

LATENT TUBERCULOSIS SCREENING AND TREATMENT:

TB or not TB

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Week 14

Educational Objectives:

1. Understand who should be screened for latent TB infection and why
2. Describe what constitutes a "positive" PPD test and why
3. Prescribe a primary effective treatment regimen for latent TB infection

Authors' Note:

Why are we worried about TB, is it still a big problem? In the United States, it is not a common problem, but globally it very much is.

In the USA (from MMWR, 2007):

- 13,293 total reported cases in USA in 2007
- From 2006 the TB rate declined 4.2% to 4.4 cases per 100,000 population, but despite the overall improvement, the rate of decline has slowed from 7.3% (1993-2000) to 3.8% (2000-2007).
- 58.5% of cases are from foreign-born persons

Case rate, 2007:

.. 2.1/100,000 amongst US born (7.8% decline since 2006, and a 71.4% decline since 1993)

.. 20.6/100,000 amongst foreign-born in US

Top four countries of origin: Mexico, Philippines, India, and Vietnam

- Five states (California, Florida, Illinois, New York, and Texas) reported more than 500 cases each for 2007; combined, these five states accounted for more than half (52.0%) of all TB cases in the U.S.

Globally (from World Health Organization) based on 2006 data:

- Overall, one-third of the world's population is currently infected with TB
- 9.2 million total reported cases in 2006, 8% of these were HIV positive.
- Compared to the United States, there are 139 new cases per 100,000 that occurred globally; although the incidence, prevalence, and death rate have been stabilizing or decreasing slowly over the last 5 years, as in the US.

- Globally, 1.7 million people die each year from TB -- Just under 5,000 deaths per day
- 86% of the burden of disease occurs in Africa, South-East Asia, and Western Pacific regions. The countries with the top total absolute number of cases respectively are India, China, Indonesia, South Africa, and Nigeria. African countries have the highest incidence rate per capita.

CASE ONE:

Mrs. Potts is a 50-year-old schoolteacher who emigrated to the U.S. 10 years ago from Vietnam. She is without any symptoms, but when some of her pupils turned up “PPD positive,” she worried that she could be infected with TB and comes to you for advice. She does not recall a previous PPD test, but says she was given the BCG vaccine as an infant in Vietnam.

Questions:

1. Should she be offered a PPD test? If so, what would constitute a “positive” result?

A decision to test is a decision to treat (regardless of age). Therefore, only those considered likely to be recently infected or are at increased risk for TB reactivation should be offered PPD testing. If not at “high risk,” one should not be tested, as the risk of reactivation is too low to warrant treatment and the inherent risks and costs. BCG history only confirms the patient is from a high risk country but does not indicate someone is at high risk of reactivation. It should not be taken into consideration when interpreting a PPD.

2. Which groups are at high risk of reactivation?

Persons at increased risk who should be tested for latent TB infection:

- Increased risk of exposure to infectious (active) cases, (e.g., close contacts at home or health care workers at facilities that treat patients with active TB)
- Increased risk of TB infection, [e.g., foreign-born persons from high prevalence countries (up to five years since emigration), homeless, incarcerated]
- Increased risk of conversion to active TB from latent TB [e.g., persons with HIV, intravenous drug abuse, end-stage renal disease, diabetes mellitus (especially poorly controlled), receiving immunosuppressants (such as infliximab or long term steroids), hematologic malignancies, s/p gastrectomy or jejunioileal by-pass]

3. So should Mrs. Potts be offered PPD testing?

No. Because she does not fall into a high-risk group, testing, and treatment are not indicated. Of note, because reactivation is significantly more likely in the first years after infection, recent converters (two years since a negative test) or recent immigrants from a high prevalence country (five years) are considered high risk for tuberculosis. If her pupils turn out to have active TB, then Mrs. Potts might be appropriate for PPD testing.

CASE TWO:

Dr. Koch is a second-year resident in your internal medicine residency program. He is a 30-year-old male, who has returned from his international health elective in Uganda four months ago. He reports all his previous annual PPDs have been negative. This year he reports a 12mm induration reaction.

4. Should he have been screened?

He was appropriately screened annually as a health care worker likely to work with patients with active TB.

5. Is this positive?

Cutoff levels are set to maximize sensitivity in groups at increasingly higher risk of infection and/or activation. Thus, the decision is made to sacrifice specificity to gain sensitivity in selected situations. In other words, a smaller amount of induration considered positive would increase sensitivity (true positive rate) such that we don't "miss cases" at the expense of lower specificity (thus a higher false positive rate).

Criteria for positive PPD:

- >5mm HIV infected
- Close contacts of active cases
- Abnormal x-ray consistent with previous TB infection
- Those on immunosuppressants (equivalent of >15mg of prednisone for at least a month, TNF inhibitors, transplant rejection drugs)
- >10mm Foreign-born recently arrived (<five years) from a country with high prevalence
- Those with medical condition that increases risk (see above in question 2)
- Intravenous drug abuser
- Homeless
- Residents and staff members of long term care facilities (skilled nursing facilities, correctional)
- Health care workers potentially exposed to active TB patients
- Children <4 years old
- Conversion of PPD within past two years
- >15mm All others

So we can see that for Dr. Koch, a 12mm reaction is indeed "positive," by virtue of being a health care worker at risk and being a recent converter. Dr. Koch, a budding statistician and gambler, wants to know what his chances of activation are if left untreated. For that matter, he also asks about the "odds" for other groups at risk.

CASE TWO CONTINUED:

6. What are Dr. Koch's chances of activation if left untreated given his age and PPD size?

The math behind the recommendations (See Table 2 of the Horsburgh article):

Lifetime risk of reactivation TB %(95% CI)
Nonconversion (not a recent converter) 6% (3-12)
Recent conversion 9% (5-15)
Immunosuppressive Therapy 12% (2-64)
Old healed TB on x-ray 31% (10-93)
Advanced HIV 58% (26-100)
Condition Relative risk of reactivation (95% CI) (Table 3)
Advanced HIV 9.9 (8.7-11.3)
Old healed TB on x-ray 5.2 (3.4-8.0)
Chronic Renal Failure 2.4 (2.1-2.8)
Infliximab therapy 2.0 (0.7-5.5)
Poorly controlled DM 1.7 (1.5-2.2)

7. What would be the next steps for Dr. Koch?

Before treatment for latent TB, active TB must be ruled out by chest x-ray. If the x-ray shows changes consistent with TB, he should have three sputum samples examined for mycobacteria before treatment. If his sputum and his symptoms are negative, treat for latent TB. If his sputum is positive, treat for active TB. If he were clinically suspicious for active TB, you may need to "rule out" more aggressively with bronchoscopic specimens.

8. If we agree that Dr. Koch should be treated for latent TB infection, what are the specific treatment regimens?

Preferred therapy: Isoniazid (5 mg/kg/day; max 300 mg) daily (or 900 mg BIW with mandatory directly observed therapy) for nine months.

Special considerations:

- Hepatitis seen in 10-20%, more common above age 50
- Symptomatic hepatitis much less common. Discontinue therapy if LFT's 3x above upper limit of normal (ULN) and symptomatic, or 5x above ULN and asymptomatic. (if need to change therapy, use rifampin as below)
- ETOH should be avoided
- Baseline LFT testing not routinely recommended except in those at high risk for hepatotoxicity [ETOH, chronic liver disease, potentially hepatotoxic medications (e.g., phenytoin), pregnancy]; otherwise, monitor clinically q month.
- Neuropathy in 2%; institute pyridoxine (10-50mg) daily in those at high risk for peripheral neuropathy (ETOH, DM, uremia, malnutrition, HIV)
- Clinical monitoring for symptoms q month (and LFTs baseline only if suspect abnormality)

Secondary therapy options if compliance a concern but can only be used if the patient is HIV negative, has normal CXR, and is not a child.

- Isoniazid as above (or 900mg BIW if directly observed therapy) for six months.
- Isoniazid (5mg/kg/day; max 300mg) daily AND rifampin 600mg daily for three month course
- Based upon meta-analysis of 5 randomized controlled trials.
- Rifampin: 600mg qday for four months, if intolerant to INH or from high incidence INH resistance countries: Vietnam, Haiti, and Philippines
- Less evidence for efficacy than INH
- Rifampin plus pyrazinamide is no longer recommended given the increased risk of hepatotoxicity.

CASE THREE:

Mrs. Ghon is Mrs. Potts' twin sister. She had a PPD placed by your colleague after hearing about the events at her sister's school. She heard your advice to her sister, so did not get the test read until now, a week later, as she noticed the area where the PPD was placed is very red. Mrs. G denies any symptoms and reports she also emigrated to the U.S. along with her sister and was given the BCG vaccine as an infant. She also cannot recall a prior PPD test.

9. Describe how to read a PPD. Is this test valid after being read so late? How does the BCG vaccine complicate your interpretation?

How to read a PPD

- Read at 48-72 hours, but up to one week is OK (so this person's reading was OK)
- By induration, not erythema. One can palpate the borders and measure, but also one can use the ballpoint pen method: On both sides of the indurated region, draw a line toward the area of induration perpendicular to the long axis of the arm until an increase in resistance is felt.
- Ignore BCG status because it means a person is from a high risk country. Only 8% of those vaccinated at birth are PPD positive 15 years later, although those who have had a BCG booster may have PPD reactions that wane more slowly. Although these cases may be difficult to interpret, they are not a valid basis for dismissing a positive reaction.
- PPD is about 80-90% sensitive
- Anergy panel not recommended (not reliable)
- Note that new modalities are on the horizon. New testing options that may help clarify this issue include the interferon gamma release assay (IGRA). IGRA's are T-cell based assays that work on the assumption that T-cells of previously TB-infected individuals will produce a high level of IFN-gamma when re-exposed to TB-specific

CASE THREE CONTINUED:

antigens. IGRA's unfortunately do not distinguish between latent and active disease, but given their specificity to TB, they may also be useful in differentiating those with non TB-mycobacteria infection. Widespread use of these tests are limited given cost, the paucity of data in immunocompromised individuals, and lack of a gold standard to determine true sensitivity, although the CDC has recommended that one specific IGRA, the QuantiFERON-TB Gold test, can be used in all circumstances that TB-skin testing would be used.

You measure carefully and find she has an indurated area of 17mm.

10. What is her chance of reactivation assuming no significant past medical history?

Her chances of reactivation depend very heavily upon her age at testing:

Induration of >15mm w/o named high risk factors (From Table 2 Horsburgh article)

Age Lifetime risk of reactivation

0-5 13%

6-15 7%

16-25 8%

26-35 7%

36-45 4%

46-55 3%

56-65 3%

>66 2%

At age 50, her chances of reactivation are very low. She should not have been screened, as she should not be treated.

11. Should she be treated?

This case reemphasizes a very important concept highlighted in question one: A decision to test is a decision to treat—regardless of age. Therefore, it is important to only offer testing in high risk groups given the high rate of false positives that will occur in the normal population (due to the low prevalence of disease in the US). These recommendations from the American Thoracic Society, CDC, and Infectious Disease Society of America also hold true for the IGRA's described in question nine. However, given the current PPD result, you should consider an informed decision with the patient and offer treatment for latent TB infection, as some patients would be concerned and would not want to accept the low risk of non-treatment, however, generally, treatment of a non-conversion positive skin test in this low-risk patient is not recommended.

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