Ind. J. Tub., 1992, 39, 171

INITIAL DRUG RESISTANCE TO ANTITUBERCULOSIS DRUGS IN URBAN AND RURAL DISTRICT TUBERCULOSIS PROGRAMME*

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Summary. The proportion of initial drug resistance (IDR) to antituberculosis drugs was estimated among new patients attending urban and rural District Tuberculosis Programme (DTP). For estimating the rural IDR, 398 smear positive patients attending DTP in Kolar district in the sears 1987-89, who were offered Short Course Chemotherapy (SCC) were taken into the study. Sputum specimens collected from them were subjected to culture and drug sensitivity tests. It was observed that IDR to any drug was 34.9% (Isoniazid 32.87% and Rifampicin 4.4%). Among the newly diagnosed urban patients attending the State TB Centre, Bangalore in the year 1985-86, IDR to any drug was 20.57% (Isoniazid 17.35% and Rifampicin 2.89%). Combined resistance to Rifampicin and Isoniazid was 1.36% in the urban clinic and 3.42% in rural DTP. Thus, resistance to Rifampicin was already present in areas where SCC was yet to be introduced, which becomes a source of concern. With the gradual introduction of SCC in NTP and treatment not being restricted strictly to the fresh cases. IDR to Isoniazid and Rifampicin assumes paramount importance and has to be monitored continuously.

Introduction

In recent times, availability of the powerful drug Rifampicin has reduced the duration of antituberculosis treatment and also increased the efficacy of treatment regimens. The Short Course Chemotherapy (SCC) regimens that contain Rifampicin are being introduced into the National Tuberculosis Programme (NTP) in a phased manner. The unsatisfactory treatment compliance in NTP and the easy availability of Rifampicin to patients, even outside of the programme, however, are factors to be taken note of, even though it is not definite how these would ultimately influence the drug resistance pattern in the clinic outpatients or in the entire population for that matter. It is, no doubt, worthwhile knowing the prevalence of drug resistance among patients who are newly reporting to the District Tuberculosis Programme (DTP), especially in places where SCC is being introduced. Though essential, it does not, however, appear feasible at present to have a nationwide surveillance of drug resistance.

In this paper, the extent of drug resistance among self reporting patients at the DTP is reported to provide baseline information on the situation at the time when SCC is just about to be implemented nationwide.

Objectives

1. To study the proportion of initial drug resistance (IDR) among urban & rural patients attending DTP.
2. To specifically investigate the extent of resistance to Rifampicin and INH, which could have an impact on the success of SCC.

Material and Methods

For this purpose, the study was conducted in an urban clinic of Bangalore city area as well as in a DTP, catering to a predominantly rural population of Kolar district.

Bangalore city TB clinic

Patients attending the Lady Willingdon State

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* Paper presented at the 46th National Conference on Tuberculosis and Chest Diseases, New Delhi 22-24 November, 1991.

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TB Centre (LWSTC), Bangalore who were >15 years of age with newly detected smear-positive pulmonary tuberculosis and had no history of antituberculosis treatment were admitted to the study. One sputum specimen was collected from each patient, and sent on the same day to the National Tuberculosis Institute (NTI) laboratory for culture of *M. tuberculosis.*

Kolar DTP

Patients attending the District Tuberculosis Centre (DTC) at Kolar and six Peripheral Health Institutions (PHIs), who were > 15 years of age with smear-positive pulmonary tuberculosis and selected for SCC according to standard DTP recommendations were taken into the study[1]. One spot specimen was collected from each patient, stored at 4°C and sent to NTI laboratory for culture.

Bacteriological Investigations

All sputa were subjected to the following:

1. Smear for AFB by microscopy.
2. Culture for mycobacteria using modified Petroff's method[2].
3. Sensitivity to Streptomycin, Isoniazid, Rifampicin and Ethambutol. The criterion used for declaring a strain as resistant was: growth of >20 colonies at the following concentrations:-

INH	:	MIC of >1µg/ml
Streptomycin	:	Resistance Ratio of >8
Rifampicin	:	MIC of >64/µg/ml
Ethambutol	:	MIC of >8/µg/ml

4. Identification tests for *M. tuberculosis* as followed in NTI laboratory[2].

Results

The study populations from Bangalore city and Kolar district are given in Tables 1 and 2. Among the total 588 culture positives from Bangalore area, 121 (20.57%) were resistant to one or the other drug. From Kolar, 102 out of 292 (34.9%) cultures were resistant to at least one drug.

The drug susceptibility results (Table 3) show that among 588 strains from Bangalore, resistance to INH was the highest (17.35%) followed by Streptomycin (4.76%) and Rifampicin (2.89%). Resistance to Ethambutol was the lowest. Similarly, from Kolar, 96 (32.87%) strains were resistant to INH, 15 (5.1%) to Streptomycin and 13 (4.4%) to Rifampicin. Tables 4 and 5 show the pattern of resistance to anti-tuberculosis drugs from Bangalore and Kolar district respectively. It is seen that single drug resistance to Ethambutol is nil in both the places.

Strains resistant to Rifampicin were further analysed (Table 6). It was observed that majority of them were resistant to INH also. The proportion of combined resistance to INH and Rifampicin was 1.36% from Bangalore area and 3.42% from Kolar district.

There was no association between age or sex of patients and drug resistance.

Discussion

The aim of this paper is to study resistance to antituberculosis drugs prevailing in a clinical situation. These estimates cannot reflect the epidemiological situation of resistance in the community. It was also possible to study the likely situation at the periphery, i.e. in a DTC and PHIs from a rural service, as compared with that in the highly urbanised set up in Bangalore city.

In Bangalore, patients with history suggestive of having taken previous chemotherapy were not taken into the study. The questioning done to elicit the history was thorough and exhaustive. The same thoroughness was not possible in Kolar, where all the newly registered patients got included in the study, irrespective of the history of previous chemotherapy because the history taking for previous treatment was casual. Hence, it is possible that some acquired drug resistance cases were included in the latter group, giving a higher estimate of resistance. In addition, the influence of a large sanatorium near Kolar DTC was also a factor. To what extent some of the not-so-formal drug regimens prescribed at the clinic attached to the sanatorium might have affected the initial drug resistance pattern of the newly diagnosed patients in DTP Kolar is a matter of conjecture. It is also possible that the people in rural area are not in a position to avail of the relatively abundant treatment opportunities usually available in urban

Table 1 *Study population from Bangalore*

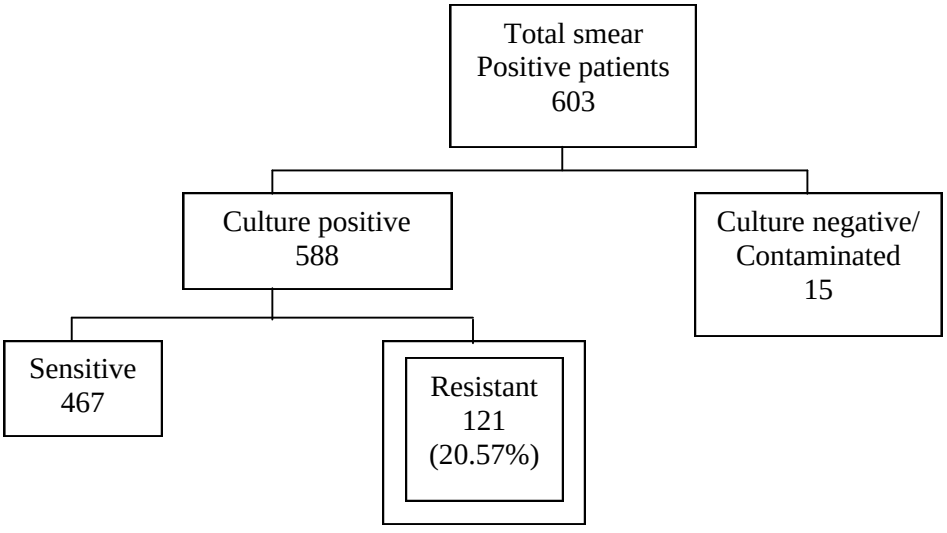

Table 2 Study population from kolar District

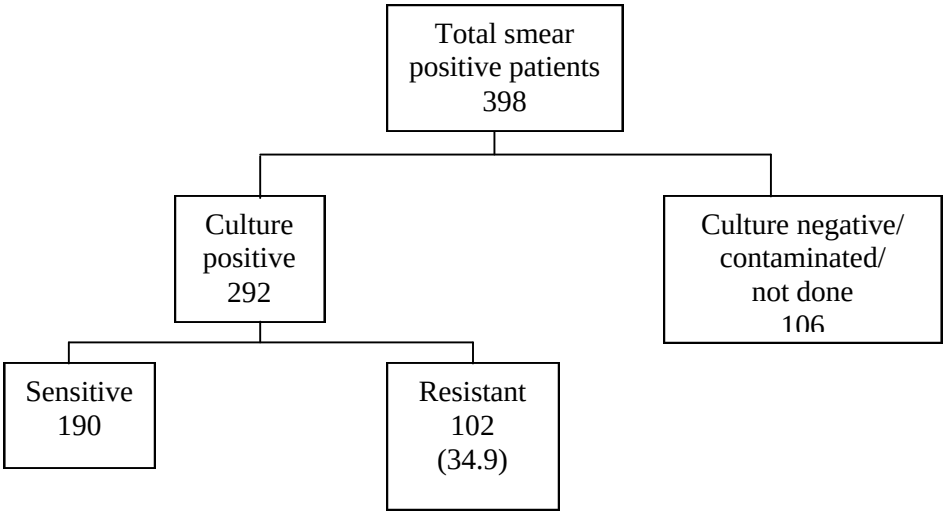

Table 3 *Drug resistance among smear positive tuberculosis patients*

Place	No. of strains	Number resistant to			
		H	R	E	S
Bangalore	588	102	17	3	28
		(17.35%)	(2.89%)	(0.5%)	(4.76%)
Kolar	292	96	13	5	15
		(32.87%)	(4.4%)	(1.7%)	(5.1%)

H = Isoniazid, R = Rifampicin, E = Ethambutol, S = Streptomycin

Table 4 *Pattern of drug resistance among patients from Bangalore*

Total	Strains resistant to						Total resistant strains
	1 drug		2 drugs		3 drugs		
588	H	74	SH	17	SHR	1	121
	R	9	HR	7			
	S	10	HE	3			
	E	0					

Table 5 *Pattern of drug resistance among patients from Kolar district*

Total	Strains resistant to						Total Resistant strains
	1 drug		2 drugs		3 drugs		
292	H	75	SH	7	SHR	2	102
	R	3	HR	7	SHE	3	
	S	3	HE	1	HRE	1	
	E	0					

Table 6 *Analysis of Rifampicin resistant cases*

	No. of strains tested	No. of strains resistant to	
		R alone	R and H
Bangalore	588	9	8(1.36%)
Kolar	292	3	10(3.42%)

areas such as clinics run by local bodies, voluntary organisations, private practitioners, etc. These, probably, are some of the reasons for a higher rate of drug resistance observed in Kolar district, as compared to the Bangalore city set up.

The combined resistance to Isoniazid and Rifampicin was 1.36% in Bangalore and 3.42% in Kolar. Siddiqi et al[3], in this context, had reported that Rifampicin resistance seemed to arise with multiple drug treatment received in the past in which Rifampicin was not necessarily included. This apparently suggested to them that prolonged anti-TB treatment predisposes to the spontaneous development of resistance to Rifampicin. Our study results have also shown that initial drug resistance to Streptomycin has not increased over a period of 15-20 years, and also that resistance to Ethambutol remains negligible. Past chemotherapy could then be surmised as the possible contributing factor for higher Rifampicin resistance in Kolar.

The problem of drug resistance has, in general, been high in developing countries[4] compared to developed countries. The resistance level in Bangalore area now is not different from what was observed a few years ago[5] or reported from elsewhere in India[6]. Initial drug resistance to Streptomycin and INH did not evoke much concern because introduction of SCC in the programme was expected to take care of resistant cases. But resistance to Rifampicin, especially in combination with INH, however infrequent, cannot be viewed similarly, because unfavourable response to treatment with SCC[7] is far more serious proposition.

The observations that (1) strains already resistant to INH and Rifampicin exist, (2) 69% of new cases are estimated to arise from those recently infected and reinfected, as reported by V.V. Krishnamurtliy et al[8] and (3) resistant strains are as infectious as the sensitive ones should be viewed with great concern. Hence, all efforts should be directed towards better treatment compliance and sputum conversion. With the quality of drug distribution and efficiency of the health system, as currently available in our country, it is debatable whether extension of SCC in the NTP at this stage is not too hasty. Toning up the case-holding, therefore, becomes a prerequisite, especially in view of the ominous possibilities of drug resistance likely to be encountered due to the haphazard implementation of SCC through a system not geared to its requirements[10].

Acknowledgement

The authors wish to thank the members of the O.R. Forum, especially Dr. A.K. Chakraborty and Mr. T.R. Sreenivas for their valuable suggestions.

They also thank the Joint Director, LWSTC, DHO and DTO, Kolar district for help at various stages of the study. They also express their sincere thanks to Mr Chauhan, Mrs N. Parimala, Mrs R. Rajalakshrni, staff of the laboratory and control section, Mr Narayana Prasad for drawings, and Miss T.J. Alamelu for secretarial assistance.

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