Diagnosis & Medical Management of TB Infection

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TB Nurse Case Management • May 6 – 8, 2025 • San Antonio, Texas

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Has the following disclosures to make:

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

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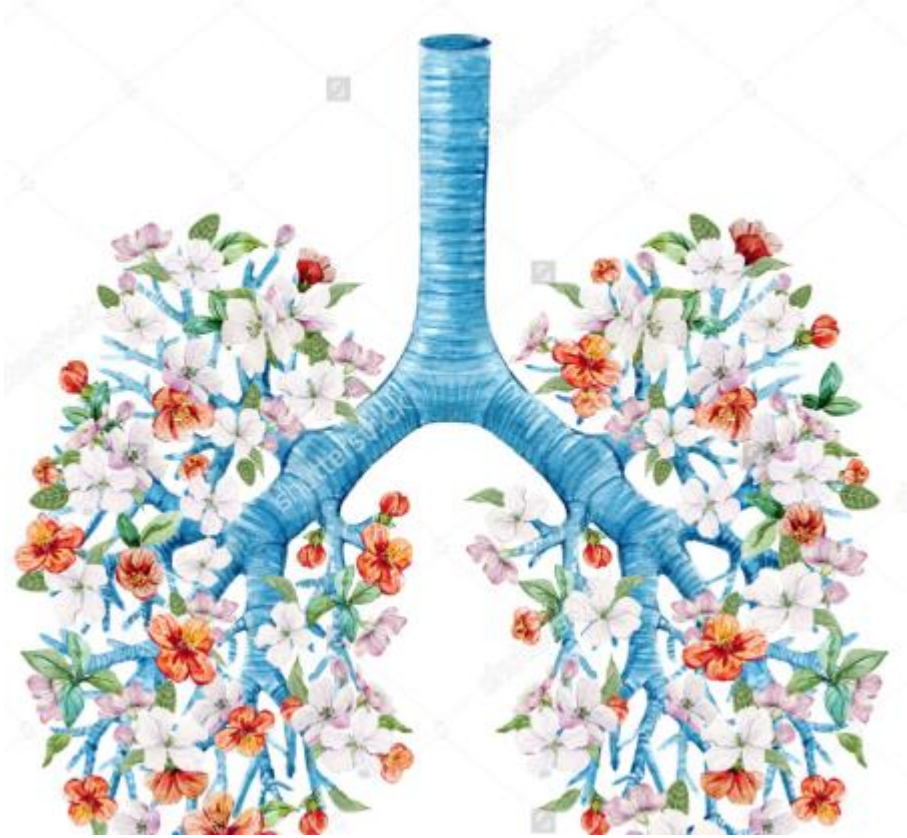

DIAGNOSIS AND MEDICAL MANAGEMENT OF TB INFECTION

TB Nurse Case Management training 5/6/2025 - 5/8/2025 San Antonio, Texas sponsored by HEARTLAND

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CDU Medical Director

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MAY 6, 2025

I have no disclosures to make

Other than

credit is given!)

shamelessly using pretty pix off the internet (but

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IDENTIFY PEOPLE **AT RISK** FOR TB INFECTION

OBJECTIVE #1

SCREENING- TARGETED TESTING-DIAGNOSIS

CURRENT RECOMMENDATIONS **FOR TREATMENT** OF TB INFECTION

OBJECTIVE #2

SCREENING- TARGETED TESTING- DIAGNOSIS OF TB INFECTION

?

WHY

WHO

WHEN

WHAT

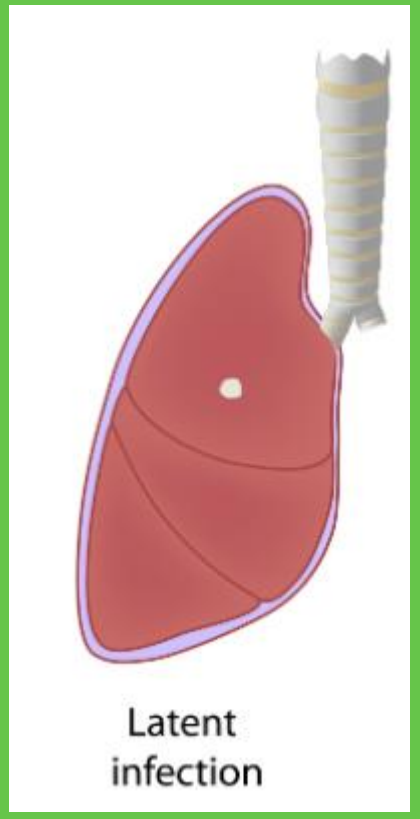
THE TB SCREENING PROCESS

Why?

first… what is TBI?

Tuberculosis infection is a state that is characterized by persistent immune response to stimulation by Mycobacterium tuberculosis (MTB) antigens with **no evidence of clinically manifest TB disease**.

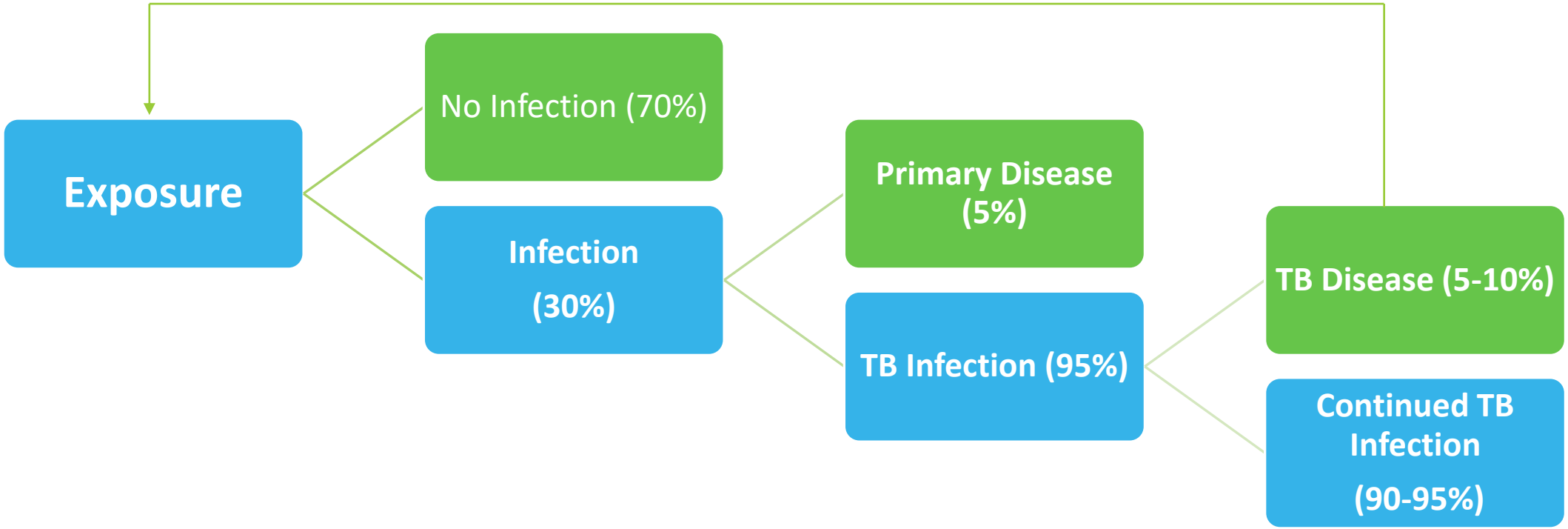
LATENT TBI



Infected with *Mycobacterium tuberculosis* but:

- No Active TB Symptoms
- Chest X-ray may be normal, or show granuloma, **stable** pleural or parenchymal scarring
- Positive TST or IGRA
- QUESTION: Can you have LTBI with a NEGATIVE TST or IGRA?

Exposure → Infection → Disease



Reproduced from slides from Charles Daley, MD

?

THE TB SCREENING PROCESS

WHY

To prevent TB disease

To Prevent TB Disease: **Find TB Infection**

LATENT TBI

QUESTION: Can you have LTBI with a NEGATIVE TST or IGRA?

Most probably!

**REMEMBER that the TST, the T Spot and the QuantiFERON -

All miss > 10 % of those with active TB

The % of those with true LTBI with negative tests unknown

LATENT TBI

People with LTBI are **NOT** infectious

90 +% chance of never getting active TB Disease

But the TB organism is alive inside the body!

LATENT TBI

- **ALIVE and in my body?!?!?!**

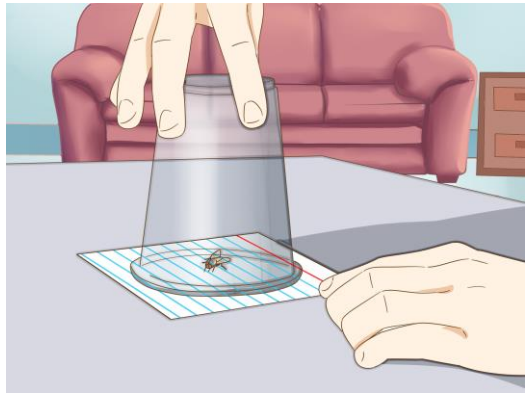
We used to think the bacteria were in a resting state or dormant but actually…

the TB Bacteria are metabolically **active and dividing.**

BUT!…

the infection is controlled by the immune system.

LATENT TB INFECTION
control & activation



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The Burden of TB in the US & Globally

USA: 13m TBI 10,347 TB disease 600 deaths (2022)

- (8% increase in cases/6% increase in rates from 2023)

Global: 2 billion TBI 10.8 million TB disease 1.25m deaths

- (1.3m were children)

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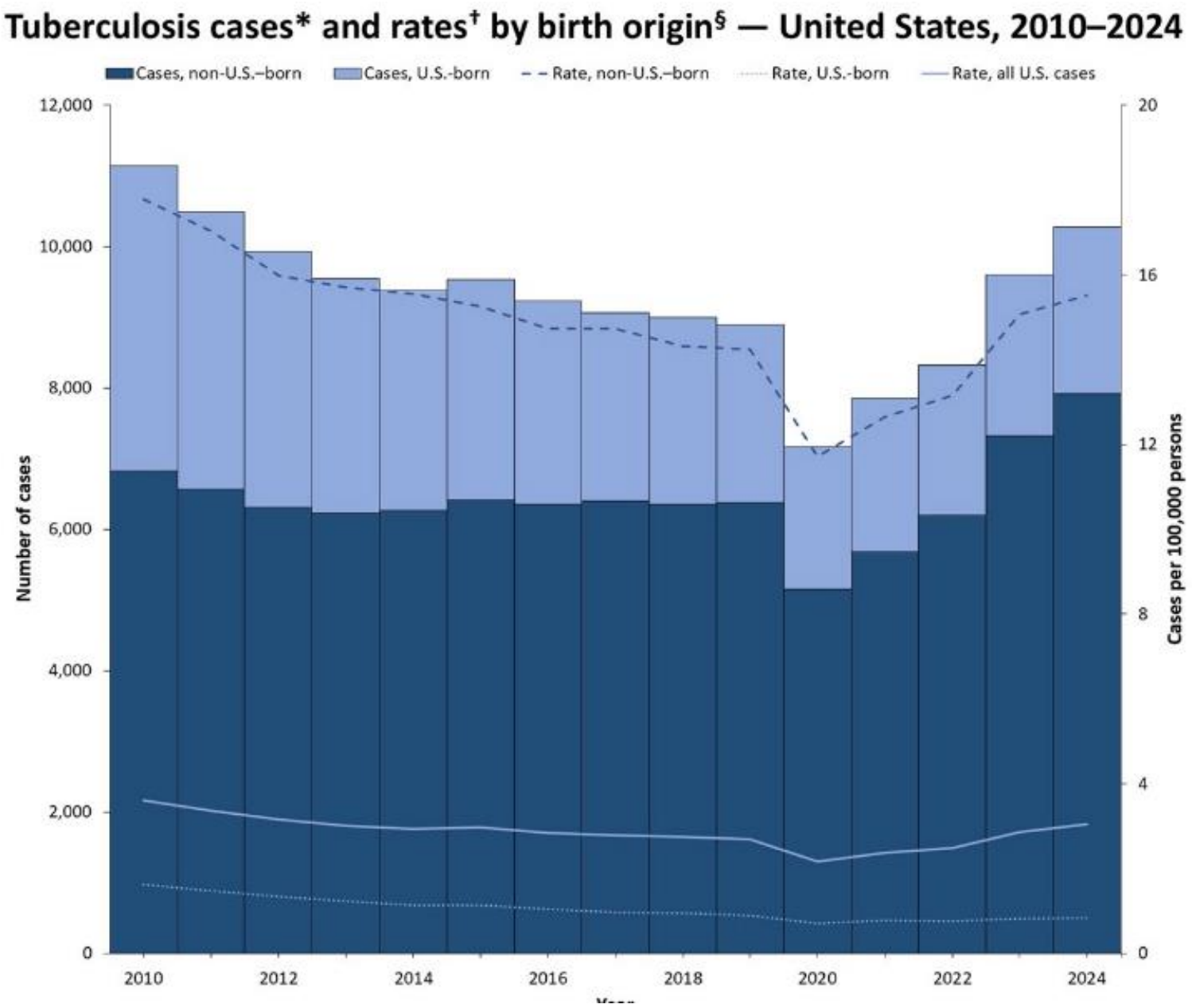

SOURCE:

https://www.cdc.gov/tb-data/2024-provisional/index.html

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WHY

WHO

WHEN

WHAT

THE TB SCREENING PROCESS

Who?

?

WHO

¿

THE TB SCREENING PROCESS

Those at risk…

*targeted testing

Who Should be Tested for TB Infection?

Targeted Testing for TB Infection

Basically…

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

@ increased RISK for INFECTION

*Contacts to active pulmonary or laryngeal TB

*People born in countries where TB is common or who travel to these countries

*Employees/residents of high risk congregate settings (Correctional facilities, long term care medical facilities, nursing homes, or other long-term care facilities)

*HCW with increased risk for occupational exposure

*Infants & children exposed to adults who are at high risk for TB

@ increased RISK for INFECTION

*HIV/AIDS
*IVDU
*DM-CKD-Silicosis
*Recent conversion (of TB test from neg to pos)
*age <5
*CXR abnormality c/w prior inadequately treated TB **(TB Class IV)**
*Smoking – active and passive
*Underweight by >10%

@ increased RISK for INFECTION

*Pregnancy and first three months post partum

*Immunosuppression

head and neck cancers
Leukemia, lymphoma
On transplant list (organ transplantation)

*Medications

- TNFα inhibitors
- Prednisone >15 mg, > 4 weeks
- Chemotherapy
- Other immunosuppressive drugs

A closer look

Contacts of Individuals with Active TB

CONTACTS: We get our contact investigators involved asap!

Among close contacts to a pt with active TB:

- 30% have TB Infection
- 1-3% have TB disease

Without TB Infection treatment:

- 10% with TBI with develop TB disease
  - Approximately 5% of contacts with newly acquired TBI progress to TB disease within 2 yrs
  - The other 5% activate > 2 years after acquisition

Examination of contacts is **one of the most effective strategies** for TBI diagnosis and TB control!

Risk of Progression to TB Disease by Age

Age @ primary infection		Risk of Disease
Birth – 12 months	TB Disease	up to 50%
	Pulmonary Disease	30-40%
	Miliary or TB Meningitis	10-20%
1-2 years	Disease	20-25%
	Pulmonary Disease	75%
	Miliary or TB Meningitis	2-5%

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Marais BJ. *Int J Tuberc Lung Dis* 2004;8:392-402

A closer look

Also:

Younger = Higher risk AND Worse Disease

Age at Infection (years)	No Disease (%)	Intrathoracic TB (%)	TB Meningitis (%)
<1	50	30-40	10-20
1-<2	75-80	10-20	2.5
2-<5	95	5	0.5
5-10	98	2	<0.5
≥10	80-90	10-20	<0.5

**Adapted from Marais et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy area. Int J Tuberc Lung Dis. 2004; 8(4):392-402*

Targeted Testing:

WE'VE COVERED

Contacts of persons with active TB

Kiddos

People with certain diseases/infections such HIV positive individuals

Injection Drug Users

Residents and Employees of high-risk congregate settings:

- Correctional facilities and Homeless Shelters
- Hospitals, Clinics, Nursing Homes, Substance Abuse Facilities

More about:

Immigrants from/travelers to high prevalence countries

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Where are our pts born?

Among persons in the United States with active TB disease who were non-US born, nearly half were born in Mexico, the Philippines, India, Vietnam, and China. The TB incidence rates in 2023 in those countries were estimated by the World Health Organization to be:

Mexico: incidence	24/100,000 (Medium)	About 17% of the TB cases
The Philippines: "	539/100,000 (High)	11.5%
India:	188/100,000 (High)	about 8%
Vietnam:	176/100,000 (High)	about 6%
China:	59/100,000 (Medium)	about 5%

(keep in mind just over half, 53% were born ELSEWHERE)

Persons who were born in, or resided in, these countries should be tested at least once regardless of how long they have resided in the United States.
When? As soon as you find out it hasn't yet been done.

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THE TB SCREENING PROCESS

?

✓WHY

✓WHO

→WHEN

WHAT

WHY? To prevent TB disease

WHO? People at high risk for exposure AND/OR

at risk for progression of TBI to TB disease

WHEN? As soon as you realize they need testing! (exposures/risks)

?

WHAT

¿

THE TB SCREENING PROCESS

Test to order?

IGRA v TST

there is no gold standard test

The TST

intradermal injection of purified protein derivative (PPD)

PPD tuberculin solution contains dozens of TB antigens

composition varies among batches

many of these antigens are present in environmental nontuberculous mycobacteria (NTM) prevalent in the US and in BCG vax

several problematic limitations of the TST

Might be easy to perform

Might not be so easy to read/interpret

Nothing beats experience!

The IGRA

detect interferon-λ (IFN-λ) release from a patient's $CD4^+$ and $CD8^+$ T- lymphocytes after stimulation by antigens found on *M tuberculosis (MTB)* complex

2 available: the **QuantiFERON-TB Gold Plus** assay (4th gen QFT; replaced the previously used & studied QuantiFERON-TB Gold In-Tube assay & other earlier QFT versions) and the **T-SPOT.TB** assay

Antigens are not in MAC/other NTMs that can rarely cause human dz, nor in M. bovis- BCG strains, but are in wild M. bovis strains

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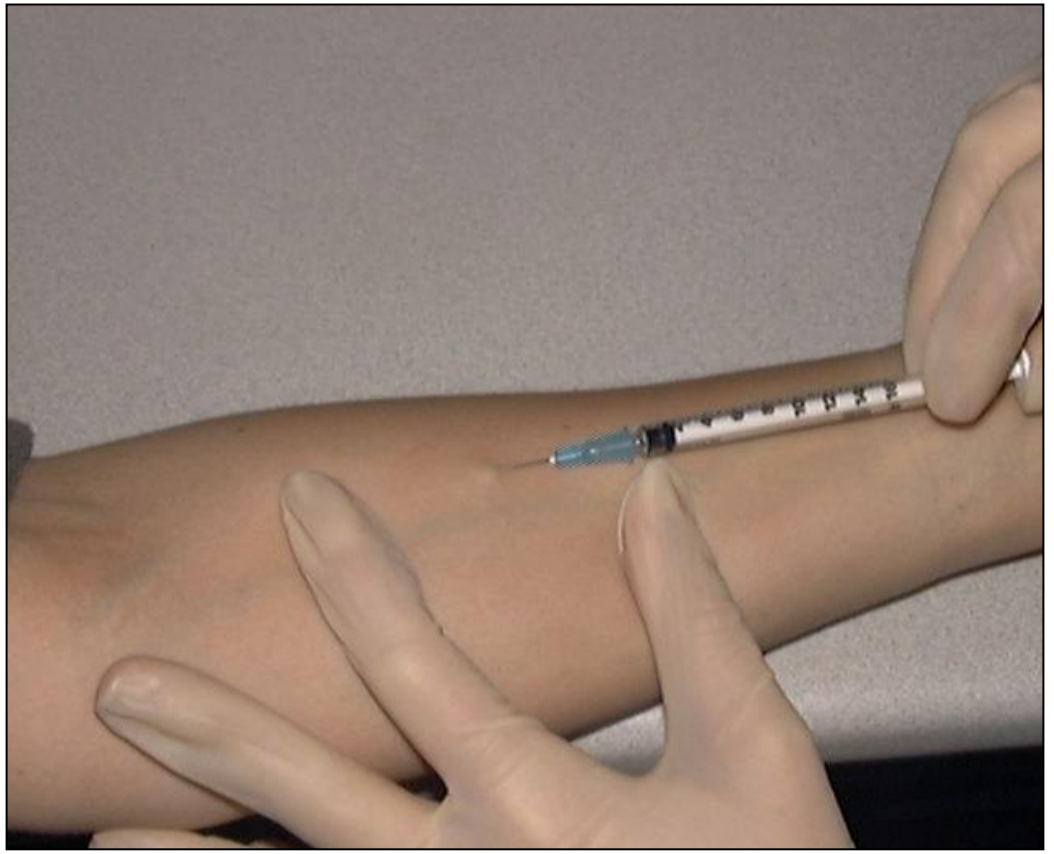
The Tuberculin Skin Test (TST)

0.1 ml of 5 Tuberculin units PPD injected intradermally; +wheal

Induration in millimeters read 48-72 hours after injection

Usually also see erythema



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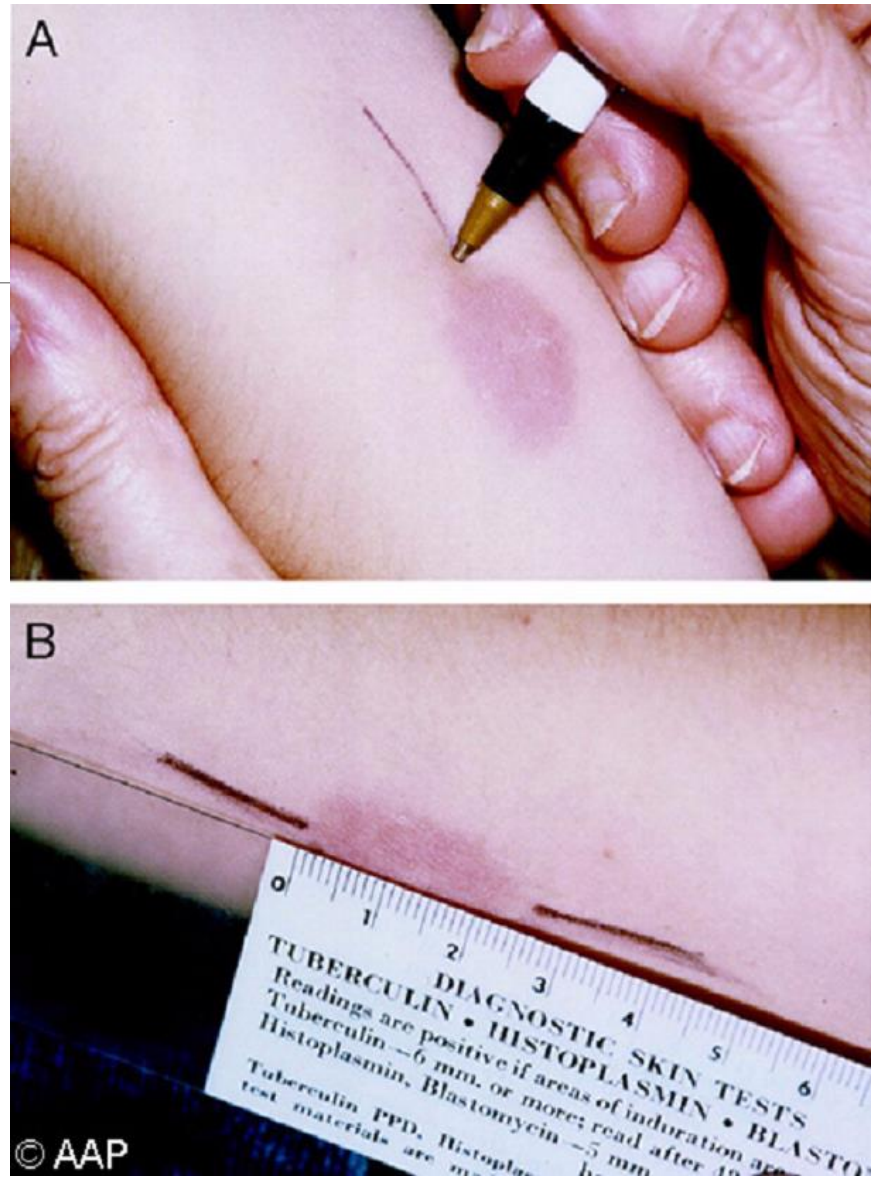
INDURATION

Measure **induration**,
not erythema



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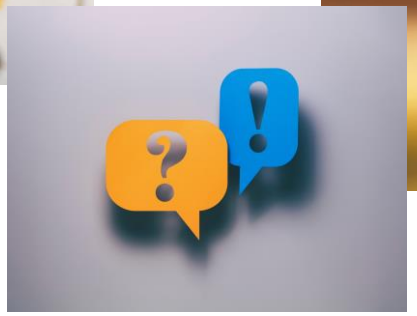
Without interpretation-

a test is just a test



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Test interpretation depends on 2 things:

the **induration** at the injection site

And

the **risk** of TBI progression to TB

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How to Classify the TST result

You must know something about your patient!

≥ 5 mm is positive in ‘high risk people’

≥ 10 mm is positive in ‘people from high-risk environments”

≥ 15 mm is positive……period

Targeted skin testing programs should only be conducted among high-risk groups

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

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

Let’s talk about IGRAs

YAY!!!

FDA Approved IGRAs

QuantiFERON®-TB Gold Plus (QFT-Plus)

- FDA approved 2017

T-Spot®.*TB* (T-Spot)

- FDA approved July 2008

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 ESAT	CFP	Environmental strains	Antigens 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	-	-

www.cellestis.com

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

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QFT GOLD PLUS

Unlike the TST, IGRAs do not cross-react with the *M. bovis* bacillus Calmette-Guérin (BCG) vaccine and NTM, with the exception of

M. kansasii,

M. szulgai, &

M. marinum

Mitogen: measures antigen-independent T-cell response

Nil: measures background IFN-λ response

TB1 primarily CD4+

TB2: both CD4+ & CD8+ T-cell response

QuantiFERON®-TB Gold Plus

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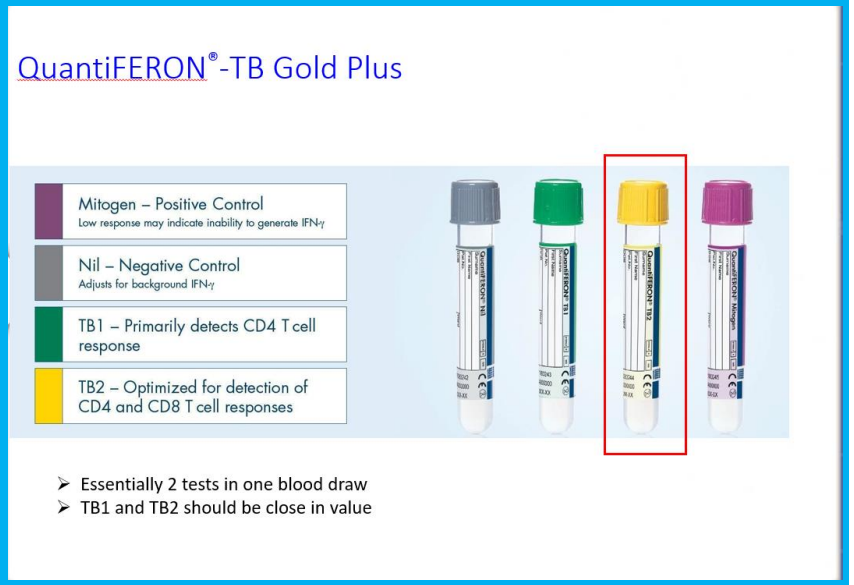
QFT GOLD PLUS



What is all this???

Mitogen: measures antigen-independent T-cell response

It has a NON-SPECIFIC stimulant to activate the immune response.

This is a reflection of the immune system

Nil: measures background IFN-λ response

There's just some in the background; if it too high then it is no good for comparison purposes; it's this difference in the 2 responses the test is looking for, test can't be read if the nil is too high as we can't tell what the immune system is doing.. The nil establishes the baseline response.

TB1 primarily CD4+; TB2: both CD4+ & CD8+ T-cell response

These tubes have specific TB antigens to stimulate a response in those who have been exposed to the MTB organisim. It requires the "memory" of the memory cells to be able to remember: this was tested earlier with the mitogen tube.

QFT Gold + interpretation

Test is indeterminate if either:

The nil is >8.0

Or

The mtiogen-Nil is <0.50

(You don't have to do the math!)

You SHOULD look at the TB1 and TB2 values

- they should not be super far apart in value

-low + is generally <1 or 1.1 (read your lab report) May consider if it is a true+ or not. FP? Retest??

Interpretation of QFT-Plus test results

Nil (IU/ml)	TB1 minus Nil (IU/ml)	TB2 minus Nil (IU/ml)	Mitogen minus Nil (IU/ml)	QFT-Plus Result	Result interpretation
≤8.0	≥0.35 and ≥25% of Nil	Any	Any	Positive	*M. tuberculosis* infection likely
	Any	≥0.35 and ≥25% of Nil			
	<0.35 or ≥0.35 and <25% of Nil	<0.35 or ≥0.35 and <25% of Nil	≥0.50	Negative	*M. tuberculosis* infection NOT likely
	<0.35 or ≥0.35 and <25% of Nil	<0.35 or ≥0.35 and <25% of Nil	<0.50	Indeterminate	Likelihood of *M. tuberculosis* infection cannot be determined
>8.0	Any				

Results table excerpted from QuantiFERON-TB Gold Plus packet insert: https://www.quantiferon.com/us/products/quantiferon-tb-gold-plus-us/package-inserts/

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	*M. tuberculosis* infection unlikely
≤ 8.0	≥ 0.35 and ≥ 25% of Nil value	Positive	ANY	*M. tuberculosis* infection **likely**
≥ 8.0	ANY	Indeterminate	ANY	Indeterminate
≤ 8.0	≤ 0.35 and or < 25% of Nil value	Indeterminate	< 5.0	Indeterminate

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Lab reports: QFT Gold Plus Results

LAB OFTEN (SOMETIMES?) GIVES YOU GOOD INFO IF YOU TAKE THE TIME TO READ IT, PARTICULARLY ABOUT INTERPRETATION & REPEAT TESTING

QUANTIFERON TB GOLD PLUS
QUANTIFERON TB GOLD PLUS POSITIVE A NEGATIVE

Interpretive guidelines:
Positive: Indicates active or latent infection by MTB complex. May also be positive with M. kansasii, M. szulgai and M. marinum. Not positive with BCG therapy. To establish a diagnosis of active disease, correlate with clinical and radiographic data.
Indeterminate: May occur from excessive levels of gamma interferon, heterophil antibodies, anergy or handling issues. Repeat analysis is recommended.
Negative: Presumptive negative for active or latent MTB infection. False negatives may occasionally be seen with impaired immune function or testing too early after exposure.

***** GAMMA INTERFERON RESULTS *****

TB1-NIL	0.378 H	IU/ML	<0.35
TB2-NIL	0.428 H	IU/ML	<0.35

Patients with an interpretation of positive and TB-nil values between 0.35 and 1.11 IU/mL should be considered low positive. Longitudinal studies of specific patients demonstrate sufficient fluctuation within this low positive range in serial testing to cause test interpretations to alternate between negative and low positive when the test results are near the cutoff value of 0.35 IU/mL. For such patients, repeat analysis after a clinically suitable period of time or alternate testing may be informative.

MITOGEN-NIL	5.860	IU/ML
NIL	0.110	IU/ML

Test	Within Range	Outside Range	Units	Reference Range

QUANTIFERON TB GOLD PLUS
QUANTIFERON TB GOLD PLUS POSITIVE A NEGATIVE

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Negative: Presumptive negative for active or latent MTB infection. False negatives may occasionally be seen with impaired immune function or testing too early after exposure.

***** GAMMA INTERFERON RESULTS *****

TB1-NIL		1.38 H	IU/ML	<0.35
TB2-NIL		1.29 H	IU/ML	<0.35
MITOGEN-NIL	>10		IU/ML	
NIL	0.04		IU/ML	

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QFT GOLD +

is not without limitations

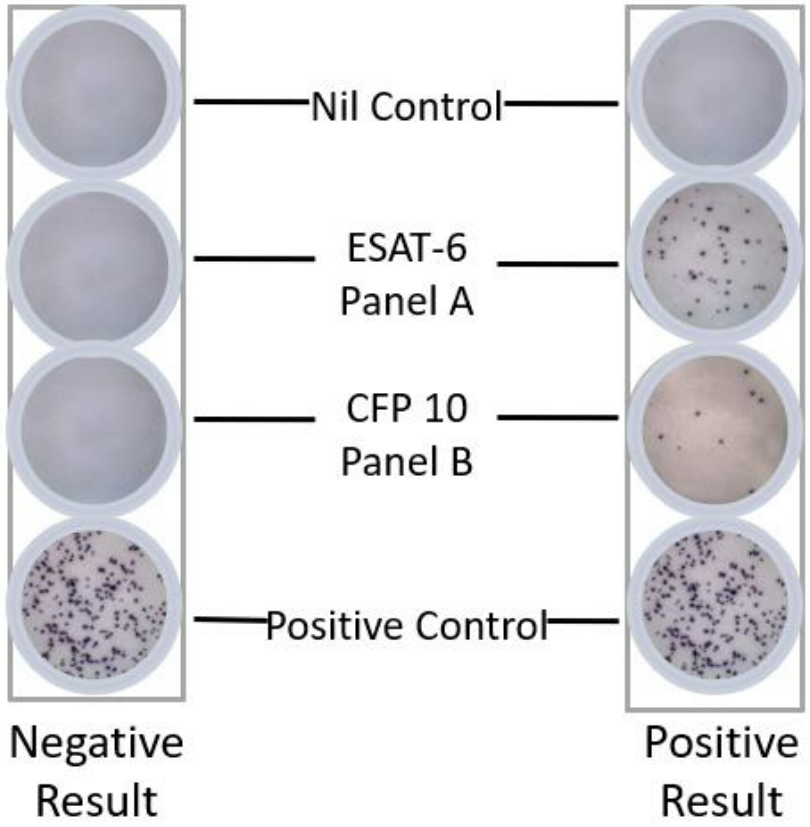
Limitations

A negative QFT-Plus result **does not preclude the possibility of *M. tuberculosis* infection or tuberculosis disease: false negative results can be due to stage of infection, co-morbid conditions that affect immune function, incorrect handling of the blood collection tubes** following venipuncture, **incorrect performance of the assay, or other individual immunological variables**. Heterophile antibodies or non-specific interferon-gamma production from **other inflammatory conditions may mask specific responses to CD4+ and CD8+ T cell antigens**. A positive QFT-Plus result **should not be the sole or definitive basis** for determining infection with *M. tuberculosis*. Incorrect performance of the assay may cause false-positive results. A positive QFT-Plus result should be followed by **further medical evaluation for active tuberculosis disease.**

T-Spot Interpretation

dark blue spots are counted

Interpretation of Results



Interpretation Criteria for the T-Spot.TB

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

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What if it is false negative?

Indeed!

Immunosuppressive states can cause this. If the body can't mount an immune response the test can be falsely negative, since both TST and IGRAs are immune-mediated tests. Even TB disease can create this situation.

It is important to evaluate the PATIENT and not just the tests.

My word regarding TB… it's a trickster. The tests can throw you off. Don't believe all the tests, ESPECIALLY if they are negative. Believe your eyes/your exam/your intuition (if it's good & developed!) in concert with test results

Downside of IGRAs

Say it isn't so!

Issues of reproducibility of results on serial performance

unexplained cases of low-level positive IGRA results reverting to negative on repeat testing

-this is known as conversion/reversion

occur among low-level results, usually between 0.35 and 1.0 IU/mL for QFT

exact cause(s) unknown

Efforts to reduce test variability through better specimen collection and handling and laboratory standardization will minimize low-level false-positive results.

Ok. But which one should I use? One is better than the other, right?

...the preponderance of evidence supports the conclusion that....

...neither is preferred over the other

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

HTTPS://WWW.CDC.GOV/TB/PHP/DEAR-COLLEAGUE-LETTERS/2025-TREATMENT-GUIDELINES.HTML

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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Lewinsohn et al. CID. 2016

New in the Diagnosis 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 if infection or progression

- Note: IGRAs are a 'better' choice:
  - When TST administration is questionable
  - In BCG vaccinated populations (increased specificity)
  - In populations with a poor rate of return (i.e., a person that is unlikely to RTC for reading)

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

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**

Also, a negative test is just a negative test; it does NOT rule out anything

IGRA points to remember

First rule of IGRA:

Don't (fully) trust a negative IGRA, *especially over other evidence!
(pro tip: never take any negative test at face value in the world of TB)
Please note: the result may be correct OR incorrect; I'm just saying to be cautious.

Does the result make sense?

The IGRA is a piece of the puzzle. *ONE PIECE* Don't overlook the other pieces!
For some, labs are Shiny and Bright objects. Oooo! Don't get distracted.

Remember, context matters. More accurate in high risk pts. More FP in low risk pts, potentially leading to unnecessary w/u &/or tx.

IGRA testing has been expanded to any pediatric age (previously was 2 years and older) **All ages now!** in the latest "Red Book" (the American Academy of Pediatrics Report of the Committee on Infectious Diseases 33rd Edition, published in 2024)

Caveat: no test is reliable for <6mo

No test (TST or IGRA) overrides clinical, epidemiologic or historical data**

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TBI is a DIAGNOSIS OF EXCLUSION

The nice thing is, you basically only have to exclude 1 disease…
tuberculosis!
Before you treat….Know the Dx

When you make a dx of TBI, you are saying the patient, to the best of your knowledge, ***does not have TB disease***
To know that, you need more than a TB test and a CXR

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Back to Basics

H&P

Talk to the patient

Examine the patient

Do they have s/sx?

TB can be almost anywhere…

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TB is weird
Do no harm
Don’t (fully) trust neg TB tests
We treat clinical TB *ALL* the time (ie, TB with negative tests or no testing done)
You can find & treat TBI… which is a dx of exclusion
You can find & dx TB
We can help you & there are tons of
superb resources.

THINGS TO KNOW & REMEMBER

A Cornerstone of TB Elimination

Treating LTBI

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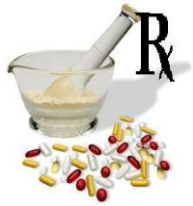
“Window Period” TB Prophylaxis After Exposure

Household contact with infectious person

- Initial TST negative
  - Window period for TST/IGRA conversion (8-12 weeks)
- CXR and physical exam normal

- **‘Window’ prophylaxis recommended:**
  - For children <5 yrs of age
  - Immunosuppressed patients, especially HIV positive
  - Patients on tumor necrosis factor-alpha blockers or other biologics
  - May prevent progression to disease during window period



Repeat TST or IGRA 8-12 wks after exposure

May stop treatment if 2nd TST (<5mm) or IGRA is negative in immunocompetent patients

Consider completion of full course of treatment in HIV + and other immunosuppressed or children < 6 months

Treating LTBI

…IF YOU HAVE RULED OUT ACTIVE TB (THE FIRST RULE)

AND YOU HAVE MADE THE DIAGNOSIS OF LTBI (NL CXR, EXAM NOT CONCERNING FOR ACTIVE TB, TEST+) THEN

DETERMINE WHAT TREATMENT OPTIONS ARE AVAILABLE FOR YOUR PT. THERE ARE 4 BASIC OPTIONS, WITH 2 CONSIDERED TO BE THE STRONGEST OPTIONS AND THE OTHER 2 ARE ACCEPTABLE ALTERNATIVES.

TO MAKE THE DECISION YOU MUST KNOW THE PMH AND MEDICATIONS, THEN DISCUSS WITH YOUR PT TO MAKE THE BEST CHOICE FOR THEM

Medication Options for TB Infection

Medication	Pills	Dose Frequency	Duration	Total Doses
Isoniazid and Rifapentine (3HP)		**Once Weekly** Directly Observed Therapy	12 Weeks	12 doses Directly Observed Therapy (Initial dose in clinic and every 4th dose in Clinic or video options)
Isoniazid and Rifampin (3HR)		**Daily**	3 months	90 doses
Rifampin (4R)		**Daily**	4 months	120 doses
Isoniazid (6H or 9H)		**Daily**	6 months Or 9 months	180 doses Or 270 doses

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TB Infection Treatment Options

CDC Recommended Treatment regimens:

- INH/Rifapentine x 3 months (3HP, weekly))
  - Once weekly DOT x 12 weeks
  - Average of 10 pills at once
- Rifampin x 4 months (4R)
  - Daily (10 mg/kg: 600 mg max)
- INH +rifampin x 3 months (3HR, daily)
  - INH daily (5 mg/kg: 300 mg max) + rifampin daily (10 mg/kg: 600 mg max)
- INH x 6-9 months (6H/9H)
  - Daily (5 mg/kg: 300 mg max) or BIW (15 mg/kg: 900 mg max)

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ATS/IDSA/NTCA. November 2018.

6H: INH monotherapy

The OG

Has the most data… and it works

Longest duration of all available regimens and the **lowest completion rate**

Highest potential for hepatotoxicity of all the regimens

Dose is 5mg/kg for adults with max 300 mg daily So if over 60 kg its 300 mg daily and **give with 50 mg vitamin B6** (pyridoxine) daily. Pts with alcoholism, diabetes, CKD, advanced age, or who are pregnant or breastfeeding and infants who are breastfed require B6 supplementation… best just to give it to everyone imho (you do you though, Ms/Mr. Independently Minded!). Lower doses for the littles.

INH available in 100 & 300 mg tablets. **Ok to crush into a slurry**

Must get 180 doses within 9 months (that's a 3m grace period. Don't tell!)

INH TBI Therapy

The standard treatment regimen for TBI has been nine months of daily INH.

- The regimen is effective and is the preferred regimen for HIV infected people taking antiretroviral therapy with drug-drug interactions that do not allow a rifamycin

- Is the option when drug-drug interactions with rifamycins are significant and must be avoided

But less than 60% complete

- Primarily due to long duration of treatment but also increased adverse effects

INH Hepatotoxicity

Asymptomatic elevation of aminotransferases: 20% of patients

Clinical hepatitis: 0.6% of patients

Fulminant hepatitis (hepatic failure)

- Approximately 4/100,000 persons completing therapy (continued INH with symptoms of hepatitis, prior INH hepatotoxicity, malnutrition).

Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

MMWR 3/5/10/ 59(08); 224-229

"Medical providers should emphasize to patients that ***INH treatment should be stopped immediately upon the earliest onset of symptoms*** (e.g. excess fatigue, nausea, vomiting, abdominal pain, or jaundice), even before a clinical evaluation has been conducted, and that initial symptoms might be subtle and might not include jaundice."

Isoniazid (INH) Dosing

Adults: 300 mg single daily dose or 900 mg twice weekly*

Children: 10-15 mg/kg single daily dose (max dose 300 mg daily)

- 20-30 mg/kg twice weekly*

Duration of treatment for TB Infection: 6 - 9 months

- 9 month regimen more effective
- 9 month regimen is very difficult to complete
- 6 months is considered adequate therapy by ATS/IDSA/CDC guidelines

- * **twice weekly treatment must be given by directly observed therapy through health department**

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INH Side Effects

Hepatotoxicity

Migraine Headaches

Gastrointestinal

- Nausea, Diarrhea, Constipation

Rash

Peripheral Neuropathy

- Pyridoxine 50mg daily can help prevent this

When not to treat

*Older than 70 or 75. Why?

- life expectancy. Tx of LTBI is based on 10 year risk of reactivation

-Medications are less tolerated in the elderly/more side effects, esp hepatotoxicity

*If they have already been treated (except under circumstances already discussed) as re-tx is not needed… bug are no longer there. Seems to confer some immunity to reinfection.

*If test is felt to be false + but -be careful!! We shouldn't be testing low risk people in the 1st place. How do you know it's false +? Maybe retest?

Contraindications

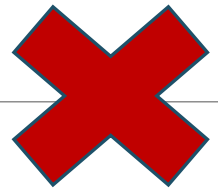
Relative contraindications (which must be considered on an individualized basis) include:

A h/o serious adverse reaction to INH and RIF

Severe liver disease

Prior tx for active TB disease or LTBI, except in recently re-exposed immunocompromised individuals or children < 5yo

Diagnostic Uncertainty



Absolute contraindication to LTBI tx

a. When it is not possible to distinguish between LTBI and active TB disease, an individual should be considered to have active TB disease until proven otherwise.

b. In such cases, a trial of multi-drug therapy for active TB disease is appropriate, with reassessment as to response to treatment at a later date (e.g. 2-3 months).

3HP: Isoniazid (INH, or H) & Rifapentine (RPT, or P)

CDC recommends for use in ages 2 and older and for use in people with HIV infection (including AIDS) on ARV meds with acceptable drug-drug interactions with RPT. Not for use in pregnancy.

This is the preferred regimen with strong recommendations with the shortest duration of therapy (12 week, which is the 3, for 3 months)

Its also the regimen with the least experience

3HP

Can be given via
DOT (directly observed) or
SAT (self administered therapy)

Wgt based regimen if <50 kg.
Max dose is 900 mg INH &
900 mg RPT
+ B6 either daily or weekly

Must get 11 doses (recommend 12) within 16 weeks to complete

Dosing for 3HP

Adults and children > 50 kg

900 mg INH once weekly

900 mg Rifapentine once weekly

Vitamin B 6 50 mg once weekly

Completion - 11 to 12 doses in 16 weeks

Children 2 – 12 years*

INH 15 mg/kg (round to nearest 50 or 100 mg tablet)

Rifapentine

- 10-14 kg: 300 mg
- 14.1-25 kg: 450 mg
- 25.1-32 kg: 600 mg
- 32.1-49.9 kg: 750 mg
- ≥ 50 kg: 900 mg

* Especially when short course is desirable; pill burden may be a problem

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Pill Burden With 3HP is Currently a Problem for Some

- Current: 10 pills (6 rifapentine, 3 INH, 1 Vit B6)
- Future: 4 pills (3 RPT/INH + 1 B6)

2xPriftin® 150mg

+

Isoniazid®

=

PH 300/300

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D., for the TB Trials Consortium PREVENT TB Study Team*

Active TB disease: 7/3986 in 3 HP arm; 15 of 3745 in 9H arm
Completion of treatment: **82.1% 3HP arm**; **69% 9 H arm**
Hepatotoxicity: 0.4% 3HP arm; 2.7% 9 H arm.

Conclusion: Use of 3 HP x 3 months was as effective as 9 months of INH and had a higher treatment completion rate.

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INH + RPT (3HP) is NOT Recommended For:

Children under 2 y/o

HIV infected persons on Antiretroviral Therapy with drug-drug interactions

Presumed INH or Rifampin Resistance in the source case

Pregnant women

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3HR: INH & RIF combination

Same length of tx as 3HP combo & shorter than mono therapies

Same interactions as RIF obvi

Can substitute RBT for RIF

At least same hepatotoxicity and perhaps more

If using, I recommend more monitoring of LFTs

Dosing same as 4R/6H (if 60+ kg that's max dose 300 mg INH + 50 mg B6 & 600 mg RIF, <60mg wgt based 5mg/kg INH, 10 mg/kg RIF) INH available in 100 & 300 mg tablets, RIF is 150 & 300 mg capsules. Can crush INH & open RIF capsules & mix into slurry if needed.

4R: Rifampin x 4 months

Rifampin monotherapy has a higher completion rate than INH monotherapy due to the shorter time frame (4m vs 6 or 9m for INH) and lower rates of hepatotoxicity

Body fluids will be discolored. Urine always, maybe rest: contacts

Dose 10mg/kg, adults 60kg+ 600 mg (max) 2 capsules daily

Must get 120 doses within 6m. 4m is ideal, but there is a (secret) 2m grace period

Numerous toxicities

- ***ALWAYS*** do drug-drug interaction checks
- RIF will make OCPs ineffective so would avoid in pts taking; condoms are not that reliable for birth control. RIF does not affect IUD
- RIF can alter methadone serum concentration so use with caution/consult with addiction specialist rx'ing
- Many interactions with antiretroviral HIV meds. If so, may be able to substitute rifabutin (RBT) instead
- PreP meds: Descovy is ok with RIF and Truvada is ok with RBT

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults

Menzies et al, N Engl J Med. 2018 Aug 2;379(5):440-453.

- Open label trial in 9 countries comparing 4 months rifampin vs 9 months INH:
  - study endpoint: prevalence of TB 28 months after randomization

- Rifampin: 3443 patients:
  - 4 active TB, 4 clinical TB

- INH: 3416 patients:
  - 4 active TB, 5 clinical TB

Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults

Menzies et al, N Engl J Med. 2018 Aug 2;379(5):440-453.

- Treatment completion:
  - Rifampin 79%,
  - INH 63% ($p < 0.001$)
- Clinically significant (drug stopped) hepatotoxic events:
  - Rifampin 0.3%,
  - INH 1.7% ($p < 0.001$)
- 4 months of rifampin was not inferior to 9 months INH for preventing development of active TB but with significantly higher completion rates and greater safety than INH.

Rifampin Dosing for TB Infection

- Adults
  - 10 mg/kg daily
  - 600 mg daily x 4 months

- Children:
  - 10 – 20 mg/kg daily x 4 months
  - Capsules 150mg/300 mg round up - use higher range
  - Higher rifampin doses well tolerated

Rifampin Treatment of TB Infection

- Pros:
  - Higher Completion Rates
  - Equally effective
  - Fewer Side Effects
  - Less Hepatotoxicity
  - Cost effective
  - Rifampin resistance uncommon
    - Globally 3%

- Cons:
  - Drug Interactions
    - Hormone Contraceptives
    - Warfarin
    - Prednisone
    - **HIV Antiretroviral agents**
    - And many more…must look up all drugs for interactions
    - Orange Body Fluids
  - Other Potential Side Effects (rare):
    - Rash
    - Thrombocytopenia
    - Anemia
    - Leukopenia
    - Allergic Interstitial Nephritis

Treatment Options for LTBI

INH +RPT once weekly	12 weeks (12 doses)
Rifampin daily	4 months (120 doses)
INH 9 daily	9 months (270 doses)
INH 6 daily	6 months (180 doses)

The longer the duration/more doses, the less likely your patient is to complete treatment

Fewer than 60% complete 9 months of INH

Should Pregnant Women Be Treated for TB Infection during Pregnancy?

A prior study showed increased risk of serious, even fatal hepatotoxicity with INH during pregnancy and the immediate post-partum period (3 months following delivery)

No study has shown increased risk of hepatotoxicity with daily rifampin

In pregnant persons who have reason for treatment of LTBI, consider daily rifampin

Monitoring should be close

- Blood work for any symptoms and hold medication
- Monitor liver enzymes and patient at every monthly visit.

Monitoring for Toxicity and Progression to Active Disease

Baseline liver enzymes – for all with risk of liver toxicity

- Those with underlying liver disease due to Hepatitis B or C or alcohol
- Those taking other potentially hepatotoxic medications
- Those with a medical co-morbidity
- Pregnant women and those in immediate post-partum (3 months) period
- Elderly
- Generally not needed for children; healthy young adults

Monitor monthly “in person” for toxicity and for evidence of progression to TB disease

- Monthly liver enzymes if baseline LFTs abnormal or above risks

Lab monitoring

General guidelines:

Baseline LFTs and monthly for all the following pts:

known liver dz/hepatitis current or past, pregnancy, substance abuse, on other hepatotoxic meds, HIV+, born in Asia or Africa

Baseline if h/o elevated LFTs, FLD, malnutrition, obesity, age >35; if baseline abnl, con't to collect monthly

CBC @ baseline if on 3HP or RIF regimen if known blood disorder or renal dz

Cr baseline & monthly if known renal dz

Pearls of Wisdom for Treating TBI

Consider the shortest regimen possible to increase the odds of completion

Be vigilant

Be supportive…..and forgiving

Take home lessons

1. Don’t treat LBTI until you are as sure as you can possibly be that it is NOT TB DISEASE.

2. If you think it is possibly TB disease, get a w/u for TB. Consult. If we can’t rule it out, we may treat for TB & assess for response.

3. When possible, chose the shorter LTBI regimen. When it comes down to daily or weekly regimen, it may come down to pt preference & habits, pill burden, etc

4. Completion is key

5. Reach out for help anytime. The goal is to get you to a point of being comfortable with treating LTBI and for assessing these pts. It takes time!

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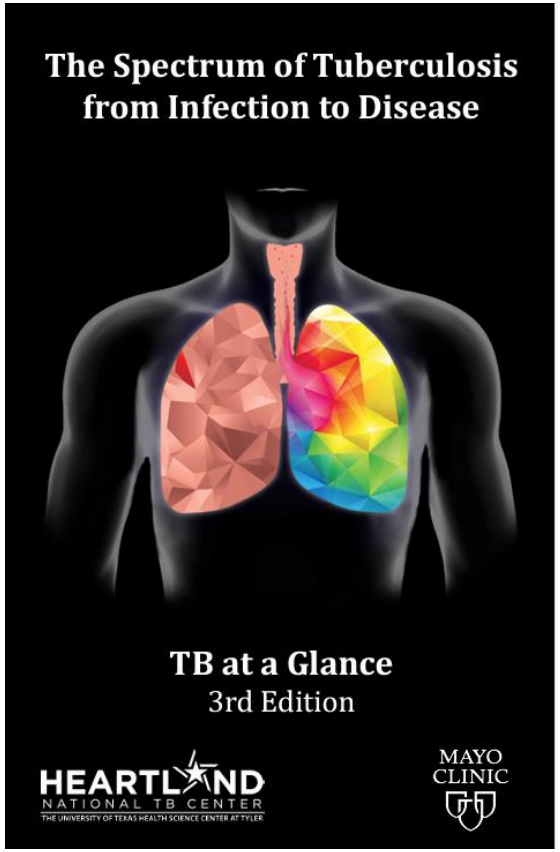

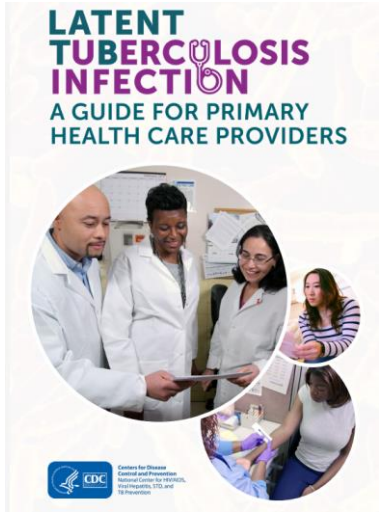

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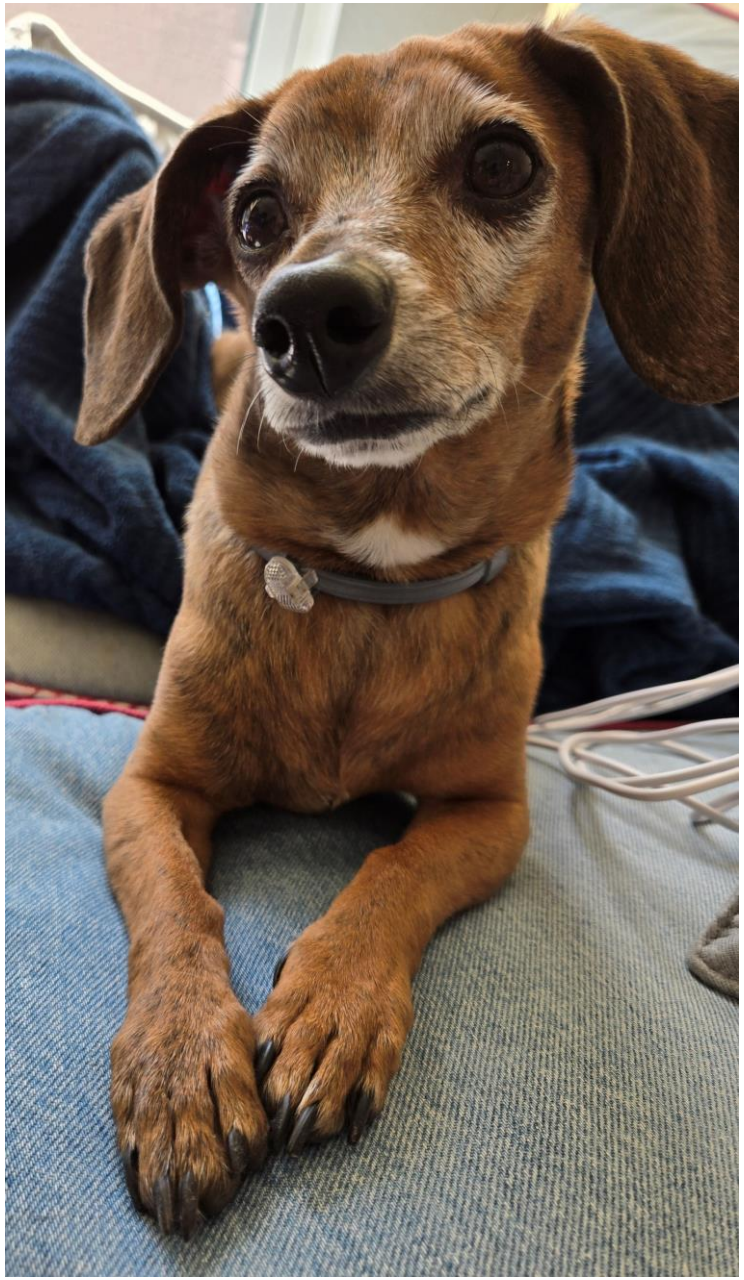
Pretty flowers from etsy clipart, fineartsamerica, freepix, adobe, dreamstime & pinterest; to find: google pretty lung flowers

Feel free to call or email. I love to talk about TB!

Questions?

And if you are tired of talking about TB, we can talk about Mr! Or your dog, I guess (just kidding! We can!)



Mr's human, aka

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Thank you for all you do!

Questions?

Thank you!

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