



TB Infection Diagnosis Recommendations

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Screening & Treating Tuberculosis Infection
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San Antonio, Texas

Lisa Armitige, MD, PhD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity





TB Infection Diagnosis Recommendations

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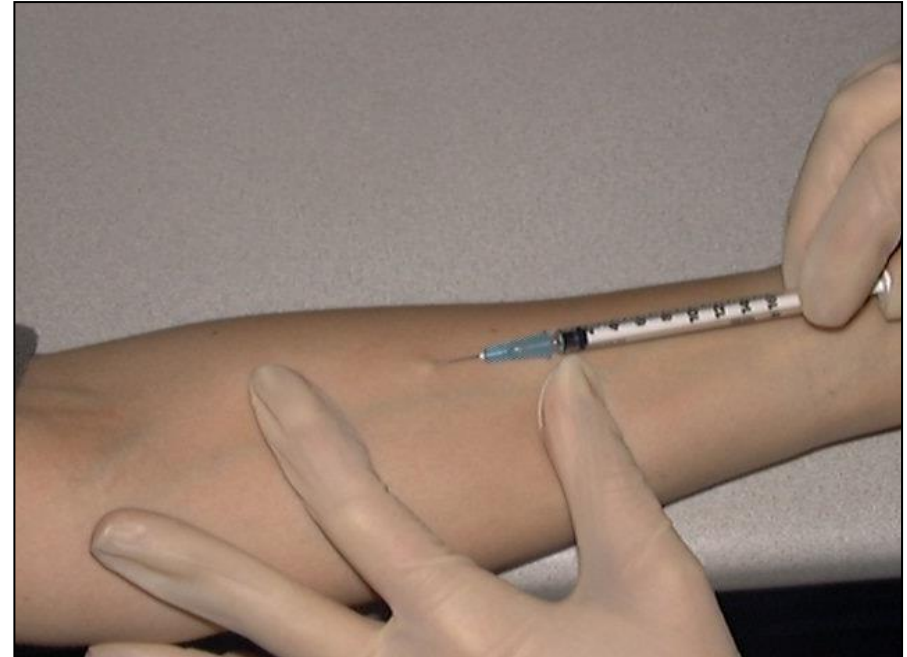
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Available Tools



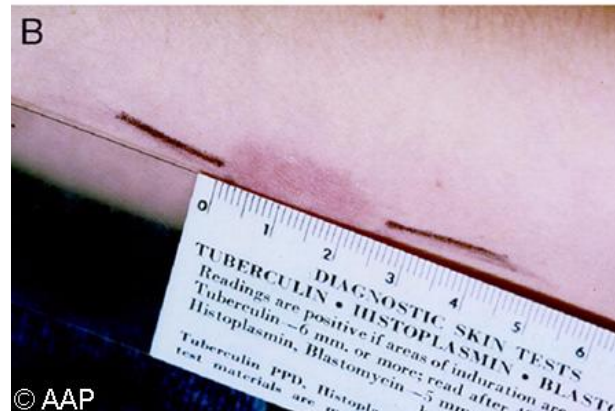
The Tuberculin Skin Test (TST)

- 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)

- 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

- Requires that you know something about the patient
- 5 mm is classified as positive in High-Risk Individuals
 - HIV/Immune suppressed
 - Recent contact with a person with infectious TB
 - Persons with evidence of old disease
- 10 mm is positive in Persons in High-Risk Settings
 - Immigrants from countries with high rates of TB (> 20/100K)
 - Residents/Employees of congregate settings
- 15 mm is positive.....period







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 (actually simulated using overlapping peptides)



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-Plus Test

Nil (IU/mL)	TB1 or TB2 Antigen minus Nil (IU/mL)	TB1 or TB2 (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



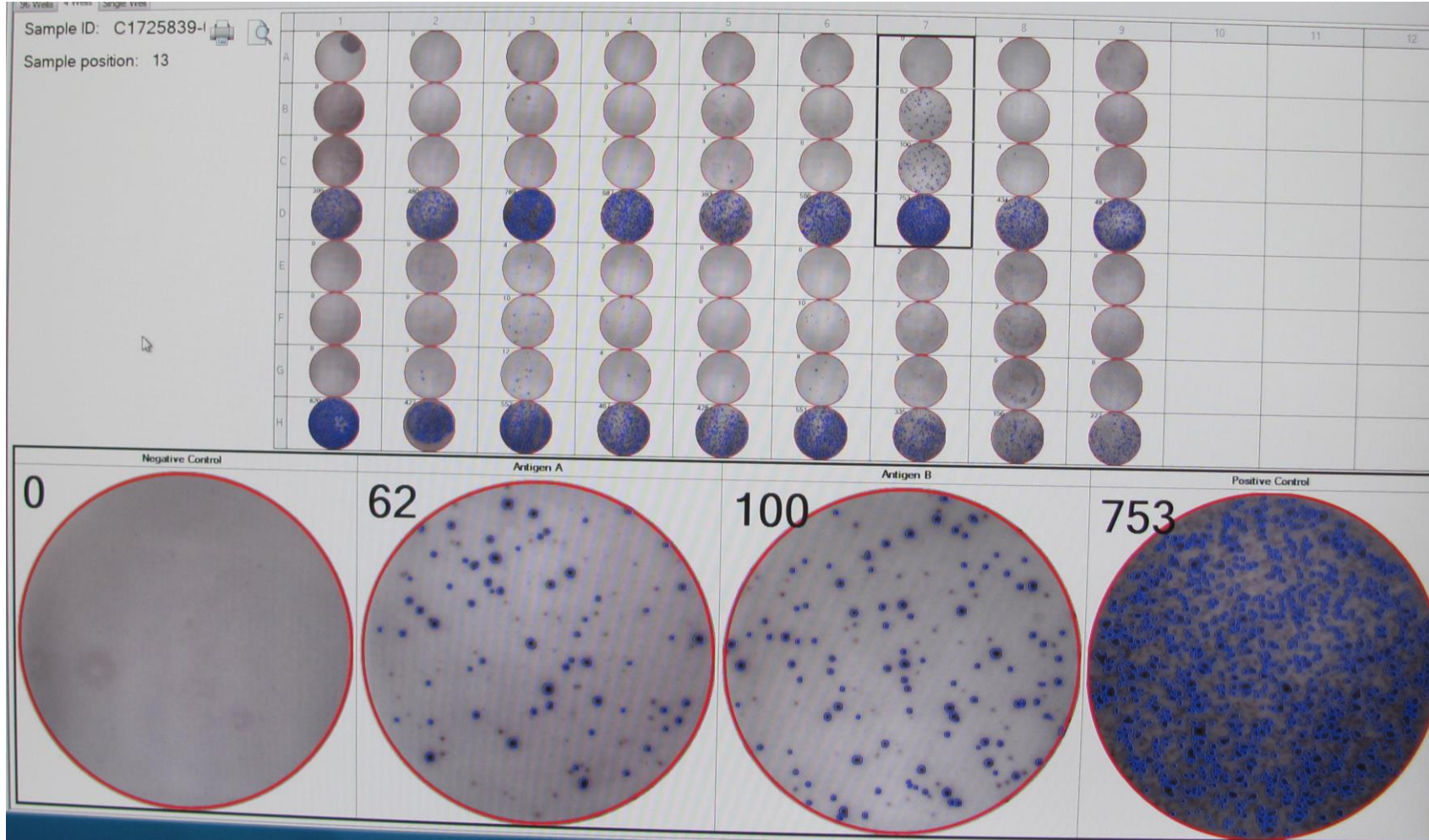
QuantiFERON-TB Gold

TABLE 2. TEST SENSITIVITY AND SPECIFICITY FOR CFP-10 AND ESAT-6 AT VARIOUS CUTOFFS IN WHOLE-BLOOD IFN- γ ASSAY

Cutoff, IFN- γ (IU/ml)	CFP-10		ESAT-6		CFP-10 and/or ESAT-6	
	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)
0.05	92.5	81.4	94.8	94.9	89.4	97.5
0.10	94.4	77.1	96.2	90.7	92.0	95.8
0.15	95.8	72.9	97.6	88.1	93.9	93.2
0.20	96.7	71.2	99.1	86.4	96.2	91.5
0.25	97.2	67.8	99.1	84.7	96.7	91.5
0.30	97.7	66.9	99.1	83.1	97.2	89.8
0.35	98.6	65.3	99.5	81.4	98.1	89.0
0.40	98.6	61.9	99.5	79.7	98.1	88.1
0.45	98.6	60.2	100.0	78.8	98.6	86.4
0.50	99.1	60.2	100.0	75.4	99.1	83.9

Sensitivity was determined on the basis of data from 118 patients with culture-positive tuberculosis, and specificity was determined on the basis of data from 213 low-risk subjects. The chosen cutoff (0.35) is in boldface.

T-Spot.TB



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



Pediatric Considerations for TB Screening

- Young immune systems, like young bodies, are growing
- By the time you have 5 candles on your birthday cake, your immune system behaves like an adult's
- There is grey area in children < 6 months of age (any test....every test), treat any positive and some negatives
- We overtreat and we are not sorry



TB Testing Take Homes

- TST expertise is fading fast
 - When can I still use it?
 - If you trust the person placing/reading it knows what they are doing
 - US born
 - No history of BCG
 - To add sensitivity
 - Repeatedly indeterminate or borderline IGRAs
- IGRAs are fast becoming the preferred screening tests for TB
 - Single visit
 - Objective result (positive or negative.....ish)
- TB screening tests are tools that add to the answer
 - They are not the answer themselves
 - They do not distinguish between TB infection (LTBI) and TB disease



Clinical Infectious Diseases

IDSA GUIDELINE



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


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Risk of Infection	Groups with Increased Likelihood of Infection with Mtb	Benefit of Therapy	LTBI Testing Strategy	
	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				
LowIntermediate (RR 1.3 -3)High (RR 3-10)				
No risk factorsClinical predisposition Diabetes Chronic renal failure Intravenous drug useChildren age less than 5 HIV infection Immunosuppressive therapy Abnormal CXR consistent with prior TB Silicosis				
Benefit of Therapy				
Not demonstratedYes				

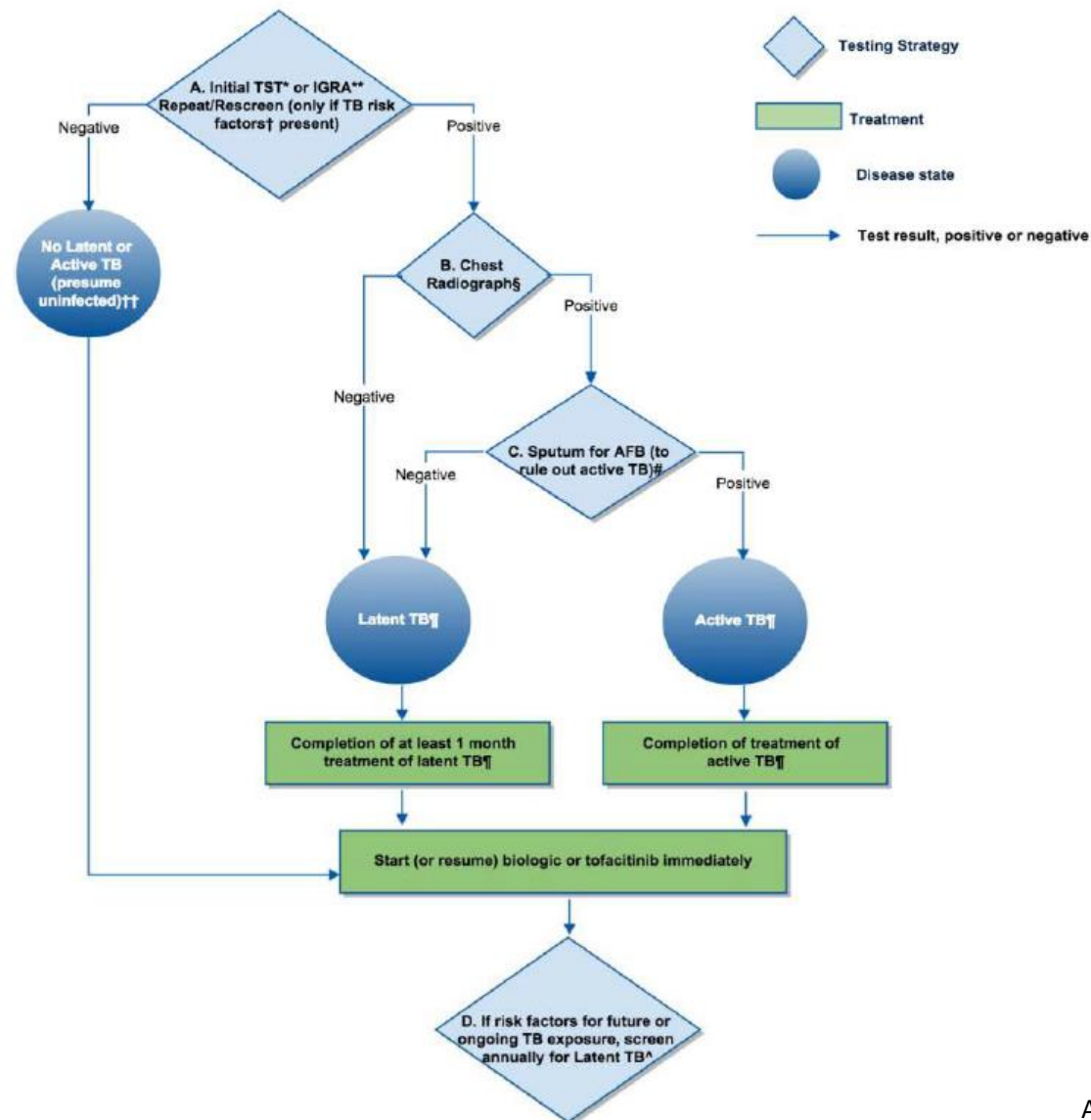
In developing a diagnostic approach for the evaluation of those with suspected LTBI, we recommend the clinician weigh the likelihood of infection, the likelihood of progression to TB if infected, and the benefit of therapy (Horsburgh, C.R., Jr., and E.J. Rubin. 2011. Clinical practice. Latent tuberculosis 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).



Group	Testing Strategy	Considerations
Likely to be Infected High Risk of Progression (TST \geq 5mM)	Adults Acceptable: IGRA OR TST Consider dual testing where a positive result from either result would be considered positive Children \leq 5 years of age Preferred: TST Acceptable: IGRA OR TST Consider dual testing where a positive result from either would be considered positive ¹	Prevalence of BCG vaccination Expertise of staff and/or laboratory Test availability Patient perceptions Staff perceptions Programmatic concerns
Likely to be Infected Low to Intermediate Risk of Progression (TST \geq 10mM)	Preferred: IGRA where available Acceptable: IGRA or TST	
Unlikely to be Infected (TST $>$ 15mM)	Testing for LTBI is not recommended If necessary: Preferred: IGRA where available. Acceptable: Either IGRA OR TST For serial testing: Acceptable: Either IGRA OR TST Consider repeat or dual testing where a negative result from either would be considered negative ²	

1. Performing a second diagnostic test when the initial test is negative is a strategy to increase sensitivity. This may reduce specificity, but the panel decided that this is an acceptable tradeoff in situations in which the consequences of missing LTBI (i.e., not treating individuals who may benefit from therapy) exceed the consequences of inappropriate therapy (i.e., hepatotoxicity).
2. Performing a confirmatory test following an initial positive result is based upon both the evidence that false-positive results are common among individuals who are unlikely to be infected with Mtb and the committee's presumption that performing a second test on those whose initial test was positive will help identify initial false-positive results.

Why, Rheumatology, Why?



World Traveler with RA

- 56 y/o WF about to be started on Humira for rheumatoid arthritis
 - She has traveled extensively, in the Peace Corp in her 20's and on humanitarian visits to Haiti, Sudan and Guatemala in the past 15 years
 - Her TST returns positive
- Do you:
 - Treat for TB infection (LTBI)?
 - Retest with an IGRA?



Recommendations

Should an IGRA or a TST be performed in individuals 5 years or older who are **likely to be infected** with *Mtb*, who have a **high risk of progression to disease**, and in whom it has been decided that **testing for LTBI is warranted**?

- Recommendation 2:

There are **insufficient data to recommend a preference for either a TST or an IGRA** as the first-line diagnostic test in individuals 5 years or older who are likely to be infected with *Mtb*, who have a **high risk of progression to disease**, and in whom it has been determined that diagnostic testing for LTBI is warranted.



Screening HCW for TB

TABLE. Comparison of 2005* and 2019† recommendations for tuberculosis (TB) screening and testing of U.S. health care personnel (HCP)

Category	2005 Recommendation	2019 Recommendation
Baseline (preplacement) screening and testing	TB screening of all HCP, including a symptom evaluation and test (IGRA or TST) for those without documented prior TB disease or LTBI.	TB screening of all HCP, including a symptom evaluation and test (IGRA or TST) for those without documented prior TB disease or LTBI (unchanged); individual TB risk assessment (new).
Postexposure screening and testing	Symptom evaluation for all HCP when an exposure is recognized. For HCP with a baseline negative TB test and no prior TB disease or LTBI, perform a test (IGRA or TST) when the exposure is identified. If that test is negative, do another test 8–10 weeks after the last exposure.	Symptom evaluation for all HCP when an exposure is recognized. For HCP with a baseline negative TB test and no prior TB disease or LTBI, perform a test (IGRA or TST) when the exposure is identified. If that test is negative, do another test 8–10 weeks after the last exposure (unchanged).
Serial screening and testing for HCP without LTBI	According to health care facility and setting risk assessment. Not recommended for HCP working in low-risk health care settings. Recommended for HCP working in medium-risk health care settings and settings with potential ongoing transmission.	Not routinely recommended (new); can consider for selected HCP groups (unchanged); recommend annual TB education for all HCP (unchanged), including information about TB exposure risks for all HCP (new emphasis).
Evaluation and treatment of positive test results	Referral to determine whether LTBI treatment is indicated.	Treatment is encouraged for all HCP with untreated LTBI, unless medically contraindicated (new).

Abbreviations: IGRA = interferon-gamma release assay; LTBI = latent tuberculosis infection; TST = tuberculin skin test.

* Jensen PA, Lambert LA, Iademarco MF, Ridzon R. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. MMWR Recomm Rep 2005;54(No. RR-17). <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5417a1.htm>.

† All other aspects of the Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings, 2005 remain in effect, including facility risk assessments to help guide infection control policies and procedures.

Suddenly Positive

- 35-year-old US-born man takes a job at new hospital in the accounting department. He has been tested annually at his old hospital job and has been TST negative for the past 10 years.
- He has a positive IGRA (nil 0, TB1-nil 0.42, TB2-nil 0.27). He has no recent travel nor known contact to anyone with TB disease.
- What should you do with him?



Recommendations

Should an IGRA or a TST be performed in individuals 5 years or older who are unlikely to be infected with *Mtb*, but in whom it has been decided that testing for LTBI is warranted?

- Recommendation 3a:

We suggest performing an IGRA instead of a TST
(*conditional recommendation, low-quality evidence*).

- Recommendation 3b:

We suggest a second diagnostic test if the initial test is positive
(*conditional recommendation, very low-quality evidence*).

Remarks: The confirmatory test may be either an IGRA or a TST. When such testing is performed, the person is considered infected only if both tests are positive.



Evaluate for Tuberculosis Disease



Initiating Treatment for LTBI

Before initiating treatment for LTBI

- Rule out TB disease
 - i.e. wait for culture results if specimen obtained
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment
- Determine current and previous drug therapy



Evaluate to Exclude Active TB Disease

- If the TST or IGRA is Positive

OR

- Child < 5 or immunocompromised person with recent exposure **even if TST/IGRA negative**
 - History
 - Physical examination
 - Chest X-Ray

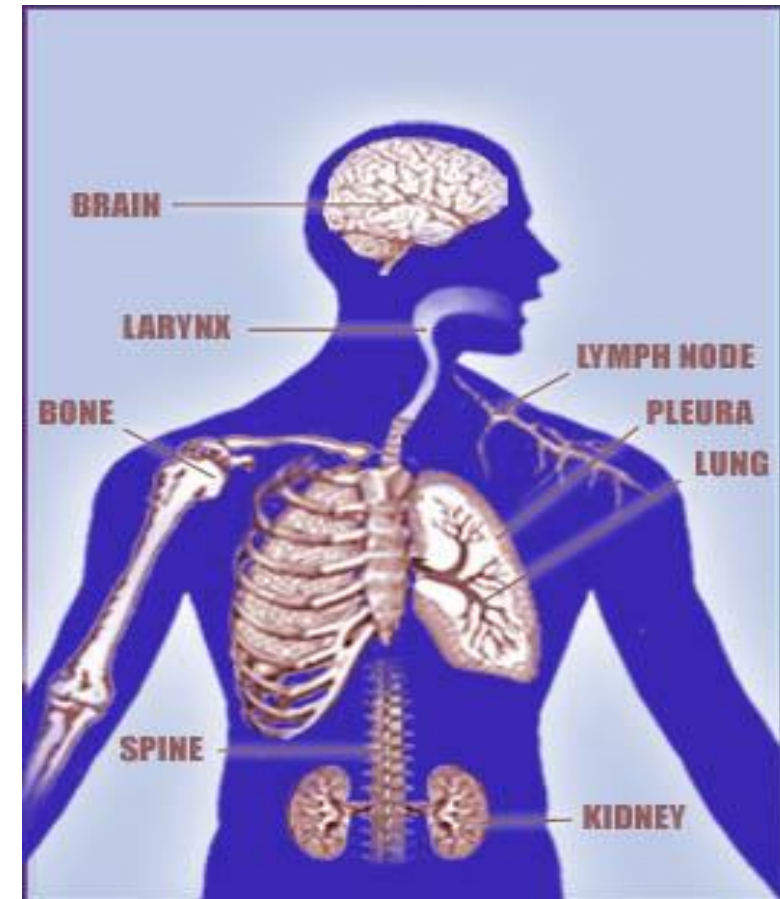


Sites of TB Disease

Lungs

Extrapulmonary:

- Larynx
- Pleural effusion
- Kidneys
- Lymphatics
- Bones & joints
- Miliary (disseminated)



Evaluation for TB

- Medical history
- Physical examination
- Testing for TB infection
- Chest radiograph
- Bacteriologic or histologic exam



Is There Evidence of Disease?

- Symptoms*

- Fever
- Chills
- Night Sweats
- Weight Loss
- Cough (dry/productive)
- Hemoptysis
- Fatigue

*** only one may be present**

Is Patient at Risk of Progression to Disease?

- Medical History:

- HIV
- Silicosis
- Chronic Kidney Disease
- Diabetes
- Immunosuppression
- Drug/alcohol/tobacco
- TB exposure



Physical Exam

- General assessment – does person look well?
- Lung exam
- Check for lymph nodes
- Palpate liver
- *In children* look at growth curve/weight/activity
- Look for anything that will complicate therapy!



Radiologic Exam

- CXR must be done **before treatment of TB Infection**
 - Must be read as normal
- Or
- IF abnormal:
 - Not consistent with Active TB
 - Stable abnormality confirmed over a 3 month period



No CXR study shows findings specific for TB

Cavitary processes suggest TB

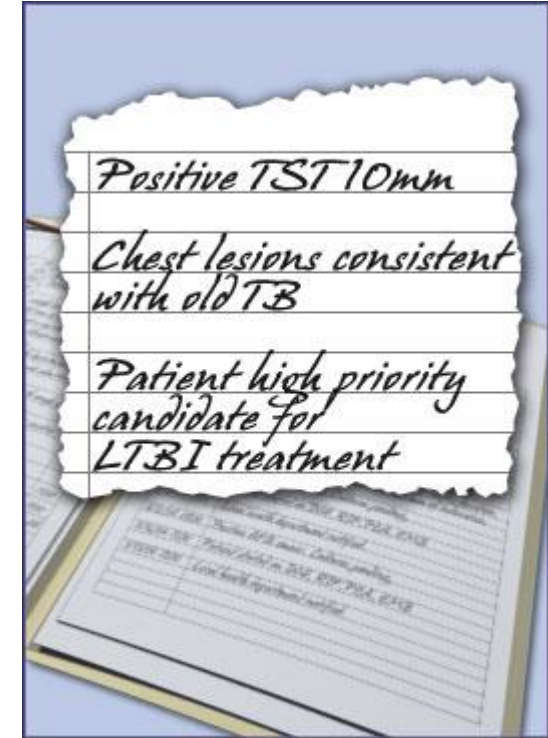
Common mimics of TB

- Non-tuberculous mycobacteria (NTM)
- fungal infection
- bacterial abscesses
- necrotic neoplasm (especially lung neoplasm)



CXR – old healed TB

- Nodules & fibrotic lesions may contain slowly multiplying bacilli = potential for progression
- CXR consistent with old TB and + TST/IGRA = high priority for LTBI treatment



*Calcified nodular lesions (calcified granuloma)
pose a very low risk for future progression*

CXR - special situations

- Pregnant women who are suspected of having or who are being evaluated for active TB disease should undergo a CXR without delay, even during the first trimester
- Patients suspected of extrapulmonary TB should have a CXR to R/O pulmonary TB



Management of Positive TST or IGRA When the CXR is Abnormal

- If Patient has NO signs or symptoms of Active TB:
 - Collect 3 sputum specimens for smears and culture
 - Evaluate for symptoms
 - If no symptoms - Wait
 - Repeat CXR after 2 – 3 months
- If CXR stable at 2 – 3 months and cultures negative, treat for TB Infection



Bacteriologic and Histologic Examinations

When lung or larynx is site of disease:

- 3 sputum specimens for AFB smear and culture
- Collected 8-24 hours apart with at least 1 early morning specimen



Bacteriologic and Histologic Examinations

Extrapulmonary Specimens

- Urine
- Cerebrospinal fluid *
- Pleural fluid *
- Pus
- Biopsy specimens

*recovery poor



**Do NOT collect
specimens in Formalin**



Laboratory Examination

- AFB smear
- AFB culture
- Nucleic acid amplification test (NAAT)
 - GeneXpert
 - Molecular Detection of Drug Resistance (MDDR)

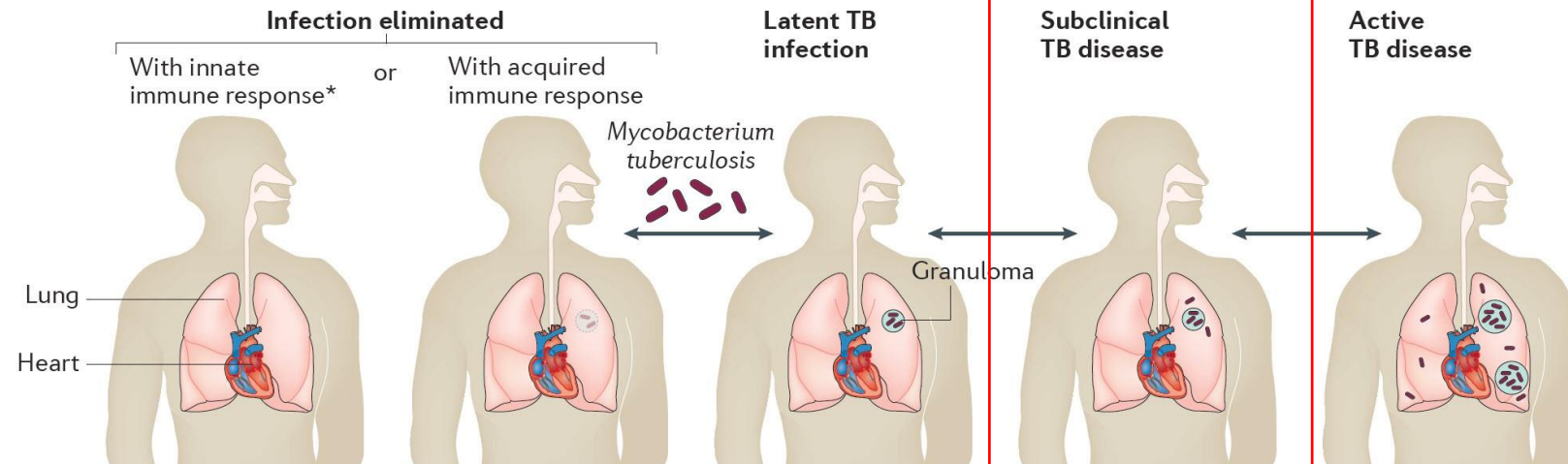


I Think This is TB.....

- 38-year-old man referred for persistent cough, abnormal CXR. Cough has been going on for 2 months, intermittently productive.
- CXR with fibronodular disease and small cavities in the RUL. IGRA positive, fungal serologies negative.
- He feels fine. No fevers, chills, no symptoms. Some weight loss (recent increase in work stress), night sweats (air condition has been acting up)
- Sputum x 3 is AFB smear negative (2 specimens NAAT negative)
- You still think this is TB....what do you do with him?



Tuberculosis Spectrum of Disease



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Management of Positive TST or IGRA When CXR is Abnormal and the Patient Has ANY Signs or Symptoms of TB

- The patient should be suspected of having TB disease
- Collect 3 sputa for smear and culture
- Consider starting standard 4 drug (RIPE) treatment
- If positive smear and/or Gene Xpert
 - Report to public health and start 4 drug (RIPE) treatment
- Never (ever!) start a treatment for TB infection in a patient with possible active TB



Pediatric TB

- The contact investigation is the life-changing event for children exposed to TB
- Every child contact under 5 y/o gets a physical exam, a CXR and a screening test
- Children mostly have paucibacillary disease, 10% smear positivity, 10-40% culture positivity
- 50% of children have no symptoms at all



TB Testing in Pregnant Persons

- Test in every instance you would test if they were not pregnant
 - HIV
 - Contact to an active case
 - Immigrant from a high-risk country
- The immune system may not react as expected
- Yes, you can/should get a CXR



Yes! You can X-ray a pregnant patient!



The American College of
Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

ACOG COMMITTEE OPINION

Number 723 • October 2017

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Committee on Obstetric Practice

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Table 2. Effects of Gestational Age and Radiation Dose on Radiation-Induced Teratogenesis ↵

Gestational Period	Effects	Estimated Threshold Dose*
Before implantation (0–2 weeks after fertilization)	Death of embryo or no consequence (all or none)	50–100 mGy
Organogenesis (2–8 weeks after fertilization)	Congenital anomalies (skeleton, eyes, genitals)	200 mGy
	Growth restriction	200–250 mGy
Fetal period	Effects	Estimated Threshold Dose*
8–15 weeks	Severe intellectual disability (high risk) [†]	60–310 mGy
	Intellectual deficit	25 IQ-point loss per 1,000 mGy
	Microcephaly	200 mGy
16–25 weeks	Severe intellectual disability (low risk)	250–280 mGy*

*Data based on results of animal studies, epidemiologic studies of survivors of the atomic bombings in Japan, and studies of groups exposed to radiation for medical reasons (eg, radiation therapy for carcinoma of the uterus).

[†]Because this is a period of rapid neuronal development and migration.

Modified from Patel SJ, Reede DL, Katz DS, Subramaniam R, Amorosa JK. Imaging the pregnant patient for nonobstetric conditions: algorithms and radiation dose considerations. *Radiographics* 2007;27:1705–22.

Table 3. Fetal Radiation Doses Associated With Common Radiologic Examinations ↵

Type of Examination	Fetal Dose* (mGy)
<i>Very low-dose examinations (<0.1 mGy)</i>	
Cervical spine radiography (anteroposterior and lateral views)	<0.001
Head or neck CT	0.001–0.01
Radiography of any extremity	<0.001
Mammography (two views)	0.001–0.01
Chest radiography (two views)	0.0005–0.01
<i>Low- to moderate-dose examinations (0.1–10 mGy)</i>	
Radiography	
Abdominal radiography	0.1–3.0
Lumbar spine radiography	1.0–10
Intravenous pyelography	5–10
Double-contrast barium enema	1.0–20
CT	
Chest CT or CT pulmonary angiography	0.01–0.66
Limited CT pelvimetry (single axial section through the femoral heads)	<1
Nuclear medicine	
Low-dose perfusion scintigraphy	0.1–0.5
Technetium-99m bone scintigraphy	4–5
Pulmonary digital subtraction angiography	0.5
<i>Higher-dose examinations (10–50 mGy)</i>	
Abdominal CT	1.3–35
Pelvic CT	10–50
¹⁸ F PET/CT whole-body scintigraphy	10–50

Conclusions

- IGRAs are becoming the TB test of choice, though the TST still has some utility
- Screening for TB should be considered in non-US born individuals who have not been previously screened or who spend significant time in higher risk countries.
- HCW screening is focused less on annual screening of low risk individuals and more on treatment of workers who test positive.
- Current TB screening tests are tools, not an answer



Questions?

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