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Prevalence of extensively drug-resistant tuberculosis among patients with multidrug-resistant tuberculosis: a retrospective hospital-based study

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Background & objective: **Extensively drug-resistant tuberculosis (XDR-TB) is a difficult-to-treat form of multidrug-resistant tuberculosis (MDR-TB). High rates of XDR-TB have been reported from India. We sought to ascertain the prevalence of XDR-TB among patients with MDR-TB treated at a tertiary care centre in New Delhi, India.**

Methods: **Case records of patients treated for MDR-TB at the All India Institute of Medical Sciences hospital, New Delhi, between 1997 and 2003 were retrospectively reviewed. All patients underwent a pre-treatment drug-susceptibility testing (DST) to first- as well as second-line drugs. XDR-TB was defined as TB caused by bacilli showing resistance to rifampicin and isoniazid in addition to any fluoroquinolone and to at least one of the three following injectable drugs: capreomycin, kanamycin, and amikacin.**

Results: **A total of 211 laboratory-confirmed cases of MDR-TB were reviewed. The mean age of the patients was 33 ± 12 yr. Fifty one (24%) patients were females. All patients were sero-negative for human immunodeficiency virus infection. Five of the 211 MDR-TB patients had XDR-TB. The prevalence of XDR-TB was 2.4 per cent among MDR-TB patients.**

Interpretation & conclusion: **Our results showed that XDR-TB was rare among patients with MDR-TB treated between 1997 and 2003 at our centre. Unreported selection bias might have been responsible for the high prevalence of XDR-TB reported in previous hospital-based studies from India.**

Key words Drug resistance - extensively drug-resistant tuberculosis (XDR-TB) - India - multidrug-resistant tuberculosis (MDR-TB) - tuberculosis

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) have emerged as significant threats to global tuberculosis (TB) control. The magnitude of the problem is evident from the fourth global report of the World Health Organization (WHO) which reported data from 81 countries across the globe[1]. Currently, MDR-TB accounts for 5.3 per cent of all TB cases in the world, with the prevalence among new and previously treated cases being 2.9 and 15.3 per cent

respectively. This report also has data on XDR-TB in which second-line drug susceptibility testing (DST) was carried out on 4012 MDR-TB isolates from 35 countries; among these, 301 (7%) were found to be extensively drug-resistant[1]. As of June 2008, 49 countries have reported laboratory confirmed XDR-TB cases to the WHO[2]. The exact prevalence of XDR-TB in most regions of the world is currently unknown. A few earlier hospital-based studies from India have reported alarmingly high rates of XDR-TB among patients with MDR-TB[3-5]. However, our personal experience in treating a large number of patients with MDR-TB is that XDR-TB would be uncommon in our setting. In order to confirm this anecdotal observation, we formally set out to ascertain the prevalence of XDR-TB among patients treated for MDR-TB at a tertiary care centre in New Delhi.

Material & Methods

The case records of patients with MDR-TB treated, during the period from 1997 through 2003, at the All India Institute of Medical Sciences (AIIMS) hospital, New Delhi were retrospectively reviewed. AIIMS is a large, tertiary level teaching hospital located in northern India. Before the initiation of treatment for MDR-TB, all patients underwent mycobacterial culture and DST at the New Delhi Tuberculosis Centre Laboratory, New Delhi. This laboratory was a supranational reference laboratory of the WHO during the study period. Cultures were done on Lowenstein-Jensen (LJ) slopes by Petroff's method[6]. Niacin test, catalase test and para-nitrobenzoic acid (PNB) test were used to identify the isolated mycobacteria. DST was carried out by the proportion method for first-line drugs and resistance ratio method for second-line drugs[7]. The tested drugs and their critical concentrations (in µg/ml) were as follows: isoniazid - 0.2, rifampicin - 40, pyrazinamide - 100, ethambutol - 2, streptomycin - 4, kanamycin - 64, ciprofloxacin - 8, ofloxacin - 8, ethionamide - 320, cycloserine - 160, para-aminosalicylic acid - 4, thiacetazone - 4, and clarithromycin - 128. MDR-TB was defined as TB caused by bacilli showing resistance to at least isoniazid and rifampicin. XDR-TB was defined as TB caused by bacilli resistant to rifampicin and isoniazid in addition to any fluoroquinolone and at least one of the three injectable second-line drugs: capreomycin, kanamycin and amikacin[8]. Human immunodeficiency virus (HIV) testing was carried out routinely in all patients.

Results

Of the 211 patients with MDR-TB, 67.4 per cent came from various States outside Delhi and 32.6 per cent from within Delhi. Most (98%, n = 207) of these patients had a history of previous treatment for tuberculosis. Only four patients were naïve to anti-tuberculous drugs. The mean age of the patients was 33 ± 12 yr; 51 (24%) patients were female. The mean body mass index was 17.3 ± 3.0 kg/m^2. All patients tested negative for HIV infection. The resistance rates to various first and second-line drugs observed are shown in Table I. Of the 211 patients, 21 patients (10%) showed resistance to one of the fluoroquinolones and 14 (6.6%) showed resistance to the injectable agent, kanamycin. Five cases of XDR-TB were detected. Thus, the prevalence of XDR-TB among MDR-TB patients was 2.4 per cent. Among the five XDR-TB patients, two patients had a definite history of previous treatment with second-line drugs; the remaining three patients had multiple previous courses of anti-tuberculosis therapy which most likely included second-line agents, but no detailed records were available. Table II shows the characteristics of the patients with XDR-TB.

Discussion

We found that XDR-TB was rare among patients treated for MDR-TB at our centre. Our findings do not support the earlier reports of frequent occurrence of XDR-TB in India. The reported prevalence of XDR-TB in these hospital-based studies varied from 7.4 - 33.3 per cent (Table III). However, a population-based study from southern India suggested a low prevalence of XDR-TB[9]; notably, DST was performed at a WHO-accredited laboratory in this study. Our findings are

Table I. Resistance rates to various first-line and second-line drugs among MDR-TB patients*

First-line drug	Resistance rate (%)	Second-line drug	Resistance rate (%)
Isoniazid	100	Kanamycin	6.6
Rifampicin	100	Ciprofloxacin	9.5
Pyrazinamide	8.1	Ofloxacin	9.0
Ethambutol	20.9	Sparfloxacin	4.8
Streptomycin	49.8	Cycloserine	4.3
		Ethionamide	3.8
		Clofazimine	1.9
		PAS	2.4
		Thiacetazone	8.7

*Note - 206 patients were tested for thiacetazone, 209 patients for cycloserine, 209 patients for clofazimine, and 208 patients for sparfloxacin. Other drugs were tested in all 211 patients.
PAS, para-aminosalicylic acid

Table II. Characteristics of the patients with XDR-TB

S.No.	Age/Sex	Body-mass index (kg/m^2)	Previous treatment for TB	Previous use of second-line drugs	Type of TB	Pattern of drug resistance
1	42 / Male	15.2	Yes	N.A	Pulmonary	R, H, K, Of, Cip, Thi
66	40 / Male	15.4	Yes	N.A	Pulmonary	R, H, S, K, Cip
100	58 / Male	17.2	Yes	N.A	Pulmonary	R, H, E, S, K, Cip, Of, Spar, Thi, Clof, Cyc, Et, PAS
142	25 / Male	16	Yes	Yes	Pulmonary	R, H, K, Cip, Of
180	24 / Male	18	Yes	Yes	Pulmonary	R, H, S, K, Cip, Of

Cip, ciprofloxacin; Clof, clofazimine; Cyc, cycloserine; E, ethambutol; Et, ethionamide; H, isoniazid; K, kanamycin; Of, ofloxacin; PAS, para-aminosalicylic acid; R, rifampicin; S, streptomycin; Spar, sparfloxacin; Thi, thiacetazone; N.A, Not available

Table III. Published studies on the prevalence of XDR-TB in India

Study	Setting	No. of MDR-TB patients	No. of HIV-infected patients	Prevalence of XDR-TB, n (%)
Mondal *et al*[3]	Tertiary care centre, Lucknow	68	Not reported	5 (7.4)
Jain *et al*[4]	Tertiary care centre, Mumbai	326	Not reported	36 (11)
Singh *et al*[5]	Tertiary care centre, New Delhi	12	All HIV-infected	4 (33.3)
Thomas *et al*[9]	Field trial, Chennai	66	Not reported	1 (1.5)
Present study	Tertiary care centre, New Delhi	211	All HIV-negative	5 (2.4)

MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis

in consonance with such an observation. The high rates of XDR-TB observed in previous hospital-based studies might be due to referral bias. Moreover, the DST was not performed at quality-assured, accredited laboratories in any of these studies. HIV infection and local failure of the control programme could have also possibly contributed to varying rates of drug-resistant TB in these studies and so is the small number of patients included in some studies.

The discrepancy in findings between the present and an earlier study[5] from the same institution can be explained by the difference in the nature of the two studies. The previous study[5] was conducted in full-blown AIDS patients and therefore, the basic study population was different from the present study. Although the present study was also hospital-based, we found that XDR-TB was rare. Notwithstanding, in our study, the DST was performed at a supranational reference laboratory. Perhaps, this might be one of the reasons for the discordant observations.

Another interesting observation was that none of the patients with MDR-TB was HIV co-infected in the present study. This finding is in agreement with previous studies on drug-resistant TB that had shown that HIV infection is not more common among drug-resistant TB patients than in the general population[10-12], although there are studies which contradict this finding[13,14]. Though there are extensive data on HIV prevalence in TB as a whole, there have been only a few studies on prevalence of HIV among MDR-TB patients from India. In a study conducted in Chennai, HIV seropositivity among MDR-TB patients was 4.42 per cent[15], which is comparable to rates of HIV observed among ordinary TB patients. It is possible that HIV co-infected patients with MDR-TB succumbed to the illness before they could be diagnosed.

There are certain limitations to the present study. First, due to its retrospective nature, the study may not truly reflect the current pattern of drug resistance. It is well known that drug resistance is a dynamic phenomenon that needs to be studied in real-time. Second, being a hospital-based study, the present observations cannot be extrapolated to the community settings. Nonetheless, the low prevalence of XDR-TB in this referral population is reassuring.

The present observation, however, should not lead to a state of complacency. Large-scale representative population-based data are urgently needed to find out the true prevalence of XDR-TB in the community. Periodic drug-resistance surveillance should become a part of the national TB control programmes. It is important to improve the laboratory infrastructure and establish a nationwide network of quality-assured laboratories capable of carrying out second-line

DST. Second-line drugs must be used judiciously and cautiously by physicians at all levels of medical care. Irrational use of second-line drugs, like adding fluoroquinolones to a first-line regimen or a failing regimen, should be avoided. Future large-scale population-based prospective studies should throw light on the prevalence of XDR-TB in the community.

Conflicts of interest

We declare that we have no conflict of interest.

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