ORIGINAL ARTICLE

Use of a Single Xpert MTB/RIF Assay to Determine the Duration of Airborne Isolation in Hospitalized Patients With Suspected Pulmonary Tuberculosis

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BACKGROUND. Hospitalized patients with suspected tuberculosis (TB) are placed in airborne isolation until 3 sputum smear samples are negative for acid-fast bacilli (AFB). The Xpert MTB/RIF assay ("Xpert") nucleic acid amplification test (NAAT) to identify *Mycobacterium tuberculosis* DNA and resistance to rifampicin is superior to AFB sputum smear microscopy for the diagnosis of TB.

OBJECTIVE. To compare the performance of a single Xpert to AFB smear microscopy for time to airborne infection isolation (AII) discontinuation.

METHODS. Consecutive patients over 17 years of age in AII for suspected pulmonary TB between October 1, 2014, and March 31, 2016, with leftover respiratory AFB samples were enrolled in this study. A single Xpert was performed on the first available sample. Demographic, clinical, and microbiological data were recorded for each patient. We compared the duration of AII using a single Xpert to AFB smear microscopy under multiple theoretical scenarios using Kaplan-Meier cumulative incidence curves and the log-rank test.

RESULTS. In total, 131 samples were included in our performance analysis of the Xpert, and 114 samples were included in our AII analysis. Overall, 81 patients (65%) were immunosuppressed, of whom 46 (37%) were positive for human immunodeficiency virus (HIV). The sensitivity and specificity of Xpert for diagnosis of *M. tuberculosis* infection were 67% and 100%, respectively. Xpert was negative in all cases of non-tuberculous mycobacteria. Use of a single Xpert reduced AII duration from a median of 67 hours per patient to 42 hours with usual reporting, to 26 hours with direct communication, and to 12 hours with immediate testing.

CONCLUSIONS. A single negative Xpert result can reduce AII duration compared to the AFB smear microscopy technique under multiple theoretical scenarios.

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The US Centers for Disease Control and Prevention (CDC) guidelines recommend airborne infection isolation (AII) for all hospitalized patients with suspected pulmonary tuberculosis (TB) until 3 respiratory specimens collected at least 8 hours apart, including 1 early-morning specimen, are confirmed to be negative for acid-fast bacilli (AFB) by smear microscopy.[1]

Compared to AFB culture for the diagnosis of TB, the AFB smear microscopy technique has a sensitivity of 20%–80%.[2] If AFB smears are negative and suspicion of TB remains, it is recommended that patients remain in AII because up to 20% of TB is spread by individuals with smear-negative TB.[3–5] Placing patients in AII to rule out TB is labor intensive, subject to delays, and associated with adverse events, poor patient satisfaction, and negative outcomes.[6] Delayed discontinuation of AII occurs in 81% of patients with suspected TB.[7]

Nucleic acid amplification tests (NAATs) have improved the accuracy of TB diagnosis and facilitate faster turnaround times, reducing time spent in AII and healthcare costs.[8–10] Xpert MTB/RIF® ("Xpert," Cepheid, Sunnyvale, CA) is an automated cartridge-based NAAT with a turnaround time of ~2 hours.[11] In pulmonary disease, Xpert has 98% sensitivity for the diagnosis of AFB smear-positive TB and 68% sensitivity for AFB smear-negative TB, with a specificity of 98%.[12]

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PREVIOUS PRESENTATION. The results of this study were presented at the Infectious Diseases Society of America Meeting 2016, on October 27, 2016, in New Orleans, Louisiana (abstract 544).

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In 2015, Xpert received FDA labeling for testing of either 1 or 2 sputum specimens in place of standard AFB smears to make decisions about AII.[13] We performed a prospective, observational study coupled with a theoretical evaluation to determine whether a negative Xpert performed on a single respiratory sample could reduce the duration of AII while optimally ruling out TB.

METHODS

Study Setting

The University of Maryland Medical Center (UMMC) is a 772-bed tertiary-care medical center in Baltimore, Maryland. Each year, ~200 patients are placed into AII for presumptive pulmonary TB, of whom 9 (on average) are ultimately found to be culture positive for *M. tuberculosis* (Mtb). The UMMC infection control policy requires that patients with suspected pulmonary TB remain in AII until 3 respiratory specimens collected at least 8 hours apart are confirmed to be AFB smear negative. Patients may be taken out of AII sooner if an alternative diagnosis is made and pulmonary TB is no longer a consideration.

Study Population

Patients over 17 years of age admitted to UMMC between October 1, 2014, and March 31, 2016, suspected of having pulmonary TB and placed in AII were eligible for study enrollment. Patients were enrolled if they had at least 1 respiratory specimen submitted for AFB smear and culture as part of their medical care, with sufficient sample leftover for testing by Xpert. Patients on antituberculous therapy for >7 days were excluded. The University of Maryland Medical Center Institutional Review Board approved this study.

Laboratory Methods and Data Collection

Respiratory samples were either expectorated or induced sputum, endotracheal aspirates, or bronchoalveolar lavage specimens. Respiratory samples received in the clinical microbiology laboratory by 7:30 AM were batched and processed once daily according to the laboratory protocol. For respiratory samples with sufficient volume, an aliquot of >0.5 mL of unconcentrated sputum was set aside for Xpert testing. For AFB smear microscopy, samples were decontaminated and concentrated, and smear microscopy was performed using auramine-rhodamine fluorescent stain. AFB culture was performed using both a Mycobacteria growth indicator tube (BACTEC MGIT 960 System, Becton Dickinson, Franklin Lakes, NJ) and Middlebrook 7H11 agar (Sigma-Aldrich, St Louis, MO).

Xpert was performed on the first available respiratory sample. Unconcentrated respiratory samples set aside for Xpert testing were deidentified and labeled with a unique study identification number. Xpert testing was performed by study personnel following the manufacturer's instructions. Xpert results were not made available to the clinical team or patients because this test has not been validated for clinical use in our institution.

Demographic, clinical, microbiologic, and radiographic data were collected from the patients' medical charts. Date–time stamps for AII initiation and discontinuation were also recorded.

Definitions and Scenarios for Airborne Infection Isolation Discontinuation

The AII initiation time was defined as time of electronic AII order entry. If this was not available, clinician and nursing provider notes were reviewed to determine the time of AII initiation. If this was unsuccessful, the first AFB smear microscopy order time was used. The AII discontinuation time was defined as the time of electronic AII discontinuation order entry. For patients discharged prior to AII discontinuation order entry, the time of discharge was used. For patients without electronic orders for AII discontinuation who remained hospitalized, nursing and provider notes were reviewed to determine the time of discontinuation. If this was unsuccessful, the result time of last AFB sputum smear was used.

In addition to recording AII initiation and discontinuation date–time stamps, we recorded the date and time that each sputum AFB sample was collected, received by the Clinical Microbiology Laboratory, processed by the clinical lab (7:30 AM daily), and results reported. Using the date–time stamps, we calculated the observed duration of AII and the time from last AFB smear reported to the time of AII discontinuation (ie, delay) for each case of AII.

To assess the potential time saved using Xpert, we calculated the duration of AII under 3 hypothetical scenarios. Because the negative predictive value (NPV) of Xpert in our study (see results) was 99%, we assumed that AII could be discontinued with the results of the first sample received in the laboratory. For this analysis, we excluded cases in for whom AII was discontinued before the first AFB smear result was reported, cases in which AII was less than 8 hours, and AII cases that were culture positive for *M. tuberculosis*.

Our first hypothetical scenario (ie, usual reporting) estimated the duration of AII if a single Xpert was used instead of AFB smear microscopy. For each patient, we used the first AFB sample received in the laboratory to calculate the time of reporting, assuming a 4-hour duration from the start of the sample processing to result entry in laboratory information system. We then added the corresponding delay in AII discontinuation to account for provider delays in discontinuation orders following negative smear results.

Our second scenario (ie, direct communication) estimated the time saved using a single Xpert instead of AFB smears, and assumed that Xpert results would be directly communicated to the healthcare provider resulting in earlier discontinuation of AII. For each patient, we added 4 hours from the start of sample processing to the results of Xpert and an additional

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hour for the discontinuation of AII following the communication of a negative result.

For our third scenario (ie, immediate testing), we assumed that samples were processed upon arrival in the clinical laboratory rather than batched and processed together the following morning. In this scenario, Xpert results would again be communicated to the clinical team with immediate discontinuation of AII. We added 4 hours to the time the sample was received in the laboratory.

Statistical Analysis

We used standard descriptive statistics to characterize our cohort. We compared the sensitivity and specificity of AFB smear microscopy to a single Xpert for diagnosis of Mtb using culture-positive TB as the reference standard. We performed a survival analysis comparing AII duration under the various hypothetical strategies using Kaplan-Meier survival curves and medians with interquartile range. The log-rank test was used to detect differences between survival curves. For our study, each episode of AII was considered separately. Statistical analysis was performed using GraphPad Prism version 5.04 software (GraphPad Software, La Jolla, CA).

RESULTS

Demographic and Clinical Features

During our study period, 275 patients were placed into AII with suspected pulmonary TB, contributing 310 distinct episodes for whom AII was used (15 patients were placed in AII multiple times during the study period). In addition, sufficient leftover respiratory samples were available for 148 episodes of AII. Of these, 17 episodes were excluded from our analysis, leaving 131 samples (from 124 patients) included in our study (Figure 1).

Patient demographic, clinical, and radiological characteristics are listed in Table 1. Overall, 58% of patients were male, and 15% were born outside of the United States. Risk factors for TB exposure included history of homelessness (16%) and prior incarceration (20%). Furthermore, 20 patients (16%) had a history of either latent TB (13 patients) or of treated active TB disease (7 patients). In addition, 65% of patients were immunocompromised, of whom the majority were infected with human immunodeficiency virus (HIV).

Microbiology

During our study period, 5 episodes (4%) of AII were AFB smear positive. Of these, 1 episode was positive for Mtb, 2 episodes were positive for *M. avium* complex (MAC), and 2 episodes were positive for *M. kansasii*. AFB cultures from 14 episodes (11%) were positive: 3 episodes (2%) were positive for Mtb; 6 episodes were positive for MAC; 2 episodes were positive for *M. kansasii*. *M. gordonae*, *M. abscessus*, and an unidentified gram-positive rod were recovered from the remaining 3 episodes.

Xpert was positive in 2 of the 3 episodes that grew Mtb on AFB culture. Using AFB culture as our reference standard, AFB smear microscopy had a sensitivity of 33% for the diagnosis of

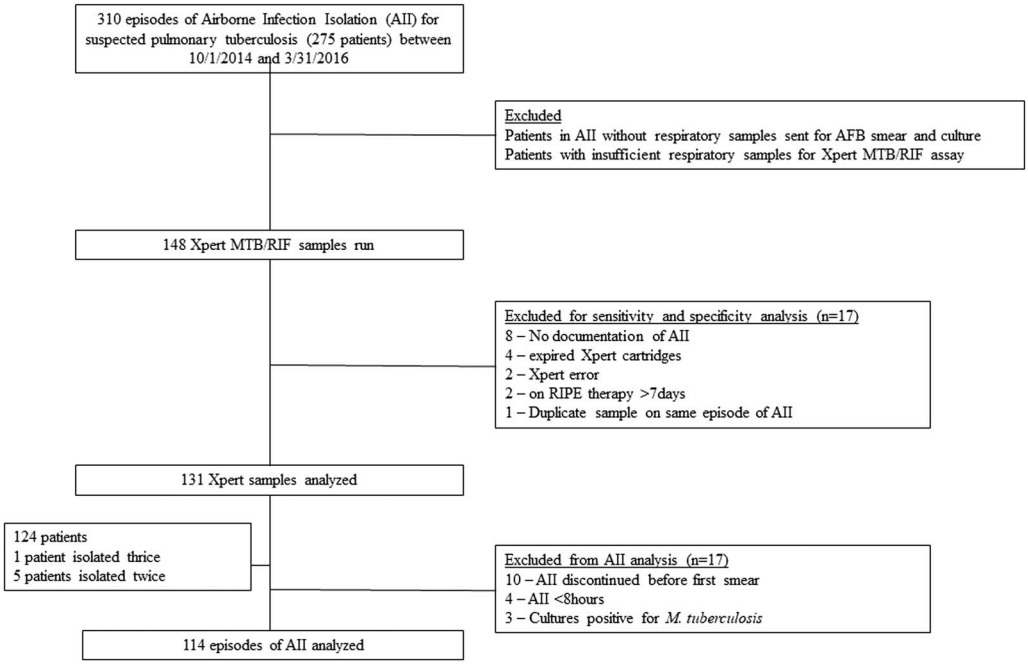

FIGURE 1. Flow diagram outlining inclusion and exclusion of study subjects for sensitivity analysis and for airborne infection isolation analysis. NOTE. AFB, acid-fast bacilli; RIPE, rifampin, isoniazid, pyrazinamide, ethambutol.

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TB, with a positive predictive value (PPV) of 20%. Xpert demonstrated a sensitivity of 67%, specificity of 100%, a PPV of 99%, and an NPV of 99%. Xpert was negative in all 11 cases (including 4 smear-positive cases) in whom non-tuberculous mycobacteria (NTM) were identified. A comparative performance analysis of AFB smear microscopy and Xpert is shown in Table 2.

TABLE 1. Demographic, Clinical, and Radiographic Characteristics

Patient Characteristics (N = 124)	No. (%)
Male	72 (58)
Foreign born	19 (15)
Race	
African American	80 (65)
Caucasian	36 (29)
Asian	7 (6)
Other	1 (1)
Homeless	20 (16)
History of incarceration	25 (20)
History of TB infection	20 (16)
History of latent TB	13 (10)
History of active TB	7 (6)
HIV positive	46 (37)
Malignancy	29 (23)
Active chemotherapy	12 (10)
Autoimmune disease	10 (8)
Solid organ or stem cell transplant	13 (10)
Symptoms (N = 131)[a]	
Fever	52 (40)
Cough	98 (75)
Night sweats	33 (25)
Hemoptysis	34 (26)
Weight loss	38 (29)
Asymptomatic	17 (13)
Imaging Findings (N = 131)[a]	
Cavitation	25 (19)
Consolidation	47 (36)
Nodular infiltrate	45 (34)
Lymphadenopathy	38 (29)
Tree-in-bud appearance	17 (13)

NOTE. HIV, human immunodeficiency virus; TB, tuberculosis.
[a]Total number refers to episodes of airborne infection. Some patients may contribute >1 episode of airborne infection isolation.

Impact of Xpert MTB/RIF Assay on Duration of AII

The NPV of a single Xpert in our study was 99%. We assumed this would rule out TB reliably, allowing the theoretical discontinuation of AII for patients with a single negative test. To determine the impact of using a single Xpert on the duration of AII, we used date–time stamps for respiratory sample collection and processing in the clinical microbiology laboratory to construct 3 hypothetical scenarios. Only 114 cases of AII were included in this analysis (Figure 1).

The observed median duration of AII using AFB smear microscopy for AII discontinuation was 67 hours (Figure 2). In the usual reporting scenario, using a single negative Xpert and allowing for a delay in AII discontinuation after results were made available resulted in a 24-hour reduction in duration of AII (median, 42.3 hours; $P < .0001$). Further reductions in AII duration could be accomplished with a single negative Xpert and prompt discontinuation of AII upon immediate communication of negative result to the clinical provider (ie, direct communication, median, 25.9 hours; $P < .0001$) and using an immediate testing and reporting strategy (ie, immediate testing, median, 11.6 hours; $P < .0001$). We calculated a total of 378 days of isolation for the patients in our study. The usual reporting, direct communication, and immediate testing scenarios demonstrated a progressive decrease in the total number of days of AII required, with 82 days of AII estimated under our immediate testing scenario.

DISCUSSION

Airborne infection isolation of hospitalized patients with suspected pulmonary TB is necessary to prevent nosocomial

TABLE 2. Comparative Performance of Xpert MTB/RIF and AFB Smear Microscopy Using AFB Culture as Gold Standard (N = 131)

	MTB Positive	MTB Negative	Total	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
AFB Smear Microscopy							
Positive	1	4	5	33.33 (0.84–90.57)	96.90 (2.25–99.15)	20 (0.51–71.64)	98.43 (94.43–99.81)
Negative	2	124	126				
Total	3	128	131				
Xpert MTB/RIF							
Positive	2	0	2	66.67 (9.43–99.16)	100 (97.16–100)	100	99.22 (96.27–99.84)
Negative	1	128	129				
Total	3	128	131				

NOTE. AFB, acid-fast bacilli; MTB, *Mycobacterium tuberculosis* culture; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval.

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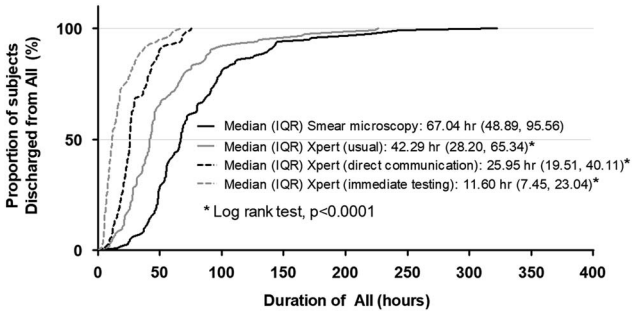

FIGURE 2. Time to airborne infection isolation (AII) discontinuation. NOTE. Kaplan-Meier cumulative incidence curve comparing time to AII discontinuation using AFB smear microscopy to 3 different scenarios using the Xpert MTB/RIF assay on a single respiratory specimen (N = 114). NOTE. IQR, interquartile range.

transmission of TB. In a study population of predominantly immunosuppressed hospitalized patients with multiple risk factors for TB, we found the Xpert superior to the AFB smear microscopy in ruling out pulmonary tuberculosis. In all patients with respiratory samples positive for NTM, Xpert was negative. Finally, Xpert could reduce the duration of AII by more than 24 hours per patient. Further reductions were possible with direct communication of negative results to clinical providers and with immediate processing of respiratory samples for analysis using Xpert.

The sensitivity of the Xpert MTB/RIF assay in our study was 67%. Despite multiple risk factors for TB in our cohort, only 3 cases of AII (2%) resulted in the diagnosis of TB, which is lower than TB detection rates reported in similar studies from the United States.[14–17] We also observed a higher than expected frequency of AFB smear-negative, culture-positive TB; 2 of 3 cases were AFB smear negative. Our results are similar to those of other groups evaluating the performance of the Xpert assay in low-incidence settings.[14–17] In one study, a single Xpert had an overall sensitivity of 85.2% for culture-confirmed TB, with a higher sensitivity in AFB smear-positive TB (96.7%) than AFB smear-negative TB (59.3%).[17] The NPV of a single Xpert in our study was 99%, which is consistent with data from low-incidence settings.[14,17] Performing a second Xpert in cases of smear-negative TB leads to a modest increase in sensitivity.[14,17]

Xpert identified 1 case of smear-negative, culture-positive TB. It successfully distinguished between NTMs and Mtb, which is an important advantage over AFB smear microscopy given the increasing prevalence of NTM infection in the United States.[18] Patients eventually diagnosed with NTM were kept in AII longer than patients with negative AFB smears and cultures (147 hours vs 74 hours). The rapid and accurate detection of true negatives in a low-burden setting can reduce duration of AII and prevent unnecessary administration of empiric therapy.

In patients with low clinical suspicion for TB, a single negative Xpert may be adequate for discontinuation of AII. In patients with high pretest probability for TB, performing a second Xpert, or keeping the patient in airborne isolation may be appropriate, even if the Xpert is negative. The risk of TB transmission in patients who are negative by both AFB smear and Xpert but are culture positive is unknown.

We have demonstrated the benefit of a single Xpert in reducing the duration of isolation under various scenarios, consistent with published data.[14,16] Our hypothetical scenarios show that direct communication of negative results to the clinical care team may reduce delays in the discontinuation of AII. The importance of direct communication between the microbiology laboratory and clinical care teams might be overlooked; communication between the microbiology laboratory and clinical care teams was necessary for a rapid multiplex NAAT to significantly impact broad-spectrum antibiotic use in bacteremic patients.[19] The increased cost of Xpert testing is offset by the significant cost savings of reducing the duration of AII.[10,14,20] However, decision making regarding the implementation of the Xpert for AII discontinuation should include microbiology laboratory workflow and staffing needs.

Our study has many strengths. It was a prospective, real-world study that used culture data to compare the performance of AFB smear microscopy with a single Xpert MTB/RIF assay. We used direct, unconcentrated respiratory specimens. In addition, many patients were at risk for developing pulmonary TB, either due to demographics and exposure or to immunosuppressive conditions, and AII was frequently used. The use of date–time stamps from clinical samples allowed us to construct hypothetical scenarios that reflect clinical practice.

Our study was limited by the theoretical estimate of time spent in airborne isolation under different scenarios. We only used leftover samples from routine clinical testing, which necessitated the exclusion of patients in AII for whom sufficient sample was not available. The number of episode of AII that were positive for TB was lower than expected, with only 3 cases of AII culture positive for TB, of which only 1 episode was smear positive for TB.

In summary, our findings suggest that a single negative Xpert may be sufficient to rule out suspected pulmonary TB (if clinical suspicion is low) in hospitalized patients from a low-incidence setting, potentially resulting in a significant reduction in AII duration.

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Potential conflicts of interest: All authors report no conflicts of interest relevant to this article.

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