Using Nucleic Acid Amplification Techniques and Routine Clinical Data to Predict Pulmonary Tuberculosis in an Urban Teaching Hospital

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A. Study Purpose and Rationale

Cases of tuberculosis in the United States, which had been declining for decades, rose again in the late 1980s. This resurgence of tuberculosis coincided with the emergence of HIV and the subsequent increase in the number s- of immunosuppressed persons living in the US. Crowded institutionalized settings such as homeless shelters or prisons are thought to be locales where tuberculosis is often transmitted from one person to another. Nosocomial transmission, or transmission of tuberculosis within health care settings, such as between in-patients or from in-patients to health care workers, was thought to play a part in this resurgence as well. Several papers noted that the identification and respiratory isolation of hospitalized patients with pulmonary tuberculosis was often delayed, and thus contributed to the nosocomial transmission of tuberculosis. The CDC subsequently published guidelines to bolster respiratory isolation efforts In hospitals and help reduce nosocomial transmission. Their guidelines recommend that patients be kept in respiratory isolation until three negative results of acid-fast bacillus smears, obtained on three separate days, have been documented.

In current practice, the criteria used by physicians to identify which patients should be isolated is rather unclear. It appears that if there is "clinical suspicion" for pulmonary tuberculosis, patients who are hospitalized are placed in respiratory isolation. This approach lowers the threshold for respiratory isolation so that patients with the disease would not be missed, and was an integral part of the public health response to the rise of pulmonary tuberculosis. The cost of placing patients in respiratory isolation, however, is not insignificant. There are financial costs to placing patients in specialty outfitted private isolation rooms. Furthermore, respiratory isolation can serve to alienate patients who are entering an unfamiliar medical environment. In addition, several studies have shown that there are significant numbers of patients with pulmonary tuberculosis who are not promptly placed in respiratory isolation during hospitalization. Thus efforts to identify clinical parameters available at time of admission to predict the presence of pulmonary tuberculosis could be of clinical value; this information could both to reduce unnecessarily isolating patients who are at low risk for pulmonary tuberculosis and ensure that patients at high risk for pulmonary tuberculosis are isolated.

A number of papers have attempted to identify such clinical parameters. Yet their impact on clinical practice has been limited. There have been some important developments in the past few years in the diagnosis of mycobacterium tuberculosis, in particular, the emergence of nucleic acid amplification assays. These assays are performed on patients' sputum samples, and they are fast. Studies show that they are very specific for mycobacterium tuberculosis and when clinical suspicion for tuberculosis is low, can also be a relatively sensitive test as well. In other words, one such test, called the E-MTD, or enhanced mycobacterium tuberculosis direct test, could augment our current attempts to better screen patients when there is suspicion for pulmonary tuberculosis.

The objective of this study is also to identify factors prospectively which may assist physicians in differentiating those patients that need to be isolated from those patients which are at very low risk for pulmonary tuberculosis and thus need not be isolated. This study, however, will add to the existing literature by incorporating the use of newer technology of nucleic acid amplification for mycobacterium tuberculosis (E-MTD) to augment traditional predictors of pulmonary tuberculosis.

B. Study Design and Statistical Analysis

This is a longitudinal, prospective study. It is observational, but also intended to study the performance of the E-MTD diagnostic test in this population. Participation in the study is not intended to affect the care of the patients. The physicians taking care of the patient will not be aware of the results of the first sputum analysis for E-MTD assay. When the decision is made to isolate the patient, usually by the physicians in the emergency room, they will be asked to notify the study coordinators. The study coordinator will then interview the admitting physicians and administer a questionnaire to the patient, obtain data, and order certain laboratory studies.

The coordinators will obtain the following information:

- Age
- Sex

- History:
- TB exposure
- Recent institutionalization (in last 3 months): jail, shelter, homeless
- History of positive PPD
- weight loss (10% in last 6 months)
- Night sweats (3 weeks)
- Fevers
- Cough
- Hemoptysis Shortness of Breath

- Physical Exam:
- Temperature (<38.5, 38,5-39, >39)
- Crackles on Exam

- Laboratory Data:
- white blood cell count
- arterial blood gas

- Chest X-Ray:

Team's Clinical Suspicion for Pulmonary Tuberculosis: probability of having pulmonary tuberculosis is rated from 0- 100%.

All patients will have sputum analyzed when the decision is made to isolate the patient. That first sputum sample will undergo standard staining for AFB and analysis for EMTD. The physicians will be blinded to the results of the E-MTD assay, so that they will not use that information to remove a patient early from isolation and/or not collect three sputum samples for smear and culture.

In total, all patients will have three sputum samples sent to the microbiology laboratory on three separate days. These samples will be stained for acid-fast bacillus and will also be sent for culture.

Univariate analyses will be performed for each of the clinical information collected at study entry.

Finally, multiple logistic regression analysis will be performed to determine if the parameters assessed are independently predictive of pulmonary tuberculosis. Using standard statistical software, each independently predictive variable including E-MTD will be weighted in order to develop a scoring system to predict pulmonary tuberculosis.

C. Study Procedures

The study procedures include routine phlebotomy at time of isolation, and this blood draw would be obtained regardless of participation in the study or not.

D. Study Drugs

None used.

E. Medical Devices

None used.

F. Study Questionnaires

The questionnaire will assess the following:

- Age
- Sex

- History:
- TB exposure
- Recent institutionalization (in last 3 months): jail, shelter, homeless
- History of positive PPD
- weight loss (10% in last 6 months)
- Night sweats (3 weeks)
- Fevers
- Cough
- Hemoptysis
- Shortness of Breath

The admitting team will also be asked to rate its Clinical Suspicion for Pulmonary Tuberculosis: rate from 0-100.

G. Study Subjects

Consecutive adult patients who are admitted to Columbia-Presbyterian Hospital and placed in respiratory isolation because of suspicion of pulmonary tuberculosis will be prospectively studied. Patients should be > 18 years of age. Vulnerable populations which might be included in the study in disproportionate numbers are patients with HIV infection since this population is at higher risk for developing active tuberculosis. They ~will be protected in that their diagnosis will be kept strictly confidential. As for other subjects, their participation will be kept anonymous and each participant will be identified by a unique random study number.

This study is not to be restricted by gender or race,

H. Recruitment of Subjects

When the decision is made by the primary physician to place the patient in respiratory isolation, that physician will approach the patient with the option to participate in the study. This will likely be the attending physician or resident physician in the Emergency Department or the resident physician of the admitting Internal Medicine team. If the patient agrees, then the study coordinator will approach the patient and discuss the nature of the study, and present to him/her the option of participating.

I. Confidentially of Study Data

All patient data will be kept confidential and will be identified by a unique study patient number. The data will be kept securely and will be accessed only by the investigators.

J. Potential Conflict of Interest

The investigators have no proprietary interest in any drug, device, or procedure under investigation and will not benefit financially or in any other way from the results of the investigation.

K. Location of the Study

The study will be located at New York Presbyterian Hospital - Columbia Campus. The two sites of the study will be in the Emergency Department and the floors of Milstein Hospital. Letters of approval will be obtained from the Chairpersons of the Department of Emergency Medicine and Internal Medicine.

L. Potential Risks

In drawing laboratory studies, there is always the small risk of bleeding and infection associated with standard phlebotomy. This risk, however, is not one incurred solely for the study, as the patient would be getting standard admission lab studies regardless of participation in the study.

M. Potential Benefits

The patient will not derive any direct benefit from the study. However, in assisting in collecting this data, the patient would contribute to improving isolation protocols in the future, and thus limiting the number of nosocomial transmission of tuberculosis and also limiting the number of patients who may be unnecessarily isolated.

N. Alternative Therapies

This study does not involve the use of experimental therapies.

O. Compensation to Subjects

None, since standard care will be given.

P. Costs to Subjects

There will be no cost to the subjects. The study is not intended to alter the participants' medical care.

Q. Minors as Research Subjects

There will be no minors participating in this study.

R. Radiation or Radioactive Substances

There will be no use of radioactive substances in this study.