Latent *Mycobacterium tuberculosis* Infection -and- Non-Tuberculosis Mycobacterial Infections

"TB or not TB"

Kenneth Woods, DO, MPH

Assistant Professor, West Virginia School of Osteopathic Medicine (WVSOM)

Adjunct Clinical Faculty, Internal Medicine Residency Program, Ohio Valley Medical Center

Chair, Department of Medicine

Medical Director, Infectious Disease

Chair, Infection Control/Prevention Committee

Chair, Antibiotic Stewardship Committee

Trinity Health System, Steubenville, Ohio

Email: kwoods@trinityhealth.com

Disclosures

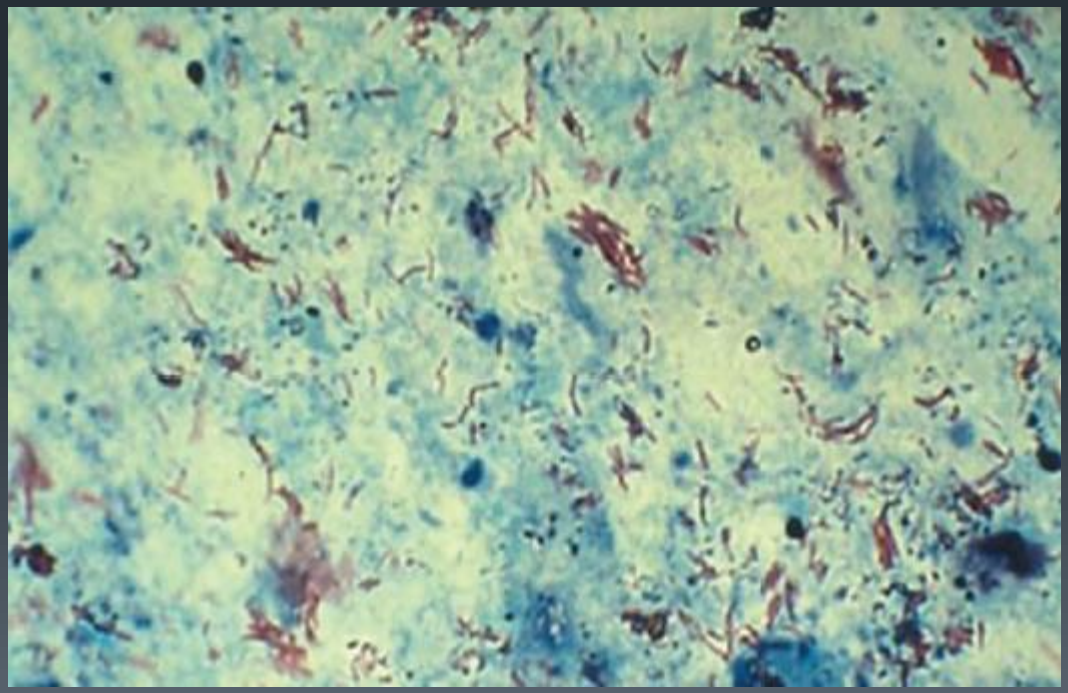
- Nothing to disclose.
- No financial relationships with Med-Pharma.

Objectives

- Define Latent Tuberculosis infection (LTBI) and practical implications in Hospitalist Medicine.
  - TB vs. LTBI
  - Who should be screened for LTBI
- Discuss diagnostic testing as it related to M.tb, TB exposure and TB risk.
  - Review available tests.
  - Interpretation of test results.
- Describe basic management of an abnormal M.tb test, PPD, TBQ, and the LTBI patient.
- Review Non-Tuberculosis Mycobacteria (NTM), and describe pathogenesis of NTM infections.

Limitations

- This is not meant to cover M.tb, which has its own conference.
- Will not cover M.tb treatment and management.



Background on TB

- TB is the leading cause of infection, morbidity/mortality worldwide.*
- ~8.6 million cases/yr and 1.5 million deaths.*
- More rare in US: <10,000 cases/yr; 2/3 being foreign born.
- *Mycobacterium tuberculosis* (M.tb) is an acid-fast bacterium that causes the disease referred to as “TB” or “TB disease”.
- TB disease is most often in the lungs or “pulmonary TB”

  -but-

  TB has infected nearly every body tissue (CNS, skin, lymphatics, organs, epididymitis, spine, pericarditis, bone marrow etc.).
- Not just a disease of immunosuppressed patients.

*CDC and WHO data.

TB risk factors

- Household or close contact/exposure to someone with TB.
- Travel to or immigration from high prevalent area.
- Resident or employee in high risk setting
  (prison, military, homeless, HCW, SNF…).
- IVDU
- HIV
- CKD
- ?DM-2
- Silicosis
- Conditions treated with immunosuppressive/immunomodulating therapies can increase risk of TB/reactivation.

M.tb Infectivity & Pathogenesis

- Person to person transmission via airborne route.
- Factors that increase risk of transmission:
  - AFB smear positive
  - Cavitary lung lesions
  - Duration of exposure
  - Exposure in poorly ventilated space (household, shelter)
  - Host susceptibility/immuno-status.
- After exposure, M.tb implants into the respiratory bronchioles or alveoli.
- Spread into the lymphatic system and hilar lymph nodes to often cause subclinical disease.
- This is when the TST/IGRA has the ability to know TB was present, which denotes LTBI.

Latent Tb Infection (LTBI)

- Latent TB or LTBI is “immunological evidence of exposure to M.tb in the absence of clinical evidence of TB disease”.
- Essentially prior exposure to M.tb without current illness caused by M.tb.
- ~2 billion people worldwide.
- ~11 million people in U.S.
- Main indication for Rx of LTBI is to prevent progression into fulminant TB disease, and to prevent transmission of this highly contagious disease.

Risk of LTBI progression into pulmonary TB

- ~6% of patients with LTBI will develop fulminant TB in their lifetime.
- ~10% per year if HIV positive.
- Greatest risk soon after exposure:
  - 50% of those that will progress to fulminant TB do so within 2 years of exposure.
- Risk increased with immunomodulatory therapy or immunosuppression, (HIV, primary def, and medication induced).
  - TNF-alpha
  - Steroids
  - DMARDS
  - Chemo
- Risk decreases with time since exposure but increases with age.

LTBI – Reason for treatment

- Decrease risk of progression to fulminant TB.
- Decrease mortality due to TB and other related complications.
- Decreased adverse effects from multiple drug therapy for fulminant TB (RIPE therapy).
- Decrease transmission of TB – public health benefits.
  - Especially important for homeless shelters, prisons, hospitals, mental and nursing care facilities.
- Increasing population on immunomodulatory therapies, at risk of reactivation and severe disease.
- WHO goal was Global eradication of TB by 2020, now 2025.

TB-Related Diagnostic Tests

Tests unrelated to Dx of LTBI – but important to know…..

- AFB Smear and AFB Culture (Acid Fast Bacilli Culture)
- M.tb or M.tb complex NAAT/PCR.
- Drug susceptibility testing.

- These are related to the workup of active TB disease, not LTBI.

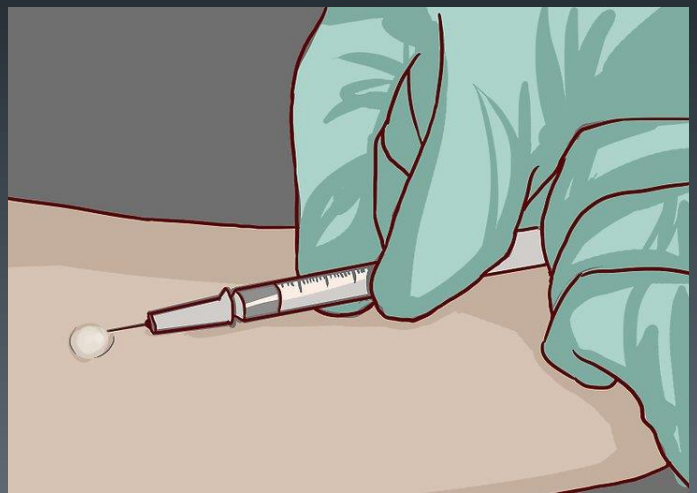
- About ‘TB rule out’…

Tests unrelated to Dx of LTBI - Exclusion of acute pulmonary TB…'TB rule out'

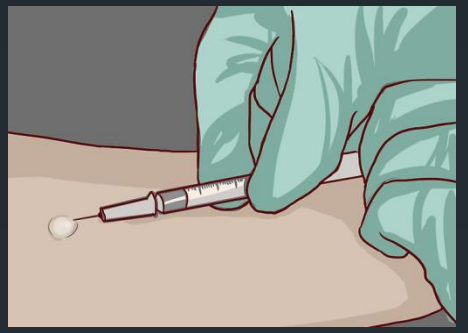
- History/Signs and symptoms evaluation.
- CXR
- Sputum AFB analysis:
  - Min of **3 sputum samples**.
    - 8h apart (≥3ml each) for AFB smear and AFB cx.
    - One should be early AM collection.
    - Both liquid & solid cx if possible, otherwise liquid alone better.
  - Sensitivity of 1 smear 53%; 2 smears 64%; 3 smears 70%.
  - NAAT/PCR done on at least 1 sputum increases sensitivity to ~96%.
- Unnecessary for ruling out acute TB: TST/PPD, IGRA (TBQ/TB-spot), PET/CT

LTBI Diagnostic Tests

- In the U.S. there are 2 commercially available types of LTBI diagnostic tests:
  1. Tuberculous skin testing = TST (PPD)
  2. Interferon Gamma Release Assay = IGRA
- Neither cannot distinguish active vs. LTBI.
- TST (PPD) no longer first line recommendation for TB screening; IGRA should be used/is recommended in most cases.



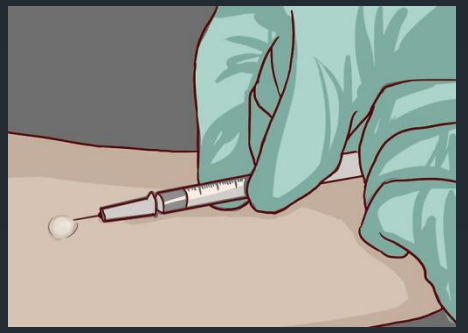
LTBI dx - TST



- TST = Tuberculous skin testing
- PPD = Purified Protein Derivative = Mantoux Test*.
- Relies on cell mediated immunity, delayed type IV hypersensitivity reaction to an inactivated bacilli tuberculin.
- Pros: cheap, readily available (?).
- Cons: Must be read 48-72h (lag time and compliance issues), interpersonal variability, lower sensitivity/specificity and can be dramatically affected by other factors (immumosuppression, BCG).

*Dr. Charles Mantoux first presented PPD in 1908

LTBI dx - TST



- Sensitivity 71-98%
  (43% if immunocompromised).
- Specificity 97% if no prior BCG vaccination.
  (60% with BCG).
- High false negative rate especially immunosuppressed, recent viral infection or recent viral vaccination.
  - To overcome the high false neg rate, it is recommended that anyone not tested with TST within 1 yr undergo 2-step TST.

Interpretation of TST/PPD

Figure 3.3
Reading the TST Correctly
Only the induration is being measured.
This is CORRECT.
The correct example below measures 10 mm.

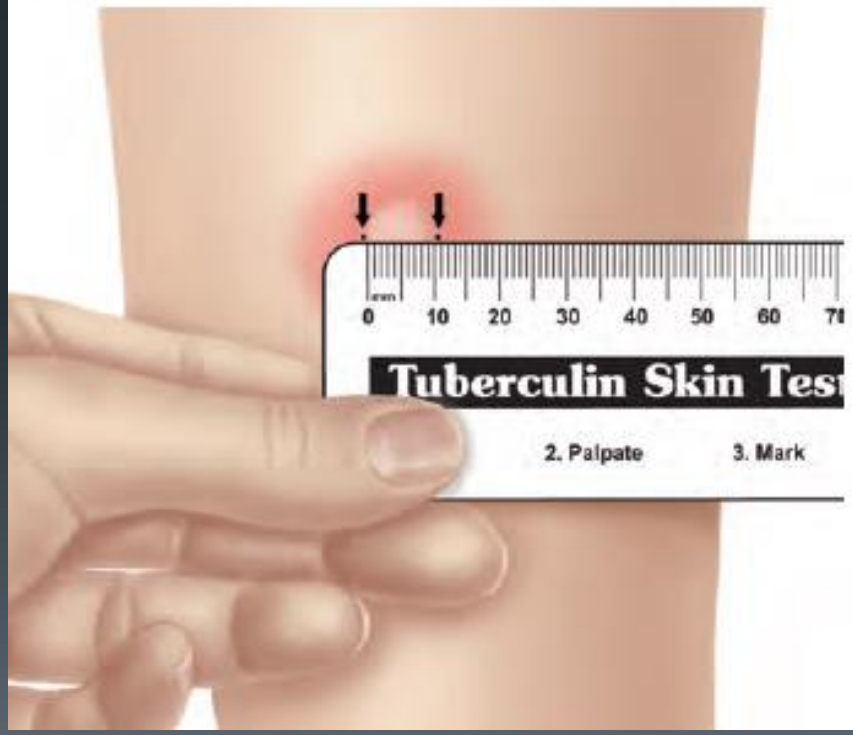


Figure 3.4
Reading the TST Incorrectly
The erythema is being measured.
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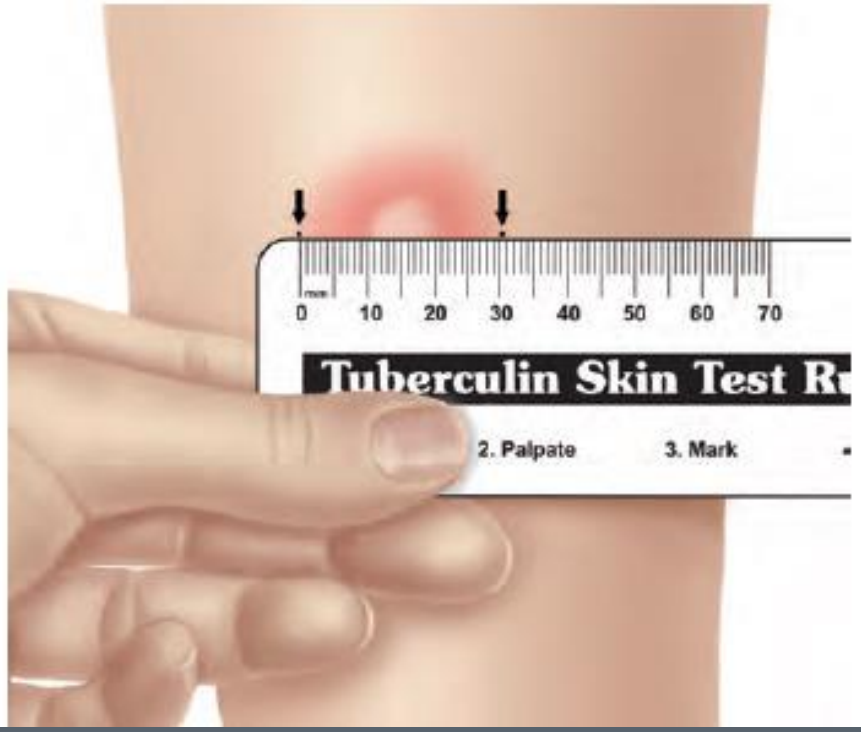
The incorrect example below measures 30 mm.



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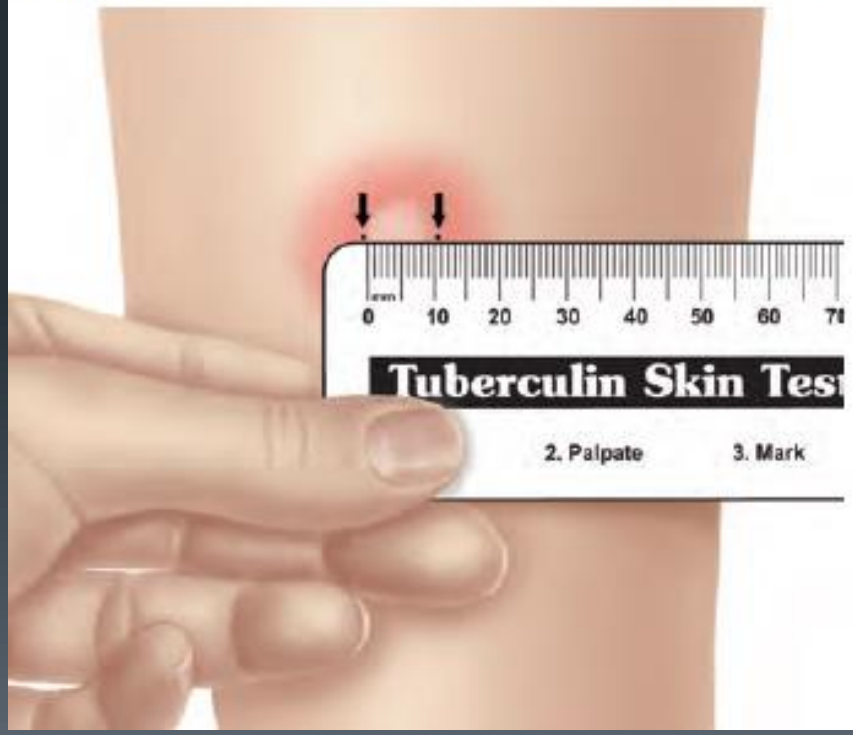

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Interpretation of TST/PPD

- >5 mm: **HIGH** risk, including exposure, immunosuppressed/HIV, highly compatible sx/sx, CXR findings, taking immunosuppressant drugs (TNF-alpha's, steroids), silicosis, children <5 y.o.[#]
  - RR of progression 3-10x the general population.

- >10 mm: **INTERMEDIATE** risk, including SNF, HCW, borne in highly endemic area, CKD, DM2, IVDU (possibly children and silicosis with normal CXR*)
  - RR of progression 1.3-3x the general population

- >15 mm: **LOW** risk, none of the above.

#ATS Guidelines

*CDC

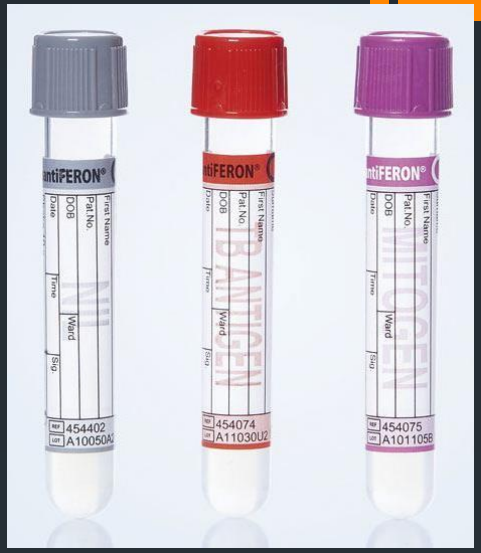
TST/PPD & BCG Vaccination

- False positive TST/PPD include NTM exposure, BCG vaccine, etc.
- CDC does not consider BCG vaccine contraindication to TST, or any variance for testing. ~however~
- TB Clinical guidelines rec. avoid TST and proceed with IGRA in everyone. BUT the guidelines state that patients with hx of BCG vaccination "should not be treated the same" as those without hx of BCG vaccination.

  Translation: IGRA is the rec. test in all patients (with or without hx of BCG vaccination) and if IGRA not available, TST is an acceptable alternative.

LTBI Dx - IGRA

- IGRA = Interferon Gamma Release Assay
  - TB spot
  - TB Quanterferon Gold
- Sensitivity >95%
- Specificity >97-99%



Interpretation of IGRA

- Positive
- Negative
- **Indeterminate ≠ intermediate!!**
  - These are invalid responses, due to high background mitogen activity, lack of T-cell response, anergy/inhibitor presence, or incorrectly performed test.
  - Possible false positive after TST, so if being used together it is recommended that IGRA be done at same time or before TST.
- No quantification ability! Higher titer ≠ higher exposure nor higher amount of disease nor higher risk of progression.

Summary Points on IGRA

- PROS:
  - Superior Sensitivity/Specificity/PPV/NPV
  - No cross reactivity with BCG.
  - Almost no cross reactivity with NTM's.
  - Faster turn around (<24h).
  - No repeat visit needed (like 48h TST check), ? Compliance.
  - Pt comfort (venipuncture vs. dermal injection)
- CONS:
  - Higher cost.
  - Availability (?)

Disconcordinate LTBI test results

- Positive TST and negative IGRA:
  - Likely false positive TST, prior NTM or similar cross reactive Ag hypersensitivity response.
- Negative TST and positive IGRA:
  - Likely IGRA is the superior test and the TST was false negative, but it is recommended to repeat IGRA prior to initiating treatment decisions.
  - Some evidence that this be considered positive for patients at HIGH risk or disease progression and initiate treatment (not universally recommended).
- Positive IGRA followed by negative IGRA:
  - Lack of evidence in this domain. Likely false positive or related to the lab cutoff criteria.

Who should be tested for LTBI and how?

- Anyone age ≥ 5 y.o. and likely to be infected with TB due to risk factors, low/intermediate risk of disease progression, or have another condition that warrants LTBI testing, hx of BCG vaccine.
- LTBI testing is not recommended in patients considered at no or low risk of TB progression, but if mandatory per law or credentialing body, than IGRA is recommended over TST.
- Patients <5 y.o. should only have TST if LTBI screening indicated.

Who should be tested for LTBI and how?

- Per the guidelines “TST is an acceptable alternative where IGRA is not available, too costly, or too burdensome”.
- Due to the higher false positive and false negative rate with TST, IGRA is still cost effective over TST due to the more accurate test, and less inappropriate secondary testing and treatment related to the TST.
- Guidelines recognize that TST may still be “more appropriate” in certain settings, factoring in mass availability, resources, cost, etc.
- Once LTBI Dx established, there is no role for repeating TST or IGRA. They are thought to be positive for life.
- Bottom line: If IGRA available, it is the recommended first line test in everyone >5 y.o. undergoing LTBI screening. When IGRA not available, TST is an acceptable alternative, but must be interpreted with care given the test characteristics.

Management / Treatment of LTBI

Management of positive LTBI test

- Per the guidelines, anyone with a positive LTBI test, should be rechecked (confirmed) with a second test
  (the same type of test is acceptable).

- **Must exclude active TB** vs. LTBI.
  - History / Signs and symptoms evaluation.
  - CXR in everyone.
  - Suggestive Sx/Sx or CXR → additional testing with sputum analysis for AFB smear/AFB cx as described earlier ('TB rule out').
  - No Sx/Sx → no sputums/AFB smears/cx are needed.

Treatment of LTBI

- First line / preferred:
  - Isoniazid (INH) 5mg/kg (300 mg max) + Pyridoxine (vit B6) 50 mg both PO daily x 9 mo.
  - Vit B6 to prevent INH induced peripheral neuropathies.

  - Children: INH 15mg/kg (300 mg max) PO daily x9 mo (vit B6 of less benefit so not needed).

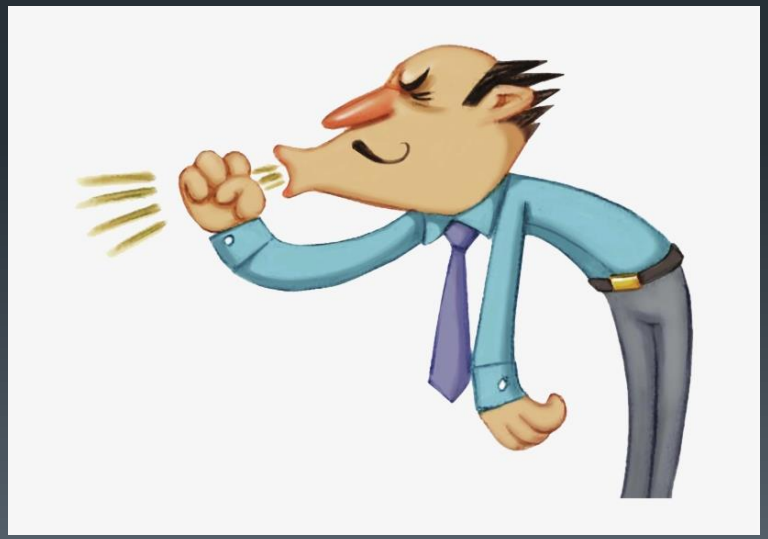
Treatment of LTBI

- Alternatives for Adults:
  1. Rifampin 10 mg/kg (max 600 mg) PO daily x 4 mo.
     - Caution: many drug interactions/tolerability.
  2. INH 5mg/kg (max 300 mg) + Rifampin 10mg/kg (max 600 mg) + vit B6 50 mg all PO daily x 3 mo.
  3. INH 15mg/kg (900 mg max) + Rifapentine 900 mg + Vit B6 50 mg all PO once weekly x 3 mo DOT (direclty observed therapy).
     - Caution: not for pregnant, HIV, noncompliant…but can also be used in children.

- These are not first line recommendations due to higher toxicity, adverse effects, or risk of treatment failure.

Non-Tuberculous Mycobacteria (NTM)

Previously called “Atypical Mycobacteria”.



Non-Tuberculous Mycobacteria (NTM)

Slow-growing mycobacteria (other than TB):

- M.avium complex (MAC)
- M.leprae
- M.kansasii
- M.xenopi.
- M.simiae complex.
- M.szulgai.
- M.malmoense,
- M.scrofulaceum,
- M.terrae/nonchromogenicum.
- M.ulcerans.
- M.haemophilum.
- M.genavense.
- Newer: M.nebraskense, M.parascrofulaceum, M.parmense, M.saskatchewanese, M.pseudoshottsii, M.seoulense, M.chimaera, M.colombiense, M.florentinum, M.arupense, M.kumamotonense, M.senuense, M.montefiorense.

Intermediate growing:

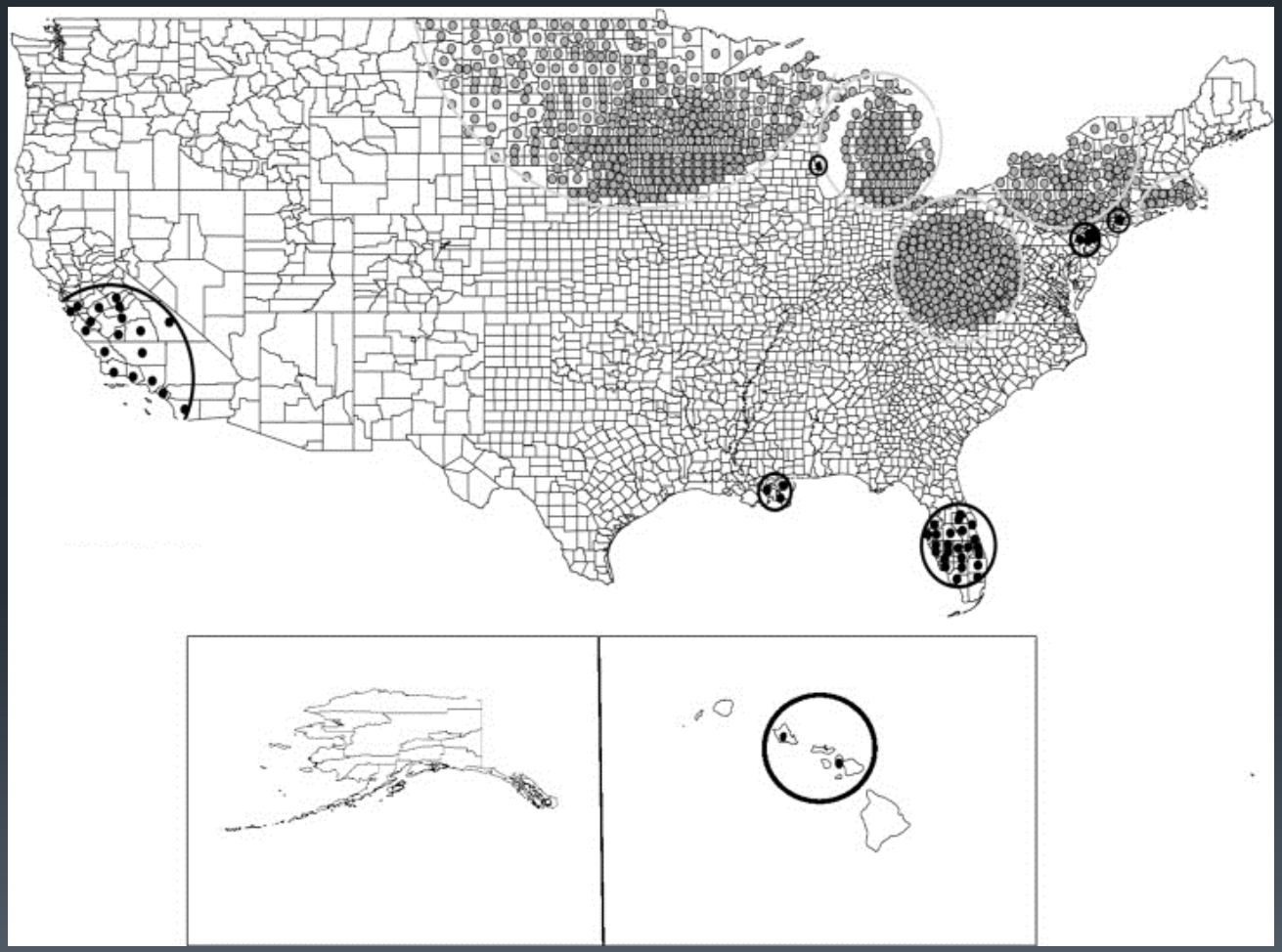
- M.marinum
- M.gordonae

Rapid growing mycobacteria (RGM):

- Non-pigmented:
  - M.fortuitum group:
    - M.fortuitum
    - M.peregrinum
    - M.senegalense
    - M.conceptionense
    - M.setense
    - M.septicum
    - M.mageritense
    - M.porcinum
    - M.houstonense
    - M.bonickei
    - M.brisbanense
    - M.neworleansense
  - M.chelonae/abscessus group:
    - M.chelonae
    - M.abscessus
    - M.immunogenum
    - M.bolletii
    - M.massiliense
  - M.mucogenicum group:
    - M.mucogenicum
    - M.aubagnense
    - M.phocaicum
- Late pigmenting or non-pigmenting:
  - M.smegmatis group:
    - M.smegmatis
    - M.wolinskyi
    - M.goodii
- Early pigmenting:
  - M.flavescense
  - M.neoaurum
  - M.vaccae
  - M.phlei
  - M.thermoresistible
  - M.canariasense
  - M.cosmeticum
  - M.monacense
  - M.psychrotolerans

Non-Tuberculous Mycobacteria (NTM)

US Hotspots



*Am J Respir Crit Care 2012

Non-Tuberculous Mycobacteria (NTM)

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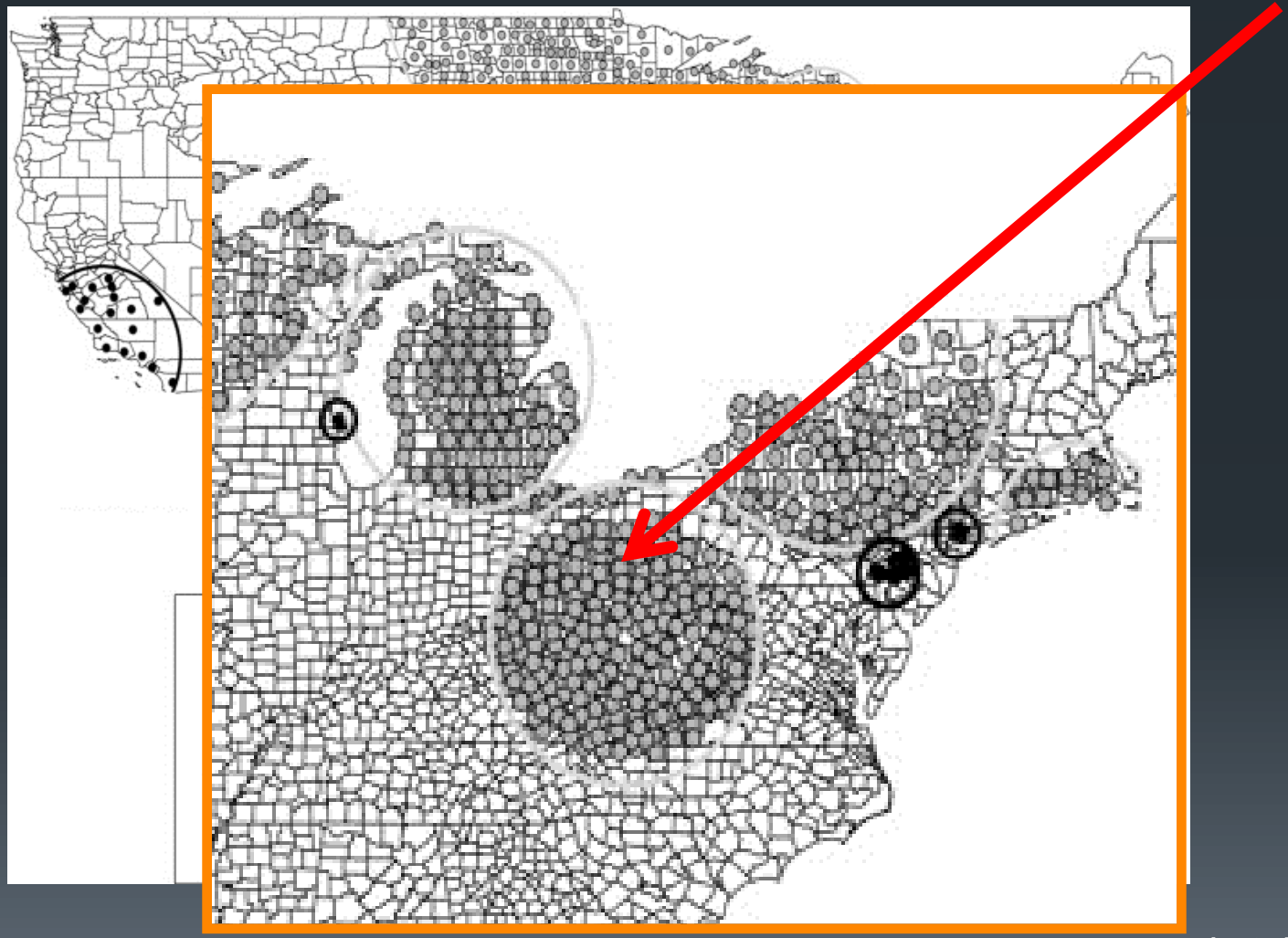

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Non-Tuberculous Mycobacteria (NTM)

- World wide distribution.
- Ubiquitous environmental pathogens in soil and water (including treated water such as drinking water, fountains, ice machines, spa's/pedicures, etc.).
- Incidence rates reported around 1.8 cases/100,000 population.
- MAC is the most common of these to cause human disease.

- Historically was a disease of AIDS patients with CD4 count <50.
- Increasing incidence of non-AIDS immunosuppressed population.
- Increased awareness/diagnostics = increased NTM disease.
- Especially high rates with TNF-α inhibitors.

Non-Tuberculous Mycobacteria (NTM)

Pathogenesis:

- Not transmissible person to person. (with exception of *M. leprae).*
  - Environment → humans via inhalational or skin inoculation.
- ~94% pulmonary infection; 3% skin; 3% other.
- Typically COPD or structural underlying lung disease but also Lady Windemere Syndrome*.

- Common contaminant in obtaining cultures.
- Positive culture ≠ disease..

*Oscar Wilde's play "Lady Windermere's Fan 1892.

Non-Tuberculous Mycobacteria (NTM)

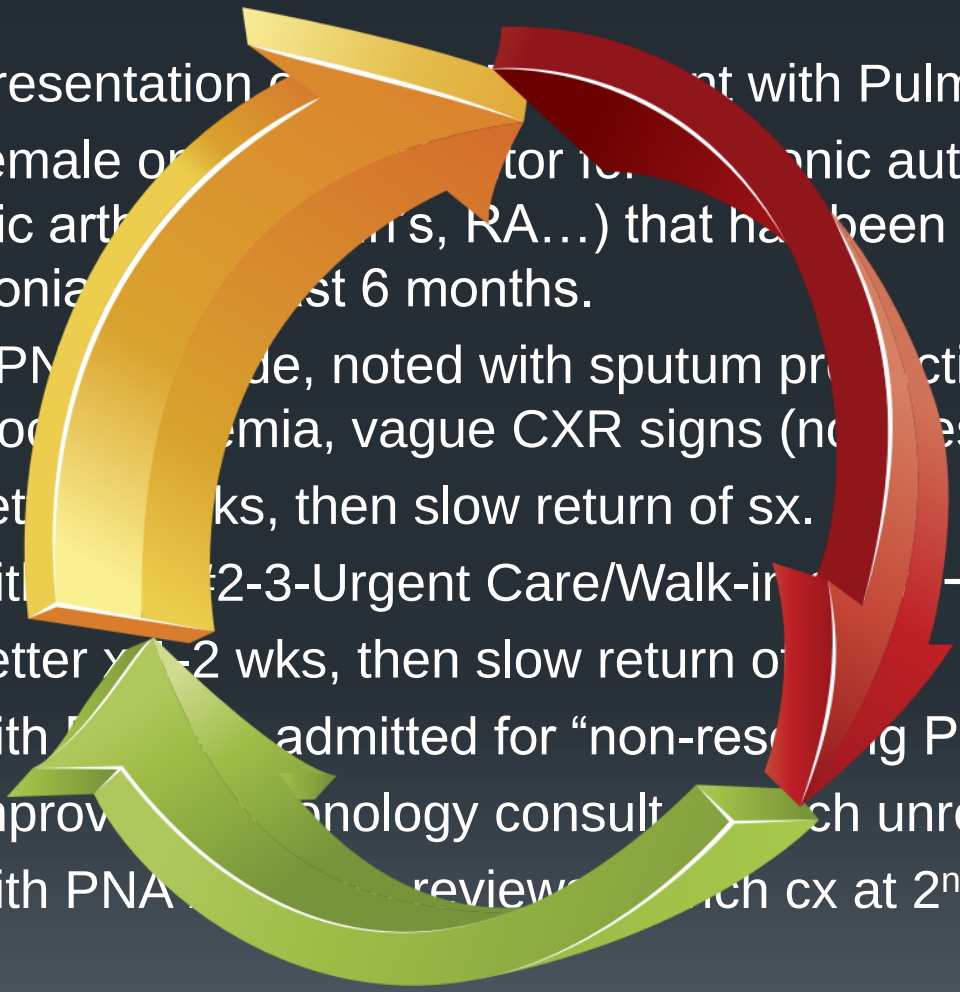
Typical presentation of non-AIDS patient with Pulmonary NTM:

- 65 yo female on TNF-α inhibitor for a chronic autoimmune disease (psoriatic arthritis, Crohn's, RA…) that has been treated 5 times for 'pneumonia' in the last 6 months.

1. First PNA episode, noted with sputum production, cough, mild normocytic anemia, vague CXR signs (nodules). PCP → abx.
   - Sx better x2 wks, then slow return of sx.
2. Dx with PNA #2-3-Urgent Care/Walk-in clinic → different abx.
   - Sx better x 1-2 wks, then slow return of sx.
3. Dx with PNA #4, admitted for "non-resolving PNA" → more abx.
   - Sx improve, Pulmonology consult. Bronch unrevealing. Sx return.
4. Dx with PNA #5, Pulm reviews bronch cx at 2nd week neg. more abx.

- EVENTUALLY week #3 bronch AFB grows MAC → ID/Pulm referral.

Non-Tuberculous Mycobacteria (NTM)



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- EVENTUALLY week #3 bronch AFB grows MAC → ID/Pulm referral.
- **Pattern of recurrent PNA → think about NTM**

Non-Tuberculous Mycobacteria (NTM)

Diagnostic criteria:

- ALL 3 MUST BE MET for diagnosis (Clinical; Radiographic; Micro)
- Per NTM Guidelines, these are all “equally important” in confirming the dx.

- Clinical:
  - Compatible illness/sx and exclusion of other etiologies.
- Radiographic:
  - CXR or CT showing bronchiectatic disease, multiple small nodules or cavitary disease c/w NTM.
- Microbiological:
  - Multiple positive sputum AFB cultures or one bronchoscopy/BAL cx or lung tissue biopsy cx.

Non-Tuberculous Mycobacteria (NTM)

Treatment:

- Confirming diagnosis does not equate to needing to treat. Decision to treat must be made with thorough discussion with the patient, comorbidities, and other factors and should be individualized.
- Treatment should only be undertaken by those experienced with treating NTM infections.
- Typically 3-drug regimen:
  1. Clarithromycin or Azithromycin
  2. Ethambutol
  3. Rifampin
- T.I.W. therapy for noncavitary disease; daily for cavitary.
- Duration – 12 months from negative AFB cx.

Non-Tuberculous Mycobacteria (NTM)

- Alternative abx's:
  - Fluoroquinolones
  - Cefoxitin
  - Doxycycline/Minocycline
  - TMP/SMX (Bactrim)
  - Linezolid
  - Aminoglycocides
  - Imipenem

- These are not first line NTM drugs, but are active.
- Active drugs very commonly used, can cause confusion w/ diagnosis, and affect AFB cultures.

Non-Tuberculous Mycobacteria (NTM)

- **Pattern of multiple recurrent pneumonias (~2-8 week cycles)??**

Think about pulmonary NTM infection!

- Ruling out NTM infection is very different than ruling out M.Tb.

- No role for airborne / negative pressure isolation
- No role for TST/PPD or IGRA/TBQ
- Usually no role for inpatient workup (takes many weeks to make the diagnosis).

LTBI and NTM Study Questions:

- Which of the following statements is true about latent Tuberculosis infection (LTBI)?
  - A. LTBI is a mild form of pulmonary TB.
  - B. LTI is a severe form of pulmonary TB.
  - C. LTBI is typically treated by a 4-drug antibiotic course such as Rifampin, Isoniazid, Pyrazinamide, Ethambutol.
  - D. LTBI is typically treated with a single drug antibiotic course such as Isoniazid.

- Why is vitamin B6 typically given with Isoniazid for the treatment of latent tuberculosis?
  - A. Prevent nausea/vomiting.
  - B. Augment the action of isoniazid antibacterial properties.
  - C. Prevent peripheral neuropathy induced by isoniazid.
  - D. Co-existing vitamin B6 deficiency is always present with latent tuberculosis.

- What is true regarding Non-Tuberculous Mycobacteria (NTM) ?
  - A. They are never pathogenic and always a contaminant on respiratory cultures.
  - B. There is no treatment for NTM infections.
  - C. Although NTM infections can be very challenging infections to both diagnose and treat, multiple treatment options are available.
  - D. NTM infections are highly contagious and warrant airborne/negative pressure isolation quarantine.

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  - D. NTM infections are highly contagious and warrant airborne/negative pressure isolation quarantine.

LTBI and NTM Study Questions:

- Which of the following statements is true about latent Tuberculosis infection (LTBI)?
  - A. LTBI is a mild form of pulmonary TB.
  - B. LTI is a severe form of pulmonary TB.
  - C. LTBI is typically treated by a 4-drug antibiotic course such as Rifampin, Isoniazid, Pyrazinamide, Ethambutol.
  - D. LTBI is typically treated with a single drug antibiotic course such as Isoniazid.

- Why is vitamin B6 typically given with Isoniazid for the treatment of latent tuberculosis?
  - A. Prevent nausea/vomiting.
  - B. Augment the action of isoniazid antibacterial properties.
  - C. Prevent peripheral neuropathy induced by isoniazid.
  - D. Co-existing vitamin B6 deficiency is always present with latent tuberculosis.

- What is true regarding Non-Tuberculous Mycobacteria (NTM) ?
  - A. They are never pathogenic and always a contaminant on respiratory cultures.
  - B. There is no treatment for NTM infections.
  - C. Although NTM infections can be very challenging infections to both diagnose and treat, multiple treatment options are available.
  - D. NTM infections are highly contagious and warrant airborne/negative pressure isolation quarantine.

Questions?

E-mail: kwoods@trinityhealth.com

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