The role of polymerase chain reaction (PCR) testing for early discontinuation of respiratory isolation for hospitalized patients with possible *Mycobacterium tuberculosis* infection

Early identification and isolation of patients with pulmonary *Mycobacterium tuberculosis* (TB) infection are essential components of any TB control plan. However, rapid diagnosis of TB has historically not been possible, because TB takes weeks to grow in culture. As a result, healthcare providers use clinical judgment to identify patients at potential risk for TB. Traditionally, patients with suspected TB are placed on airborne isolation until 3 successive sputum acid-fast bacilli (AFB) smears are negative. This practice comes with great expense. Only a fraction of patients placed in airborne isolation for suspected TB are ultimately confirmed to have TB. Obtaining and examining sputum samples takes, on average, 5 days to complete and costs an additional $2000 per patient (1). Furthermore, airborne isolation increases risk of adverse events for patients (2).

A polymerase chain reaction (PCR) test called Gene Xpert MTB (“Xpert”, Cephied, Sunnyvale CA) was initially developed to aid in rapid diagnosis of TB infection and detection of drug resistance. The FDA approved Xpert for use in place of serial AFB smears to help with decision making about the timing of discontinuation of empiric use of airborne isolation precautions in 2013. This month’s newsletter will:

- Discuss the evidence for using Xpert results in isolation strategies for suspected TB
- Compare and contrast the utility of AFB smear tests and PCR test results
- Discuss how your facility may benefit from the use of PCR for managing isolation of patients with suspected TB.

**PCR in addition to smears: The evidence**

Three studies have evaluated the utility of Xpert compared to sputum smears and the impact of Xpert testing on the duration of airborne isolation in patients with suspected TB.

The first study, done by Chassion et al. (3), prospectively and hypothetically evaluated the impact of the addition of a single Xpert test to sputum samples on duration of airborne isolation in a cohort of 237 patients requiring respiratory isolation for TB at San Francisco General Hospital over a one-year time period. A total of 142 isolated patients provided sputum for AFB smears, Xpert testing, and culture. In total, 10 patients had positive cultures for *Mycobacterial* species; 9 of 10 patients had culture-positive TB (9/142). Eight of these nine patients had both a positive AFB smear and a positive Xpert PCR test. One patient had a negative AFB smear, a negative Xpert PCR test, and a positive culture for TB. One
additional patient had a positive AFB smear, but negative Xpert PCR test and cultures revealed a non-tuberculosis mycobacterium.

The authors also hypothetically estimated the cumulative amount of isolation time saved if a single Xpert PCR test were used to guide decisions about airborne isolation discontinuation. They concluded that addition of Xpert PCR test to diagnostic strategies would have saved 258 days of isolation for the 133 patients with possible TB who were isolated during the study period but turned out to have negative evaluations.

Lippencott et al (2) performed a similar prospective cohort study to evaluate the time to airborne isolation discontinuation in patients with suspected TB using 4 different strategies: (a) 3 negative AFB smears, (b) 1 negative Xpert PCR test, (c) 2 negative Xpert PCR tests, or (d) 3 negative Xpert PCR tests. Treating physicians were blinded to Xpert PCR test results. A total of 206 patients were admitted for TB evaluation during the study period. These 206 patients provided 546 samples for AFB smear and culture and 505 samples for Xpert analysis. Six patients (6/206) had culture-confirmed TB. The use of the result of single Xpert PCR test to guide discontinuation of isolation missed 1 case of TB. The remaining 3 strategies identified all patients with culture-confirmed TB. The authors concluded that requiring 2 consecutive Xpert tests would 1) identify all cases of TB and 2) result in significantly shorter duration of isolation compared to AFB smear method (68 hrs vs. 41.8 hrs). An important limitation of this study was the use of hypothetical times to estimate reductions in the duration of isolation.

Floe et al (1) evaluated the effect of combining Xpert PCR testing with traditional AFB smears on 1) duration of time on isolation and 2) the comparative sensitivity and specificity of the two diagnostic tests in a cohort of 1274 Danish patients with culture-positive TB during 2002-2011. Ultimately, Floe et al identified 12 “discordant” smear positive/PCR negative patient results. However, the sputum sample used for smears was NOT the same sample as the one used PCR in these 12 patients. Also the, sputum samples that were smear positive in these 12 patients were “low grade” positive tests. The authors concluded that use of initial single PCR sputum test of sputum would: 1) shorten isolation by approximately 3 days per patient, and 2) provide a relatively safe and sensitive way to diagnose TB. However, there were important limitations to this study: 1) all study results came from a reference laboratory that processed a high volume of TB samples, and 2) this was a retrospective study that did not evaluate baseline isolation practices. Furthermore, the authors did not analyze concordance rates between 2 or more PCR results and smears—a step likely to improve sensitivity of the PCR test in patients with low grade smears.

**Compare and contrast: Smear versus PCR**

Xpert PCR testing for TB is more sensitive than AFB smear tests and, as discussed above, it leads to earlier discontinuation of airborne isolation for patients than when isolation discontinuation is based on results of AFB smears. However, Xpert PCR test technology is more expensive and requires specially trained staff. Therefore, Xpert may not be practical or cost-effective for hospitals with few cases of suspected TB.
Table 1. Comparison between conventional testing methods and Xpert PCR for the diagnosis of TB

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<tr>
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<th>Smear</th>
<th>Xpert PCR</th>
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<tr>
<td><strong>Sensitivity</strong></td>
<td>Approx. 60% for single smear (requires 10 to 4 CFU for + stain!)</td>
<td>98% for smear +/culture + TB</td>
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<td></td>
<td></td>
<td>76% for smear-/culture +TB</td>
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<tr>
<td><strong>Specificity</strong></td>
<td>Not specific for TB</td>
<td>99-100% specific for TB</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$</td>
<td>$$$</td>
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<td><strong>Validation</strong></td>
<td>Valid on multiple sample types: sputum, BAL, and gastric samples can all be used</td>
<td>Only validated for sputum. BAL, gastric samples cannot be not tested</td>
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<td><strong>Work time</strong></td>
<td>Approximately 1.5 hrs of tech labor, but usually a half a day to complete.</td>
<td>3 hours total: 1 hr technician set-up time, 2 hours for the run</td>
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<tr>
<td><strong>Other considerations</strong></td>
<td></td>
<td>Requires in-house validation and training prior to use</td>
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<td></td>
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<td>Requires an adequate volume of sputum samples—ie, running daily batches</td>
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**Should your facility use Xpert PCR test?**

Hospital personnel should ask the following questions prior to initiating Xpert testing.

1. **How many patients with suspected TB are placed on isolation per month or per year?**

   The cost-benefit of Xpert testing depends on the annual number of patients that are placed in isolation for TB evaluation. One study estimated that, after initial costs, Xpert testing can save approximately $2200 per hospitalized patient hospitalized that is placed on respiratory isolation for possible TB (4). However, the authors of another study pointed out that cost savings occurs only if Xpert tests are run daily 5 days a week (3).

2. **Does your institution have the “platform” for PCR testing in use in your laboratory?**

   If your laboratory currently uses Xpert for *Clostridium difficile* testing, the initial costs of initiating Xpert testing for TB will be substantially reduced. If not, initial costs of initiating sputum PCR testing will be considerable.

   Regardless if your facility currently uses the Xpert PCR “platform”, the use of Xpert PCR testing must be validated at your institution prior to adoption for daily use.

3. **Does your institution have available trained personnel to perform Xpert PCR tests on a daily basis?**

   Trained microbiology personnel are a prerequisite for the cost-effective use of Xpert PCR testing for TB a part of your local TB plan. The lack of such personnel who can consistently perform PCR testing on a daily basis, makes this option cost-ineffective.
DICOM Recommendations:

There is good evidence that Xpert PCR testing for TB is more sensitive and specific than AFB smears, and that 2 negative PCR results have an excellent negative predictive value to rule out TB. Hospitals that perform Xpert PCR testing on 2 sequential sputum samples collected from patients with suspected TB will experience substantial cost savings through early discontinuation of isolation in patients with negative test results. However, your hospital laboratory must have adequate numbers of trained personnel to support daily PCR runs, and a sufficiently large number of patients admitted for TB evaluation each year. For example, a hospital that cares for 200 patients with suspected TB could expect to save about $500,000 a year by using Xpert PCR testing for TB (4). We recommend that hospitals undertake a careful, institution-specific cost analysis before using Xpert PCR testing for TB as a basis for their local TB control plane. If they decide to use Xpert PCR testing, recommend this approach:

- Two sputum samples should be collected from patients placed in isolation for possible TB. These samples should be collected at least 8 hours apart sent for AFB smear, Xpert PCR test and CULTURE.
- Isolation can be discontinued, regardless of AFB smear results, if a patient has 2 negative Xpert PCR test results,
- Isolation should be continued, regardless of sputum smear results, if a patient has a positive Xpert PCR test result for TB.
- Xpert PCR test is an addition to, not a substitute for, current TB diagnosis practices. See below table for details.

Recommendations for Discontinuation of Airborne Isolation for Patients with Suspected Tuberculosis:

<table>
<thead>
<tr>
<th>Isolation Status</th>
<th>Traditional use of AFB Smears</th>
<th>Use of Gene Xpert PCR</th>
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<tr>
<td>When to discontinue isolation</td>
<td>3 consecutive sputum AFB smears obtained at least 8 hours apart are negative</td>
<td>2 Gene Xpert PCRs obtained at least 8 hours apart are negative, regardless of smear status</td>
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<tr>
<td>Culture</td>
<td>All samples sent for culture</td>
<td>All samples sent for culture</td>
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<tr>
<td>Other</td>
<td>Sputum is a good quality sample</td>
<td>Sputum is a good quality sample</td>
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References: