DRUG RESISTANT TUBERCULOSIS — THE EMERGING SCENARIO

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ABSTRACT

During the period April 1992 to September 1994 a total of 2288 patients of pulmonary tuberculosis were treated at our centre. *M. tuberculosis* could be isolated from the sputa of 1037 patients (45.3%). All the isolates were subjected to indirect susceptibility testing using drug incorporated Lowenstein-Jensen medium slants. A total of 142 (13.7%) patients showed drug resistance. Single drug resistance was observed in 86 (8.3%) patients whereas resistance to two or more drugs was observed in 56 (5.4%) patients. Patients showing initial drug resistance were more in number (83 cases) than those showing acquired drug resistance (59 cases). Resistance to streptomycin was commonest (8.3% of isolates) followed by isoniazid (5.7%) and rifampicin (5.0%). Multiple drug resistance was mostly acquired (71.4% of drug-resistant isolates).

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KEY WORDS : Antitubercular agents; Drug resistance microbial; Tuberculosis.

Introduction

After 113 years of discovery of the causative organism, tuberculosis still marches ahead as one of the mightiest killers of the human race. The old enemy has acquired a reinforced armoury in the form of drug resistance which is proliferating not only in third world countries but also in other countries with strong scientific and financial might [1-4]. Emergence of drug-resistance has reduced the efficacy of treatment to almost the level of the pre-chemotherapeutic era [6] and is a limiting factor in our attempts to cure individual patients and, thereby, to eradicate the disease from the community. These patients will eventually form the pool which will spread the drug-resistant strains in the community [7]. The problem of drug-resistance is to a large extent due to acquired resistance and can be prevented by ensuring adequate management with an appropriate regimen [7-9].

We in the Armed Forces deal with a patient population which is fairly different from the usual cohort of tuberculosis patients found in any other tuberculosis clinic. This study has been carried out to estimate the prevalence and pattern of drug-re-

sistance in the Armed Forces. In our patient population we had soldiers from all parts of the country. We also had small group of patients composed of family members of serving personnel.

Material and Methods

The study included sputum samples from 2288 cases of pulmonary tuberculosis treated at the Military Hospital (Cardiothoracic Centre), Pune during the period April 1992 to September 1994. Early morning sputum samples from all patients, irrespective of previous history of drug intake, were cultured on Lowenstein-Jensen (LJ) slants on 3 successive days after concentration by modified Petroff's method using 4 per cent NaOH. LJ slants were incubated at 37°C for primary isolation of mycobacterial strains. Slants were examined once a week for 8 weeks for evidence of growth. Identification tests for mycobacteria were carried out on the isolates as followed in the NTI laboratory [10]. Indirect drug susceptibility tests for streptomycin (S), INH (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) were performed on the isolates by incorporation of required drug concentration into LJ medium before inspissation and subsequent inoculation of the slants with standardized inocula

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and incubation at 37°C. The pH of the medium containing pyrazinamide was adjusted to 4.85 before inspissation. Reading of the slants was carried out after 4 weeks. The strains were declared resistant if 20 or more colonies were observed in slants with the following drug concentrations :

INH $\geq$ 5 mg/L

Streptomycin (resistance ratio) $>$ 8

Rifampicin $>$ 64 mg/L

Pyrazinamide $>$ 100 mg/L

Ethambutol $>$ 8 mg/L

For the purposes of this study the types of resistance [11] were defined as:

(a) Initial resistance - drug resistance in patients who deny any previous chemotherapy. (b) Acquired drug resistance - wherein the patients initially had drug-susceptible bacilli which later became drug resistant due to inadequate or inappropriate chemotherapy or due to irregular drug ingestion. (c) Primary resistance - when previously untreated patients were found to have drug-resistant organisms. (d) Multi-drug resistance (MDR) - any patient showing resistance to two or more anti-tubercular drugs was considered to have multi-drug resistant tuberculosis (MDR-TB).

In primary resistance the patients is infected with a strain already resistant to one or more drugs whereas acquired (or secondary) resistance emerges during therapy. The identification of primary resistance may be unreliable owing to the failure of the patient or his medical records to mention previous antitubercular therapy. It is therefore preferable to refer to this as initial drug resistance when the first isolate from the patient is found to be resistant.

TABLE 2

Initial/acquired resistance (n=1037)

	Single		Double		3 or more		Total	
	I	A	I	A	I	A	I	A
S	37	4	14	17	0	14	51 (59.3)	35 (40.7)
H	21	3	9	15	0	11	30 (50.8)	29 (49.2)
R	2	12	8	17	0	13	10 (19.2)	42 (80.8)
Z	6	0	1	2	0	4	7 (53.8)	6 (46.2)
E	1	0	0	1	0	2	1 (25.0)	3 (75.0)

I = Initial, A = Acquired

(Figures in parenthesis indicate percent)

Results

Culture of 6864 sputum samples from 2288 patients yielded growth in 1037 patients (45.3%). All isolates were identified as *M. tuberculosis* (MTB). Of these 1037 isolates, 895 (86.3%) were sensitive to all drugs whereas 142 (13.7%) showed resistance to one or more anti-tubercular drugs. Of 142 patients having drug resistant isolates initial resistance was observed in 83 (58.5%) and acquired resistance in 59 (41.5%). Among these 142 patients single drug resistance was commonest and was observed in 86 (60.6%) patients whereas resistance to two or more drugs was observed in 56 (39.4%) patients (Table 1). The pattern of resistance observed is depicted in Tables 1 and 2. Streptomycin resistance was observed in 86 of the 1037 patients (8.3%) whereas single drug resistance to this drug was observed in only 4 per cent patients. Similarly INH resistance was observed in 59 (5.7%) patients which included 2.3 per cent

TABLE 1

Pattern of drug resistance

Total No. Tested	No. of strains resistant to			Total resistant
	1 drug	2 drug	3 or more	
1037	S - 41	SH - 15	SHR - 8	142
	H - 24	SR - 14	SRZ - 3	
	R - 14	RH - 9	SHE - 1	
	Z - 6	SZ - 2	SHRZ - 1	
	E - 1	RZ - 1	SHRE - 1	
		RE - 1		
Total	86	42	14	

cases having single drug resistance to INH. Rifampicin resistance was found in 52 (5%) patients with single drug resistance being present in 1.4 per cent of patients. In only 13 patients MTB showed resistance to pyrazinamide and in only 4 to ethambutol. MDR-TB was observed in 56 cases of which 40 (71.4%) showed acquired resistance.

Acquired drug-resistance was also observed in all 21 patients who were family members of serving personnel and attended out-patient departments of various hospitals irregularly. We had two definite cases of primary-resistance in contacts (family members) of patients with MDR-TB. One patient was the wife of a serving soldier with multi-drug resistant tuberculosis and other was the son of a known case of multidrug-resistant tuberculosis. Both index cases and contacts showed excellent therapeutic response.

Discussion

Development of drug-resistance has been noted since the beginning of the chemotherapeutic era [8,11]. However, today in the nineties, the problem seems more acute and likely to reach alarming proportions in the near future [5,8,9]. We had the unique opportunity to assess the pattern of drug-resistance in a distinct subset of patient population which is different from many other groups studied. Majority were members of the defence and paramilitary services and, therefore, were exposed to antitubercular drugs only after reaching a reasonably sound diagnosis. However, we had a small group of 21 patients who were family members of serving personnel and were referred to us after varying periods of unsupervised OPD treatment.

Overall culture positivity was 45.3 per cent. The prevalence of drug resistance in the isolates was 13.7 per cent. This was definitely lower than the figures quoted by other authors [5,12,13]. This can be explained by the fact that the vast majority of our patients were from a disciplined community thus minimising the chances of indiscriminate exposure to antitubercular agents prior to reporting to the hospitals.

Out of the 5 first-line drugs tested, incidence of resistance to streptomycin was the highest and observed in 86 (8.3%) patients. Out of these 54 (52.3%) showed additional resistance to other drugs. This is to be higher than the figures quoted

by Chandrasekaran [12,14]. The free supply, wide availability in almost all peripheral treatment centres, and indiscriminate use seem to be the important contributing factors for higher incidence of streptomycin resistance in the Armed Forces. Initial resistance to streptomycin was observed in 4.9 per cent patients which is lower than the incidence of 7.4 per cent observed by Trivedi [5].

Resistance to INH was observed in 59 (5.7%) patients which included 2.9 per cent initial drug resistant cases. This is much lower than the incidence of 17.4 per cent initial resistance to INH observed by Chandrasekaran [12]. Overall higher incidence of INH resistance was observed by Trivedi (13.9%) and Chandrasekaran (17.3%) [5,14].

Rifampicin resistance was observed in 52 (5%) patients including 42 (4%) showing acquired rifampicin resistance (Table 2). In comparison to the study by Trivedi (5) where primary rifampicin resistance was nil, we had a higher incidence of 1 per cent. However, our incidence was lower than 3 per cent quoted by Chandrasekaran [12]. Our figures are slightly more than the figure of 0.6 per cent of initial resistance to rifampicin quoted by Jain [9]. Acquired resistance to rifampicin of 4 per cent (42/1037) observed by us is much lower in comparison to the figure of 33.3 per cent quoted by Jain [9].

The lower levels of resistance to rifampicin and INH can be explained on the basis of the patient population of our study. The incidence of resistance to pyrazinamide and ethambutol were 1.2 per cent and 0.4 per cent respectively.

Acquired resistance was observed in all 21 patients who were family members of serving personnel and were attending various hospital OPD's irregularly. As has been rightly observed by various authors, acquired drug resistance contributes to a large extent to the problem of drug resistance and is preventable [1,7-9]. Acquired resistance develops when patients are treated with an inadequate regimen or fail to take a regimen appropriately [1]. It is worth noting the observations of Chandrasekaran that the incidence of drug resistance was more in rural patients where indiscriminate use of rifampicin-INH combinations by quacks has made the situation grim [14]. Similarly

irregular treatment also aggravates the problem of drug resistance [2,3,8,9].

As has been brought out in our study 71.4 per cent MDR-TB belonged to acquired resistance group. Although second-line anti-tubercular drugs are available for treatment of MDR-TB, these drugs are expensive, generally more toxic and significantly less effective, hence cure is possible in only a limited proportion of such cases [2,7]. The prevalence of high incidence of drug-resistant tuberculosis in family members makes the serving soldier highly vulnerable to contacting multidrug-resistant tuberculosis. The remedy, therefore, lies in ensuring regular treatment of family members as well so as to achieve a quick and dependable sterilizing effect.

We had two cases of primary drug resistant tuberculosis in family contacts of MDR-TB. Drug resistant disease may also occur because the patient initially had primary drug resistant disease and reflects ongoing transmission, suggesting a need for improved case-finding and containment (1). This has been established in a prospective study by Steiner [15].

The most effective method, therefore, of dealing with drug-resistant tuberculosis is to prevent its development by ensuring that drug-susceptible tuberculosis is treated appropriately (1). In this regard the recommendations of the Advisory Council for the Elimination of Tuberculosis, a national advisory committee to the United States Secretary of Health and Human Services for initial management of patients with tuberculosis will go a long way [3]. These recommendations include the following :-

- (a) In-vitro drug susceptibility testing on initial isolates from all patients with tuberculosis.
- (b) The initial treatment regimen should have four drugs to ensure that patients with unsuspected drug resistance are adequately treated while results of susceptibility testing are awaited.

- (c) Directly observed therapy to ensure adherence to medication regimen.

Early diagnosis followed by appropriate therapy of tuberculosis cases, therefore, offers the best chance of cure and simultaneously reduces the likelihood of drug-resistant tuberculosis and its transmission in the community.

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