Original Article

Drug-resistant tuberculosis: Study of clinical practices of chest physicians, Maharashtra, India

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ABSTRACT

Background: Patients suffering from drug-resistant tuberculosis (DR TB) avail of private care since Programmatic Management of DR TB (PMDT) is not universally available in India. Management of DR TB is challenging and involves great expertise. Chest physicians (CPs) play a major role in this area. The study was undertaken with the objective to see whether the practices of CPs comply with current guidelines and to identify areas where they could be involved to improve access to PMDT. **Materials and Methods**: For this cross-sectional study, CPs from Mumbai and Nagpur, Maharashtra, India, were given pretested questionnaires to be filled in and returned. **Observations**: Of 70 enlisted CPs, 29 (41%) responded. Twenty-six (89%) respondents used the drug susceptibility test (DST) for diagnosis: private labs and hospitals were preferred; 9 (31%) used standard treatment, 15 (51%) switched to individual treatment after starting standard therapy and 12 (41%) started empirical treatment later switched to individual treatment as per the WHO guidelines. Seven consultants (10%) used in addition drugs from alternative systems of medicine for immune modulation and adverse drug effects. Eighty-six per cent CPs monitored treatment by smear examination, 51% by culture and 93% used X-rays. Reported case holding in the form of regular follow-up consultation visits was around 70%, treatment success estimated to be between 30% and 70%, and deaths around 30%. Adverse drug reactions were reported in around 30% cases. **Conclusion**: This study shows that most private CPs generally comply with current guidelines for management of DR TB. Accreditation of private labs for DST, involving CPs in diagnosis, treatment and monitoring of patients through public private partnerships can improve access to PMDT.

KEY WORDS: Chest physicians, compliance, DR TB, guidelines, practices

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INTRODUCTION

In 2008, an estimated 390 000–510 000 cases of multidrug-resistant tuberculosis (MDR-TB) emerged globally (best estimate, 440 000 cases).[1,2] Despite progress in programmatic management of drug-resistant TB (PMDT), globally fewer than 30,000 cases (approximately 6%) were successfully diagnosed and notified.[1,2] In India, the PMDT is in infancy although the Revised National Tuberculosis Control Program has 100% coverage and has achieved case detection rate and treatment success rate targets. It is estimated that approximately 110,000 MDR-TB cases will need second-line treatment in India.[3] It will be long before universal access to second-line drugs (SLD) will be available. Thus, patients detected as having drug-resistant TB (DR TB) will continue to seek private care in the foreseeable future.

Management of DR TB is challenging and involves considerable expertise. Chest physicians (CPs), thus, play a major role in management of DR TB. Use of quality assured laboratories for diagnosis, standard drugs with good bioavailability used in rational combinations and adherence to treatment are some of the prerequisites of good management.

The authors thought it relevant to study the practices of

CPs in managing DR TB and their compliance with current guidelines. The findings of this study will enable program managers to understand issues and evolve strategies to involve this group of consultants in PMDT.

MATERIALS AND METHODS

Study Setting
Mumbai and Nagpur the two cities in one of India's largest state of Maharashtra were selected for the study. Nagpur has been implementing the PMDT since 2007 through the public sector, Mumbai was selected for implementing PMDT in the public sector in the second phase and training of public health staff has been completed.

Study design and Sample
This cross-sectional study involved consenting CPs managing DR TB. As no comprehensive list was available, CPs were listed from the membership registers of various professional bodies including the Association of Medical Consultants, Indian Chest Society, and Local Medical Associations. A total of around 70 consultants were proposed to be interviewed. The study was carried out between December 2008 and June 2009.

Survey tool
A pre-tested, structured schedule was prepared for carrying out the study. The questionnaire included information of general profile of the treating chest physician, their practices related to diagnosis, treatment, monitoring and evaluation, and perception regarding DR TB. Initially, it was proposed to conduct interviews at the consultant's clinic by prior appointment. However, this strategy failed as consultants due to their busy work schedules did not give appointments and if they did, could not give adequate time to the interviewer. The tool was then redesigned to facilitate responses to be filled in by the consultants at their convenience. The questionnaire was left at the CPs clinic to be collected at a later date. In Mumbai, the questionnaire was sent through e-mail to be filled and returned electronically.

The study was sanctioned by the Institution's Ethics Committee.

Data and analysis
The data was entered on SPSS on receipt of the responses and entries were rechecked after all data was obtained and entered. Analysis was performed through cross tabulations of variables using the descriptive statistics function of SPSS analysis.

Observations
A total of 29 (41%) of the enlisted 70 (50 from Mumbai and 20 from Nagpur) CPs responded, 15 from Mumbai and 14 from Nagpur. Of these, only two were female. Most of the consultants were in private practice (26/29), 3 were in fulltime government service. Of the 26 private consultants, 12 were also associated with NGOs and 6 with Government and Academic Institutions. Clinical experience varied with 14 consultants having more than 10 years experience [Table 1].

The average number of TB patients seen in a month was 68 (range 3–200) and that of DR suspects was 8 (range 0–35). The number of TB patients or DR suspects seen by the Consultants was not related to the level of clinical experience.

Table 2 shows the responses to issues in management of DR TB.

Suspicion of DR TB through a combination of clinical, bacteriological, and radiological presentations was reported by 26 CPs, Clinical and radiological presentations by 8 and only clinical presentation by 6 CPs.

Twenty-one of 28 (75%) CPs confirmed DRTB by DST only, 2/28 (7%) only through therapeutic trial and 5/28 (18%) used both DST and therapeutic trial of SLD in some cases to confirm drug resistance. Therapeutic trial was resorted to in cases of EPTB or non-availability of sputum specimen for culture and where clinical and or radiological suspicion was high.

Preference of lab
22/27 respondents sent DST specimen to private labs, 1 also to a NGO run lab and only 5 (all from Nagpur) referred to the Intermediate Reference Laboratory. All CPs preferred DST to both first- and second-line TB medicines.

Treatment strategies
24/29 Consultants responded to this section. The respondents treated DR TB through three distinct strategies: 9/24 used standard second-line treatment throughout; 12/24 would start empirical treatment and individualize on DST reports and 15/24 would start standard second line treatment, wait till DST reports and start individualized treatment. The choice of strategy would depend on the prior drug history, availability of DST reports, and clinical condition of the patient. This approach resulted in application of more than one strategy by the respondents.

Table 1: Clinical experience and the type of practice of the 29 respondents

Particulars		Mumbai	Nagpur	Total
Total CPs interviewed		15 (2 Females)	14	29
Years in practice	1 – 5	1	2	3
	6 – 10	3	3	6
	11 – 15	3	0	3
	16 – 20	3	1	4
	> 20	5	2	7
	Not responded	0	6	6
Type of practice*	Private	13	13	26
	NGO/charitable	11	1	12
	Government	5	4	9
	Academic institution	5	4	9

*Some CPs are involved in more than one type of practice

Among the SLDs, CPs preferred to use drugs from each of the five groups of anti TB medicines [Table 3], including drugs like amoxicillin–clavulinic acid combination, clofazimine, linezolid, macrolides like clarithromycin and roxithromycins. Group 5 SLDs were included in the treatment by 15 respondents.

Medicines being expensive, seven CPs directed the patients to NGOs for free or subsidized medicines.

Seven CPs used medicines other than allopathic along with the second-line treatment as immune modulators.

Table 2: Responses by chest physicians: Management of DR TB*

Particulars	Mumbai	Nagpur	Total
Diagnosis (*n* = 28)			
Suspicion of DR TB (28)			
Clinical	2	4	6
Clinical + radiological	3	5	8
Clinical + radiological + bacteriological	15	11	26
Confirmation (28)			
DST only	11	10	21
DST + therapeutic trial	4	1	5
Therapeutic trial only	0	2	2
Lab type (27)			
Private lab	15	7	22
NGO lab	1	0	1
Govt. lab	0	5	5
Treatment (*n* = 24)			
Standard	7	2	9
Empirical followed by individualized	7	5	12
Standard followed by individualized	7	8	15
Alternative therapy (*n* = 24)			
Ayurvedic	2	3	5
Homeopathic	1	1	2
Unani	0	0	0
Siddha	0	0	0
Reasons for surgery (*n* = 24)			
Localized lesions	12	9	21
Haemoptysis	7	8	15
Non response to treatment	5	3	8
Others	15	14	29
No surgery		2	2
Monitoring and follow up (*n* = 29)			
AFB culture only	0	0	0
AFB smears only	9	1	10
AFB smears + culture	6	9	15
X-rays only	0	2	2
X-rays + bacteriology	15	10	25
Clinical	15	12	27#

#Two respondents relied only on clinical follow up, *More than one response by an individual. DR TB: Drug-resistant tuberculosis, DST: Drug susceptibility test, AFB: Acid-fast bacillus, NGO: Non-governmental organization

Five used Ayurvedic medicines and two homeopathic treatment. Additionally, two CPs reported using other allopathic medicines.

Surgery in DR TB

22 of the 24 respondents considered surgical intervention during the course of treatment. Twenty-one would advise surgery for localized lesions, 15 for severe haemoptysis, and 8 for non-response to medicines. Other reasons for surgical intervention provided by the respondents included: aspergillomas, bronchiectasis, broncho-pleural fistulae, empyema, lymph node excision, and lung volume reduction to improve quality of life.

Twenty CPs stated that they hospitalize patients during treatment. Several reasons for hospitalization were mentioned: severe haemoptysis (mentioned by 19), adverse drug events (mentioned by 14), co-morbid conditions such as diabetes, renal or respiratory failure (mentioned by 5). No CP admitted their patients for purpose of observation of treatment as required by the national guidelines.

Monitoring and assessment of treatment success through bacteriology was reported by 25/29 (83%) CPs (15 by Acid-fast bacillus (AFB) Smears + Culture and 10 AFB Smears alone). In addition to bacteriology, all 25/29 CPs used X-rays. Two CPs used radiology exclusively to monitor treatment and two relied only on clinical follow up.

Of the 27/29 CPs who decided to change treatment at some time during the course, 17 changed therapy for treatment failure, 17 for adverse drug events, and 1 each for issues of cost and availability of SLDs.

Consultants reported uniformly good case holding in the form of regular follow-up consultation visits. This was irrespective of the clinical experience in years—majority of the consultants reported regular follow-up visits by more than 70% patients. The CPS did not document treatment outcomes, they were asked to estimate the proportion of MDR TB patients under their care with successful treatment outcomes in the range of less than 30%, 30–70%, or above 70%. All respondents reported treatment success in the range 30–70%, and deaths were reported to the extent of 30%. Adverse drug events were reported in around 30% cases. Default, although not measured, was attributed to high cost of drugs and shopping for health.

Table 3: Alternative method of grouping anti-tuberculosis agents (adapted from World Health Organization)

Grouping	Drugs
Group 1: First-line oral agents	Isoniazid, rifampicin, ethambutol, pyrazinamide, rifabutin
Group 2: Injectable agents	Kanamycin, amikacin, capreomycin, streptomycin
Group 3: Fluoroquinolones	Moxifloxacin, levofloxacin, ofloxacin
Group 4: Oral bacteriostatic second-line agents	Ethionamide, prothionamide, cycloserine, terizidone, ρ-amino salicylic acid
Group 5: Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	Clofazimine, linezolid, amoxicillin/ clavulanate, thioacetazone, imipenem/ cilastatin, high-dose Isoniazid, clarithromycin

WHO: World health organization, MDR-TB: Multidrug-resistant TB

Twenty-eight of the 29 consulting CPs were willing to participate in case notification protocols.

DISCUSSION

Ours is the first study from India reviewing clinical practices of private CPs for DR TB and assessing their compliance to current guidelines. An important limitation of our study was the small numbers who responded to our questionnaire. Our initial strategy of personal interviews had to be changed as it was extremely difficult to get appointments for the interviews and even when consultants consented, they could not devote adequate time. We managed to get 29 of the 70 (41%) CPs enlisted to respond. In a similar survey carried out in UK, 72% physicians responded.[4]

Drug Susceptibility Testing is essential for the diagnosis of DR TB. 26/28 (93%) responding CPs in our study confirmed DR TB through DST to both first- and second-line drugs mostly at private laboratories (only 5 CPs sent their patients to the Intermediate Reference Laboratory at Nagpur). Two of 28 (7%) did not comply with the guidelines for diagnosis and started SLD on mere clinical or radiological suspicion. Failure to confirm by DST may lead to avoidable expenses and may amplify drug resistance and increase drug-related morbidity. In cases in whom smears and cultures are negative with a strong clinical and radiological suspicion of drug resistance and in extra-pulmonary cases, one may be justified to resort to a therapeutic trial with SLDs as done by 7/28 (25%) of the respondents. Early and correct diagnosis of drug resistance is essential to prevent its spread. There is thus an urgent need to improve access to diagnosis through accreditation of private laboratories.

PMDT advocates periodic cultures to assess treatment response. 15/29 (54%) of CPs complied with this guideline. In resource-limited settings like ours, cultures may not only be an avoidable financial burden but may also lead to delays in decisions. This could be the plausible explanation for 10/29 (36%) of CPs using sputum smears without cultures for monitoring treatment. A recent follow-up study in India[5] has shown that sputum smears could be used as a surrogate for culture to monitor treatment. Larger studies need to be designed to assess the role of sputum smears in monitoring treatment. This would prevent delay in decision making and may also be cost-effective. X-rays alone are poor prognostic indicators. Notwithstanding this, two respondents (7%) relied only on X-rays and additionally two CPs only on clinical response. They did not use smears or cultures to monitor treatment.

Our data show that the treatment strategies followed are in line with the current WHO recommended guidelines which are: (1) standardized treatment whenever reliable DST is not readily available; (2) standardized treatment followed by individualized treatment where DST testing is reliable and easily accessible, and (3) empirical treatment

followed by individualized treatment.[6] None of the respondents used strategy other than these although in various combinations. However, in formulating the regimen, 52% CPs used drugs from group five [Table 3] that are not recommended for routine use for MDRTB treatment by WHO.[7] Referrals to NGOs providing subsidized second line drugs may be an issue of concern for quality of care as there is no knowledge about their practices. This can be a subject for future research.

In a meta-analysis[8] of 26 trials with a total 4959 patients reporting end of treatment outcomes, 62% of patients met the definition of successful treatment, while 11% died and 8% failed therapy. The default rate was 13%, while 2% had their care transferred to another jurisdiction. A tertiary referral hospital in New Delhi, India,[9] where standard therapy was used reported 67.9% cure, 14.3% deaths, 17.9% defaults, but no failures among patients who had completed a 2-year treatment course. The reported outcomes in our study compare well with these although they may not be accurate as documentation practices were not studied.

Alternative systems of medicine such as Ayurveda and Homeopathy claim to have good immune system modulators. Seven of 24 (29%) CPs reported use of drugs for this purpose: 5—Ayurvedic medicines and 2—homeopathic medicines. A survey among a heterogeneous group of family physicians reported use of alternative medicines in treatment of tuberculosis by 20 of 104 surveyed (19%). Controlled studies using alternative therapies as adjuvant to SLDs to boost immunity and alleviate adverse drug effects are needed to record evidence of improving cure rates and quality of life of DR TB patients as has been shown in a study in an HIV cohort in Mumbai.[10]

In a recently published study, general practitioners from a large slum in Mumbai were found to be lacking in knowledge of correct prescription practices.[11] However, higher training bestows higher responsibility and specialists like CPs are expected to comply with guidelines. Our group of CPs, although not representative due to the small numbers, is reasonably compliant with the prevailing guidelines in managing patients. There will always be an intrinsic gap between individual patient management and that of large populations which needs to be acknowledged and understood by policy makers.

Limited health budgets have hampered implementation of PMDT in India. This limited access will compel patients from all socio-economic backgrounds to approach private consultants for care. Since the practices of CPs are mostly compliant with the current guidelines, the program will benefit by enlisting their support in areas where they are proficient such as in diagnosis and clinical monitoring. CPs could also be involved as members of the diagnostic committees as has been done in Philippines where specialists have been empanelled on local/regional TB

Diagnostic Committees for diagnosis of sputum negative cases.[12] Access to PMDT could be improved through public–private partnerships involving CPs, NGOs, and pharmaceutical industry to establish a model cost sharing drug delivery system on lines of antiretroviral therapy (ART) programs that have been researched in Mumbai and Chennai.[13] These linkages will not only improve access but also have the potential to ensure quality of care and prevent XDR TB.

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