

Nucleic Acid Amplification Testing in the Diagnosis of Suspected Pulmonary Tuberculosis

A. Study Purpose and Rationale:

Airborne isolation for patients with suspected pulmonary tuberculosis (TB) is costly. Nevertheless, maintenance of patients with suspected TB on isolation is standard because of the high risk of transmission. The current approach to ruling out TB for the purposes of discontinuing isolation involves serial testing over three consecutive days of sputum samples via staining and microscopy for acid-fast bacilli (AFB) followed by culture for AFB. Because final AFB culture results can take up to 8 weeks, management decisions are often made based on the serial sputum smears, including whether to maintain patients on isolation.¹ However even obtaining sputum smear results requires several days. If there was an alternative diagnostic test to serial stained smear microscopy that could be performed more rapidly, but was not less sensitive, it is possible that a less costly and time consuming alternative approach to isolating patients for suspected TB could be developed.

The sensitivity of stained smear microscopy for AFB is reported as 50-80% for a single sample, and this increases with testing multiple samples, while the sensitivity of sputum culture for AFB is reported as 80-85%, again increasing with repeated testing². Nucleic acid amplification (NAA) tests are PCR based tests that can be used in the diagnosis of TB. There are two NAA tests that have been FDA approved for the testing of AFB smear-positive samples. The sensitivity of these tests in smear-positive samples is reported as approximately 95%, in smear-negative samples as approximately 50%, and overall sensitivity is reported as 75-80%^{3,4}. Currently, there is no consensus about the most appropriate way to use NAA testing in the diagnosis and management of TB⁵.

The purpose of this study is to test the hypothesis that NAA testing on one sputum sample for patients being worked up for suspected pulmonary tuberculosis is as accurate as serial AFB smear testing for the purposes of determining the need to maintain respiratory isolation while awaiting definitive culture results.

B. Study Design and Statistical Procedures

This will be a prospective study to evaluate the accuracy of NAA testing on the first sputum sample of patients maintained on airborne isolation for suspected pulmonary TB compared to serial stained smear microscopy for AFB. This will be a single center study performed at Milstein Hospital at Columbia University Medical Center (CUMC). The study subjects will be patients admitted to CUMC who are placed on airborne isolation for suspected pulmonary TB and who do not already have established diagnoses of TB.

All decisions regarding testing and treatment of study subjects will be made by the treatment team without consultation with any members of the study team. For any sputum samples sent to the laboratory for testing sufficient sputum specimen is available and in addition to testing ordered by the treatment team, if not already ordered by the treatment team NAA testing will be performed on the first sample, and if not already ordered by the treatment team AFB staining and microscopy and AFB culture will be performed on the first three samples.

Study subjects will only be included for statistical analysis if at least three sputum samples are obtained, and there is sufficient sputum specimen to perform all of the above described testing. For the purposes of the study, patients will be considered to have a positive NAA test if the first sputum sample is positive, they will be considered to have a positive AFB smear test if any of the first three stained smears for microscopy is positive, and they will be considered to have a positive AFB culture if any of the first three culture specimens is positive.

In order to power the study, it was assumed that in cases where results of the NAA test and the sputum smear microscopy test differed, 67% of the time, the NAA test would be correct based on the gold standard of AFB culture, and 33% of the time smear microscopy would be correct. Using a one-sample chi-square test for 80% power, for alpha of 0.05, 71 patients would be required in the group of patients in whom the NAA and smear test results differed. Assuming a sensitivity and specificity of 75% and 99% respectively for AFB smear and a sensitivity and specificity of 95% and 100% respectively for NAA in smear-positive patients and 50% and 99% respectively in smear-negative patients, at least 378 total subjects will be required.

C. Study Procedures

CUMC does not have a good system in place for obtaining induced sputum, so usually early morning sputum samples are used for the purposes of diagnostic testing. NAA testing will be performed using the Gen-Probe MTD test. Otherwise, study procedures will be as described above.

D. Study Drugs or Devices

N/A

E. Study Questionnaires

N/A

F. Study Subjects

Inclusion Criteria: All patients admitted to CUMC who are placed on airborne isolation for TB

Exclusion Criteria: Patients with known diagnosis of TB

G. Recruitment

N/A

H. Confidentiality of Study Data

All study data will be maintained on password-protected computers and secure storage media. Study subjects will be assigned a unique identifying number, and no private health information will be stored.

I. Location of Study

CUMC - Milstein Hospital.

J. Potential Risks

Although the study team will not communicate with the treatment team, it is possible that the treatment team will make clinical decisions based on tests performed on the sputum samples that were not ordered by them, and this carries a potential risk.

K. Potential Benefits

As in the case of potential risk, the treatment team will make clinical decisions based on tests performed on the sputum samples that were not ordered by them, and this could benefit the subject.

L. Alternatives

N/A

M. Compensation and Cost to Subjects

N/A

N. Minors and Research Subjects

As subjects will be patients admitted to Milstein Hospital, they will be older than 18 years of age.

O. Radiation or Radioactive Substances

N/A

References

1. Centers for Disease Control and Prevention (CDC). Health disparities experienced by black or African Americans--United States. *MMWR Morb Mortal Wkly Rep.* 2005;54(1):1.
2. Board of Directors, July 1999. *Diagnostic Standards and Classification of Tuberculosis in Adults and Children.* *Am J Respir Crit Care Med.* 2000;161(4 Pt 1):1376.
3. Dalovisio JR, Montenegro-James S, Kemmerly SA, et al. Comparison of the amplified Mycobacterium tuberculosis (MTB) direct test, Amplicor MTB PCR, and IS6110-PCR for detection of MTB in respiratory specimens. *Clin Infect Dis.* 1996;23(5):1099.
4. Dilworth JP, Goyal M, Young DB, et al. Comparison of polymerase chain reaction for IS6110 and Amplicor in the diagnosis of tuberculosis. *Thorax.* 1996;51(3):320.
5. Rapid diagnostic tests for tuberculosis: what is the appropriate use? American Thoracic Society Workshop. *Am J Respir Crit Care Med.* 1997;155(5):1804.