Changing TB Isolation Practices: Consensus Statement Concerning the Incorporation of Molecular Testing

<table>
<thead>
<tr>
<th>Facility</th>
<th>Location</th>
<th>Time Period</th>
<th>Total Cases</th>
<th>Resistance Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital A</td>
<td>Miami</td>
<td>1988-91</td>
<td>65</td>
<td>INH, RIF (EMB, ETA)</td>
</tr>
<tr>
<td>Hospital B</td>
<td>NYC</td>
<td>1989-91</td>
<td>35</td>
<td>INH, SM (RIF, EMB)</td>
</tr>
<tr>
<td>Hospital C</td>
<td>NYC</td>
<td>1989-92</td>
<td>70</td>
<td>INH, RIF, SM (EMB, ETA, KM, RBT)</td>
</tr>
<tr>
<td>Hospital D</td>
<td>NYC</td>
<td>1990-91</td>
<td>29</td>
<td>INH, RIF (EMB, ETA)</td>
</tr>
<tr>
<td>Hospital E</td>
<td>NYS</td>
<td>1990-91</td>
<td>7</td>
<td>INH, RIF, SM (EMB, ETA, KM, RBT)</td>
</tr>
<tr>
<td>Hospital F</td>
<td>NYC</td>
<td>1990-91</td>
<td>16</td>
<td>INH, RIF, SM (EMB, ETA, KM, RBT)</td>
</tr>
<tr>
<td>Hospital I</td>
<td>NJ</td>
<td>1990-92</td>
<td>13</td>
<td>INH, RIF (EMB)</td>
</tr>
<tr>
<td>Prison System*</td>
<td>NYS</td>
<td>1990-92</td>
<td>42</td>
<td>INH, RIF (SM, EMB, ETA, KM, RBT)</td>
</tr>
</tbody>
</table>

Total Cases = 277

*24 Prison cases are also counted with Hospital C

INH=Isoniazid; RIF=Rifampin; SM=Streptomycin; EMB=Ethambutol; ETA=Ethionamide; KM=Kanamycin; RBT=Rifabutin
Staff TST in Four Hospitals with MDR-TB Outbreak

<table>
<thead>
<tr>
<th>TESTED</th>
<th>CONVERSION</th>
<th>PERCENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>13</td>
<td>33</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>50</td>
</tr>
<tr>
<td>108</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>50</td>
</tr>
</tbody>
</table>

MDR-TB in Healthcare Workers

11 were HIV-positive
8 were HIV-negative

9 died

7 were HIV-positive
6 deaths related to MDR-TB
2 were HIV-positive deaths due to cancer and drug overdose

Median Age 37
What factors contributed to the outbreak?

Breakdown of Source Control

- Convergence of highly susceptible, immunosuppressed patients with patients with active tuberculosis
- Delayed recognition of tuberculosis
- Delayed recognition of multidrug resistance
- Delayed initiation of effective anti-tuberculosis therapy
- Lapses of infection control practices
  - Delayed isolation
  - Poor ventilation
  - Lapses in respiratory isolation
  - Inadequate duration of isolation
  - Inadequate precautions for cough-inducing procedures

- Recommended the Use of Administrative, Respiratory Protection and Engineering Procedures to prevent nosocomial transmission of TB

Removing Patients From A.I.I.

- Traditionally used 3 sputum smears, at least one collected in the early morning
  - Recommendation of 3 negative smears to remove from isolation not based on performance studies but historical data on risk of transmission from smear negative cases (30-50% of positive PPDs among smear (+) vs ~5% among smear (-)) as well as studies showing sensitivity of smears to diagnose TB (~50-60%)¹

¹ Sepkowitz CID 1996:23:954-62
Infectiousness of TB

- Not all patients with active TB are contagious
  - Only about 20-50% of patients with TB are thought to be able to transmit disease (1-3)
  - Those that are contagious can and at times do infect a lot of individuals-"super transmitters"
  - Need to identify those that are contagious especially in congregate setting where the spread of TB may be even greater given the environment (especially in hospitals or other environments where there are immunosuppressed individuals)

2. Snider et al ARRD 1985:325
3. Riley et al ARRD 1962:511

Infectiousness

- Directly related to number of bacilli-laden droplets expelled into the air
- Infectiousness usually declines rapidly with treatment
  - However, some remain infectious for weeks or months
Infectiousness

Patient factors associated with infectiousness:

• Coughing
• Cavity in the lung
• Sputum smears positive for acid-fast bacilli (AFB)
• TB disease of the lungs, airway, or larynx
• Undergoing cough-inducing or aerosol-generating procedures
• Not receiving adequate therapy
• Culture positive


• Recommended the Use of Administrative, Respiratory Protection and Engineering Procedures
  • Published studies have documented the effectiveness of these guidelines with a decrease in the number of occurrences of nosocomial transmission with a concomitant decrease in the number of staff conversions\textsuperscript{1,2}

\textsuperscript{1}Grant Am J Infect Control 1998;26:224-31
\textsuperscript{2}Welbal et al. Am J Infect Control 2009;37:668-73
Hospitalization for TB

- Cohort studies have estimated that 50%–75% of TB patients are hospitalized for TB, and 83% of these hospitalizations occur at the time of TB diagnosis.

- From 1995 to 2006, the number of hospitalizations with a principal diagnosis of TB decreased 41% from 15,000 to 8,800; the number of hospitalizations with a secondary diagnosis of TB decreased 10% from 55,000 to 49,700.

- The average length of stay for a TB hospitalization is between 9 to 17 days, and the estimated cost per hospitalization is $6,000 to $27,000.

Problems with Isolation

- Patients are kept on average 5-7 days in isolation for TB
- Limited number of A.I.I. rooms in most facilities
- A systemic review showed patients in isolation tend to:
  - Be seen less by HCWs
  - Have an 8 fold increase in adverse effects
  - Have a negative perspective of their care

- Delay in getting the proper procedure performed
- Most people admitted into isolation DO NOT HAVE TB
Removing Patients From A.I.I.

- Traditionally used 3 sputum smears collected daily in the early morning
  - Took a long time so studies were performed suggesting collection can be performed every 8 hours
  - Not sensitive 50-90%
  - Not specific 70-90% (depending on NTM and TB prevalence)

Notice to Readers

Update: Nucleic Acid Amplification Tests for Tuberculosis

On September 30, 1999, the Food and Drug Administration approved a reformulated Amplicor Mycobacterium Tuberculosis Direct Test® (MTD) (Cepheid®, Sunnyvale, California) for detection of Mycobacterium tuberculosis in acid fast bacillus (AFB) smear-positive and smear-negative respiratory specimens from patients suspected of having tuberculosis (TB). MTD and one other nucleic acid amplification (NAA) test, the Amplicor® Mycobacterium Tuberculosis Test (Amplicor) (Roche® Diagnostic Systems, Inc., Branchburg, New Jersey), previously had been approved for the direct detection of M. tuberculosis in respiratory specimens that have positive AFB smears. This notice updates the original summary published in 1996 (1) and provides suggestions for using and interpreting MTD, which were not included in the initial product documentation of MTD. TB.

MMWR 7/7/2000
Removing TB suspects from respiratory isolation: Efficiency of a single sputum NAAT compared to serial smears

Processing: 7 days; NAAT 6 days; broth medium monitored 7 days
NAAT (first specimen) - AFB and culture (3 specimens) - 493 pt [46 TB]

<table>
<thead>
<tr>
<th></th>
<th>Tuberculosis (46)</th>
<th>No TB (447)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Sputum NAAT</td>
<td>High ROTT (35)</td>
<td>Low ROTT (11)</td>
</tr>
<tr>
<td>Positive</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Negative</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

ROTT = Risk of TB transmission

GenExpert A.I.I. Studies

- In a prospective study of 139 patients (10 cases of TB) admitted to rule out TB (30% HIV+)\(^1\), serial sputum AFB smear microscopy and a single concentrated sputum Xpert had identical sensitivity (89%) and similar specificity (99%) referenced to culture positivity.

- In another study of 207 admissions to A.I.I. (23% HIV+)\(^2\), Xpert detected 5 of 6 culture-confirmed cases on the initial submitted specimen; the sixth culture-positive case was detected on a second specimen. Sensitivity again was similar for Xpert and AFB smear: 93%.

FDA Approval of GenExpert for A.I.I.

- “In February 2015, the U.S. Food & Drug Administration (FDA) approved a change in the package insert for the Xpert to reflect expanded claims related to A.I.I.. According to this change, negative results using this assay on “either one or two sputum specimens” can be used as an alternative to examination of serial acid-fast stained sputum smears to aid in the decision to discontinue A.I.I. for patients with suspected pulmonary TB”
Diagnosis of TB

- Detection of organisms
  - Need to have enough biomass to identify the organism
WE ARE NOT GOING TO SPEAK TODAY ABOUT NUCLEIC ACID AMPLIFICATION TECHNIQUES FOR THE DIAGNOSIS OF TB

• MUST DISTINGUISH AS THESE SCENARIOS ARE BEING CONFUSED IN THE TB COMMUNITY
• DISTINGUISH BETWEEN A DIAGNOSTIC TOOL AND A DECISION MAKING TOOL
• HOWEVER IN THE PROCESS OF MAKING A.I.I. DECISIONS STILL MAY BE TRYING TO DIAGNOSE TB AS INDICATED

Xpert MTB/Rif for Airborne Isolation Decisions

It is a tool trying to predict infectiousness which in hospitals has been traditionally done by 3 negative smears AND the clinical appropriateness to be removed from isolation
NTCA/APHIL White Paper

- Represents a significant document which is meant to be a practical consensus statement for the implementation of the FDA approval for the GenExpert for its Airborne Infection Isolation indication
Community Standard for GenExpert for A.I.I.

- It will be up to each state TB program in partnership with Hospital Infection Control Practitioners to “set the community standards” for the use of GenExpert for A.I.I. through their program’s Policies and Procedures (Recommended Operating Procedures)


- Dr. John Bernardo- “Consensus Statement on the Use of Cepheid Xpert MTB/RIF® Assay in Making Decisions to Discontinue Airborne Infection Isolation in Healthcare Settings”
- Dr. David Warshauer- “Working with Your Laboratory”
- Dr. Neha Shah- “Xpert Consensus Statement: The Algorithm”
Infectiousness and Tuberculosis

• The infectiousness of a TB patient is directly related to the number of droplet nuclei carrying *M. tuberculosis* (tubercle bacilli) that are expelled into the air.
  ▪ ... Infection occurs when a person inhales droplet nuclei containing *M. tuberculosis*

• Quantitative Sputum Smear Microscopy traditionally has been used as an index of infectiousness. However:
  ▪ Limited sensitivity (10⁻³ CFU/ml); non-specificity
  ▪ Poor turnaround time

* CDC, 2005. Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health-Care Settings

John Bernardo, MD

Current Practice

- Persons with presumed pulmonary tuberculosis are placed into airborne infection isolation (A.I.I.) and are assessed by smear microscopy on 3 respiratory specimens collected 8–24 hours apart
  - Three AFB-smear negative sputum samples generally are used to support clinical decisions to discontinue A.I.I.

Direct Detection of MTb Complex: Nucleic Acid Amplification Testing (NAAT)

- **NAA assays: 3 platforms approved by FDA**
  - Amplicor®-Roche: DNA
  - MTD®-GenProbe: r-RNA
  - Cepheid-GeneXpert MTB/RIF®: DNA
- **Advantages**
  - High sensitivity & specificity for MTb complex
  - TAT generally ≤ 48 hr
- **Disadvantages**
  - $ Costly
  - No indication of viability of organism or of susceptibility
- **FDA-approved ONLY for respiratory secretions (sputum, bronchial)**
  - Smear +/- patients, ≤ 7 days therapy (Xpert® sputum in adults only; July, 2013)
- **“Off-label” use**
  - Non-respiratory applications

* No longer manufactured

**GeneXpert® MTB/RIF**

- Closed, self-contained and automated platform
- rt-PCR-based amplification of MTb DNA: Molecular Beacons
  - 131 CFU/mL clinical LOD
  - Rapid TAT: 2-4 hours
- Boehme NEJM 9/9/10: 1730 pulmonary TB suspects
  - Sensitivity: 551/561 sm-pos (98.2%); 124/171 sm-neg (72.5%)*
  - Specificity: 604/609 (99.2%)

* increased to 90% with repeat testing

---

**Nucleic Acid Amplification Testing and A.I.I. Decisions**

- In February, 2015, the FDA approved a change in the package insert for the GeneXpert to reflect expanded claims related to A.I.I.*

Specifically:

... results using this assay on “either one or two sputum specimens” can be used as an alternative to examination of serial acid-fast stained sputum smears to aid in the decision to discontinue All for patients with suspected pulmonary TB.

* CDC. MMWR, 2/26/2015
Xpert and A.I.I. Labelling Change:
The Basis

- Improved sensitivity and specificity of NAA versus sputum AFB smear in early detection of culture-confirmed pulmonary TB in adults.
  - Negative NAA test results (Xpert and other platforms) from 1 or 2 sputum specimens are highly predictive of results of 2 or 3 AFB sputum smears being negative
  - Use of NAA could provide cost savings by reducing patient time in All and length of hospital stay
- Data (unpublished* at time of FDA approval) from 3 countries
  - Xpert versus sputum smear and culture: In 638 US participants
    - Sensitivity (culture-pos MTB)
      - First Xpert: 85.2% (96.7% in AFB sm-pos; 59.3% in AFB-sm-neg sputum)
      - 2nd Xpert: 91.1% (100% sm-pos, 71.4% sm-neg)
    - NPV (neg Xpert, sm and culture neg MTB)
      - First Xpert: 99.7%
      - 2nd Xpert: 100%


Xpert and A.I.I. Labelling Change:
The Details

- Patient selection: Tuberculosis is a real diagnostic consideration
- Sputum Quality: Critical both for the diagnosis of pulmonary TB and for the performance of this assay
  - Spontaneously expectorated sputum: should be representative of secretions from the lower respiratory tract; should appear purulent (not saliva)
  - Induced sputum: purulence is desirable, but induced sputum may have the appearance of saliva, due to the saline
- Laboratory Considerations
  - Follow protocol for collection, transport, and processing of raw sputum
  - NAA testing is not a substitute for smear microscopy and culture
    - Samples still must be submitted for diagnostic purposes – isolation, identification and drug susceptibility testing – and for genotyping.
How to collect a spontaneously produced sputum sample*

- Coach the patient and supervise at least for the first sputum
- Patients should understand that sputum is material that is brought up from the lungs - nasal secretions and saliva or spit are not acceptable
- Sputum should be collected in an airborne isolation room or a negative-pressure sputum collection booth, or it may be collected outdoors

The patient should follow these steps:

1. Rinse the mouth with filtered bottled, or sterile water. Tap water may contain nontuberculous mycobacteria and should not be used.
2. Inhale deeply, and exhale slowly. Repeat 2 more times.
3. After the 3rd breath, inhale completely and try to cough hard to produce sputum from deep in the lungs. You may feel a rattle or tickle as the sputum moves up from the lungs into your throat.
4. Expectorate the sputum into a sterile cup. When you have at least 5 mL (1 teaspoon) of sputum, replace the lid on the container and tighten it so it does not leak.
5. Remain in the booth or room until you are cleared to leave.

* NTCA and APHL Consensus Statement, Appendix IIb; see Appendix IIa for Nebulized Sputum Induction

Interpretation of Results

- Results must be interpreted the context of the clinical and radiographic presentation and the clinician’s suspicion for infectious TB
  - Test sensitivity is subject to a variety of factors:
    - sampling (e.g., poor specimen quality)
    - inappropriate transport and processing of the specimen
    - errors in performance of the assay
    - errors in labelling or reporting
- Results are reported to the requesting clinician and to infection control as either:
  - “*Mycobacterium tuberculosis* complex Detected”,
  - “*Mycobacterium tuberculosis* complex NOT Detected”, or
  - “Invalid” (test failure)
- Decisions to remove a person from A.I.I. must comply with local jurisdictional public health laws and regulations where applicable

John Bernardo, MD

Xpert and A.I.I. Decisions

**STEP 1.**
- Collect sputum for AFB smear microscopy, AFB culture, and Xpert

Positive Xpert result:
- AFB smear detected
- TB likely
- Continue A.I.I.

Negative Xpert result:
- AFB smear not detected
- TB unlikely
- Infectious TB not excluded
- Continue A.I.I.

One Step Xpert:
- TB unlikely
- Continue A.I.I.

**STEP 2.**
- Correct nasal swab specimen at least 1 hour after first specimen for AFB smear microscopy, AFB culture, and Xpert

Positive Xpert result:
- AFB smear detected
- TB likely
- Continue A.I.I.

Negative Xpert result:
- AFB smear not detected
- TB unlikely
- Infectious TB not excluded
- Continue A.I.I.

Note: This algorithm is intended to complement PPD testing. AFB smear results are not used to determine TB status. AFB culture results are used to confirm the presence of AFB in the specimen.
Limitations

- This FDA-approved application applies only to the Xpert assay performed on raw sputum or concentrated sputum sediment prepared from expectorated or induced sputum.

- Collection of quality sputum specimens is critical to obtaining accurate Xpert, AFB smear, and culture results.

- NAA testing should NOT be used solely to determine when a laboratory confirmed case of pulmonary TB can be released from A.I.I.

- This application applies only to A.I.I. in healthcare facilities.

- FDA labelling approval was based upon research investigations of persons aged 18 years and older.

Acknowledgments

The A.I.I. Working Group:

Emily A. Anderson
Heidi Behm
Maria Dalbey
Phil Griffin
Kenneth C. Jost
Quratulain Kizilbash
Diana Nilsen
Randall Reves
Max Salfinger

David Ashkin
Robert L. Brawley
Andrea Forman
Frances Jamieson
Jimmy Keller
Maureen Murphy-Weiss
Susan Ray
Barbara Russell
Caitlin Reed

Co-Chairs:
John Bernardo
David Warshauer

NTCA:

Jennifer Kanouse
Donna Wegener

APHL:

Anne Gaynor
Paul Zell

CDC:

Neha Shah
Brian Baker

John Bernardo, MD

07/20/2016

GeneXpert

- Easy to use FDA approved automated real-time PCR system
- Available in many laboratories
  - Used for other infectious agents in addition to *M. tuberculosis* complex
Specimen Requirements

- Quality specimen and adequate volume are critical
- Expectorated or induced sputum
- Specimen requirements may vary among laboratories
  - One specimen for both Xpert and smear/culture, 5-10 ml
  - Allows interpretation of Xpert in conjunction with AFB smear result
- Two specimens
  - One for Xpert, 1-2 ml
  - Separate specimens for smear/culture

Reporting

- MTB Detected
- MTB Not Detected
- Invalid
  - Presence or absence of MTB could not be determined due to failure of the control
- Rifampin resistance detected
- Rifampin resistance not detected
- Rifampin resistance indeterminate
Reporting

• May include interpretive comments
  – E.g. A result of MTB not detected indicates infectious TB is not likely. Make the decision to discontinue airborne infection isolation in conjunction with clinical data.

• Who to report to?
  – Health care provider
  – Infection preventionist
  – TB Control Program
  – Local Public Health

Turn-around Time Expectations

• Will vary with how laboratory is structured and staffed
  – Xpert system available onsite and raw sputum tested----2-3 hr
  – Xpert system offsite and raw sputum tested
    • Factor in transport time plus 3-4 hr
  – Xpert performed in the Mycobacteriology lab using processed sediment ----5 – 24 hr
Xpert Consensus Statement
Part 1
The Algorithm

Neha Shah, MD MPH
Tuberculosis Control
California Department of Public Health
Centers for Disease Control and Prevention

July 2016

Disclosures

• No affiliation or financial relationship with any of the tests or companies mentioned in this presentation

• This presentation does not necessarily represent the official position of the US Centers for Disease Control and Prevention
Case 1

- 91 year old male from Philippines
- Remote history of TB per patient
- Hemoptysis but no other TB symptoms
- Xpert positive

- Discontinue Isolation?
Case 1

- 18 year old male from China
- IGRA negative
- CXR with LUL calcification consistent with granuloma disease
- Xpert negative
Case 2

- Second Xpert negative
Case 2

18 year old from China
IGRA negative
CXR with LUL calcification consistent with granuloma disease

Discontinue isolation?

Positive Xpert result:
- Mtb complex detected
- TB likely
- Stop Xpert testing and continue A.I.I.

Negative Xpert result:
- Mtb complex not detected
- Infectious TB not likely
- Make the decision to discontinue A.I.I., in conjunction with clinical data

Invalid Xpert result:
- Continue A.I.I. and use AFB smear results with Xpert result and clinical judgment to make decision to discontinue A.I.I.
Case 3

- 18 year old male from China
- IGRA positive
- CXR with LUL calcification consistent with granuloma disease
- Nonproductive cough
- Xpert negative
Case 3

• Second Xpert negative
Case 3

- Discontinue isolation?

- What if he had hemoptysis instead of dry cough?

- What if it was winter time and everyone in dorm had a cough?

- What if he was smear positive?
Case 3

- Discontinue isolation?

- REPORT TO HEALTH DEPARTMENT

Case 4

- 40 year US-born individual
- TST positive
- Had minimal contact to TB case
- Nonproductive cough
- CXR: minimal infiltrates RML
- Xpert negative
Case 4

- **Second Xpert positive**
Case 4

**Summary**

- Historically 3 smears used to determine discontinue of A.I.I.
- Can now use Xpert
- Consensus statement developed to assist with determining criteria to discontinue isolation
Summary

• DO NOT use consensus statement as a diagnostic algorithm

• If smells like TB, it is still TB

• Keep public health TB program aware of any suspected TB cases

Thank you