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Evaluation of Xpert MTB/RIF assay: diagnosis and treatment outcomes in rifampin resistant TB

리팜핀내성 결핵의 진단과 치료에서 Xpert MTB/RIF assay의 임상적 유용성 평가

2016 년 2 월

서울대학교 대학원

의학과 내과학 전공

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A thesis of the Degree of Master of Medicine

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February 2015

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A thesis submitted to the Department of Internal Medicine in partial fulfillment of the requirements for the Degree of Master of Medicine at Seoul National University College of Medicine

November 2015

Approved by Thesis Committee:

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ABSTRACT

Introduction: The Xpert MTB/RIF assay is endorsed by the World Health Organization for detection of rifampicin (RIF)-resistant tuberculosis (TB). The aim of this study was to evaluate Xpert for its diagnostic accuracy in detecting RIF-resistant TB and its impact on treatment outcomes.

Methods: Patients with available phenotypic drug susceptibility test (DST) results and those in whom RIF-resistant pulmonary TB was diagnosed using Xpert were evaluated. Xpert's accuracy and turnaround time (TAT) for determining RIF-resistant TB was calculated. The TATs for treatment between patients diagnosed with RIF-resistant TB by Xpert and those diagnosed without the assay (phenotypic DST group) were compared.

Results: In 321 patients, when phenotypic DST was used as the gold standard, the sensitivity and specificity of Xpert for RIF-resistance diagnosis was 100% and 98.7%, respectively, while the positive and negative predictive values were 86.2% and 100%, respectively. The Xpert group had a much shorter interval from initial evaluation to commencing second-line anti-TB drugs (64 vs. 2 days, $P<0.001$), and negative conversion of mycobacterial cultures (197 vs. 62.5 days, $P<0.001$) than did the phenotypic DST group.

Conclusions: Xpert was accurate at diagnosing RIF-resistance in this setting of intermediate TB burden and low level of RIF-resistance. Xpert might reduce disease transmission by shortening sputum culture conversion times for patients with RIF-resistant TB.

Keywords: Xpert MTB/RIF, drug-resistant tuberculosis, diagnostic accuracy

Student number: 2014-21105

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INTRODUCTION

Tuberculosis (TB) remains one of the leading infectious causes of mortality worldwide. TB control is a key challenge for global public health, but efforts have been seriously hampered by the emergence of drug-resistant isolates of *Mycobacterium Tuberculosis* (1, 2). Multidrug-resistant TB (MDR-TB), defined as the disease caused by *M. tuberculosis* that is resistant to at least isoniazid (INH) and rifampicin (RIF), caused around 210,000 deaths worldwide in 2013, and is associated with poor outcomes despite prolonged treatment (1, 3).

With MDR-TB, delayed diagnosis is an important risk factor associated with increased transmission and poor clinical outcomes (4, 5). Because RIF-resistant *M. tuberculosis* is also likely to be resistant to INH, early detection of RIF-resistance is critical for proper management of MDR-TB. Accordingly, recent efforts have been focused on developing rapid tests not only for diagnosing TB but also drug-resistance (6, 7).

The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), an automated, single-cartridge-based nucleic acid amplification test using RT-PCR detection of the TB-specific *rpoB* gene, represents an important advance in the field of rapid molecular diagnosis of TB and drug resistance. The test enables simultaneous identification and detection of TB and RIF-resistance to be completed within 2 hours (8, 9). Because of its high accuracy and speed, the Xpert MTB/RIF assay was recommended for use by the World Health Organization (WHO) for the rapid detection of TB, as well as for detecting

RIF-resistance, and current guidelines recommend initiation of MDR-TB treatment with second-line drugs when RIF-resistance is repeatedly detected by this assay (3, 10).

Despite the Xpert MTB/RIF assay having good overall concordance with conventional phenotypic drug susceptibility tests (DST), limited data is available on its turnaround time (TAT) and the impact of the assay on treatment outcomes in clinical practice for patients with RIF-resistant TB. Furthermore, controversy remains on how this assay should be implemented in different health care systems and settings (11). The aim of this study, therefore, was to validate the diagnostic accuracy, TAT, and clinical impact of the Xpert MTB/RIF assay in diagnosis and treatment of RIF-resistant pulmonary TB in South Korea, a country with an annual TB incidence of 97 per 100,000 people, and 2.7% MDR among newly diagnosed TB patients in 2013 (1).

MATERIALS AND METHODS

1. Study design

We retrospectively reviewed the medical records of patients who were diagnosed with pulmonary TB for which conventional phenotypic DST results were available between January 1, 2011 and August 31, 2014 at Seoul National University Hospital, a tertiary referral hospital in South Korea. Using the data from a consecutive series of patients *with M. tuberculosis*-positive results from the Xpert MTB/RIF assay as well as available phenotypic DST results, we evaluated the accuracy and TAT of the Xpert MTB/RIF assay for detecting RIF-resistance, and the difference in clinical outcomes between patients diagnosed with RIF-resistant TB using the Xpert MTB/RIF assay and RIF-resistant TB patients for whom this assay was not used for diagnosis. The design of this study was approved by the Institutional Review Board of Seoul National University Hospital.

2. Accuracy of the Xpert MTB/RIF assay for detection of RIF-resistance

To evaluate the diagnostic accuracy of the Xpert MTB/RIF assay for detecting RIF-resistance in comparison to conventional phenotypic DST as the reference standard, we selected patients who had received *M. tuberculosis*-positive Xpert MTB/RIF assay results whose sample had also been tested by phenotypic DST. The sensitivity, specificity, positive predictive value (PPV),

negative predictive value (NPV), positive likelihood ratio and negative likelihood ratio of the Xpert MTB/RIF assay using respiratory specimens for diagnosis of RIF-resistance and MDR were calculated.

3. TAT and clinical impact of the Xpert MTB/RIF assay on treatment of RIF-resistant TB

The TAT of the Xpert MTB/RIF assay for determining RIF-resistance was compared with that of conventional phenotypic DST among patients in whom the Xpert MTB/RIF assay as well as the phenotypic DST were performed. Additionally, to evaluate the clinical impact of the Xpert MTB/RIF assay on treatment of RIF-resistant pulmonary TB, the time from the first TB test to initiation of second-line anti-TB drugs and the time to negative conversion of mycobacterial culture were compared between patients diagnosed with RIF-resistant pulmonary TB with the Xpert MTB/RIF assay (Xpert group) and those diagnosed without this assay (phenotypic DST group). Treatment of RIF-resistant TB in both groups was individualized according to their contact history, previous treatment, and DST results. WHO definitions were used to define the treatment outcomes (5, 12). Treatment success was defined as bacteriological cure or successful completion of treatment, and unfavourable outcome was defined as treatment failure, default, or death from any cause (11).

4. Laboratory processing of specimens

The Xpert MTB/RIF assay was performed and interpreted according to the manufacturer's instructions and the protocols suggested were strictly followed. All respiratory specimens were pretreated with equal volumes of N-acetyl-L-cysteine-sodium hydroxide (NALC–NaOH, 1% final concentration). Tests were commenced within 24 h of specimen collection and were performed by two certified full-time laboratory technicians who were blind to the results of the other tests. When phenotypic DST was requested, the absolute concentration method was used as a gold standard for detection of RIF-resistance (defined as ≥1% bacterial growth in Löwenstein–Jensen medium at a concentration of 40.0 μg/ml) (13, 14).

5. Statistical analyses

To determine the diagnostic accuracy of the Xpert MTB/RIF assay for detecting RIF-resistance, we calculated sensitivity, specificity, PPV and NPV, positive and negative likelihood ratios using phenotypic DST as a reference; 95% confidence intervals (CIs) were used. Clinical data from the patients comprised medians and interquartile ranges (IQR) for the age and time variables, and means and standard deviations for other continuous variables. Fisher's exact test and the χ^2 test were used for comparisons between categorical variables, and independent *t*-tests and Mann–Whitney tests were used to compare continuous variables. P-values of < 0.05 were recognized as statistically significant. All analyses were performed using SPSS software, version 19.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Accuracy of the Xpert MTB/RIF assay for diagnosis of RIF-resistance

In total, 321 patients who were Xpert MTB/RIF assay-positive for detection of *M. tuberculosis* and were also culture-positive and for which phenotypic DST results were available were included in the analysis. The median age of the patients was 56 years (IQR: 38-71 years) and 196 (61.1%) were male. Sixty patients (18.7%) had a history of TB treatment and 52 (16.2%) had diabetes. Using conventional phenotypic DST as the gold standard, the sensitivity and specificity of the Xpert MTB/RIF assay for diagnosis of RIF-resistance were 100% and 98.7%, respectively, while PPV and NPV were 86.2% and 100%, respectively (Table 1).

Table 1. Diagnostic accuracy of Xpert MTB/RIF for detecting rifampicin resistance among 321 culture-positive pulmonary TB patients using conventional phenotypic drug susceptibility testing as the gold standard

Rifampicin resistance detection	Diagnostic accuracy (n/N) (95% CI)
Sensitivity, %	100 (25/25) (86.7–100)
Specificity, %	98.7 (292/296) (96.6–99.5)
Positive predictive value, %	86.2 (25/29) (68.3–96.1)
Negative predictive value, %	100 (292/292) (98.7–100)
Positive likelihood ratio, %	74.0 (28.0–195.9)
Negative likelihood ratio, %	0 (not applicable)

CI: confidence interval

Among the 29 patients who had positive Xpert MTB/RIF assay reports of RIF-resistance, four (13.8%) turned out to be susceptible to RIF (false-positive) according to the phenotypic DSTs. Additionally, two (6.9%) were RIF-resistant but susceptible to isoniazid, while 17 (58.6%) and six (20.7%) patients were diagnosed with MDR- and XDR-TB, respectively (Table 2). The PPV of the Xpert MTB/RIF assay for diagnosing MDR-TB was 79.3% (23/29). The Xpert MTB/RIF assay was performed only once for all but one of the 29 patients, and the results in that patient were identical (i.e., resistant

to RIF).

Table 2. Resistance profiles based on phenotypic drug susceptibility testing among 29 pulmonary TB patients with rifampicin-resistance detected by the Xpert MTB/RIF assay

Resistance profile based on phenotypic DST, n (%)	Rifampicin resistance detected by Xpert MTB/RIF assay (N=29)
Rifampicin sensitive	4 (13.8%)
Rifampicin resistant, but not MDR	2 (6.9%)
MDR	17 (58.6%)
Without resistance to FQ or injectable drugs	13 (44.8%)
With resistance to FQ	4 (13.8%)
With resistance to injectable drugs	0 (0%)
XDR	6 (20.7%)

DST: drug-susceptibility test, MDR: multidrug-resistant, FQ: fluoroquinolone, XDR: extensively-drug resistant

2. Comparison of Xpert MTB/RIF and phenotypic DST TATs

Among the 321 patients for whom the results of both the Xpert MTB/RIF assay and the phenotypic DST were available, the median TAT from the time of initial request of an Xpert MTB/RIF assay to receiving its laboratory report was 0 days (IQR 0-0.5). This was a significantly shorter time than that of the conventional phenotypic DST based on sample culture (median 78.5 days, IQR 63.5-92, $P < 0.001$). The median TAT from initial evaluation to provision of the Xpert MTB/RIF assay results to the duty physician was one day (IQR

0-4.5). This TAT was also significantly shorter than that of the conventional phenotypic DST (median 92.5 days, IQR 71-113.5, P = 0.001) (Table 3).

Table 3. Turnaround time of the Xpert MTB/RIF assay and phenotypic drug susceptibility test to detect rifampin-resistance

	Laboratory report of results, days, median (IQR)	*p*-value*	Confirmation of results by duty clinician, days, median (IQR)	*p*-value*
Xpert MTB/RIF assay	0 (0-0.5)	Ref.	1 (0-4.5)	Ref.
Phenotypic DST	78.5 (63.5-92)	<0.001	92.5 (71-113.5)	<0.001

IQR: Interquartile range, DST: drug susceptibility test

**p*-values are from comparisons between the Xpert MTB/RIF assay and phenotypic drug susceptibility test

3. Clinical impact of the Xpert MTB/RIF assay on treatment of rifampicin-resistant TB

Baseline demographic and clinical characteristics were similar between patients diagnosed with RIF-resistant pulmonary TB using the Xpert MTB/RIF assay (Xpert group) and RIF-resistant pulmonary TB patients diagnosed without Xpert MTB/RIF (phenotypic DST group). There was no significant difference in the proportions of the drug-resistance profiles between the two groups. The proportion of patients for whom second-line anti-TB medications were initially started was higher in the Xpert group (72% *vs*. 28%, P=0.002) (Table 4).

Table 4. Clinical characteristics of pulmonary TB patients diagnosed with rifampicin-resistant TB with or without use of the Xpert MTB/RIF assay

Characteristics	Diagnosed as rifampicin-resistant TB using Xpert (n=25)	Diagnosed as rifampicin-resistant TB without using Xpert (n=25)	*p*-value
Age, years, median (IQR)	42 (30-62.5)	52 (36.5-64.5)	0.187
Sex, male, n (%)	15 (60.0)	16 (64.0)	0.771
BMI, mean±SD	21.1±3.8	21.9±4.0	0.511
Current or ex-smoker	13 (52.0)	14 (56.0)	0.777
History of previous TB treatment			0.734
Never treated for TB	12 (48.0)	12 (48.0)	
Received only first-line TB drugs in the past	8 (32.0)	6 (24.0)	
Received second-line TB drugs in the past	5 (20.0)	7 (28.0)	
Comorbidities			
Diabetes mellitus	4 (16.0)	5 (20.0)	0.713
Chronic kidney disease	1 (4.0)	1 (4.0)	1.000
Malignancy	3 (12.0)	4 (16.0)	0.684
Characteristic of lung lesion, n (%)			
Cavitary lung lesion	14 (56.0)	9 (36.0)	0.156
Bilateral lung lesion	16 (64.0)	12 (48.0)	0.254
Treatment initiated with second-line anti-TB drugs, n (%)	18 (72.0)	7 (28.0)	0.002

IQR: interquartile range, BMI: body mass index

A diagnosis of RIF-resistant TB obtained via the Xpert MTB/RIF assay resulted in the following: a significantly reduced time from the point of specimen request to initiating second-line anti-TB drugs (2 *vs.* 64 days, P<0.001), time to change to second-line anti-TB drugs from initiating first-line drugs (1 *vs.* 73.5 days, P<0.001), time from specimen request to negative conversion of a mycobacterial culture (62.5 *vs.* 197 days, P<0.001), and time from initiation of TB treatment to negative conversion of culture (61.5 *vs.* 196 days, P=0.001). Despite not reaching statistical significance, use of the Xpert MTB/RIF assay appeared to reduce the time from initiation of second-line anti-TB drugs to negative conversion of culture (61 *vs.* 147 days, P=0.07). The number of successfully treated patients was 17 (68%) in the Xpert group, and 13 (52%) in the phenotypic DST group (P=0.301) (Table 5).

Table 5. Comparison of turnaround times and treatment outcomes for patients diagnosed as having resistance to rifampicin with or without Xpert MTB/RIF assay analysis

Variables	Patient diagnosed with RIF-resistant TB using Xpert (n=25)	Patient diagnosed with RIF-resistant TB not using Xpert (n=25)	*p*-value
Interval from specimen request to beginning 2nd-line anti-TB drugs, days (IQR)	2 (1-5.5)	64 (24.5-103)	<0.001
Interval from initiating 1st-line drugs to change to 2nd-line anti-TB drugs, days (IQR)	1 (1-2)	73.5 (45.75-105.5)	<0.001
Interval from specimen request to negative conversion of culture, days (IQR)	62.5 (41-79)	197 (111.5-282)	<0.001
Interval from initiation of anti-TB drugs to negative conversion of culture, days (IQR)	61.5 (41-76.5)	196 (82.5-269)	0.001
Interval from initiation of 2nd-line anti-TB drugs to negative conversion of culture, days, (IQR)	61 (38-76)	147 (38-233)	0.072
Treatment outcomes, n (%)			0.301
Treatment success	17 (68.0)	13 (52.0)	
Unfavourable outcome (failure, death, default)	5 (20.0)	10 (40.0)	
Still on treatment	3 (12.0)	2 (8.0)	

RIF: rifampicin, IQR: interquartile range

DISCUSSION

Through this study, which was performed in South Korea, where the prevalence of MDR among new TB cases was 2.7% in 2013, we have shown that the sensitivity, specificity, PPV, and NPV of the Xpert MTB/RIF assay for the diagnosis of RIF-resistant *M. tuberculosis* were 100%, 98.7%, 86.2%, and 100%, respectively (1). Additionally, the PPV of the Xpert MTB/RIF assay for detecting MDR-TB was 79.3%.

Previous studies have raised concerns about the low PPV of rapid RIF-resistance testing (including the Xpert MTB/RIF assay) in countries with a low prevalence of RIF-resistance and MDR-TB. The PPV for detecting RIF-resistance in *M. tuberculosis* is expected to diminish significantly when the prevalence of RIF-resistance falls below 5%, and a PPV of 59.5% is expected in a setting where the prevalence of RIF-resistance is 3% (9, 15). However, PPVs in such settings are expected to have improved when the latest generation (G4) Xpert MTB/RIF assay was introduced in 2011 (16, 17). In fact, the 86.2% PPV estimated in the present study for analysis of the results from the latest generation Xpert MTB/RIF assay, has exceeded previous values in settings with similar prevalence of RIF-resistant TB (9). These data support the WHO recommendation for the use of the Xpert MTB/RIF assay for diagnosis of RIF-resistant pulmonary TB, as well as policies based on the use of this assay for diagnosis of drug-resistant TB in settings where the incidence of TB and RIF-resistance are similar to those in South Korea (3, 9, 10).

In this study, among the patients who tested positive for RIF-resistant *M. tuberculosis* by Xpert MTB/RIF, 6.9% (2/29) turned out to be resistant to RIF, but susceptible to INH. These patients were susceptible to all other first-line TB drugs other than RIF. This result is similar to that of a recent study from a setting with a low prevalence of RIF-resistance which reported RIF-monoresistance among 6.3% of the patients who were RIF-resistant by the Xpert MTB/RIF assay (16). Because retaining an INH treatment regimen could be helpful for such patients, the importance of developing rapid and accurate diagnostic tools for the detection of resistance not only to RIF, but also to INH should not be underestimated.

Previous studies have shown that use of the Xpert MTB/RIF assay can shorten TB test result TATs, thereby hastening the initiation of TB treatment. A large majority of the TB patients included in such studies had drug-susceptible TB (18, 19). Our study, which focused on patients with RIF-resistant TB, showed that the Xpert MTB/RIF assay TAT for detection of RIF-resistance was much shorter than that of the phenotypic DST (0 *vs*. 78.5 days). The clinicians on duty also noted a shortened time-to-confirmation period (92.5 to 1 days). In turn, these benefits reduced the following parameters: 1) the interval from initial evaluation for pulmonary TB to beginning second-line anti-TB drug treatment (from 64 to 2 days); 2) the interval from initial evaluation to negative conversion of mycobacterial cultures (from 197 to 62.5 days); and, 3) the interval from initiation of anti-TB treatment to negative conversion of mycobacterial cultures (from 196 to 61.5 days). Reductions in these parameters are important because they would decrease transmission of

drug-resistant TB, while also possibly improving treatment outcomes and long-term survival (4, 20).

However, the results of our study did not confirm an improvement in treatment outcomes among patients for whom the Xpert MTB/RIF assays were performed, although the treatment success rate appeared to be higher (68% *vs.* 52%). In fact, two previously reported prospective studies also failed to show any improvements in the treatment outcomes of pulmonary TB patients, despite earlier initiation of treatment in these people (11, 19). The results of our study might be explained as follows. First, the potential benefits of the Xpert MTB/RIF assay on treatment outcomes were possibly masked by the small number of patients included in the study (i.e., 25 patients per group). The second possible explanation is that treatment outcomes are composite measures that can be influenced by various factors other than the time taken to initiate treatment (e.g., treatment compliance, drug susceptibility profiles, treatment regimens) (4). Nevertheless, the importance of achieving a negative sputum culture within a shorter time period, that is, a shorter infectious period, for patients with RIF-resistant TB diagnosed by Xpert MTB/RIF should be underscored because this would be hugely beneficial in preventing transmission and control of drug-resistant TB (4).

Because co-infection with HIV is a well-known risk factor for the higher incidence and mortality rates seen among MDR-TB patients, prior studies have focused mainly on evaluating the effectiveness of Xpert MTB/RIF in settings with a high prevalence of HIV and HIV/TB co-infections (4, 21). Indeed, previous prospective studies have reported that the benefits of the

Xpert MTB/RIF assay were particularly evident among HIV patients co-infected with TB that had low CD4 cell counts (11). In our study, because there was a low incidence of HIV and HIV/TB co-infections (0.1 per 100,000 population in 2013), there were no HIV patients included in the analysis comparing TAT and treatment results between the Xpert group and the phenotypic DST group (1). Therefore, the benefits of Xpert MTB/RIF shown in our study provides evidence that even in settings with a very low incidence of HIV/TB co-infections, programmatic use of Xpert MTB/RIF would benefit the control of RIF-resistant TB.

To interpret our results correctly, we should take into account the limitations of this study. First of all, because of the retrospective design of this study, the Xpert MTB/RIF assay was based on an individual physician's decision to use it, rather than on predefined criteria. Although this approach provided a unique opportunity to compare the clinical parameters for RIF-resistant TB patients diagnosed by assistance with or without the Xpert MTB/RIF assay, selection bias might exist. Conducting the study in a single centre might also be considered a limitation. However, because this study was performed in a centre where treatment compliance in drug-resistant TB patients is excellent, with low default rates, our results may correctly reflect the outcomes expected when Xpert-based TB control programs are properly established (22).

The main strength of this study is that the data come from a real clinical setting in South Korea, a developed country, with intermediate TB burden and a low proportion of MDR among newly diagnosed TB patients. Limited data evaluating the usefulness of Xpert MTB/RIF-based algorithms for detection

and treatment of drug-resistant TB in settings of intermediate or low TB and MDR burden make it difficult to establish TB control policies based on programmatic use of the Xpert MTB/RIF assay (23). This study should provide relevant information to help guide policy recommendations in South Korea and other countries.

In conclusion, the Xpert MTB/RIF assay was fairly accurate in the diagnosis of RIF-resistance in a setting of intermediate TB burden and a low proportion of RIF-resistance. Use of the assay has potential to reduce disease transmission by shortening the time for culture conversion of sputum among patients with RIF-resistant TB.

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국문 초록

서론: 현재 세계보건기구는 Xpert MTB/RIF assay 를 결핵 및 리팜핀내성 결핵의 진단에 적극적으로 사용할 것을 권고하고 있다. 그러나 Xpert MTB/RIF assay 의 이용이 실제 임상에서 약제내성 결핵의 진단 및 치료에 어떠한 영향을 미치는지에 대해서는 자료가 부족하다.

방법: Xpert MTB/RIF assay 를 진단에 이용하였고, 실제 결핵균 동정 결과가 있는 환자들의 의무기록을 분석하여 Xpert MTB/RIF assay 의 리팜핀내성 결핵에 대한 진단 정확도와 진단까지 걸리는 시간을 알아보았고, Xpert MTB/RIF assay 를 이용하여 약제내성결핵이 진단된 환자들과 검사를 이용하지 않고 진단된 환자들을 비교하여 각종 치료지표에 차이가 있는지 분석하였다.

결과: 총 321 명의 환자들을 분석한 결과, Xpert MTB/RIF 는 리팜핀내성 결핵을 진단하는 있어 100%의 민감도와 98.7%의 트깅도를 보였으며, 양성예측도와 음성예측도는 각각 86.2% , 100%였다. 더불어 Xpert MTB/RIF assay 를 약제내성결핵 진단에 이용하였을 경우, 이용하지 않은 경우에 비하여 통계적으로 유의하게 환자 방문시부터 2 차 결핵약제를 시작하게 되는 시간 (64 일 -> 2 일), 그리고 결핵균이 음전까지의 시간 (197 일 -> 62.5 일)이 단축됨을 알 수 있었다.

결론: 결론적으로 Xpert MTB/RIF assay 는 실제 임상환경에서 높은 정확도로 리팜핀내성 결핵을 진단하고, 약제내성결핵을 치료하는 데에 있어 긍정적인 효과를 보였다. 이를 근거로 약제내성결핵의 진단 및 치료에 있어 Xpert MTB/RIF assay 의 적극 사용할 것을 권고할 수 있을 것이다.

주요어 : Xpert MTB/RIF, 약제내성 결핵, 진단 정확도

학 번 : 2014-21105