculin skin test. In individuals that are low risk, such U.S.-born healthcare workers that have had no exposure to tuberculosis, IGRAs are more likely to result in false positive results.

And this problem is magnified when the test is performed serially as a screening tool because IGRA's inversion definition based on the crossing of a threshold and we know that number of sources of variability can cause crossing of that threshold, so -- they are more susceptible to false positive results.

Bob Barrett: Doctor, how well do Interferon Release Assays perform in those subjects with infection and those without infection?

Dr. Niaz Banaei: So, for a long time we were using surrogates, a latent tuberculosis infection, because there is no gold standard for latent TB infection. And when we use surrogates such as active tuberculosis, the sensitivity of Interferon Gamma Release Assays is in the order of 80 percentile and if the subject is immunocompromised, that number even goes down further.

And more recently people have been able to conduct contact investigation studies to follow people after exposure for a number of years and performed that IGRA testing in the beginning of the study and wait several years to see who develops active tuberculous.

So using active TB as a reference standard for prior infection in those studies, the sensitivities are in the order of 50, 60, and 70 percentile. There is only one contact investigation study out of Germany that showed a really high sensitivity for diagnosis of latent tuberculosis infection.

So based on the best type of reference standard, that one can use, the sensitivity ranges from 50% to 70% for latent tuberculosis infection.

Bob Barrett: Do you think that changes in diagnostic cutoffs would increase the utility of Interferon Gamma Release Assays?

Dr. Niaz Banaei: So, changing the cutoffs has been recommended and adopted by several institutions in North America. However, my personal belief is that changing the cutoff is not going to be the solution to this problem.

For example, in one study, when the cutoff was increased for a QuantiFERON assay from 0.35 to 1 international units per mil, although they reduced the number of false positive results that they got in low risk individuals, they also lost a significant fraction of those subjects that had a persistent positive results.

Meaning that these individuals were probably infected and by increasing the cutoff they were now being missed. And as I mentioned the sensitivity of assays already low for latent TB infections and by further increasing their cutoff, we are risking to further decrease the sensitivity of this assay.

So my personal belief is that, instead of changing the cutoffs, the solution is to actually eliminate sources of variability. Over the recent years a number of sources of variability have been identified. These include pre-analytical sources, analytical sources, manufacturing sources and immunological sources.

And some of them are random sources, so there isn't anything that we can do about them, but a good number of them are actually, they can be predicted and so by further standardizing the assay and eliminating these sources of variability, I think we can improve further the reproducibility at the accuracy of the assay compared to what we have right now.

Bob Barrett: Doctor, what challenges do practitioners and occupational health programs using Interferon Gamma Release Assays face on a daily basis?

Dr. Niaz Banaei: Well, every day as we test thousands of low risk healthcare workers in the U.S. and also other groups that are obligated to undergo testing, as with any test even with those tests that have a good specificity, we are going to get more and more individuals that have false positive results.

And these individuals are referred to practitioners and occupational health physicians, who then have to investigate these individuals.

It starts out by doing risk assessment, doing a chest x-ray, bringing these people back for a second test. In some instances, these individuals are referred to their primary care providers for prophylactic therapy.

So, as you can imagine, the problem is that potentially we are exposing these individuals who don't have an infection to toxic therapy which they don't need, and as it's already stated, with its own consequences.

So it's enormous challenge that the clinicians have to deal with and if we can avoid it, it would improve their work on daily basis.

Bob Barrett: Has the situation improved over the years?

Dr. Niaz Banaei: Well the IGRAs were introduced in the past decade, and prior to that most people were using the tuberculin skin test which has a better defined conversion definition.

With the IGRAs, as I described earlier, their conversion definition is not as well developed and therefore just to do sources of variability, one can have a false positive result.

And so in my opinion, it actually in those groups that are undergoing serial testing such as low risk healthcare workers, the problem is actually worse now than before because we have a higher number of individuals that convert when they get tested on annual basis.

The other problem is that, the quality of the reagents in IGRAs hasn't been particularly as good as it should be. We have had several instances where various institutions have experienced false results or false indeterminant results because of the quality of the reagents that were provided to them.

Bob Barrett: Well finally, doctor, how can regulatory agencies and the manufacturers improve the process?

Dr. Niaz Banaei: Well I think the regulatory agencies can do a better job demanding better quality assurance of the testing reagents, and the manufacturers themselves can also do a better job, ensuring the quality of reagents that are being put out.

And clearly with the existing procedures that are in place, they are not sufficient because we have, over the years, experienced false testing because of the quality of the reagents.

And so these are relatively fixable issues that can be addressed by improving the quality assurance.

Bob Barrett: Dr. Niaz Banaei is from the division of infectious diseases and geographic medicine and Medical Director of the Clinical Microbiology Laboratory at Stanford University. He is been our guest in this podcast from *Clinical Chemistry.*

I am Bob Barrett. Thanks for listening.