



TB Infection: The Old and The New

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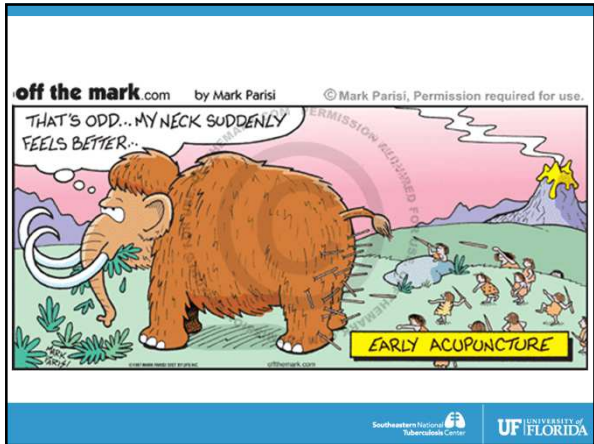
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Objectives

At the completion of this session, participants will be able to:

- Select the appropriate diagnostic test for patients suspected of tuberculosis as an initial step in the clinical management of the disease
- List three different treatment modalities for latent TB infection to enable providers to support patients through to completion of therapy

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THAT'S ODD... MY NECK SUDDENLY FEELS BETTER...

PERMISSION REQUIRED FOR EARLY ACUPUNCTURE

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Case: Mrs. H

- 72 year old F – from the Philippines
 - Living with daughter in the U.S. for 3 months
- C/O cough x several months (reddish tinge lately)
 - Lost ~18 pounds over 4 months
 - Night sweats and fevers
- Known contact to father
 - Father treated for TB when she was a child
- Current HX: IDDM
- Immigration screening
 - CXR reported as fibronodular changes in the RUL
 - Cultures negative



MENTIMETER QUESTION #1 TB or Not TB?


- Yes
- No



TB or TB Infection?

- Symptoms of TB disease
- Exposure to a person who has infectious TB or has other risk factors for exposure to TB
- Risk factors for developing TB disease
- TB infection or TB disease in the past





Remember:
Every case of TB was once a contact!

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THINK TB....
(and evaluate accordingly)

Diagnosis of *M. tuberculosis* infection

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What About the Contacts?

- High risk for progression in first two years
- Daughter has three children
- ages 4, 6, and 12
- Now what would you do?



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Methods for Detecting *M. tb* Infection

1. Mantoux tuberculin skin test (TST)
 2. Interferon Gamma Release Assays (IGRAs):
 - QuantiFERON-TB Gold In-Tube (QFT-GIT)[®], and
 - T-Spot.^{TB}[®]
- These tests do not exclude LTBI or TB disease
 - Decisions about medical/public health management should not rely only on TST/IGRA results, but consider TB risk, setting, patient and source case factors



MENTIMETER QUESTION #2 Testing for TB

What test do you use to diagnose TB infection?

- A. TST
- B. QuantiFERON
- C. T-Spot





Tuberculin Skin Testing





Mantoux Tuberculin Skin Test

- Tuberculin is made from proteins derived from inactive tubercle bacilli
- 0.1 ml of 5 tuberculin units of liquid tuberculin are injected in the intradermal space
 - Usually the forearm
- Most people who have TB infection will have a reaction at injection site


HCW administering Mantoux TST

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Mantoux Tuberculin Skin Test (2)

- Area should be examined within 48 to 72 hours by a trained HCW
- Reaction is an area of induration (swelling) around injection site
 - Induration is ONLY measured in millimeters ONLY
 - Erythema (redness) is not measured





Only the induration is measured

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Factors that May Affect the TST Reaction

Type of Reaction	Possible Cause
False-positive	<ul style="list-style-type: none"> • Non-tuberculous mycobacteria • BCG vaccination • Using wrong solution (i.e., tDap, dTap) • Measurement or interpretation
False-negative	<ul style="list-style-type: none"> • Anergy • Viral, bacterial, fungal co-infection • Recent TB infection • Very young age; advanced age • Live-virus vaccination • Overwhelming TB disease • Renal failure/disease • Lymphoid disease • Low protein states • Immunosuppressive drugs • Problems with TST administration

Mantoux Tuberculin Skin Test and BCG Vaccine

- People who have been vaccinated with BCG may have a false-positive TST reaction
- Individuals should always be further evaluated if they have a positive TST reaction



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TB Testing Programs with TST

- Many residential facilities, health care settings, corrections, etc. have TB testing programs (and still use TST)
- Tested at baseline
 - Two-Step
 - Booster Phenomenon

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MENTIMETER QUESTION #3

Facility TB Testing programs should include:

- A. TST or IGRA Test
- B. Screening
- C. Both

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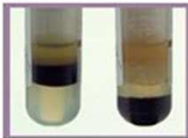
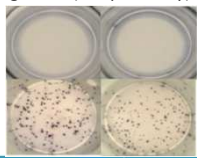
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Interferon Gamma Release Assays



Interferon Gamma Release Assays


- Whole blood test using purified antigens from MTB to stimulate lymphocytes (CD4) to produce interferon-gamma (IFN- α)
 - QuantiFERON tests (QFT) measures level of IFN- α in cells
 - TSPOT measures # of cells producing IFN- α (ELISpot assay)



QFT vs T-SPOT Results


QFT-GIT	T.SPOT.TB
Positive (> 0.35 IU/mL)	Positive (> 8 spots)
Negative (< 0.35 IU/mL)	Negative (< 4 spots)
Indeterminate	Borderline (5-7 spots)
-Low mitogen	Invalid
-High nil	-Low mitogen
Failed	-High nil
-Inadequate blood volume	Failed
-Broken tube	-Inadequate blood volume
-Delayed incubation	-Broken tube
	-Delayed incubation



IGRA: General Points


- **Highly specific:** (~95% in low TB incidence areas)
 - Both QFT and T-SPOT are substantially more specific than PPD since they contain antigens not found in BCG
 - Distinguish most NTM
 - o Except *M. Kansasii*, *M. marinum*, *M. szulgai*, *M. flavescens*
 - o PPD contains large number of mycobacterial proteins not specific to *M. tuberculosis*
- **Sensitivity:** T-SPOT.TB assay appears higher than QFT or TST (90%, 80%, and 80%, respectively)
 - Sensitivity diminished by HIV infection, immunosuppression, and in children

Pai et al. Clinical Microbiology Reviews, 2014

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Advantages for using an IGRA (as compared to the TST)


- Single patient visit
- Results available in ~24 hours
- No booster phenomenon
- Laboratory test - not affected by HCW bias
- IGRA results not affected by BCG vaccine

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IGRA Limitations

- Indeterminates
- Test discordance between tests more common than concordance among those with + tests
- Delay in IGRA conversion compared to TST may account for some discordant TST/IGRA results in recently exposed contacts

Ghassemieh, American Journal of Respiratory and Critical Care Medicine, 2016; 194 (4):493-500.
Dorman, Am J Respir Crit Care Med. 2014;189(1):77-87
Ranelli, J Clin Microbiol 54:845-850.

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Candidates for testing and treatment of LTBI

1. Exposure risk
 - Persons with risk for recent infection with *M. tuberculosis*
2. Medical risk
 - Persons with risk of progression to active TB if infected with *M. tuberculosis*

CDC. MMWR Recomm Rep. 2010 Jun 9;48(RR-04):S1.
 Latent Tuberculosis Infection: A Guide for Primary Health Care Providers
<http://www.cdc.gov/tb/publications/rb/targetedtesting.htm>

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Criteria for classifying positive LTBI diagnostic test

Positive IGRA or TST 5mm induration or more is considered positive in:	Positive IGRA or TST 10mm induration or more is considered positive in:
<ul style="list-style-type: none"> HIV-infected persons Recent contacts to a person with infectious TB People with fibrotic changes on a CXR consistent with old TB Organ transplant recipients People who are immunosuppressed for other reasons (e.g., taking the equivalent of >15mg/day of for more than one month, or taking TNF-α antagonists) 	<ul style="list-style-type: none"> Recent immigrants from high TB prevalence countries Injection drug users Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities).
Positive IGRA response or a TST 15mm of induration or more is considered positive in:	
<ul style="list-style-type: none"> A person who has no risk factors for TB* 	

*Although skin testing programs should be conducted only among high-risk groups, certain individuals may require skin testing for employment or school attendance. An approach independent of risk assessment is not recommended by CDC or the ATS.

No Gold Standard to Confirm LTBI

- TST and IGRA are *indirect* markers of infection

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Treatment for TB Infection Options

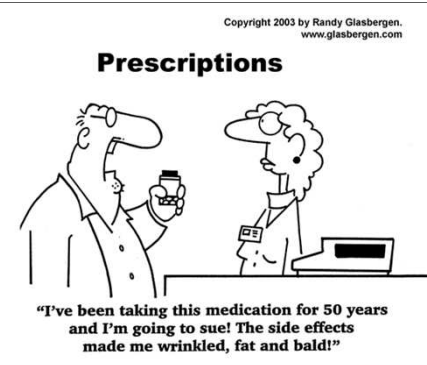
Isoniazid (INH)	Rifampin (RIF)	3HP – INH & RIF
x 9 months	x 4 months	x 12 weeks

Not in order of priority!

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Prescriptions



"I've been taking this medication for 50 years and I'm going to sue! The side effects made me wrinkled, fat and bald!"

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Clinical Practice Guidelines for the Diagnosis and Treatment of TB Infection

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Clinical Infectious Diseases Advance Access published December 8, 2016
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,^{1,2} Michael K. Leonard,^{3,4} Philip A. Lebowitz,^{5,6} David L. Cohen,^{7,8} Charles L. Daley,⁹ Ed Desmond,¹⁰ Joseph Keam,¹¹ Deborah A. Lewinsohn,¹² Ann M. Lounsbury,¹³ Gerald H. Mannes,¹⁴ Richard J. O'Brien,¹⁵ Madhukar Pal,¹⁶ Luca Riccobelli,¹⁷ Max Salfinger,¹⁸ Thomas M. Shinnick,¹⁹ Timothy S. Sterling,²⁰ David M. Wenzel,^{21,22} and Erik S. Wiersma²³

Joint Statement	<ul style="list-style-type: none"> • CDC • ATS • IDSA
Partners	<ul style="list-style-type: none"> • American Academy of Pediatrics • Association of Public Health Laboratories
Harmonization w/ concurrent and overlapping guidelines	<ul style="list-style-type: none"> • AAP Red Book • CDC IGRA Guidelines update • CDC Nucleic Acid Amplification Testing Guidelines update

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Latent TB Infection Treatment Regimens | 2018 CDC Recommendations

Drugs	Duration	Interval	Comments
Isoniazid and Rifapentine	3 months	Once weekly ¹	<ul style="list-style-type: none"> Not recommended for persons who are: <ul style="list-style-type: none"> • Less than 2 years old • Living with HIV/AIDS and taking antiretroviral medications with clinically significant or unknown drug interactions with rifapentine • Presumed infected with INH- or RIF-resistant M. tuberculosis, and • Women who are pregnant or expect to become pregnant within the 12 week regimen.
Rifampin	4 months	Daily	<ul style="list-style-type: none"> Not recommended for persons who are: <ul style="list-style-type: none"> • Living with HIV/AIDS and taking antiretroviral medications with clinically significant or unknown drug interactions with rifampin (rifadion may be used as a substitute) • Presumed infected with RIF-resistant M. tuberculosis, and • Women who are pregnant or expect to become pregnant within the 4 month regimen.
Isoniazid	6 months	Daily	Not recommended for persons who are presumed infected with INH-resistant M. tuberculosis.
Isoniazid	6 months	Twice weekly ²	Not recommended for persons who are presumed infected with INH-resistant M. tuberculosis.
Isoniazid	9 months	Daily	Not recommended for persons who are presumed infected with INH-resistant M. tuberculosis.
Isoniazid	9 months	Twice weekly ²	<ul style="list-style-type: none"> Preferred treatment for: <ul style="list-style-type: none"> • Persons living with HIV/AIDS and taking antiretroviral medications with clinically significant or unknown drug interactions with once-weekly rifapentine or daily rifampin, • Pregnant women (with pyridoxine/vitamin B6 supplements) Not recommended for persons who are presumed infected with INH-resistant M. tuberculosis. Preferred treatment for pregnant women (with pyridoxine/vitamin B6 supplements)

¹Use Directly Observed Therapy (DOT) or Self-Administered Therapy (parentally administered SAT to children)
²Use Directly Observed Therapy (DOT)
 Note: Due to the reports of severe liver injury and deaths, CDC recommends that the combination of rifampin (RIF) and pyrazinamide (PZA) should not be offered for the treatment of latent TB infection.

<https://www.cdc.gov/tb/topic/treatment/lbti.htm>

9 months Isoniazid

- >20 randomized, placebo-controlled trials of INH for LTBI treatment involving >100,000 subjects
- ~60% reduction in TB
 - Results based on total study populations treated, regardless of how regularly medication was taken
 - Reduction highest during year of treatment
- ~90% when analyses limited to participants who took INH for most of treatment year
- Protection lasted 20 years after treatment

Foreman, S. H. 1970. *Bull Tuberc* 26:28-106.
 International Union Against Tuberculosis Committee on Prophylaxis. 1992.
 Bull World Health Organ 60:555-64.

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TB Infection Treatment 9 months Isoniazid

- INH action:
 - **Bactericidal**, especially for rapidly dividing cells; inhibits Mycobacterial cell wall synthesis; active against intracellular and extracellular *M.tb*
- Dose: 300mg daily, self-administered
- Completion rate of 6-9 mo. INH: 20-60%
- Drug Interactions

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Isoniazid: Safety


- 10-20% develop transient, asymptomatic liver enzyme abnormalities (most not clinically significant)
- Hepatotoxicity ~ 0.1%-0.5%
 - Increased risk with age, liver disease, HCV, alcohol use, prior INH hepatotoxicity, other hepatotoxic meds
 - Mortality 0.3/1000 (increases w/ age, alcohol use)
- Peripheral neuropathy uncommon at 5 mg/kg
 - Give vit B⁶ 10-50 mg/day for persons with diabetes, uremia, alcoholism, malnutrition, HIV, pregnancy, seizures, signs and symptoms of peripheral neuropathy

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TB Infection Treatment Rifamycins

- **Bactericidal** against dormant and semi-dormant bacteria that characterize LTBI (persisters)
 - (*INH only active against replicating bacteria*)

- Rifampin
- Rifabutin (RBN)
- Rifapentine (RPT)



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Four months Rifampin Monotherapy (4R)

- Open label RCT of 4R vs 9H for preventing TB
- More than 6800 adults in nine countries
 - 4R not inferior to 9INH for prevention of active TB
 - 4R treatment completion rate higher than 9H
 - 4R group had significantly lower incidence of adverse events of grades 3 to 5, particularly hepatotoxic adverse events.

Menzies et al. N Engl J Med 2018; 379:440-453



Rifampin (4R)

- Dose: 600 mg daily x 4 months self-administered
- High completion rates: 60-91%
- Well-tolerated: Mild rashes, GI sx, **ORANGE** body fluids
- Low hepatotoxicity
- Hypersensitivity syndrome
 - “Flu-like” symptoms (fever, malaise, myalgias)
 - Anemia, thrombocytopenia
 - More common with intermittent doses
- Carefully rule out TB if used in HIV, avoid with ART
- Rifabutin 300mg may be substituted if drug interactions



Rifamycins – Drug Interactions

http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm

- | | |
|--------------------------------|----------------------|
| • Oral anticoagulants | • Dapsone |
| • Oral contraceptives | • Diazepam |
| • Cyclosporine | • Digoxin (oral) |
| • Glucocorticoids | • Diltiazem |
| • Itraconazole | • Disopyramide |
| • Ketoconazole | • Doxycycline |
| • Methadone | • Fluconazole |
| • Midazolam or triazolam | • Haloperidol |
| • Phenytoin | • Losartan potassium |
| • Quinidine | • Nifedipine |
| • Theophylline | • Nortriptyline |
| • Verapamil | • Sulfonylureas |
| • β-Adrenergic blocking agents | • Tacrolimus |
| • Chloramphenicol | • Tocainide |
| • Clarithromycin | |



3HP Precautions

- Possible neutropenia, increased liver enzymes, hypersensitivity reactions (fever, dizziness, musculoskeletal pain, rash, pruritus)
- Drug interactions with other meds via cytochrome P450 enzymes – avoid with methadone, coumadin and hormonal birth control
- Counsel women to add or switch to a barrier method if using oral birth control pills

CDC, 3HP Recommendations; http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?_id=mm6048a3_w

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NEVER START WITH ONE DRUG


NO Symptoms of TB Disease

General

- Fever
- Chills
- Night sweats
- Weight loss
- Appetite loss
- Fatigue
- Malaise

Pulmonary

- Cough lasting 3 or more weeks
- Chest pain
- Coughing up sputum or blood



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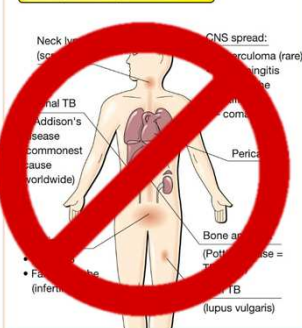
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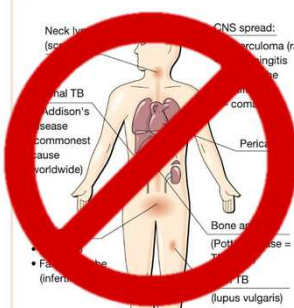
NEVER START WITH ONE DRUG

NO Symptoms of Extrapulmonary TB Disease

General

- Can have both pulmonary and extrapulmonary TB!

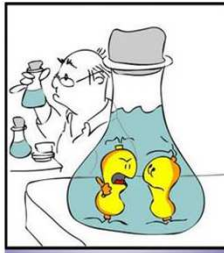




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1-800-4-TB-INFO!!



I'M FED UP WITH THIS GUY - LET'S BECOME PATHOGENIC



Resources

- 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 <https://academic.oup.com/cid/article/doi/10.1093/cid/ciw694/2629583/Official-American-Thoracic-Society-Infectious>
- Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis *MMWR* 2009; 58 (01): 7-10.
- Guidelines for the Diagnosis for LTBI in the 21st Century <http://globaltb.njms.rutgers.edu/downloads/products/guideltbi.pdf>
- Guide to the Application of Genotyping to Tuberculosis Prevention and Control, <http://www.cdc.gov/tb/programs/genotyping/manual.htm>
- Lardizabal AA, Reichman LB. 2017. Diagnosis of latent tuberculosis infection. *Microbiol Spectrum* 5(1):TNM17-0019-2016. doi:10.1128/microbiolspec.TNM17-0019-2016.



Resources *Fact sheets*

- Testing for TB, http://www.cdc.gov/tb/publications/factsheets/skintest_eng.htm
- A New Tool to Diagnose Tuberculosis: The Xpert MTB/RIF Assay, http://www.cdc.gov/tb/publications/factsheets/testing/xpert_mtb-rif.htm
- Recommendations for Human Immunodeficiency Virus (HIV) Screening in Tuberculosis (TB) Clinics, <http://www.cdc.gov/tb/publications/factsheets/testing/hivscreening.htm>
- Interferon-Gamma Release Assays (IGRAs) - Blood Tests for TB Infection, <http://www.cdc.gov/tb/publications/factsheets/testing/igra.htm>
- Tuberculin Skin Testing <http://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm>
- Diagnosis of Tuberculosis Disease <http://www.cdc.gov/tb/publications/factsheets/testing/diagnosis.htm>
- Targeted Tuberculosis Testing and Interpreting Tuberculin Skin Test Results, <http://www.cdc.gov/tb/publications/factsheets/testing/skintestresults.htm>