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NTM-TB INSIGHTS

May 2016

Dr. Charles L. Daley Honored with the American Thoracic Society World Lung Health Award

Charles Daley, MD, chief of the Division of Respiratory and Mycobacterial Infections at National Jewish Health, received the 2016 World Lung Health Award for his efforts around the world to improve diagnosis and treatment of patients with tuberculosis, the world's most deadly infectious disease. For more than two decades, Dr. Daley has worked with physicians, hospitals, health ministers and others to stop the spread of tuberculosis in countries around the world, from Russia to China, India to South Africa. He currently holds leadership positions in the World Health Organization and the Stop TB Partnership. A significant focus of his current efforts is improving patient access to second-line antibiotics for drug-resistant tuberculosis.

The World Lung Health Award is given to an individual with recognized contributions to improving world lung health in the area of translational or implementation research, delivery of healthcare, continuing education or care of patients with lung disease, or related political advocacy with a special emphasis on efforts that have the potential to eliminate gender, racial, ethnic, or economic health disparities worldwide.

Congratulations Dr. Daley on your well-deserved ATS World Lung Health Award!

American Academy of Pediatrics Guidelines for the Use of Interferon-γ Release Assays in Children

For decades, the only available test for tuberculosis (TB) infection in children was the tuberculin skin test (TST). The TST has many limitations, including difficulty in administration and interpretation, the need for a return visit by the patient, false negative results caused by immune suppression, and false-positive results caused by cross-reaction with many nontuberculous mycobacteria (NTM) and *Mycobacterium bovis* Bacille Calmette-Guérin (BCG) vaccines. As a result, there are problems with both the sensitivity and specificity of the TST, especially for children who are more likely to be exposed to environmental NTM and to have had a recent BCG vaccination.

Interferon-γ release assays (IGRAs) are blood tests that measure ex vivo T-lymphocyte release of interferon-γ after stimulation by antigens specific for *Mycobacterium tuberculosis*. An American Academy of Pediatrics technical report, Interferon-γ Release Assays for Diagnosis of Tuberculosis Infection and Disease in Children, published in December, 2014 **(Pediatrics 2014;134:e1763-e1773),** reviewed available data about the performance and interpretation of the IGRAs in children, especially compared with that of the TST, and gave guidance to pediatricians on the use of these tests in children.

Two commercial IGRA tests are widely available: QuantiFERON-TB Gold In-Tube (QFT; Cellestis/ Qiagen, Carnegie, Australia) and T-SPOT.TB (T-SPOT; Oxford Immunotec, Abingdon, United Kingdom). These tests measure the response to two (T-SPOT) or three (QFT) antigens found on *M. tuberculosis* that are not present on most NTM, including the ubiquitous *Mycobacterium avium* complex and *M. bovis* BCG. As a result, one would expect the IGRAs to be more specific than the TST, yielding fewer false-positive results. Unfortunately, as with the TST, the IGRAs do not distinguish between TB infection and TB disease, and immune suppression diminishes the sensitivity of both tests. The **Table 1** shows a comparison of many characteristics of both tests' methods. Given the limitations of both methods, it should be stressed that only children who have a risk factor for TB infection, have a disease or condition that may require significant therapeutic immunosuppression, or are suspected of having TB disease should be tested with either method. Risk factor assessment should be done before testing is performed.

As there is no gold standard test for TB infection (or latent tuberculosis infection as it often is called), it is not possible to determine the exact sensitivity and specificity of either test method; estimates are based on studies of persons with culture-proven TB disease and studies using proximity to an infectious case as a surrogate for likely TB infection. However, the published studies measuring the sensitivity of both the TSTs and the IGRAs in children were performed mainly in high burden countries with children who have culture-positive TB disease, which is often immunosuppressing; many also had malnutrition and helminthic infection, which also can lower test sensitivity. It is not clear that the low sensitivity of the IGRAs as measured in these studies is an accurate measure of the sensitivity in otherwise healthy children with TB infection.

Based on the sum of published studies, the IGRAs have higher specificity than the TST and will produce fewer false-positive results, especially in children who have received a BCG vaccine or been exposed to environmental NTM. However, it does not appear that the IGRAs have a significant advantage over the TST in sensitivity. Unfortunately, there remains hesitancy to use the IGRAs in children younger than 3 years of age due to a relative lack of published data for the performance of IGRAs in this age group, for whom test sensitivity is paramount because they have the highest rate of untreated TB infection progressing rapidly to TB disease.

Strategies for the use of the TST and IGRAs in children with a risk factor for TB infection are outlined in the **Figure 1**. Some points of emphasis are:

- For children 5 years of age and older, either a TST or IGRA can be used in any situation.
- For children 5 years of age and older who have received a BCG vaccine, one of two strategies can be used:

    1. An IGRA can be used and the result acted on.

    2. A TST can be performed. If the result is negative, no further testing or evaluation is necessary; if the TST result is positive, an IGRA can be performed and its result acted on.

- When testing for TB infection, some experts use an IGRA in children 2-4 years of age, especially if they have received a BCG vaccine (to avoid false-positive results with the TST). However, most experts do not routinely use an IGRA in children younger than 2 years of age because of lack of data for this group.
- For children diagnosed with an immunosuppressing disease or who are about to start significant immunosuppressive therapy, testing should be performed with either a TST or an IGRA even in the absence of a TB risk factor. If the child has a TB risk factor, testing should be performed with both a TST and an IGRA, and any positive result should be further evaluated and treatment strongly considered.

- When evaluating a child of any age for TB disease, both a TST and one or both of the IGRAs can be performed to maximize sensitivity.

Jeffrey R. Starke, MD, Professor of Pediatrics, Baylor College of Medicine & Director, Children's Tuberculosis Clinic, Texas Children's Hospital, Houston, Texas. Dr. Starke is also a co-editor for the recently published Handbook of Child and Adolescent Tuberculosis, *2016. Oxford University Press, United Kingdom.*

TABLE 1 Comparison of the TST and IGRAs

Characteristic	TST	IGRA
Antigens used	Many; PPD	3 (QFT) or 2 (T-SPOT)
Sample	Intradermal injection	Blood draw
Patient visits required	2	1
Distinguish between LTBI and TB disease	No	No
Cross-reactivity with BCG	Yes	No
Cross-reactivity with NTM	Yes	Only rare species[a]
Differing positive values by risk	Yes (5-10-15)	No
Causes boosting	Yes	No
Subject to boosting by previous TST	Yes	Possible
Durability over time (stays positive with or without treatment)	Yes	Unknown
Difficulties with test reproducibility	Yes	Yes
Relative cost	Lower	Higher
Location of need for trained staff	"Bedside"	Laboratory
Estimated specificity in BCG-unvaccinated children	95% to 100%	90% to 95%
Estimated specificity in BCG-vaccinated children	49% to 65%	89% to 100%
Estimated sensitivity (confirmed TB disease)	75% to 85%	80% to 85%
Estimated sensitivity (clinical TB disease)	50% to 70%	60% to 80%

[a] *M marinum, M kansasii, M szulgai,* and *M flavescens.*

Permission received from the American Academy of Pediatrics to reproduce Table 1.

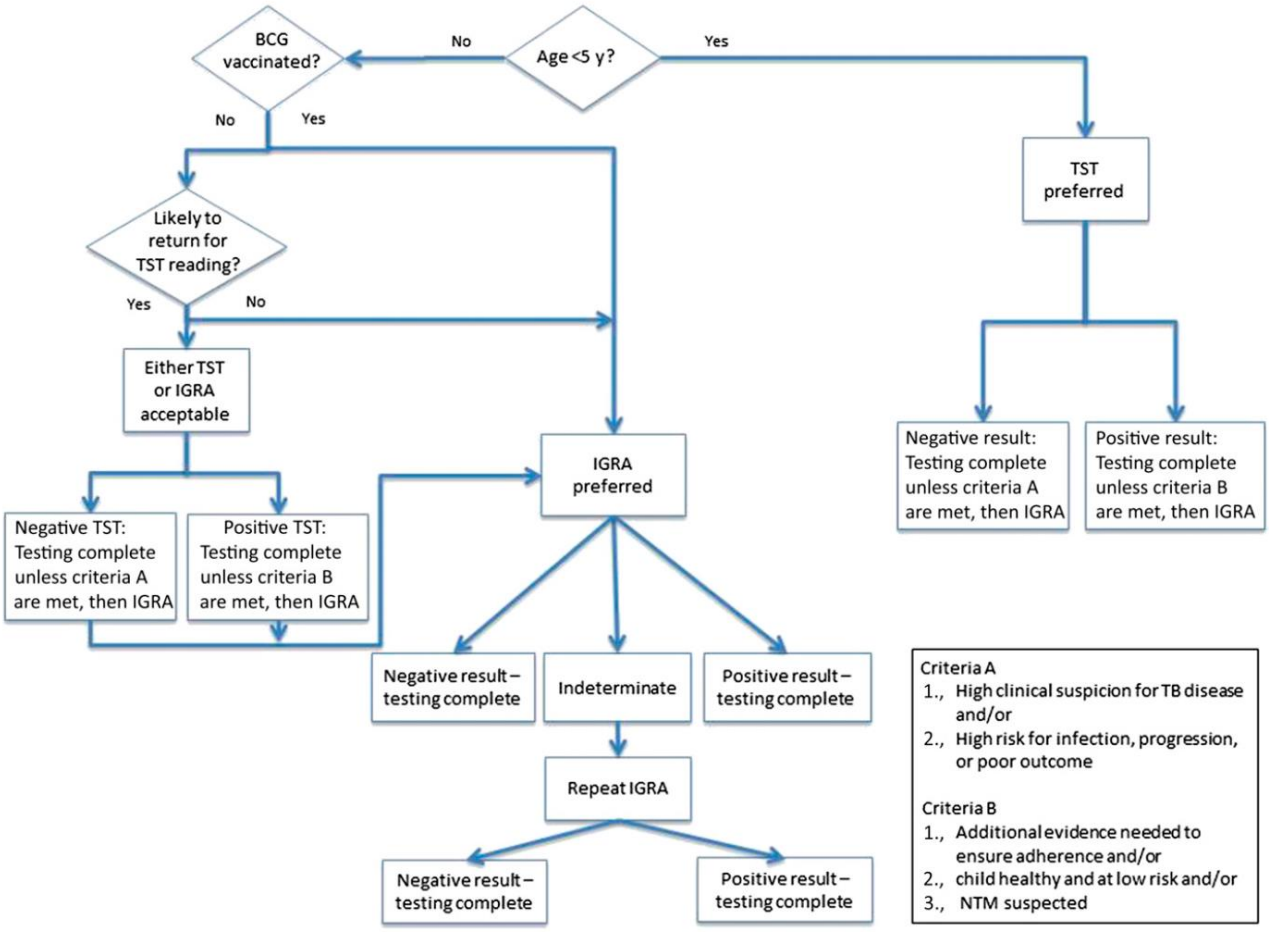
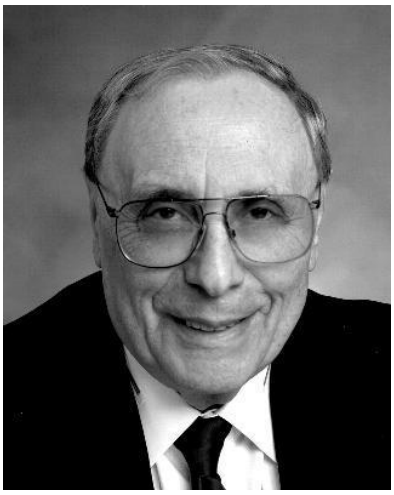


FIGURE 1
An algorithm for the use of the TST and IGRAs in children. Entry into the algorithm assumes that the child has at least 1 risk factor for TB infection.

Permission received from the American Academy of Pediatrics to reproduce Figure 1.

In Memory of Leonid Heifets (1926-2015)



Dr. Heifets was a true leader in the laboratory diagnosis of tuberculosis and nontuberculous mycobacteria (NTM). He came to National Jewish Health in 1979 as a research fellow, progressed to the Kramer Foundation Professor in Clinical Mycobacteriology, and was the Director of the Mycobacteriology Laboratory from 1980 to 2012.

Leonid was born on January 5, 1926 in Belarus to parents in the medical field: his father was a physician and his mother a pediatric nurse. At age 15 (in 1941), pending the German attack from the west, Leonid's father sent him off to Somarkand, Uzbekistan to avoid conscription and to continue his education. After World War II, Leonid transferred to the Moscow Medical Institute, graduating with his M.D. in 1947 and, subsequently, he was awarded his Ph.D. in 1953 (Infectious Diseases, Epidemiology and Microbiology). From 1957 to 1969, Dr. Heifets was the Head of Laboratory for Study of Efficacy of Bacterial Preparations - Metchnikoff Scientific Research Institute of Vaccines and Sera, Moscow and from 1969-78: Senior Researcher at Central Research Institute of Tuberculosis, Russian Academy of Medical Sciences – Moscow.

On the occasion of the passing of Dr. Mayer Goren, Dr. Heifets wrote a letter to the Editor of the Intermountain Jewish News in 2005 explaining how he emigrated from the Union of Soviet Socialist Republics (USSR) in 1978, settled for a few months in Italy and how Mayer Goren, Richard Bluestein (then President of the now National Jewish Health) and Reuben Cherniack (then chairman of the Department of Medicine at the now National Jewish Health) helped him with his fellowship and employment in Mayer's laboratory. Dr. Goren was a world-renowned chemist working on elucidating the secrets of the cell wall of mycobacteria. When being met by Dr. Goren at the Stapleton airport in Denver, Colorado on January 23, 1979, Leonid later proclaimed: "It was my new birthday!"

Dr. Heifets authored or co-authored more than 150 scientific publications and many book chapters. He also published his own book entitled *Drug susceptibilities in the chemotherapy of mycobacterial infections* in 1991. His contributions were referenced more than 5,000 times by other scientists. As his contributions to the field of mycobacteriology are many fold, 3 particular ones stand out:

- **Revolutionized *in vitro* antimicrobial susceptibility testing for novel agents for tuberculosis.**
  Heifets L: Qualitative and quantitative drug-susceptibility tests in mycobacteriology. Am Rev Respir Dis. 1988 May;137(5):1217-22.

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  Heifets LB, Cangelosi GA: Drug susceptibility testing of *Mycobacterium tuberculosis*: a neglected problem at the turn of the century. Int J Tuberc Lung Dis. 1999 Jul;3(7):564-81.

- **Created a novel system to perform antimicrobial susceptibility testing for pyrazinamide.**

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- **Established the definitive methodology for *Mycobacterium avium* complex antimicrobial susceptibility testing.**
  Siddiqi SH, Heifets LB, Cynamon MH, Hooper NM, Laszlo A, Libonati JP, Lindholm-Levy PJ, Pearson N: Rapid broth macrodilution method for determination of MICs for *Mycobacterium avium* isolates. J Clin Microbiol. 1993 Sep;31(9):2332-8.

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Dr. Heifets was also a great storyteller and book writer: *From Russia with tales and confessions to discovering America* (2009), *African Exposure* (2010), *The second coming of the white plague* (2013), and *Murder in the Lab* (2014). Hearing him tell his story of Green Eggs is one you can never forget [Heifets L. Three stories about green eggs. Story Three: Green Eggs and Vodka. Int J Tuberc Lung Dis. 2000, Volume 4, Number 12, December 2000, pp. 1188-1189]

Leonid Heifets passed away on May 15, 2015 at the age of 89. He was one of a kind and is truly missed.

Acknowledgement: Barbara Griss and Peggy Cruse, Library & Knowledge Services, National Jewish Health

Max Salfinger, MD, Executive Director Advanced Diagnostic Laboratories & Director, Mycobacteriology and Pharmacology Laboratories, National Jewish Health, Denver, Colorado

Recent Staff Publications

Koh WJ, Jeong BH, Jeon K, Kim SY, Park KU, Park HY, Huh HJ, Ki CS, Lee NY, Lee SH, Kim CK, Daley CL, Shin SJ, Kim H, Kwon OJ. Oral Macrolide Therapy Following Short-term Combination Antibiotic Treatment for *Mycobacterium massiliense* Lung Disease. Chest. **2016 May** 7. [Epub ahead of print]

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Meetings/Conferences/Lectures

- **21st Annual Regional Allied Health Conference**, September 9, 2016; Molly Blank Conference Center at National Jewish Health Main Campus. For more information and registration: **www.njhealth.org/AlliedHealthCare**
- **Carolyn and Matthew Bucksbaum NTM Lecture Series for Providers**, September 15-16, 2016; Molly Blank Conference Center at National Jewish Health Main Campus. For more information and registration: **www.njhealth.org/2016NTMProviders**
- **Carolyn and Matthew Bucksbaum NTM Lecture Series for Patients and Families**, September 17, 2016; Molly Blank Conference Center at National Jewish Health Main Campus. For more information and registration: **www.njhealth.org/2016NTMPatients**

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