

Inconsistency in the reporting of antitubercular drug susceptibility tests in an endemic region

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ABSTRACT

Background: Individualized treatment for multidrug-resistant tuberculosis (MDR TB) is associated with improved outcomes. Therapy needs to be tailored to drug susceptibility testing (DST) results. We present our observations on the inconsistency in DST reporting in an endemic region with a high prevalence of MDR TB. **Methods:** We retrospectively analyzed 118 DST reports from 10 different laboratories. **Observations:** Of 118 patients, only 79 (67%) had DST reports with results to all first-line drugs, a fluoroquinolone (excluding ciprofloxacin), all aminoglycosides, and a polypeptide. Twenty-one (18%) isolates did not have DST reports for all first-line drugs; 4 (3%) did not have DST reports for any second-line drugs; 9 (8%) did not have DST reports for a fluoroquinolone; and 31 (26%) did not have DST reports for all second-line aminoglycosides and polypeptide. **Conclusion:** Inconsistencies were observed in several of the 118 DST reports. A case is made for sensitization toward standardization and completeness in TB DST reporting in India.

KEY WORDS: Drug resistance, drug susceptibility testing, tuberculosis

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INTRODUCTION

Multidrug-resistant (MDR) tuberculosis (TB) is endemic in India, with nearly 71,000 pulmonary MDR TB cases notified in 2014.^[1] MDR TB therapy requires prolonged administration of antitubercular medications with the attendant challenges of default, loss to follow-up, adverse reactions to medications, and treatment failure, which in turn may amplify drug resistance. It is, therefore, essential to begin appropriate antitubercular therapy as soon as possible after diagnosis, and tailor therapy to drug susceptibility testing (DST) results, which improves outcomes (individualize treatment).^[2,3] Consequently, valid and consistent DST is central to the effective management of MDR TB.^[2,4]

Evidence-based guidelines recommend performing DST to all first-line drugs, isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin, and, where multidrug resistance is detected, to a panel of second-line drugs that must include all aminoglycosides, capreomycin (due to reported cross resistance), and a fluoroquinolone of choice (only one may be tested due to extensive cross resistance).^[5-7] The WHO recommends DST to first-line drugs using an automated liquid culture system.^[5,7] DST methods to most second-line drugs have not yet been standardized.^[2] The selection of drugs for testing must be guided by local susceptibility patterns and treatment policies.^[5]

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In the Mumbai region, India, there is a high prevalence of preextensively drug resistant (pre-XDR) TB, with a majority of isolates exhibiting resistance to fluoroquinolones, including ofloxacin and moxifloxacin. There is also a high prevalence of resistance to ethambutol, pyrazinamide, streptomycin, and ethionamide. Resistance to aminoglycosides and polypeptides is less prevalent.^[8,9]

Here, we present our observations on the inconsistency in DST reporting in an endemic setting with a high prevalence of pre-XDR and XDR TB.

METHODS

We retrospectively analyzed the DST reports of 118 MDR TB patients who presented to us over a period of 5 years. DSTs were performed at 10 different laboratories by one or more of the following methods: phenotypic methods (*in vitro* DST on Löwenstein-Jensen medium by the resistance ratio method or using the BD BACTEC™ MGIT™ 960 System) or by genotypic resistance profiling (Cepheid TB GeneXpert® System or Hain Lifescience GenoType MTBDR*plus* and GenoType MTBDR*sl* Systems).

RESULTS

Of 118 patients, only 79 (67%) had DST reports with results to all first-line drugs, a fluoroquinolone (excluding ciprofloxacin), all aminoglycosides, and a polypeptide.

Fifty-two of the 118 patients (44%) had only MDR TB, 51 (43%) pre-XDR TB, and 12 (10%) XDR TB while three (3%) could not be classified beyond multidrug resistance. Of the three unclassifiable isolates, two were not tested against second-line aminoglycosides, polypeptides, and fluoroquinolones, and the susceptibility of one to fluoroquinolones was reported as “indeterminate” (the isolate was tested by line probe assay-Hain Lifescience GenoType MTBDR*sl*).

Three MDR TB isolates (3%) were not tested against ethambutol and pyrazinamide. Four (3%) isolates were not tested against any second-line drug, despite two of these being resistant to all tested first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide, and

streptomycin). Four (3%) isolates were not tested against any aminoglycoside or capreomycin. Eight (7%) isolates were tested against only kanamycin, but not against amikacin or capreomycin. Ten (9%) did not have actionable reports to fluoroquinolones (nine untested and one reported as “indeterminate”), and 5 (4%) were not tested against the WHO group 4 drugs (ethionamide, cycloserine, and para-aminosalicylic acid). The number of isolates that were not tested against specific drugs, and the number of pre-XDR TB, XDR TB, and unclassifiable isolates among these are shown in Table 1. The observed compliance with current guidelines is shown in Table 2.^[5,6]

DISCUSSION

MDR TB treatment regimens must include at least five effective drugs, including an injectable (aminoglycoside or polypeptide), a fluoroquinolone (excluding ciprofloxacin, which is no longer recommended), and at least two other second-line drugs.^[10,11] The individualization of treatment with tailoring of antitubercular therapy to DST results has been shown to improve treatment outcomes.^[2]

DST to isoniazid and rifampicin shows good reliability and reproducibility while it is less reliable and reproducible for pyrazinamide, ethambutol, and streptomycin. Although DST methods to most second-line drugs have not yet been standardized, guidelines recommend liquid culture DST to aminoglycosides, polypeptides, and fluoroquinolones as they yield fairly reliable and reproducible results.^[5-7]

Complete DST is performed for only 25% of MDR TB patients in India.^[1] We observed inconsistency and incompleteness in DST reporting in several of the 118 patients who presented to us. For patients with incomplete DST reports, drugs need to be instituted empirically, rendering the exercise and expense of susceptibility testing inadequate. Also, once growth is reported on TB culture, laboratories often request the treating teams to choose the drugs to which sensitivity testing is desired. We ask if this practice is appropriate and can be improved upon to make reporting standardized.

Mycobacterium tuberculosis takes up to 6 weeks to grow on culture and may take an additional 4 weeks to yield a

Table 1: Number of isolates not tested against specific drugs and the number among each that were multidrug resistant, preextensively drug resistant, extensively drug resistant, or unclassifiable

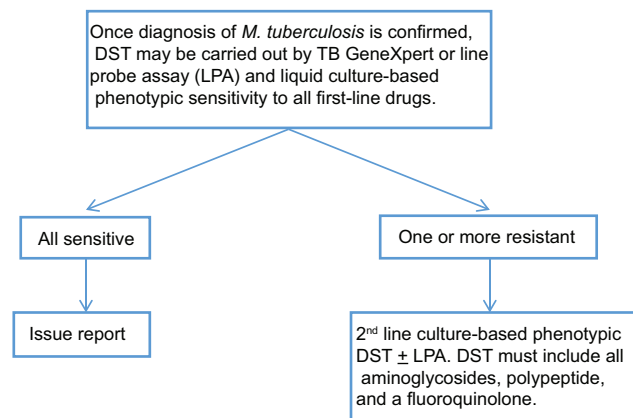
Drug	Not tested (%)	Indeterminate (%)	MDR	Pre-XDR	XDR	Unclassifiable
Ethambutol	3 (2)	0	2	1	0	0
Pyrazinamide	21 (18)	0	13	5	1	2
Streptomycin	9 (8)	0	5	4	0	0
Kanamycin	6 (5)	0	4	0	0	2
Capreomycin	13 (11)	0	10	1	0	2
Amikacin	30 (25)	0	21	6	1	2
Ethionamide	14 (12)	0	8	4	0	2
Cycloserine	100 (85)	0	58	28	11	3
PAS	13 (11)	0	7	3	0	3
Fluoroquinolone	9 (8)	1 (1)	7	0	0	3

PAS: Para-aminosalicylic acid, MDR: Multidrug resistant, XDR: Extensively drug resistant

Table 2: Observed compliance with guidelines

Guideline	Observation (total n=118)
DST must be carried out against all first-line drugs for MDR TB isolates	21 (18%) isolates did not have DST reports for all first-line drugs
DST against second-line drugs must be carried out for MDR TB isolates	4 (3%) isolates did not have DST reports for any second-line drug
DST must be performed against a fluoroquinolone where MDR TB is suspected	9 (8%) isolates did not have a DST report for a fluoroquinolone
DST must be performed against all second-line aminoglycosides and polypeptide where MDR TB is suspected	31 (26%) isolates did not have DST reports for all second-line aminoglycosides and polypeptide
Ciprofloxacin is no longer recommended for antitubercular therapy	DST against ciprofloxacin was reported for 2 (2%) isolates

MDR: Multidrug resistant, TB: Tuberculosis, DST: Drug susceptibility testing

**Figure 1:** Suggested workflow for laboratories performing drug susceptibility testing

DST report. This duration equals nearly half the intensive phase of treatment. The association between *in vitro* susceptibility of most antitubercular drugs, their use in therapy, and consequent treatment success has been demonstrated.^[2,9] We, therefore, believe that it is important to have a complete and actionable DST report. Where DST is a distinct possibility, it must be carried out completely in a standardized manner to ensure appropriate and adequate antitubercular therapy is prescribed.

For MDR TB, particularly in an endemic region, DST must be attempted to all first-line drugs as well as to a panel of second-line drugs that may be selected by the laboratory based on guidelines, local susceptibility patterns, and availability. Susceptibility to drugs from the different WHO groups may be carried out in a sequential manner as advised by guidelines to ensure cost-effectiveness.^[5,6]

An indeterminate result must be reassessed by another phenotypic or genotypic method. A laboratory workflow as outlined in Figure 1 has been proposed so that the precious sample obtained by TB culture may be appropriately utilized.^[5,6]

CONCLUSION

We present a case for sensitization toward standardization and completeness in TB DST reporting.

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Conflicts of interest

There are no conflicts of interest.

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