

Diagnosing Drug-Resistant Tuberculosis with the Xpert®MTB/RIF. The Risk for Rifampin Susceptible Cases

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Abstract

Setting: Tuberculosis clinic in México. **Objective:** Since the Xpert®MTB/RIF does not detect resistance to isoniazid, our objective was to emphasize the need for additional drug susceptibility testing. **Design:** A prospective study. All patients with an Xpert®MTB/RIF and a positive tuberculosis culture with drug susceptibility testing were included. **Results:** 70 patients were included. Forty-two (60%) had a history of previous treatment for TB. Fourteen patients (20%) had a strain resistant to isoniazid (H), twelve of them (85.7%) with a history of TB treatment in the past vs. 2 (7.1%) among new cases ($p = 0.028$). Four patients (5.7%) had resistance to rifampin (R); three of them were previously treated cases. Additionally, six patients with a negative Xpert test (8.6%) had a positive MGIT culture; three of them were resistant to H (the 3 were poly-resistant). Two patients with a positive Xpert®MTB/RIF test without R resistance were phenotypically multidrug-resistant. **Conclusion:** Isoniazid resistance is associated with overall increased treatment failure, relapse, and acquired multidrug resistance in patients treated with regimens containing only first-line tuberculosis drugs. It is urgent that national TB programs implement the necessary infrastructure to complement the Xpert®MTB/RIF results with DST either by phenotypic or genotypic methods.

Keywords

Diagnosis, Tuberculosis, Isoniazid, Failure, Relapse

1. Introduction

One of the main obstacles for the control of tuberculosis worldwide is the lack of

accessibility to laboratory diagnosis. Globally, notifications of newly diagnosed TB cases in 2014 represented 63% of the 9.6 estimated incident cases. The best estimate of the gap between notifications of new episodes of TB (new and relapse cases) and incident cases was 3.6 million cases [1].

Compounding the problem, increasing drug resistance also poses a grave threat to TB control, since traditionally it requires more sophisticated laboratory infrastructure. However, the development of Xpert®MTB/RIF a real-time PCR (rt-PCR) assay that can both diagnose TB and detect rifampicin resistance concurrently, has revolutionized the diagnosis of drug-resistant tuberculosis (DR-TB). The simplicity for the user makes this an assay that can be widely implemented outside centralized laboratories [2]. The assay has been endorsed by the World Health Organization (WHO) since 2010 and its 2015 policy statement recommends that the Xpert®MTB/RIF should be available to all who need it and prioritized for persons at risk of multidrug-resistant TB (MDR-TB) and HIV-associated TB. Very importantly, in the same policy statement WHO emphasizes that DST for anti-TB medicines other than rifampicin should also be offered [3]. Developing countries with high burden of DR-TB have had preferential access to acquire the equipment and supplies at discount prices which has allowed for the global expansion of the test [4]. From 2010 to the end of 2015, more than 16.2 million Xpert®MTB/RIF cartridges have been procured by eligible customers in the public sector, covering 122 high burden developing countries [5].

The WHO algorithm for interpreting the results from Xpert®MTB/RIF tests [4] specifies that if the Xpert®MTB/RIF shows no mutation for rifampin resistance, the patient should be treated with the WHO recommended first-line treatment. Unfortunately, some of the regions with the highest burden of DR-TB do not have access to other drug-susceptibility testing (DST) in-country, either by phenotypic or genotypic methods. Rifampin resistant cases detected by the Xpert®MTB/RIF, will be treated as multidrug-resistant, frequently without the benefit of DST for second-line drugs. Another problem arising from this diagnosis strategy, hardly ever mentioned, is that patients tested with the Xpert®MTB/RIF with a rifampin-sensitive strain will not be tested further and will be treated with first line drugs. If the strain is resistant to isoniazid (a more frequent event than that of rifampin resistance) the patient will be exposed to what it amounts to rifampin monotherapy during the four-months of the continuation phase of the regimen, situation that creates a high risk of extending resistance to rifampin and treatment failure. This problem has been addressed in the 2017 WHO TB guideline, stating that due to the fact that the Xpert®MTB/RIF lacks the ability to test for isoniazid resistance, providers must be vigilant about this possibility and, if it is suspected, test for isoniazid susceptibility and treat accordingly [6].

Our objective was to determine the presence of phenotypic resistance to first line drugs other than rifampin, in patients without rifampin resistance in the Xpert®MTB/RIF test in a region with high burden of DR-TB.

2. Patients and Methods

The study was carried out at the Tuberculosis Clinic of the Tijuana General Hospital. Tijuana (population 1.6 million) is located at the border with the United States of America, and has the highest rate of tuberculosis in Mexico (60×10^5) and a multidrug-resistant TB (MDR-TB) rate of 3.9% [7]. Patients are referred from peripheral clinics in the city when considered at risk for DR-TB. From 31 August 2015 through 30 April 2017 every patient that was tested with the Xpert®MTB/RIF and also processed for culture and drug susceptibility tests was included in the database.

Sputum sample were collected at the clinic and immediately processed for smear microscopy and the Xpert®MTB/RIF test according to the manufacturer instructions. The remaining sample was decontaminated-digested (MycoPrep™) and processed for liquid and solid culture (MGIT 960®/Lowenstein Jensen/Stonebrink) and subsequent drug-susceptibility testing in positive cultures. Data was analyzed with the SPSS statistical analysis software Ver. 24 (IBM SPSS Statistics®).

Ethics Approval

Ethics clearance for the study was obtained from the Ethics Committee of the Tijuana General Hospital, Tijuana, Mexico. Written informed consent was obtained at the moment of sputum collection.

3. Results

A total of 70 patients with an Xpert®MTB/RIF test and a positive MGIT culture were included (patients without a MGIT culture or without growth in their culture were excluded). Mean age for the group was 38.0 ± 13.1 years; 42 (60%) were males. Forty-two patients (60%) had a history of previous treatment for TB. Fourteen patients (20%) were smear negative (and culture positive); sixteen (22.9%) were positive 1+, 17 (24.3%) were 2+ and 23 (32.9%) were 3+.

Fourteen patients (20%) had a strain resistant to isoniazid (H); twelve of them (85.7%) had a history of TB treatment in the past vs. 2 (7.1%) among new cases ($p = 0.028$). Four patients (5.7%) had resistance to rifampin (R); three of them were previously treated cases. Three of the four R resistant cases detected by the Xpert®MTB/RIF were MDR. **Table 1** shows the resistance profile of every drug-resistant case.

Six patients with a negative Xpert test (8.6%) had a positive MGIT culture; three of them were resistant to H (the 3 were poly-resistant). Two patients with a positive Xpert test without R resistance were phenotypically MDR.

4. Discussion

The Xpert®MTB/RIF system has transformed the diagnosis of rifampin resistance and MDR-TB, from a process that took months, to one that requires less

Table 1. Resistance profile of drug-resistance cases.

Drug (s)	Number of resistant cases	Overall (%)
Isoniazid (H)	5	7.1
Rifampin (R)	1	1.4
Pyrazinamide (Z)	10	14.2
Streptomycin (S)	4	5.7
H+Ethambutol (E)	2	2.8
S + H + Z	3	4.3
S + H + R + E	1	1.4
H + R	1	1.4
S + H	1	1.4
H + R + Z	1	1.4

than 2 hours. It has given regions without access to formal laboratories and the ability to rapidly detect R resistant cases, and referred them for appropriate treatment. However, some regions (usually those with higher burden of drug-resistance), not having access to other DST, once the test is reported negative to resistance to rifampin, treat patients with a first-line drug regimen without further testing. In regions with high rates of DR-TB this can represent a serious problem.

It is well known that the vast majority of rifampin resistant patients will have a MDR-TB strain. For example, in a report from Haiti, 86.9% of patients with rifampin resistance detected by the Xpert®MTB/RIF were later proved to have MDR-TB due to simultaneous resistance to isoniazid (INH) [8], while a report from Zimbabwe found that 85.2% of patients detected with the Xpert®MTB/RIF as resistant to rifampin were actually MDR [9].

Non-MDR H resistance is remarkably prevalent globally (9.5% of all TB cases), and although the prevalence of H resistance is much higher than that of R, detection of H-resistance has received lower priority, largely because the clinical impact of H mono-resistance is less pronounced than that of R. Dekinger *et al.*, in a theoretical transmission model concluded that detection of H-resistance has minimal impact on transmission of TB, MDR-TB, and H mono-resistant TB [10]. Nevertheless, a large meta-analysis by Menzies *et al.*, shows that when patients with mono-resistance to H are treated only with first line drugs, treatment failure rates range from 18% - 44% [11]. The same meta-analysis found an increment of acquired drug resistance of 5.1 times in patients with INH-resistant disease vs. those with drug-susceptible disease (95%CI 2.3 - 11.0) [11].

A large data base from the WHO has estimated, as mentioned, that more than 80% of R resistant isolates are MDR-TB [12], while by comparison, an average of less than 40% of INH-resistant strains is MDR-TB [13] and therefore, more than 60% of H resistant cases are R sensitive.

H is highly bactericidal in rapidly dividing bacteria; the drug provides great initial killing activity at the start of antituberculosis treatment, after which rifampin largely takes over in terms of bactericidal activity, and rifampin and pyrazinamide then act as sterilizing drugs [14].

We have found that in a region with high burden of DR-TB, a high proportion of the cases with a rifampin-susceptible result by the Xpert®MTB/RIF had culture-proven resistance to INH (2 of them were actually MDR) and would have been treated with a 6-month regimen that included only first line drugs and a continuation phase of 3 times per week dosing if the only test for DR-TB would have been the Xpert®MTB/RIF. Also almost 9% of the patients with a negative Xpert test (which would have been diagnosed as non-TB cases) had a positive culture and half of those were resistant to H.

Isoniazid resistance is associated with overall increased treatment failure, relapse, and acquired multidrug resistance in patients treated with regimens containing only first-line tuberculosis drugs [11]. This problems will be worse in settings with high prevalence of poly-drug resistance (isoniazid resistance associated with resistance to pyrazinamide or ethambutol, or both), which can cause even higher rates of failure and relapse [15]. This is not a local or regional problem, since resistance to isoniazid without resistance to rifampin has been reported worldwide, especially in regions with high burden of drug resistant TB [16]. It is urgent that national TB programs implement the necessary infrastructure to complement the Xpert®MTB/RIF results with DST either by phenotypic or genotypic methods.

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Conflicts of Interest

None declared.

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