Latent Tuberculosis in Adults: From Testing TO Treatment

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Tuberculosis Factoids & Milestones

• The most common adult infectious cause of death worldwide
• Humans serve as the only natural reservoir
• One third of the world’s population infected
• Someone dies of TB every 15 seconds
• TB is diagnosed every 4 seconds
• M.Tb. complex contains *M. tuberculosis*, *M. bovis*, *M. africanum* and *M. microti*
Tuberculosis Factoids & Milestones

• Causative agent of tuberculosis was discovered by Robert Koch 1882, used it to expound Koch’s postulates.
• Paul Ehrlich discovers the acid fast property of M.Tb that same year.
• Koch discovers tuberculin in 1890.
• Roentgen invents/disCOVERS X-rays
• Mantoux test 1907
• Treatment progressed through fresh air, pneumothorax, plombage and eventually chemotherapy
Transmission of TB

- Transmission is by airborne ‘droplet nuclei’
- Rate of transmission related to:
  - ‘infectious particle density’
  - dilution of infected air
  - duration of exposure & proximity to index case
  - the ‘inoculum’ (patient cough frequency and vigour)
- Also depends on smear-status of patient. Smear negative patients are nearly 80% less infectious than smear positive patients
Pathogenesis of TB

- Primary infection usually self-limited followed by variable period of latency.
- At site of implantation the infection is contained and the emphasis is on regional self-limited lymphatic spread, occult bacteremia seeding apical and non-respiratory sites (renal, bones, etc.)
- Requires about 18-24 months for cellular immunity to completely mature (memory).
Latent Tuberculosis is the presence of *Mycobacterium tuberculosis* bacilli in the absence of any signs, symptoms, radiographic or microbiologic evidence of TB disease.
Latent vs. Active TB

- About 5% of newly infected people cannot contain the infection and develop primary/progressive disease within 1-2 years after infection.
- 95% have LTBI of which 90% never get disease and 5% reactivate their post-primary state in immunocompetent hosts.
- In contrast, HIV patients have a 10% yearly risk of reactivation.
Latent vs. Active TB

Exposure to an Infectious Case of TB

Primary Infection

Primary or Progressive Primary Disease

≈ 5%

Latent Infection

≈ 95%

Hypersensitivity Reactions

≈ 90%

Postprimary TB due to Reactivation

≈ 5%

No Disease

Nonrespiratory

Respiratory

New Infections

* The probability of disease is much greater than 5% in patients with a severe immunocompromising condition such as HIV/AIDS.
Epidemiology Pearl

- In low prevalence countries most post-primary active TB disease is due to re-activation
- In endemic countries it’s difficult to sort re-activation from primary re-infection
Patients with LTBI usually have a positive TST and/or IGRA and a normal CXR (or evidence of healed granulomatous disease)
Risk Factors for TB Infection (PPD +)

• The risk of TB infection in a population is related to the number of infectious cases and the duration of infectiousness
• Each smear + case infects a mean of 10 people per year
Risk for Progression to TB If Infected

- Age is a large determinant: peaks under 5 year and again at 19 and also the risk increases at 75+ years
- Intensity of exposure (3.5x higher for smear positive contact)
- Time since infection (50% of cases within first 2 years)
TB Epidemiology

- In the U.S. there were 5.1 cases per 100,000 residents in 2003
- Contrast with 3.8 cases / 100,000 in 2009
- Canada has 5.2 / 100,000 vs 4.7 / 100,000 for the same years (total cases 1599 in 2009)
- Peel region has between 9-11 cases / 100,000 residents
Targeted TB (TST) Testing is the Preferred Method of ‘Screening’

- Targeted testing is essential as a TB prevention and control strategy
- Detects patients who would benefit from treatment if test is positive
- Discourages testing of low-risk populations
- Effective and efficient use of resources
My LTBI Framework

The proper way to conceptualize LTBI has everything to do with inherent risk of a) truly being infected, b) the chance of developing active disease in the near or distant future, c) patient preferences, and d) future re-exposure risk†
Indications for Tests to Dx TB Infection

- There are 3 general situations when risk of disease, if infected, are increased:
  - Recent infection (most commonly close contacts of patients with active contagious pulmonary TB), OR, new Canadians within 2 years of landing*
  - Increased risk of reactivation from immunocompromise (HIV, RheumRx, Chemotherapy, renal failure, diabetes)
  - When there is radiographic evidence of old healed inactive and previously untreated TB

*If arriving from country of high TB incidence
When Should I Not Do A TST?

- TST contraindicated in:
  - Severe prior blistering TST reactions
  - Those with active TB
  - Those previously treated for TB
  - Those with major viral infections
  - Prior positive TST
Be Very Selective in Canada, Not so Much in Peel Region

• In low-risk populations *pro forma* testing is discouraged because of the low PPV of the TST; the risks of Rx are likely to outweigh any perceived benefit

• Also, futile to test if there is no *a priori* commitment to treatment or monitoring
The TST

- The Intra-dermal Tuberculin Skin Test
- Mantoux technique:
- Tubersol® 5 Tuberculin Units (5-TU) of Purified Protein Derivative Standard (PPD-S)
- Should be positive (induration) in previously infected hosts
- Results from a CMI DTH within 48-72 hrs
- Newly infected hosts should convert within 3-8 weeks
How to Read the TST

- Disregard erythema
- Measure only induration
- Do not round up
- Record results in ‘mm of induration’, record no induration as ‘0 mm of induration’
- Record the date, the patient name, the reader and provide copy to patient
Can I Still Do A TST If...?

- The following can receive a TST
  - Those taking <15mg of prednisone less than 2-4 weeks
  - Those who are pregnant or breast feeding
  - Those immunized on same day with any vaccine or immunized with live attenuated vaccine after 4 weeks
  - Those with a history of a positive TST that is not documented. A documented positive TST should not be repeated
False Negative TST

- There are several reasons for a false negative test:
  - Technical
  - Biologic
    - Immune suppression due to severe illness or medications, viral illness, HIV or any condition with impaired CMI, TNF-α inhibitors, malnutrition, active TB, age less than 6 months
False Positive TST

- Previous Non-Tuberculous Mycobacterial infection
- BCG vaccination after the age of 1
- Probably okay to ignore BCG up to age 6
- Risk of false-positive increases in proximity to vaccination
**Interpretation of TST**

- <5 mm = negative, 5-9 mm only in HIV, close contacts, FN disease on CXR, on TNF-α inhibitors or chemo), >10mm = positive in everyone else

- Interpretation should be best using a combination of size, PPV (different from sensitivity) and risk of disease

- In Canada, for most people a cutoff of 10 mm of *induration* has the optimal sensitivity (90%) and specificity (95%)

- PPV is based on pre-test probability and Specificity

- Affected by ‘endemicity’, MOTT, and BCG vaccine
The BCG Dilemma

- BCG vaccine can be ignored if given before age 1
- The younger the person was when inoculated the less likely a positive TST is due to BCG
- BCG during age 1-5 still results in only 10-15% FP TSTs, after age 10 ignore if given in infancy
- BCG may be considered cause of FP TST if person is Canadian born non-Aboriginal or from a low TB incidence country
Web Based TB Resources

- BCG atlas developed by M. Pai, R. Menzies and colleagues at McGill University: [www.bcgatlas.org](http://www.bcgatlas.org)
Interpretation of Sequential TST
(The Problem of Non-Specific Variation)

- Clinical circumstances are the most helpful guide in determining conversion (versus booster variability)
- But generally accepted if:
  - a prior test was <5mm and is now 10mm or greater.
  - in select circumstances (e.g. highly contagious source case) an increase of 6mm or more is accepted
  - a prior test was between 5-9mm the definition of conversion is more controversial (conservative approach is increase of 6mm
Booster And 2-Step TST Principles

- A single test may illicit little response but stimulate an anamnestic immune response such that a repeat test within 1 week to 1 year will result in a positive test.
- A 2-step TST should be performed between 1-3 weeks:
  - In people who will require regular interval testing
  - In people following exposure to an infectious TB case
  - If discrete exposure, the dates are accurate and time is <3wks (before a true seroconversion can occur). This will establish the true baseline.
- Need not be repeated*
Interpretation of A 2-Step TST

- A 2-step TST is considered positive if the second test is 10mm or greater
- Patients should be sent for evaluation
- Patients with positive 2-step TSTs have about half the risk developing TB than patients with an initial positive test, (more likely in older pts)
- Q: How to manage a patient who had a step-1 between 5-9mm and a step-2 of 10mm or more but increased less than 6mm (e.g. 9mm 11mm)?
Who to Refer for Further TB Evaluation

- People with a TST >5mm, <10mm
  - and an abnormal CRX
  - or high risk factors (HIV-AIDS, close contact of active case, CRF on hemodialysis, silicosis, transplant)
- People with a positive TST (10mm or more)
  - or mild- moderate- risk factors (recent immigration, low-dose steroids, high TB incidence country of origin, consideration for TNF-α inhibitors)
Who to Refer for Further TB Evaluation

- Recent skin-converters
- Occupational skin-converters
- Referrals from Health Canada and Canada Immigration
- Contacts of active cases:
  - with symptoms compatible with active TB
  - with recent skin-conversion (within 8 weeks)
A Word About LTBI in The Elderly Population

- TB case rates increase with age among all racial and ethnic groups.
- Screening for TB in LTC facilities is recommended with a CXR.
- Incidence of TB disease is two to seven times higher among nursing home residents in some areas than among demographically similar persons in other settings.
- Studies indicate that unsuspected transmission of *M. tuberculosis* in nursing homes/facilities presents a risk to residents and workers.
- Risk of INH adverse event is significantly increased in patients >65 [OR6.4] (Menzies, CMAJ 2011).
Treatment of LTBI

- Isoniazid 5mg/kg (max. 300 mg) PO qd (+ vitamin 25mg B6) for 9 months (c. 0.001 % AE, far less for SAE) (Level I)
  - 9INH with >80% adherence showed 93% protection
- Rifampin 600 mg PO qd for 4 months (still level III evidence)
  - More cost effective if compliance hits 65%, more efficacious if compliance hits 74%
  - 6R with unknown adherence showed 100% protection
- Medications are free from Public Health
- Patient should be provided with documentation of any/all TB assessments and interventions

Menzies, Thorax 2010
My preference is to *not* offer LTBI treatment for residents that travel to countries of high TB prevalence with a frequency greater than every 3-5 years.
Initial Choice of LTBI Regimen

- Rifampin 600 mg/d x 4 mo as good as INH 300 mg/d for 9 mo
- However, if any suspicion of active TB risky to use Rifampin monotherapy empirically due to possibility of inducing resistance
- Any radiographic abnormalities warrant an initial sputum induction
The Rifapentine Study

• INH-RPT weekly for 12 weeks as DOT is as effective as other regimens for TB prevention and is more likely to be completed (3 RCTs)

• 270 daily doses of INH (<60% adherence) vs. 12 once-weekly doses of INH-RPT (long $t_{1/2}$). DOT under the ensures adherence to the regimen and facilitates safety monitoring

• CDC recommends monitoring for adverse effects of the new INH-RPT regimen, even though it was well-tolerated in treatment trials
Candidates for INH-RPT

- Healthy persons aged 12 years or older who have LTBI and factors predicting development of TB:
  - recent exposure to contagious TB
  - documented seroconversion
  - radiographic findings of healed pulmonary TB.
- HIV-infected patients who are otherwise healthy and ARV naive
- Can be considered for the following patients:
  - correctional settings
  - clinics for recent immigrants
  - homeless shelters
  - who are unlikely to complete 9 months of daily INH
WOHS Management of LTBI

• In our TB clinic, every LTBI patient gets:
  - an initial consultation
  - induced sputa*
  - a baseline CXR/low-dose CT chest
  - risk factor stratification
  - PPH demographic snapshot and case management (education, forms, etc.)
  - monthly f-up for side effect surveillance
  - baseline & monthly LFTs and initial HIV test†

*If abnormal radiology and considering Rifampin, or working up active TB
†We are actively working toward this goal
The Commercial IGRAs

- Quantiferon -TB Gold In-Tube®
  - Whole blood is incubated with M. tb antigens, and the resulting production of IFN-\(\gamma\) is measured using an ELISA

- T-SPOT.TB ®
  - Peripheral blood mononuclear cells are incubated with M. tb antigens and the number of T-cells producing IFN-\(\gamma\) are measured using an ELISPOT assay
IGRA Considerations

- **Advantages**
  - Excellent specificity unaffected by BCG vaccination
  - Quality control
  - One visit
  - No risk of serious skin reactions

- **Disadvantages**
  - Cost
  - Need to be processed within 12 hours
  - Hasn’t been around for 100 years
  - Available?
Indications For IGRA (CDC)

- Neither TST nor IGRAs should be used to test persons at low risk for infection or progression to active TB if infected, unless they are at increased risk in the future. When testing low-risk patients, the test with the greatest specificity should be chosen.
- The most suitable test or combination of tests to diagnose *M. tuberculosis* infection should be chosen based on the reasons and the context for testing, test availability, and overall cost effectiveness.
- An IGRA may be used instead of a TST in all situations in which the CDC recommends the TST as an aid in diagnosing *M. tuberculosis* infection.
- IGRA is preferred for testing groups that have low rates of returning to have TST read and for those who have received BCG. In the latter group, the tuberculin skin test has a higher false-positive rate.
- IGRAs or TST may be used to test recent contacts of persons with infectious tuberculosis.
- IGRAs or the tuberculin skin test may be used for periodic screening for occupational exposure.
WOHS TB Clinic
Approach to IGRA

- Always start with the TST
- *Close contact*, TST positive but low pre-test probability of having recently acquired LTBI and have no other risk factors for progression to active disease, IGRA can be used as confirmatory test
- *Immunocompromised* person, TST negative, IGRA positive then consider therapy
WOHS TB Clinic
Approach to IGRA

- Low risk person, TST +, IGRA - no therapy
- Low risk person
  - TST done for school or employment, no history of TB contact, no clinical condition that increases risk of reactivation, normal CXR
- (TST positive immigrants from high TB incidence countries, no history of TB contact, no clinical condition that increases risk of reactivation, normal CXR)*
Thank You - The End

- Thanks for attending
- Questions....