Review Article

DRUG RESISTANT TUBERCULOSIS NEW DIRECTIONS AND NEW DETECTION TOOLS

Salman H. SIDDIQI

Key words: Drug resistant tuberculosis

Ever increasing drug resistance in tuberculosis, from MDR (multi drug resistant) to XDR (extensively drug resistant) and the new reports of TDR (totally drug resistant), is a great threat[1]. In some of high burden countries like India, there are reports that more than 50% treated patients carry MDR strains and 5% of those are XDR and this situation is increasing[2]. Culture-based drug susceptibility test (DST) has come a long way. The use of solid medium used to take 5−6 weeks for results. Introduction of liquid medium, such as BACTEC MGIT, has reduced this time to only 2−4 weeks for complete detection and DST with 10−20% increase in the sensitivity of positive detection[3]. This is a significant help in the patient management.

Molecular-based tests have further reduced the time. Recently introduced Gene Expert is simple and detects TB and Rifampicin (RIF) resistance in about 2 hours, while another test, Hain's GenoType detects TB as well as resistance to RIF and Isoniazid (INH) but it is comparatively more time consuming and cumbersome. These tests are a great help in the management of new TB cases by rapid diagnosis and detection of MDR. However, these tests are for initial screening as the sensitivity of these for smear-negative and culture-positive cases is rather low. In the study carried out by FIND (Foundation for Innovative New Diagnostics), the sensitivity of Xpert was 98% for smear-positive, 72% for smear-negative, and 90−93% for RIF resistance[4]. Major shortcoming of these tests is inability to detect drug resistance of other first-line and second-line drugs. Hain's GenoType MTBDR*sl* detects resistance to Fluoroquinolone, Amikacin (AMK), Kanamycin (KAN), Capreomycin (CAP), and Ethambutol (EMB) but the sensitivity of several of these drugs is questionable.

WHO has recommended that most of the rapid molecular tests are good screening tests and thus, these tests do not eliminate the need of culture and DST and for culture-based tests liquid medium should be used wherever it is possible[5)6)].

A comprehensive CDC study is ongoing to detect gene mutations for resistance by sequencing and its relationship with DST results. Resistant TB strains are collected from all over the world and are tested for gene mutation for resistance in *rpoB* (RIF), *katG* &/or *inhA* (INH), *embB* (EMB), *pncA* (Pyrazinamide: PZA), *gyrA* (Ciprofloxacin: CIP and Ofloxacin: OFX), *rrs* or *eis* (KAN), *rrs* (AMK), *rrs* &/or *tylA* (CAP). A recent publication indicates that the sensitivity of detection of genetic resistance as compared to the culture-based tests was less than 90% for EMB, PZA, CIP, OFX, KAN and CAP, while at 95% cutoff only RIF agreed[7]. This is a limitation for existing molecular tests for the detection of drug resistance.

At present liquid medium (MGIT) is the best choice for second-line DST and for the detection of MDR and XDR (WHO). Several multi-center studies have been carried out to establish procedure and critical test concentrations[8)〜12)]. The critical concentrations establlished and WHO recent recommendation (unpublished) are given in the Table.

In summary, molecular tests help significantly in rapidly screening TB and MDR cases. Recommendations are to have a two-tier system. Molecular tests help in early diagnosis and screening MDR but ultimately all the clinical specimens should be tested for culture and DST as this is the most sensitive and accurate method. Liquid medium is preferred over the solid medium. Second-line DST should be perfomed only by liquid medium.

References

1) Velayati AA, Masjedi MR, Farnia P, et al.: Emergence of new forms of totally drug resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug resistant strains in Iran. Chest. 2009 ; 136 : 420−425.

Consultant Mycobacteriologist (several organizations)

Correspondence to: Salman H. Siddiqi, 15 Glencoe Manor Court, Sparks, Maryland, USA. (E-mail: siddiqi122@gmail.com)
(Received 5 Oct. 2012)

Table Recommended Critical Concentrations for Second-line Drugs in MGIT

Drug	Drug Concentrations μg/ml					WHO
	Study 1	Study 2	Study 3	Study 4	Study 5	
Amikacin	1.0	1.0	1.0	1.5	1.0	1.0
Kanamycin	ND	2.5	ND	ND	2.5	2.5
Capreomycin	2.5	2.5	1.25	2.5	2.5	2.5
Ethionamide	5.0	5.0	ND	5.0	5.0	5.0
Protionamide	2.5	2.5	2.5−5.0	ND	ND	2.5
Ofloxacin	2.0	2.0	1.0	ND	2.0	2.0
Moxifloxacin	ND	1.0	0.125	ND	0.25	0.5/2.0
Levofloxacin	ND	ND	ND	1.5	ND	1.5
Rifabutin	0.5	ND	0.5	ND	0.5	NA
PAS	ND	4.0	ND	ND	4.0	4.0
Linezolid	1.0	ND	ND	ND	1.0	1.0

2) Paramasivan CN, Rehman F, Wares F, et al.: First- and second-line drug resistance among previously treated tuberculosis patients in India. Int J Tuberc Lung Dis. 2010 ; 14 : 243.

3) Rodrigues C, Shenai S, Sadani M, et al.: Evaluation of the BACTEC MGIT 960 system for recovery and identification of *Mycobacterium tuberculosis* complex in a high thorough put tertiary care center. Indian J Med Microbiol. 2009 ; 27 : 217−221.

4) Boehme C, Nabeta P, Hillemann D, et al.: Rapid molecular detection of tuberculosis and rifampin resistance. New England J Med. 2010 ; 363 : 1005−1015.

5) WHO Policy Statement: Use of liquid TB culture and drug susceptibility testing (DST) in low and medium income settings. 2007.

6) WHO Policy Statement: Molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis. 2008.

7) Campbell PJ, et al.: Molecular detection of mutation associated with first-line and second-line drug resistance compared with conventional drug susceptibility testing of *M.tuberculosis*. Antimicrob Agen Chemother. 2011 ; 55 : 2032−2041.

8) Rüsch-Gerdes S, Pfyffer GE, Casal M, et al.: Multicenter Laboratory Validation of the BACTEC MGIT 960 Technique for Testing Susceptibilities of *Mycobacterium tuberculosis* to Classical Second-line Drugs and Newer Antimicrobials. J Clin Microbiol. 2006 ; 44 : 688−692.

9) Rodrigues C, Jani J, Shenai P, et al.: Drug susceptibility testing of *Mycobacterium tuberculosis* against second-line drugs using the BACTEC MGIT 960 system. Int J Tuberc Lung Dis. 2008 ; 12 : 1449−1455.

10) Kruuner A, Yates MD, Drobniewski FA: Evaluation of MGIT 960-Based Antimicrobial Testing and Determination of Critical Concentrations of First- and Second-Line Antimicrobial Drugs with Drug-Resistant Clinical Strains of *Mycobacterium tuberculosis*. J Clin Microbiol. 2006 ; 44 : 811−818.

11) Lin SYG, Desmond E, Bonato D, et al.: Multicenter evaluation of BACTEC MGIT 960 system for second-line drug susceptibility testing of *Mycobacterium tuberculosis* complex. J Clin Microbiol. 2009 ; 47 : 3630−3634.

12) Sharma M, Thiberts L, Chedore P, et al.: A Canadian Multicenter Laboratory Study for Standardized Second-line Antimicrobial Susceptibility Testing of *Mycobacterium tuberculosis*. J Clin Microbiol. 2011 ; 49 : 412−416.