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Factors associated with treatment failure in T.B. patients at National Tuberculosis Centre

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Sixty patients with sputum smear positive tuberculosis who had failed on anti tuberculosis treatment were examined at the National Tuberculosis Centre. Information on treatment history, clinical features and demographic data were collected by a standardized questionnaire and from treatment records. Sputum culture and sensitivity results were reviewed to determine patterns of resistance. Factors which appeared to be important in patients with treatment failure included cavitory disease, a previous history of relapse, repeated defaulting from treatment, and adverse effects from drugs. Ninety eight percent of patients were resistant to one or more drugs. Sixty seven percent had multi-drug resistant TB, with resistance to isoniazid and Rifampicin. Treatment failure and multi-drug resistance occurs because patients are given inadequate treatment by health workers. Inappropriate drug combination, inadequate doses and insufficient duration of treatment, together with inadequate education and lack of supervision of patients produce this problem. It is important that health workers managing patients with tuberculosis treat them according to nationally approved guidelines, with strict supervision of treatment, particularly in the intensive phase of treatment.

Keywords: TUBERCULOSIS, DRUG RESISTANCE, TREATMENT FAILURE.

INTRODUCTION

Modern anti tubercular drug can cure most tuberculosis (TB) cases if an effective combination of drugs, in proper doses is used for a sufficient period of time. However in practice many cases are not cured. The cure rate of TB cases in many developing countries is below 50%, while WHO recommended target is 85 %, to be achievedby the year 2000.[1] The estimated treatment completion and cure rate in Nepal is 40 %.[2] Recently it has been observed that the problem of drug resistance is increasing, the causes being poor case holding, low cure rate, improper use of anti tubercular drugs and uncontrolled use of TB medicine in the market.[3] The development of primary and acquired drug resistance leads to treatment failure.[4] Treatment failure cases are those who remain sputum positive five or more months after the start of treatment. These cases remain as a source of infection in the community and may transmit disease to others with multidrug

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resistant bacilli. Such cases are very dangerous for the community. For the physicians, it is a difficult decision to choose the most appropriate regimens in the treatment of failure cases. If the previously used drugs are known, we should use at least two new drugs which have not been used before. The culture and sensitivity report may help if available during the treatment. The culture and sensitivity report has its own limitation in the developing countries. In Nepal this facilities are available only in two places of Kathmandu. In the management of failure cases prevention will be better than cure. Treatment of a failure case is very expensive and difficult. We do not have published data on the prevalence of treatment failure cases. One author has reported 8.7%[4] Reports from the NTC clinic, suggest that initial resistance rate is found in 5% of the patients and overall acquired resistance rate is 52.5 % at least to one drug.[2]

This report has been prepared from the retrospective study of the treatment failure cases attending National Tuberculosis Centre Clinic(NTC), from October 1989 to March 1992. NTC clinic is a referral centre for the country, especially for treatment failure cases. The aim of the study was to determine the causes leading to failure of chemotherapy and related factors responsible for secondary drug resistance, so that we might be able to improve in the future and prevent the emergence of drug resistance.

METHODS AND MATERIALS:-

All sputum positive cases registered during October 1989 to March 1992 at NTC clinic were included. Patients whose sputum microscopy was persistently positive five or more months after the start of treatment, disregarding the type of regimen, were included in this study. Cases whose culture and sensitivity reports were available, were interviewed in the clinic, within the period of six months (Jan. 1992 to July 1992). A format was prepared and filled in using a standardized questionnaire including demographic data and previous history of anti tubercular treatment. Information was collected by asking the patients, relatives, and reviewing available old treatment records. Care was taken to avoid re-inclusion of the same patient on the subsequent visit to the clinic.

Bacteriological Procedures:-

Isolation and identification of mycobacterium were carried out according to a standarised procedure.[5] Tests of sensitivity to Isoniazid, Rifampicin, Streptomycin, Ethambutol and Thiacetazone were performed on 1% Ogawa media containing drugs on various concentration and 1% Ogawa media free of drug was taken as control. The strains were considered resistant to the respective anti-tubercular drug if the growth was observed at the following concentration.[6]

Isoniazid	1 microgram / ml.
Streptomycin	20 microgram / ml.
Rifampicin	50 microgram / ml.
Ethambutol	5 microgram / ml.
Thaicetazone	10 microgram / ml.

RESULT

The total number of sputum positive cases registered during Oct. 1989 to March 1992 at NTC clinic was 3,464, of those 126 (3.3%) cases were registered as treatment failure cases. The sixty cases whose culture and sensitivity reports were available were interviewed and data were analysed.

Results of the study are shown in Table I to IV

A) DEMOGRAPHIC DATA:-

Table I. Demographic Information

Characteristic		Number	%
Sex			
	Male	39	65.0
	Female	21	35.0
Age			
	15-25	8	13.3
	26-35	26	43.3
	36-45	10	16.7
	> 45	16	26.7
Level of education			
Illiterate		25	41.7
Primary		32	53.3
High School Degree		2	3.3
Degree		11	1.7

B) CLINICAL FEATURES :-

Table II. Clinical Features

Characteristic		Number	%
Duration of Illness (Years)			
	1 - 4	28	46.7
	4 - 8	22	36.7
	> 8	10	16.7
Duration of Sputum Positivity (Years)			
	< 1	16	
	1 - 2	34	
	> 2	10	
Radiological Features		36	60
Cavitory Lesions		24	40
Non cavitory Lesions			
History of Family Contact			
	Yes	20	33.3
	No	40	66.7

C) TREATMENT HISTORY:-

Table III. Treatment History

Characteristic		Number	%
Episodes of default from treatment (n = 38)			
	1	15	39.4
	2	9	23.8
	3	4	10.5
	> 3	10	26.0
Causes of default (n = 38)			
	Social problem	8	21.0
	Ignorance	11	28.9
	Biological	8	21.0
	Financial	9	23.7
	Distance	2	5.3
Episodes of relapse (n = 22)			
	1		
	2		
History of adverse reaction to drugs (n = 60)			
	Thiacetazone	15	
	Streptomycin	8	
	Pyrazinamide	3	
	PAS	2	
Duration of treatment (Years)			
	1 - 2	15	25.0
	2 - 4	35	58.3
	4 - 6	7	11.7
	> 6	3	5.0
Drugs used			
	Isoniazid	60	100.0
	Rifampicin	60	100.0
	Streptomycin	57	95.0
	Ethambutol	59	98.3
	Pyarazinamide	53	88.3
	Thiacetazone	50	83.3
	PAS	12	20.0
	Ethionamide	1	1.7
	Ciprofloxacin	1	1.7

Out of sixty cases 39 (65 %) were male and 21 (35 %) were female, no one was below 15 years of age. Sixty percent of cases belongs to the most economically productive age group of 26 - 45 years and 42 % of cases were illiterate and 53 % had primary level of education, which shows majority of them had lower educational status (Table No.I).

More than 50 % of cases were suffering from disease for more than four years. 27 % 0f cases were sputum positive for 5 to 12 months, 57 % of cases for 12 to 24 months and 16 % of cases for more than 24 months (Table No. II) and 33.3 % of cases gave the history of contact among the close family members. These findings indicate high risk of infection from chronic execrators of TB bacilli..

Another interesting finding was that 60 % of cases had cavitory lesions in the X-ray chest (Table No. II). Report of NTC clinic showed ,18 % of TB cases had cavitory lesions and report from Army Hospital showed 33 % of cases had cavitory lesions.[7] The patients with the cavitory disease should be treated with extra care to cure them.

Past history of treatment showed that 63 % of cases had defaulted from treatment and 60 % of them had defaulted twice or more. The common causes of defaulting were ignorance, financial problems and the side effects of the drugs (Table No.III).

The history of disease relapse was a common factor among these group of cases, 47 % of cases giving a history of disease relapse in past. Such cases need extra-care during the treatment. WHO has recommended that Category 2 regimen of, (2 SHRZE + 1HRZE + 5HRE) should be given under full supervision.[8]

Drug toxicity was observed among 46.6% cases which is quite high.

Four cases had diabetes as an associated disease, three cases had pneumothorax as complication of tuberculosis and two cases were operated for peptic ulcer. The widely used drugs were isoniazid and rifampicin, as all the cases had used these two drugs for various periods of time. Fifty eight percent of cases had treatment for 2 - 4 years, 17% had for more than 4 years and 25 % had less than two years. These cases were using anti tubercular treatment for a long duration without much benefit. The regimen used were not fixed ,various combination of drugs used were for different period and frequent change of regimen was observed.

D) RESULTS OF DRUG SENSITIVITY:

The culture and sensitivity result showed that 98.4 % of cases developed resistance to one or more drugs only, except one case showed sensitivity to all the drugs. Resistance to Rifampicin was highest at 90 %. Single drug resistance occurred 3.3 % of cases. Two drugs resistance was observed among 16.8 % of cases, most of these had the combination of Rifampicin and isoniazid resistance 33% had resistance. to three drugs, 28.3 % of cases to four drugs and 16.6 % of cases to all five drugs (Table No. IV).

98 % of isoniazid resistance was associated with Rifampicin and other drugs. 67 % of cases had combination of Rifampicin and isoniazid. Rifapicin resistance was always in combination with other drugs .

There were three cases who had never used Streptomycin but showed resistance, two had the history of contact with a patient with drug resistance in past.

Table IV Patterns of drug resistance

Characteristics		Number	%
Number of drugs resistant			
	0	1	1.7
	1	2	3.3
	2	10	16.7
	3	20	33.3
	4	17	28.3
	5	10	16.7
Resistance to drugs	Isoniazid	44	73.3
	Rifampicin	53	88.3
	Streptomycin	33	55.0
	Ethambutol	33	55.0
	Thiacetazone	38	63.3
Combined resistance to isoniazid (INH)			
	INH alone	1	1.7
	INH + rifampicin	40	66.7
	INH + streptomycin	23	38.3
	INH + ethambutol	23	38.3
	INH + thiacetazone	23	38.3

DISCUSSION

Information was available from only 60 cases out of the 126 registered as treatment failure cases. It is possible that substantial bias has occurred, with higher level of drug resistance reported than in all the treatment failure cases. However, even if this were so, the corrected rate of drug resistance would still be very high, and a matter of great concern.

The common factors observed among the treatment failure cases were, presence of cavitory lesions, previous history of relapse, repeated defaulting from treatment and adverse effects of drugs. These were the factors responsible to decrease the patient 's adherence to treatment leading to drug resistance and treatment failure. In addition the treatment regimens used were not fixed, there was frequent change of regimens and the treatment was not supervised. Maximum acquired resistance was found to rifampicin, which may be the result of wide spread use of this drug. rifampicin resistance was always associated with other drugs. Initial rifampicin resistance has been reported in 2.5 % of patients in Nepal.[2] It has been reported that resistance to Rifampicin occurs rapidly in 2-3 months if used alone.[6] The relation between the development of resistance and duration of anti tubercular treatment was not so significant.

The large number of patients with resistance to Isoniazid and Rifampicin is a matter of great concern, as by definition they have multidrug resistance.[9] These patients present a great challenge to the National Tuberculosis Program, as they are very difficult to cure, and spread a very dangerous form of disease.

Acquired resistance commonly develops as result of inadequate treatment regimens provided by the health workers, poor case holding and misuse of anti tubercular drugs in the private sectors.[3] It is very important to avoid improper, unsupervised and careless use of the precious drug like Rifampicin in the treatment of tuberculosis. Each and every dose of Rifampicin should be supervised as we do not want to loose it by creating resistance . Proper combination of drugs should be used for proper duration of time and national recommended regimens should be used. Care should be taken while treating a relapse or defaulter cases by using WHO approved or national regimen ,under supervision and extensive motivation of

the patients. The problems are high defaulter rate, freely available anti tubercular drugs of various quality in the market which can be prescribed by any one. There was no fixed national regimen in the past. According to revised NTP policy, we have national recommended regimens which have to be followed. Every health worker should try to cure all the new cases with effective treatment . Extra care should be taken while treating relapse and defaulter cases. We must avoid improper, unsupervised, careless use of Refampicin. Lastly extensive motivation of the patients is needed.

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