TB or not TB? Newer assays settle in

William Check, PhD

March 2013—Though tuberculosis is primarily diagnosed and treated in the public health system, there's a need for greater knowledge about TB in the private sector, says Sundari Mase, MD, MPH, of the CDC's Field Services and Evaluation Branch, Division of Tuberculosis Elimination. Among private physicians, she says, "there is little institutional knowledge about TB." When Dr. Mase sees patients, often she'll note diagnostic delays in recognizing TB, "delays that occur because physicians aren't thinking about TB."

One example: lymph node biopsies. "It happens all the time," she says, "that a patient is sent for a lymph node biopsy, which goes to a pathologist. On readout, there is granulomatous disease, but no one has thought about the possibility of TB, so the specimen is not sent for TB culture. The patient is sent to me, and I have to make a diagnosis of TB on clinical presentation and the pathology report without a culture." In these circumstances, Dr. Mase says, the patient could go from one physician to another seeking a diagnosis until someone realizes this could be TB.

"It would be good to have greater knowledge of TB among clinicians and pathologists," she says. "Once the tissue is in formalin, we can no longer get a culture." While molecular tests work on formalin-fixed specimens, the yield for TB is low. "There are very few organisms in the specimen," Dr. Mase says. "There are generally not a lot of TB organisms in the lymph node, so it is hard to pick up." Dr. Mase has sent four pathology specimens for molecular testing; all were negative.

Dr. Mase

While many areas in TB diagnosis and management remain unchanged, a major advance has taken place in testing for latent TB infection. Several years ago, in vitro blood tests were approved that recognize the presence of TB infection by release of interferon-gamma (interferon-gamma-release assays, IGRAs) ("Tuberculosis no longer skin deep," CAP TODAY, November 2008). Data have accumulated on the performance of these assays in relation to the historical standard, tuberculin skin testing (TST), so that the place of IGRAs in diagnosing TB in various populations is now becoming clear. The CDC published updated guidelines in 2010 on the use of IGRAs; those guidelines are still the governing document (*MMWR*. 2010;59[No. RR-5]:1–25). Says Dr. Mase, "For diagnosis of latent TB infection, interferon-gamma-release assays are recommended for all situations in which we have used tuberculin skin testing."

People working in this area speak well of the IGRAs. Scott Lindquist, MD, MPH, director of health for the Kitsap (Wash.) Public Health District, says for him, as a public health person, the limitations of tuberculin skin testing are an important consideration. "It's a very old method, and frankly it does not perform well." He's excited about the newer technologies, which he describes as "not so new anymore." Published data show that IGRAs perform well, he says. In particular, "Specificity of IGRAs tends to be higher than that of the skin test."

Dr. Lindquist

Cost is an issue: IGRAs are more expensive. “However,” Dr. Lindquist says, “when you look at the higher false-positive rate with the skin test, it means you have to do more chest x-rays and possibly offer more people medication. In the long run, you need to ask which is more cost-effective.” There are good data, he adds, about the greater cost-effectiveness of IGRAs. (See, for example: Nienhaus A, et al. *BMC Health Serv Res*. 2011;11:247.)

The higher specificity of IGRAs comes from their not giving a positive result for those who have received BCG vaccination (Bacillus Calmette-Guérin), whereas tuberculin skin testing does. Charles L. Daley, MD, head of the Division of Mycobacterial and Respiratory Infections at National Jewish Health in Denver, says, “When we started to adopt IGRAs in the public sector, we saw about a 30 percent decrease in the rate of positivity compared to skin tests, historically speaking, in foreign-born persons. In this population, savings from the increased accuracy of [IGRAs] probably pays for their increased cost.”

The private sector may see similar savings. “Screening for latent infection is increasingly becoming part of private medicine because of significant funding cuts to the public sector,” Dr. Daley says. And as IGRAs become more available in the private sector, more screening will be done there, he adds. Already rheumatologists are screening arthritis patients for latent TB infection with IGRAs before instituting anti-TNF therapy, and gastroenterologists are screening prior to biological therapy for inflammatory bowel disease.

Higher specificity is an important advance, in the view of Julie Higashi, MD, PhD, director of the TB Control Section in the San Francisco Department of Public Health. “People feel much more comfortable with a result when they don’t have to worry about false-positives from vaccination,” she says.

Dr. Daley

Michael Wilson, MD, director of laboratories for Denver Health Medical Center, cites three advantages of IGRAs: First, they are one-stop tests: Patients don’t need to return to have their results read, as they do with skin testing. Second, the results are more objective than those of a skin test. With the TST, there can be reader variability. Last, the tests are not affected by previous vaccination with BCG.
(Dr. Wilson emphasizes that TST and IGRAs are tests that were designed for detection of latent TB, not clinically active cases.)

The 2010 CDC guidelines do not state a preference for either method—TST or IGRA. “Results of studies examining sensitivity, specificity, and agreement for IGRAs and TST vary with respect to which test is better,” the Expert Committee noted. Its members concluded, “ … [both] TSTs and IGRAs … may be used as aids in diagnosing *M. tuberculosis* infection.”

Two of the CDC scientists who prepared the 2010 guidelines, both of whom are in the Division of Tuberculosis Elimination, wrote in a recent editorial, “A number of cost-effectiveness studies have been performed in different populations, and the results are inconsistent” (LoBue PA, Castro KG. *JAMA*. 2012;308:241–242). Their conclusion:

“TST has not outlived its usefulness.”

Whether to continue to use TST or to adopt an IGRA depends on several factors:

- the prevalence of TB in your population(s).
- the incidence of foreign-born in your population(s).
- how common BCG vaccination is in your population(s).
- the reliability of a return visit in your population(s).
- whether you can realize programmatic savings from IGRAs’ higher specificity.

Each hospital must make its own decision about how to do annual TB screening of its health care workers, Dr. Higashi says. “I would say that the majority still use skin testing. It is still unusual to see hospitals using IGRAs, which are more advantageous in higher-risk groups who have had BCG vaccination and in people who can’t be depended on to return for a skin test reading.”

Dr. Mase says many TB control programs have switched to IGRAs because of the economics. Others have reverted to skin testing because of limited resources. “It depends on your population,” she says. “If you are running a program in a setting where you have a high rate of foreign-born, there might be greater savings from IGRAs. But if you are working in a situation with mainly U.S.-born, such as homeless persons, you might not see that cost saving.”

Dr. Wilson agrees with the need to know the demographics of patients and employees before it can be known which method is better. “We just participated in a five-year multicenter screening study with CDC in a very low-risk population. It turns out that skin testing and IGRAs have different roles, not that one is always better than the other,” he says. “For high-risk patients in a TB clinic, IGRAs are better. If you are in a high-incidence area you would probably screen employees with an IGRA. But in Denver, where the incidence of TB is so low in the general population, you would end up getting more false-positive results.” At Denver Health Medical Center, TST is used for employee screening, whereas IGRAs are used in the Metro TB Clinic, in the HIV clinic, and in high-risk obstetric patients and foreign-born patients from high-incidence countries.

Dr. Lindquist says the real value of IGRAs is in foreign-born individuals who have had BCG vaccination. “So we use them pretty universally [in that population] even if someone doesn’t have the ability to pay.” The Kitsap Public Health District does not use IGRAs in all groups, however. Interferon-gamma-release assays are not approved in the under-five population, for instance. Dr. Lindquist also has questions about using IGRAs in those who are HIV-positive. “So there is still a role for skin testing,” he says, “as long as you understand its limitations.”

Dr. Higashi

In San Francisco, Dr. Higashi sees the entire spectrum of TB. “We serve the whole city and county,” she says. “We cover active and latent TB. We see all patients who are TB suspects.” Those with latent TB are generally referred in from community health clinics. Some clinics do skin testing, Dr. Higashi says. A smaller group has the ability to do IGRAs. “We get referrals for people with a positive skin test or a positive blood test.”

The advantage of the latter for San Francisco’s Department of Public Health is that the city and county have a

large population of people born in a country with endemic TB who had the BCG vaccination. “In this era, where we are looking for ways to become more efficient, to concentrate services as much as possible in the populations that need them the most, the blood test allows us to eliminate people who would have a positive skin test due to vaccination,” Dr. Higashi explains. “In the foreign-born population, we see one-half to two-thirds fewer positive tests with interferon-gamma-release assays.”

San Francisco also has a large urban population that is marginally housed or homeless. “We have a shelter program for TB testing,” Dr. Higashi says. “It is difficult for some shelters and other service providers to ensure that clients and patients come back for reading of their skin test.” While the cost-effectiveness of IGRAs, for which only one encounter is needed, has not been rigorously studied in these settings, Dr. Higashi says, she believes they are somewhat cost-effective in some populations. “We have had a huge number of staffing cuts over the last few years,” she says. “To some extent we have been able to maintain clinic services because [IGRAs] allow us to triage and reduce the number of chest x-rays and the number of patients we put on isoniazid.”

Dr. Higashi’s clinic also gets referrals from primary testing of HIV-positive persons. “Community clinics do both skin testing and/or a blood test in that population. We need to maximize sensitivity in those with HIV,” she says. Studies of those who are immunocompromised, including individuals with HIV, have been confined to relatively small samples. Immunocompromised persons include those scheduled for organ transplantation or for cancer chemotherapy. If a patient is about to be immunosuppressed, the clinician has to know whether the patient has latent TB so he or she can treat the infection during immunosuppressive therapy.

It may happen that a person has both a TST and an IGRA and the results are discordant. “A lot of our work in the last five years has been learning how to manage discordant results,” Dr. Higashi says. “For someone with a normal immune system who has received BCG and who has a positive skin test and a negative IGRA, we are confident and comfortable to let the IGRA finding drive our diagnosis. For any patient with an immunocompromised condition, we have to be careful what we do with discordant results.”

Puzzling results can arise with IGRAs during serial testing, especially in low-risk populations. For instance, in health care workers tested annually, TST has a less than one percent conversion rate. A far higher apparent conversion rate, five percent to six percent, has been seen with IGRAs. “That is a repeatability issue with blood tests,” Dr. Higashi says. “We now understand that better in the context of screening and are developing better guidance on how to handle these apparent conversions. A lot of that five percent is probably not true conversion.”

Dr. Daley calls this variability “wobble.”

Dr. Wilson

“This is still an issue in low-risk populations,” he says. “Whether it is short term—six weeks, or six months or one year—we still see this problem. They appear to be false conversions. When we re-test they are negative. And if we re-test again, they are still negative. Most of these people have no risk or history of exposure.” A high rate of reversion from positive to negative with IGRAs was seen in a multicenter study, coordinated by Dr. Daley, of more than 2,500 health care workers. None developed TB regardless of the test result, even though very few were treated.

An institution that chooses to use an IGRA has two commercial choices: QuantiFeron-TB Gold and its newer In-Tube version (Cellestis, a Qiagen company, Valencia, Calif.) and T-Spot.TB (Oxford Immunotec Limited, United Kingdom).

T-Spot requires isolated WBCs rather than whole blood, which can be more technically demanding. On the other hand, T-Spot may be more sensitive in those who are immunocompromised. Says Dr. Mase, “Between QuantiFeron Gold In-Tube and T-Spot, which assay a program adopts depends on variables such as cost and ease of implementation.”

Whether it is TST or IGRA that is used for TB testing, an important challenge remains: identifying individuals who will progress from latent TB to active infection. “Our current consensus is that IGRAs are as predictive as skin testing,” Dr. Daley says. “The problem is that neither one is very good.” Fewer than five percent of persons who are positive on TST or IGRA will progress to active disease. “We need a test that is 80 percent to 90 percent predictive,” Dr. Daley says. “The whole point is to treat and prevent progression while avoiding inappropriate therapy.”

Dr. Lindquist agrees. “What we really need for TB care,” he says, “is a rapid diagnostic that is accurate and that identifies those patients who will go on to active disease.”

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