Latest TB testing guide set forth by ATS, CDC, IDSA

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March 2017—Testing for latent *Mycobacterium tuberculosis* infection and active tuberculosis disease remained relatively unchanged for many years. Screening for latent infection depended on an initial positive tuberculin skin test, and evidence for active TB required a positive culture for *M. tuberculosis* complex. New tests altered this picture in the past five years. For diagnosis of latent infection, interferon-gamma release assays have taken a major role. And nucleic acid amplification testing is becoming a mainstay for establishing a diagnosis of TB.

These assays took their place as part of the official recommendations for the detection of latent *M. tuberculosis* infection and diagnosis of TB in a newly published guideline (Lewinsohn DM, et al. *Clin Infect Dis.* 2017;64[2]:e1–e33). "Development of a new guideline was motivated by the availability of interferon-gamma release assays and some new molecular tests," says Gail L. Woods, MD, a professor of pathology at the University of Arkansas for Medical Sciences and chief of pediatric pathology at Arkansas Children's Hospital, Little Rock. She was a member of the guideline committee of the American Thoracic Society, Infectious Diseases Society of America, and the CDC.


Dr. Daley

The guideline lagged behind laboratory practice to some extent because of the rapidity with which information about these new tests was acquired. "There has been a lot of innovation since the last guideline [published in 2000]," says Charles L. Daley, MD, also a member of the guideline committee, "most notably interferon-gamma release assays and some molecular-based diagnostics for actual TB." This made it necessary to update the recommendations. "Unfortunately, the update took a long time because so much was happening in the field of diagnostics," says Dr. Daley, chief of the Division of Mycobacterial and Respiratory Infections at National Jewish Health in Denver. "It has been a moving target. We were hard put to know when to stop and say that's it, we're not accepting any more data."

Between the two reasons to screen—to detect active disease and cure it to stop transmission, and to find latent disease and treat it to prevent progression to active disease—the greater focus in U.S. tuberculosis programs is to find those with latent infection. For this, interferon-gamma release assays have become a major tool. They are in vitro T-cell–based assays that measure interferon gamma release by sensitized T cells in response to highly specific *M. tuberculosis* antigens.

"There is at least one instance in which IGRAs are better [than tuberculin skin tests]," Dr. Daley says.

That is in persons who have received BCG (bacillus Calmette-Guérin) vaccination, in whom a positive tuberculin skin test is not meaningful. “That is a pretty strong area of improvement of IGRAs over tuberculin skin testing,” Dr. Daley says, because most countries outside the U.S. administer BCG vaccination routinely.

Four conditions need to be met to justify primary use of an IGRA: a person age five or older who is likely to be infected with *M. tuberculosis*, a low or intermediate risk of disease progression, a decision that testing for latent infection is warranted, and a person who has received BCG vaccination or is unlikely to return to have his or her tuberculin skin test read. If even one of these conditions is not met, the tuberculin skin test, or TST, could be used, Dr. Woods says. That is important because IGRAs are much more expensive than TST. At this time, TST is also preferred in children under age five.

Among those who are unlikely to return to have the TST read are undocumented immigrants, who are often mobile, and homeless persons, whom Dr. Daley called “the classic group” for this condition. In addition, jails sometimes release prisoners before their skin tests can be read. For this reason, some jails have gone to chest x-ray (which cannot detect latent infection) to detect active *M. tuberculosis* disease, since active disease is the main concern. “It doesn’t help a jail to know that an inmate is latently infected,” Dr. Daley says.

Testing is warranted in those who have had a known exposure to a person infected with *M. tuberculosis*, those entering the U.S. from an area with a high prevalence of TB, HIV-infected patients, and those who are immunocompromised from other conditions, such as chronic renal failure or intravenous drug use. Prisoners could also qualify for testing.

There is an active program to test some who go through the formal process to immigrate to the U.S., including refugees, Dr. Daley says. In this program the IGRA is used because most come from countries where BCG vaccination is administered. For persons entering the U.S. to work for a period, there is no formal testing requirement, though companies can test if they choose. “In Canada they screen all persons staying in the country for six months or more,” Dr. Daley says.

Many health care institutions require staff to be screened for latent *M. tuberculosis* infection, even though many employees are in a low-risk group. Dr. Woods is required to get tested even though she has minimal, if any, patient contact and does not process patient specimens. In contrast, it is reasonable to screen laboratory personnel who work in a mycobacteriology laboratory.

“Hospitals generally screen health care workers,” Dr. Daley agrees, noting that in some institutions TST is used because health care workers can be relied on to return.

When talking about screening health care workers, inevitably the issue of serial testing arises. “During the time that this document was put together, we obtained data on serial testing with the IGRA assay, mostly in health care workers,” Dr. Daley says. Typically the tuberculin skin test is performed annually in this population. Studies began to show that in this very low-risk population in the U.S., serial testing could lead to false-positive results. This finding was not surprising. “If you take any test and repeatedly screen a low-prevalence population you will get false-positives,” Dr. Daley notes.

“We published data several years ago from serial screening of health care workers with three tests—Quantiferon, T-Spot, and TST,” Dr. Daley says. “We saw conversion in all three groups. But conversion was highest with the IGRA. We don’t know why that is. Usually false-positives on the IGRA revert to negative with repeat testing. Maybe that’s because we don’t have the correct definition of

conversion for this test. With the skin test we require a specific change, for instance, an increase in 10 mm of induration. We have to see a certain increase in positivity to call it a conversion. We don't have that with IGRAs. So maybe we simply don't have the right definition yet."

Dr. Daley and his colleagues went one step further: They asked what would happen if they changed the definition of conversion with the IGRA. "In our study," he explains, "we had to require a very large increase in positivity with the IGRA to get to the same rate of conversion as we saw with TST. That is not a reason not to use IGRAs. They are fairly new and we are still looking for the best way to use them." As with all tests, there is a tradeoff between specificity and sensitivity. With no gold standard, however, it is not known which results are true.

"The issue for us," Dr. Daley says, "is what happens after a positive diagnostic test, either an IGRA or TST. We do a chest x-ray, and if that is positive, we collect sputum and isolate the patient. Even if those tests are negative, we treat the patient for months with drugs that have some toxicity. So that is expensive and possibly harmful." Looked at from the other direction, a false-negative result in a low-risk population is not so bad, in Dr. Daley's view. "We won't miss many cases," he says. "So a false-positive is what we are more concerned about in low-risk populations."

Because of these concerns, the guideline committee asked the Centers for Disease Control and Prevention to re-evaluate screening practices in the United States.

Screening of health care workers at National Jewish is, paradoxically, less of an issue than it is in some other places. "In this field," Dr. Daley says, "we have always said that you don't get TB from the patient you know is infected, but from the patient you don't know about. And here, where we mostly treat patients who are already diagnosed with multidrug-resistant TB, we know they are coming way ahead of time." Fortunately, Dr. Daley says, "We don't really see many cases. There are not many cases of TB in the U.S. anymore." As a result, they are going through a change in policy to performing less frequent screening of health care workers.

In contrast, "If you go to a place like Denver Health, which treats indigent populations, that is where health care workers are exposed to TB, in the emergency department and on the medical wards," he says.

A guideline on whom to screen will be out in about a year, Dr. Daley says. "It is moving very slowly, partly because WHO came out with a guideline on this subject, which is the first time they have put out a guideline on latent *M. tuberculosis* infection. From a global perspective, this was a significant step. They were acknowledging that there are groups everywhere in the world that we should be screening and treating. That was a real change in WHO policy." It will be difficult to adhere to this guideline in resource-poor countries, he noted.

Although the incidence of active tuberculosis in the U.S. is low, Dr. Woods and Dr. Daley say accurate diagnosis and keeping up with changes in the guideline are important.

"We still do have active TB [in the U.S.]," Dr. Daley says. "It is a complicated and difficult issue. In terms of the diagnostic approach to active TB, we did not make major changes."


Dr. Woods

Dr. Woods points out that diagnosing active tuberculosis is entirely different from diagnosing latent infection. “It doesn’t hurt to get an IGRA or do TST, but they won’t make the diagnosis. You have to do culture for *M. tuberculosis* and a smear and in some cases a nucleic acid amplification test.”

Once a patient has a positive TST or IGRA, the clinician has to rule out active disease by asking about symptoms—cough (particularly if the patient is coughing blood), fever, and weight loss. Next would be a chest x-ray. “If any of these investigations is positive, you need to continue with testing for disease,” Dr. Woods says. “It is crucial to rule out active disease before you treat for infection because the most popular choice [for latent infection] is a one-drug regimen, which you wouldn’t use for active TB.”

There is one change in the workup of active TB. “We did recommend that people use NAAT [nucleic acid amplification tests] to try to more rapidly identify *M. tuberculosis* in respiratory specimens,” Dr. Daley says. “They were previously recommended to be used but they weren’t used in the U.S. as much as they should. We were quite delayed in adopting rapid molecular tests. I think we are catching up now.” Appropriate NAATs, the guideline says, include the Hologic Amplified Mycobacteria Tuberculosis Direct test and the Cepheid Xpert MTB/RIF test. The Cepheid test detects presence of *M. tuberculosis* and rifampin resistance mutations in two hours.

Could the policies to identify and deport the undocumented in the U.S. detrimentally affect public health programs to screen those with a risk of having latent infection and TB disease? “I’m pretty sure that’s going to happen,” Dr. Daley says. “What we in public health provide is a safe haven for people who require care. We have used that to find latent infection and TB. We could even discuss with people that treatment will take so many months and ask whether they would be here for that time, and they could answer truthfully. Now I don’t think they will show up.”
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