



Tuberculosis Screening and Testing

Lisa Y. Armitige, MD, PhD

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Lisa Y. Armitige, MD, PhD

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Lisa Y. Armitige, MD, PhD

Co-Medical Director

Heartland National TB Center

Associate Professor

Internal Medicine/Pediatrics/Adult Infectious Disease

University of Texas Health Science Center at Tyler

Who Should be Tested for TB Infection?

Targeted Testing for TB Infection

The simplified version:

- Persons who are at increased risk for *M. tuberculosis* infection
- Persons at increased risk for progression to active disease if infected with *M. tuberculosis* (even if not at increased exposure risk)

And those who tend to be tested in addition:

- Persons tested for administrative reasons (e.g., mandatory employment testing)
- Persons with symptoms of active TB disease (fever, night sweats, cough, and weight loss)



Who Should be Tested for TB Infection?

Targeted Testing for TB Infection

- Contacts of persons with active TB
- HIV positive individuals
- Immigrants from high prevalence countries
- Injection Drug Users
- Residents and Employees of high risk congregate settings:
 - Correctional facilities and Homeless Shelters
 - Hospitals, Clinics, Nursing Homes, Substance Abuse Facilities
- Newest Category:
 - Patients considering treatment with TNF- α Antagonists
- Children exposed to high-risk adults or environments



Contacts of Individuals with Active TB

- Among close contacts to a TB Case:
 - 30% have TB Infection
 - 1-3% have active TB disease
- Without TB Infection treatment:
 - 10% with TB Infection with develop Active TB
 - Approximately 5% of contacts with newly acquired TB Infection progress to TB disease within 2 years
 - The other 5% activate > 2 years after acquisition
- Examination of contacts is one of the most effective strategies for TB Infection diagnosis and TB control!

Percent Risk of Disease by Age

Age at Infection	Risk of Active TB
Birth – 1 year*	43%
1 – 5 years*	24%
6 – 10 years*	2%
11 – 15 years*	16%
Healthy Adults	5-10% lifetime risk
HIV Infected Adults ⁺	30-50% lifetime

*Miller, Tuberculosis in Children Little Brown, Boston, 1963

⁺WHO, 2004



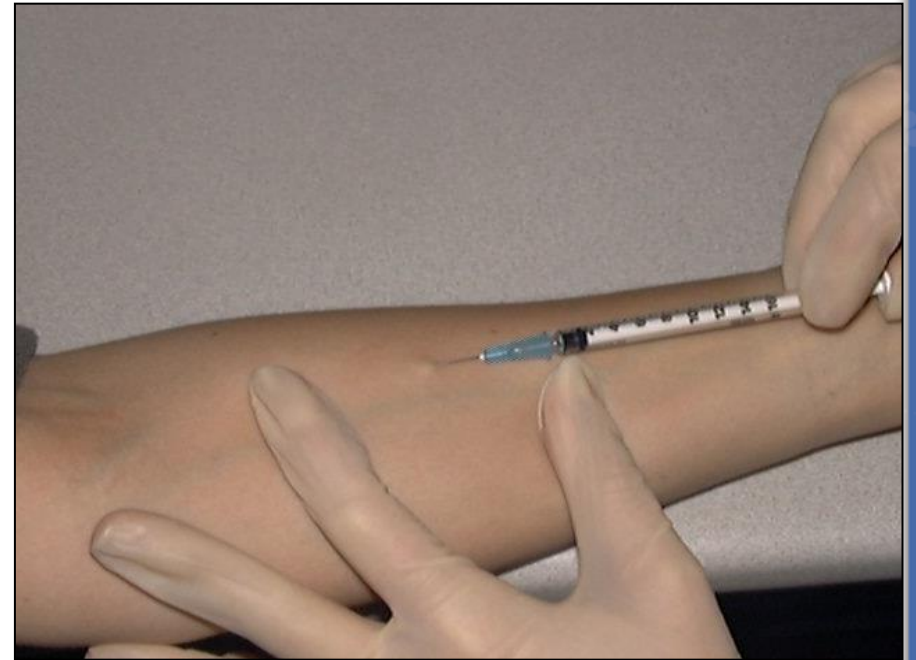
TB Infection Diagnostics

- TB Skin Test (TST)
- Interferon Gamma Release Assays (IGRA)



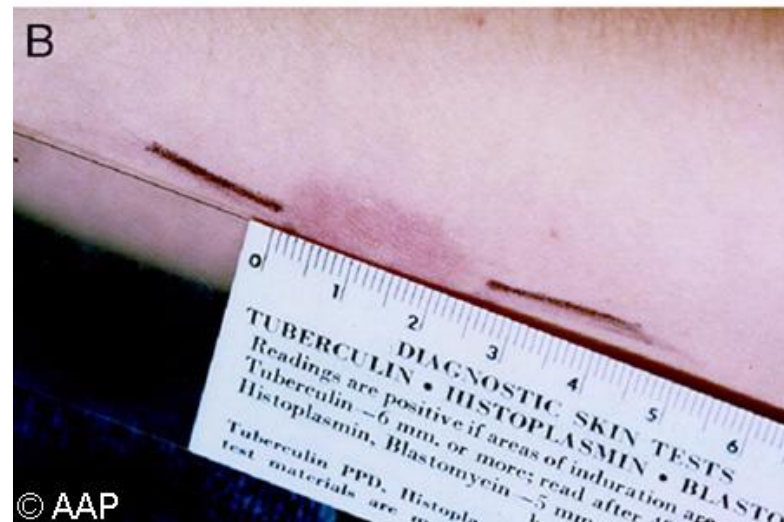
The Tuberculin Skin Test (TST)

- 0.1 ml of 5 TU PPD tuberculin injected intradermally
- **Induration** in millimeters read 48-72 hours after injection



Reading the TB Skin Test

Measure **induration**,
not erythema!!!



© AAP

TB Skin Test (TST)

- Pros:

- Inexpensive
- Simple to perform
(if you know what you are doing....
and know how to herd cats.....)

- Cons:

- Must return in 48-72 hrs
- Interpretation is somewhat subjective
- False Negatives:
 - Elderly
 - Immunosuppressed
- False Positives:
 - Low risk populations
 - Non-tuberculous mycobacteria
 - BCG vaccination



Classifying the Tuberculin Reaction

5 mm is classified as positive in

- HIV-positive persons
- Recent contacts of TB case
- Persons with fibrotic changes on chest radiograph consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients



Classifying the Tuberculin Reaction

10 mm is classified as positive in

- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories



Classifying the Tuberculin Reaction

15 mm is classified as positive in

- Persons with no known risk factors for TB
- Targeted skin testing programs should only be conducted among high-risk groups



Let's talk about IGRAs



Antigens for Newer Generation IGRAs

- Negative control or nil (e.g., saline, heparin)
- Positive control or mitogen: non-specific immune response stimulator (e.g., phytohemagglutinin)
- *M. tuberculosis*-specific antigens
 - Unlike PPD used in TST, do not cross-react with BCG or NTM (some exceptions)
 - ESAT-6, CFP-10, TB 7.7 (actually simulated using overlapping peptides)



Antigens for Gamma-Release Assays

Tuberculosis complex	Antigens		Environmental strains	Antigens	
	ESAT	CFP		ESAT	CFP
M tuberculosis	+	+	M abcessus	-	-
M africanum	+	+	M avium	-	-
M bovis	+	+	M branderi	-	-
BCG substrain			M celatum	-	-
gothenburg	-	-	M chelonae	-	-
moreau	-	-	M fortuitum	-	-
tice	-	-	M gordonii	-	-
tokyo	-	-	M intracellulare	-	-
danish	-	-	M kansasii	+	+
glaxo	-	-	M malmoense	-	-
montreal	-	-	M marinum	+	+
pasteur	-	-	M oenavense	-	-
			M scrofulaceum	-	-
			M smegmatis	-	-
			M szulgai	+	+
			M terrae	-	-
			M xenopi	-	-



FDA Approved IGRAs

- QuantiFERON[®]-TB Gold Plus (QFT-Plus)
 - FDA approved 2017
- T-Spot[®].TB (T-Spot)
 - FDA approved July 2008



QuantiFERON[®]-TB Gold Plus

Mitogen – Positive Control

Low response may indicate inability to generate IFN- γ

Nil – Negative Control

Adjusts for background IFN- γ

TB1 – Primarily detects CD4 T cell response

TB2 – Optimized for detection of CD4 and CD8 T cell responses



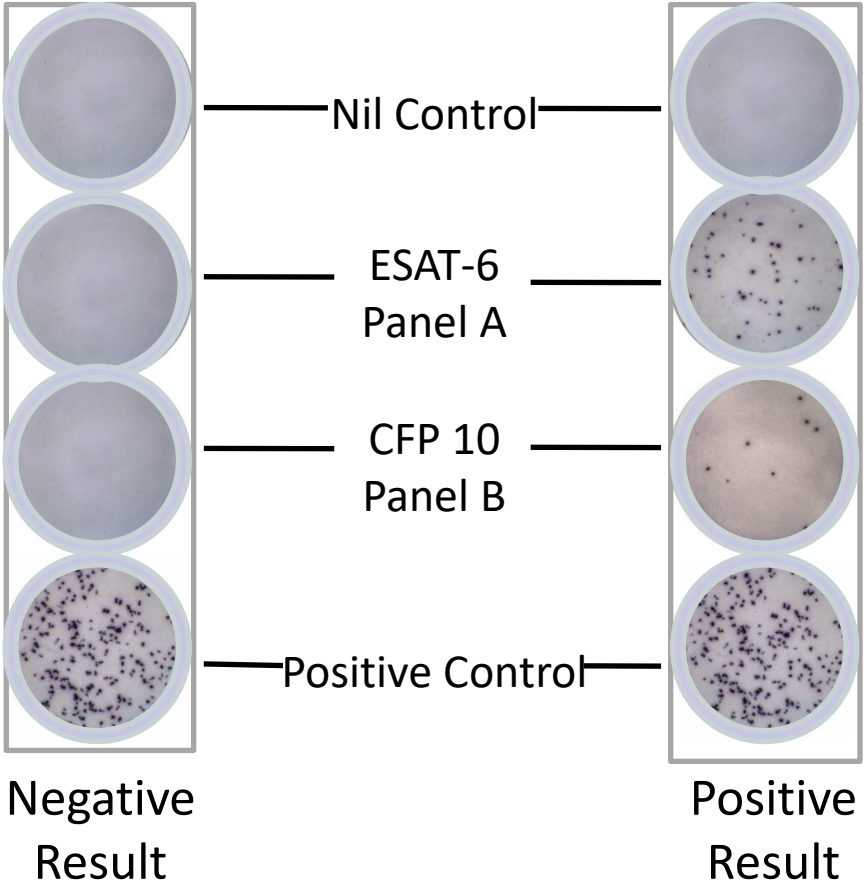
- Essentially 2 tests in one blood draw
- TB1 and TB2 should be close in value

Interpretation Criteria for the QFT-GIT Test

Nil (IU/mL)	TB Antigen minus Nil (IU/mL)	QFT-GIT (IU/mL)	Mitogen	Interpretation
≤ 8.0	≤ 0.35 or $< 25\%$ of Nil value	Negative	≥ 5.0	<i>M. tuberculosis</i> infection unlikely
≤ 8.0	≥ 0.35 and $\geq 25\%$ of Nil value	Positive	ANY	<i>M. tuberculosis</i> infection likely
≥ 8.0	ANY	Indeterminate	ANY	Indeterminate
≤ 8.0	≤ 0.35 and or $< 25\%$ of Nil value	Indeterminate	< 5.0	Indeterminate



Interpretation of Results



Interpretation Criteria for the T-Spot.TB

Result	Nil*	TB Response# #	Mitogen++	Interpretation+
Positive	≤ 10 spots	≥ 8 spots	Any	<i>M.tuberculosis</i> infection likely
Borderline	≤ 10 spots	5, 6, or 7 spots	Any	Uncertain likelihood of <i>M. tuberculosis</i> infection
Negative	≤ 10 spots	≤ 4 spots		M Tb infection unlikely
Indeterminate	> 10 ≤ 10	Any < 5 spots	Any < 20 spots	Uncertain likelihood of <i>M. tuberculosis</i> infection



Indeterminate and Borderline Results

- Indeterminate
 - Negative control result is too high
 - High background production of IFN- γ
 - Positive control result is too low
 - Immunocompromised patients may not respond to mitogen
- Borderline (T-Spot only)
 - Falls within borderline zone close to negative/positive cut point



(New) ATS/CDC/IDSA Guidelines



Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children

David M. Lewinsohn,^{1,a} Michael K. Leonard,^{2,a} Philip A. LoBue,^{3,a} David L. Cohn,⁴ Charles L. Daley,⁵ Ed Desmond,⁶ Joseph Keane,⁷ Deborah A. Lewinsohn,¹ Ann M. Loeffler,⁸ Gerald H. Mazurek,³ Richard J. O'Brien,⁹ Madhukar Pai,¹⁰ Luca Richeldi,¹¹ Max Salfinger,¹² Thomas M. Shinnick,³ Timothy R. Sterling,¹³ David M. Warshauer,¹⁴ and Gail L. Woods¹⁵

¹Oregon Health & Science University, Portland, Oregon, ²Emory University School of Medicine and ³Centers for Disease Control and Prevention, Atlanta, Georgia, ⁴Denver Public Health Department, Denver, Colorado, ⁵National Jewish Health and the University of Colorado Denver, and ⁶California Department of Public Health, Richmond; ⁷St James's Hospital, Dublin, Ireland; ⁸Francis J. Curry International TB Center, San Francisco, California; ⁹Foundation for Innovative New Diagnostics, Geneva, Switzerland; ¹⁰McGill University and McGill International TB Centre, Montreal, Canada; ¹¹University of Southampton, United Kingdom; ¹²National Jewish Health, Denver, Colorado, ¹³Vanderbilt University School of Medicine, Vanderbilt Institute for Global Health, Nashville, Tennessee, ¹⁴Wisconsin State Laboratory of Hygiene, Madison, and ¹⁵University of Arkansas for Medical Sciences, Little Rock

Groups with Increased Likelihood of Infection with Mtb		Benefit of Therapy	LTBI Testing Strategy	
Risk of Infection ↑	Household contact or recent exposure of an active case	Yes	Likely to be Infected Low to Intermediate Risk of Progression (TST ≥ 10mM)	Likely to be Infected High Risk of Progression (TST ≥ 5mM)
	Mycobacteriology laboratory personnel	Not demonstrated		
	Immigrants from high burden countries (>20 / 100,000)	Not demonstrated		
	Residents and employees of high risk congregate settings	Yes		
	None	Not demonstrated	Unlikely to be Infected (TST > 15mM)	
Risk of Developing Tuberculosis if Infected →				
		Low	Intermediate (RR 1.3 -3)	High (RR 3-10)
		No risk factors	Clinical predisposition Diabetes Chronic renal failure Intravenous drug use	Children age less than 5 HIV infection Immunosuppressive therapy Abnormal CXR consistent with prior TB Silicosis
Benefit of Therapy				
			Not demonstrated	Yes

In developing a diagnostic approach for the evaluation of those with suspected LTBI, we recommend the clinician weigh the likelihood of infection, the likelihood of progression to TB if infected, and the benefit of therapy (Horsburgh, C.R., Jr., and E.J. Rubin. 2011. Clinical practice. Latent tuberculosis infection in the United States. The New England journal of medicine 364:1441-1448). Recommendations were formulated for each of the three groups illustrated above. These groups are concordant with current recommendations for the interpretation of the TST (2000. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recomm Rep 49:1-51).

Current Diagnostic Guidelines

- Decisions to test or treat are based on likelihood of infection and likelihood of progression
- IGRAs are recommended for testing for TB infection in individuals ≥ 5 years old with low or moderate risk of infection or progression
 - Notes: IGRAs are a 'better' choice
 - When TST administration is questionable
 - In BCG vaccinated populations (increased specificity)
 - In populations with a poor rate of return
- Testing in low-risk populations is still not recommended. When it is necessary, such as required HCW screenings, use an IGRA
- In populations at high risk for infection or progression, either a TST or IGRA is appropriate
- UPDATE! American Academy of Pediatrics Red Book suggests IGRA use in children at any age



Pearls for TST vs. IGRAs

- Discordance between the TST and IGRAs has been measured up to 20% in patients known to be infected with Mtb. Don't order both tests, pick the right test to start with!
- The tests are not perfect. They provide one piece of your whole picture when assessing a patient, not the 'answer'.
- No test (TST or IGRA) overrides clinical, epidemiologic or historical data





37 y.o. male from Eritrea. Entered U.S. 10/15/2016
05/13/2019 Tspot (+)



32-year-old
wife/mother

No prior TB test

05/02/2019
TSpot (+)



17 mo. old
Male

No prior TB
test (U.S. Born)

05/04/19
TST (+) 14 mm



3-year-old
Male

06/11/2018
Tspot (-)

05/04/2019
TST (+) 15 mm



4-year-old
Female

06/11/2018
Tspot (-)

05/04/2019
TST (+) 18mm



13-year-old
Female

05/08/2018
TSpot (-)

05/02/2019
TSpot (+)



15-year-old
Male

05/02/2018
Tspot (+)

No current
testing

