IMPROPER ANTI-TB TREATMENT- ALMOST CERTAIN RECIPE FOR MDR-TB

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ABSTRACT

BACKGROUND

Tuberculosis being a very important global health issue, is posing new challenges in the form of drug resistant tuberculosis, particularly MDR-TB which is predominantly a man-made phenomenon. Inadequate anti TB treatment due to various patient related, drug related or National TB Control Program related problems, appear to be the leading cause of this menace. Present study was conducted, with the objective of identifying the various factors in the history of past anti TB treatment, which could have led to emergence of drug resistant tuberculosis.

METHODS

This was an observational cross-sectional study, done on 116 adult patients, of both genders who attended Department of Pulmonary Medicine, MLN Medical College, Allahabad from August 2015 to August 2016, for starting standard re-treatment regimen under Revised National Tuberculosis Control Program (RNTCP). All patients were subjected to sputum smear microscopy and Cartridge Based Nucleic Acid Amplification Technique (CB-NAAT), to determine their current disease and rifampicin sensitivity status. Pregnant women and patients with diabetes mellitus, HIV seropositivity, liver disease, kidney disease, psychiatric illnesses were not included in study. Adequacy of previous anti TB regimen taken, and causes of treatment interruption if any, were determined, by a detailed clinical history. All data obtained was further subjected to relevant statistical analysis, to determine results.

RESULTS

Out of the 116 patients enrolled, 37 were found to be having MDR-TB, and remaining 79 were non MDR-TB patients. It was found that patients, who had to take anti TB treatment more than once in past, were more likely to develop MDR-TB ($p=0.00001$). We also found that, chances of MDR-TB are highest if patients take inadequate anti TB regimen in inadequate doses, while it is least, if adequate regimen is taken in adequate doses ($p=0.00113$). Regarding treatment interruption, it was found that, majority of patients interrupted in third month, during continuation phase of treatment, because they did not perceive any clinical improvement to the treatment they were taking. Apart from this cause, our study also found that early improvement of symptoms, adverse effects of anti TB drugs used, and financial burden were also important causes of treatment interruption with subsequent adverse consequences.

CONCLUSIONS

Basic objective of any anti TB treatment should be good and effective treatment of drug sensitive tuberculosis. Anti TB regimen used, must be adequate in terms of drug combination, dosages and duration, along with treatment compliance of patients to prevent the emergence of drug resistant tuberculosis. Role of health care provider is very important in ensuring the compliance to treatment, by repeated motivation and counselling, which helps the patient to tide over the psychological and social stress of prolonged treatment. Substance abuse and addictions, which create treatment complications and compromise the outcome, could also be managed in a proper way. Patient counselling also helps in preventing the spread of disease in society by educating the patient about cough hygiene and etiquettes.

KEY WORDS

Improper Treatment, MDR-TB

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BACKGROUND

Tuberculosis remains a major global health problem, and ranks as second leading cause of death worldwide.¹

India is the highest tuberculosis burden country in the world and accounts for nearly one-fifth of global burden of tuberculosis,² and this problem is further complicated by emergence drug resistant strains of *Mycobacterium tuberculosis*. These may be Multi-Drug Resistant (MDR), non-MDR drug resistant or Extensive Drug Resistant (XDR) bacilli. Anti TB drug resistance can be defined as temporary or permanent capacity of TB bacilli to remain viable and multiply in the presence of drug concentration that would normally destroy or inhibit the growth of the bacilli. Drug resistant individual is a patient whose TB disease is due to tubercle bacilli, which are resistant in vitro, to at least one anti TB drug, according to accepted laboratory methods. Any strain with 1% (the critical proportion of bacilli) resistant to any of anti TB drugs, is classified as resistant to that particular drug.

Natural drug resistance in *M. tuberculosis* occurs by random, single step, spontaneous mutation at low but

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predictable frequency, in large bacterial populations. These spontaneous mutations occur at a frequency of approximately 1 in 10^5 - 10^8 bacilli, which at first sight gives impression that probability of dual mutation is minimal, but given enormous bacterial masses in pulmonary cavities, it may present a serious threat of emergence of drug resistant bacilli. The TB bacilli develop drug resistance by selective growth of resistant mutants, and incidence of drug resistant cases depends on number of bacilli and drug resistant mutants in the cavities of lungs. Irregular treatment, inappropriate drug combination in regimens, inadequate drug dosages or addition of single drug to a failing regimen, allows the selective growth of resistant mutant bacilli resulting in acquired drug resistance.

According to Global Tuberculosis Report 2015, of World Health Organisation, it is estimated that about 3.3% of new TB cases and 20% of previously treated cases have MDR-TB. In this report, India, Indonesia and China alone accounted for 23%, 10% and 10% of total cases respectively. Multi Drug Resistant tuberculosis (MDR-TB), caused by *M. tuberculosis*, resistant to at least rifampicin and isoniazid, with or without resistance to other anti TB drugs, is among the most worrisome elements of pandemic of antibiotic resistance. Globally about three percent of all newly diagnosed tuberculosis patients have MDR-TB, and this proportion is higher among patients who have previously received anti-TB treatment, reflecting the dire need of an effective program, with robust system of drug sensitivity guided treatment, to ensure complete cure. While host and genetic factors may probably contribute, but incomplete and inadequate treatment is the most important factor leading to the development of MDR-TB.

MDR-TB, is predominantly a man-made phenomenon, and arise due to inadequate treatment of drug sensitive tuberculosis. This problem mainly develops when standard six month regimen for new cases of drug sensitive TB is wrongly prescribed or wrongly taken.³ Causes of inadequate treatment could be:⁴ (a) program or provider related like non-compliance to treatment guidelines, inadequate training of staff and unmonitored treatment; (b) drug related like poor quality, non-availability and wrong dosages; (c) patient related like poor adherence, poverty, adverse drug reactions, malabsorption and substance abuse.

Studies conducted in this regard by Sharma SK et al⁵ and Thomas A et al⁶ to determine causes of MDR-TB, found history of incomplete and inadequate treatment as a major risk factor. The South Indian study of Thomas A et al, reported the relapse rate of 12.3%, and majority of relapse occurred during first six months, and major risk factors associated with relapse were irregularity, initial drug resistance, smoking and alcoholism, which added to adverse effect and decreased bioavailability. These findings are further supported by the microbiological fact that *M. tuberculosis*, when exposed to inadequate, interrupted and sub therapeutic serum levels of anti TB drug, undergoes mutation to develop acquired drug resistance.

Our present study was conducted, with aim of determining various factors of past anti TB treatment in clinical history of TB patients, which could have impact in development of MDR-TB.

METHODS

Present study comprised of patients attending the Department of Pulmonary Medicine, MLN Medical College, Allahabad, during the period from August 2015 to August 2016.

Study Design

This was an observational cross-sectional study, with aim of assessing the association of MDR-TB with various factors in past history of anti TB treatment.

Case Selection

All patients aged above 18 years, of either sex, with pulmonary tuberculosis enrolled for starting standard re-treatment regimen, under Revised National Tuberculosis Control Program (RNTCP), were enrolled in this study as per inclusion and exclusion criteria.

Inclusion Criteria

Patients who failed, relapsed or defaulted on anti TB treatment in past, and enrolled under RNTCP for re treatment.

Exclusion Criteria

1. Patients not giving consent for participation in the study.
2. Pregnant women.
3. Patients with co-morbid conditions, like diabetes mellitus, seropositive for HIV, kidney disease, liver disease and psychiatric illness.

Data Collection and Analysis

Detailed history of past anti tuberculosis treatment was taken, with particular emphasis on adequacy of anti TB drug regimen, duration and dosages. History was further elaborated to determine various causes and frequency of treatment interruption if any. All patients were subjected to cartridge based nucleic acid amplification test (CB-NAAT), to make confirmatory diagnosis of rifampicin resistance, which is taken as surrogate of MDR-TB under RNTCP.

Investigations

1. Haematological investigations (Hb, TLC, DLC and GBP), liver function test and kidney function test.
2. Bacteriological test by sputum smear examination for *M. tuberculosis* by LED fluorescence microscope.
3. Sputum test for CB-NAAT.
4. Chest radiograph postero-anterior view.

Statistical Analysis

The data collected were analysed statistically using IBM SPSS Statistics software, version 20. Chi-square test was used as the test of significance. A p-value of < 0.05 was considered significant.

RESULTS

A total of 116 patients were selected from OPD and ward of Department of Pulmonary Medicine. Out of these patients, 37 were MDR-TB and 79 were non MDR-TB. Their detailed history revealed various facts, which were found to be statistically significant.

How many Times Patient took ATT in Past	MDR- TB (n=37)		Non MDR-TB (n=79)	
	Number	Percent	Number	Percent
Once	8	21.62	61	77.21
Twice	13	35.13	15	18.98
Thrice or more	16	43.24	3	3.79

Table 1. Distribution of MDR-TB Among Patients with Previous History of ATT Intake (Among Patients at Start of Re-Treatment Regimen)

p=0.00001

Regimen/ Dose of Previous ATT (n=116)	MDR-TB (n=37)		Non MDR-TB (n=79)		p-Value
	No.	%	No.	%	
Inadequate Regimen and Inadequate Dose (n=7)	7	100	0	0	0.000
Inadequate Regimen and Adequate Dose (n=17)	7	41.17	10	58.82	0.374
Adequate Regimen and Inadequate Dose (n=5)	2	40	3	60	0.691
Adequate Regimen and Adequate Dose (n=74)	18	24.32	56	75.67	0.020
Detail not Reliable (n=13)	3	23	10	76.92	0.469
Table 2. Association of MDR-TB with Adequacy of Previous Anti TB Treatment (Among Patients at Start of Re-Treatment Regimen)					
P=0.00113					

Reason for Interruption	No. of Patients (n=45)	Percentage
Drug adverse effect	12	26.66
Loss of work / wages	2	4.44
No improvement	16	35.55
Long duration treatment	1	2.22
Early improvement	14	31.11
Table 3. Reason for Treatment Interruption		

Patient Interrupted Treatment in which Month	No. of Patients who Interrupted Treatment (n=45)	Percentage
1 st Month	4	8.88
2 nd Month	7	15.56
3 rd Month	21	46.67
4 th Month	8	17.78
5 th Month and more	5	11.11
Table 4. Timing of Treatment Interruption		

Table 1, shows that among patients who were required to take ATT more frequently in past, were more likely to develop MDR-TB, and this association was found to be statistically significant. The chi-square value of data was 39.75 and p-value 0.00001. This study showed that proportion of MDR-TB is 100% among patients who took inadequate regimen along with inadequate doses, while it was least in those, who took adequate regimen with adequate doses, and this association was also found to be statistically significant, with chi-square value of data as 18.18 and p-value 0.00113.

In this table 3, we see that 16 patients interrupted treatment, because they found no improvement in their symptoms. These figures highlight the importance of close monitoring, counselling and repeated motivation.

This table 4, reveals that maximum patients interrupt treatment during continuation phase 75.55% (n=34), and that too in 3rd month of treatment 46.67% (n=21).

DISCUSSION

Treatment of tuberculosis patient, should include judicious use of anti TB drugs, supervised and preferably individualized treatment, focused clinical, radiological and bacteriological follow up and use of surgery at appropriate juncture. The key to successful elimination of tuberculosis is early treatment of cases with optimum anti tuberculosis chemotherapy, which if administered poorly, could lead to selective growth of resistant mutants among bacillary population, and subsequent development of drug resistance. Therefore, regular treatment by combination chemotherapy of three or more anti TB drugs, among new cases of tuberculosis, results in cure, while irregular treatment, inadequate drugs, inadequate drug dosages, or addition of single drug to a failing regimen leads to acquired drug resistant tuberculosis.^{7,8}

Apart from adequacy of anti TB treatment, patient compliance is very important to achieve good results. Present study found that no clinical improvement on treatment, was

most common cause of treatment interruption, followed by early improvement, drug induced adverse effects, loss of work and long duration of treatment. Earlier works on this issue, found early clinical improvement to treatment, drug related problems and migration as the major cause of treatment interruption.^{9,10,11,12}

Our additional finding, that majority of patients defaulted in 3rd month of anti TB treatment, is in congruence with the finding of earlier studies, on this issue.^{9,10} This is generally the time, when patients feel fit and healthy, consider the treatment unnecessary and tend to default. Here lies the role of counselling and repeated motivation on part of health care provider, as this incomplete treatment would not only lead to unacceptably higher rates of clinical and bacteriological relapse, but also pose serious risk of emergence of drug resistant bacilli, death, disability and spread of infection in society.

A very important aspect observed in our study, pertaining to treatment default, adverse drug reactions, treatment failure and emergence of drug resistance; was substance abuse. We found that proportion of MDR-TB was 25% among patients who were either tobacco smokers or alcoholic, while it was 40% among those who were both smokers and alcoholics, highlighting the fact that both addictions simultaneously have additive effect in increasing the risk of MDR-TB, among patients of tuberculosis. Heavy alcohol use strongly influences both the incidence and the outcome of the disease. It is supposed to be linked to altered pharmacokinetics of drugs used in the treatment, social marginalization and drift, depression and other psychological problems, higher rate of re infection, higher rate of treatment defaults and ultimately resulting in emergence of drug resistant forms of tuberculosis.

These findings in our study, have very clearly established the important role of counseling of tuberculosis patients, to improve their compliance to treatment. Since treatment of tuberculosis is a prolonged one, involving several months; ignorant and illiterate patients are very prone to default, further highlighting the role of health visitor, DOT provider and other care givers to properly educate, and repeatedly motivate these patients.

Patient counselling has greater role in educating the patient regarding spread of disease in society. In our study we found that about 50% patients were not counselled about the nature of disease, that it spreads from person to person, through aerosol transmission during coughing. Here it should be emphasized that there is a need to educate the tuberculosis patient, regarding cough hygiene and etiquette, of keeping a cloth on mouth while coughing or visiting the hospital seeking health care. A concerted effort is required by the treating team, both medical and para medical, to counsel each patient about the risk of transmission of disease in household, particularly to children, elderly and pregnant women and in society at large. Patients should also be told about the benefits of practicing good cough etiquette.

Entire focus of Revised National Tuberculosis Control Program (RNTCP), is and should be complete and effective treatment of drug sensitive tuberculosis, which in turn would prevent emergence of drug resistant tuberculosis, particularly MDR-TB. This menace of MDR-TB, drains heavily on health care resources of society, because its management is a challenge as it needs to be treated by experienced clinicians at specialized centers equipped with reliable laboratory services,

for mycobacterial culture and in vitro sensitivity testing to guide the selection of second line anti TB drugs, which are expensive, potentially toxic and comparatively less effective than first line drugs, in achieving bacteriological cure.

Anti TB Chemotherapy must be given optimally by-

1. Ensuring adequate absorption of drugs,
2. Selection of appropriate combination of drugs in adequate dosages,
3. Timely diagnosis and management of adverse effects of drugs,
4. Strict adherence to treatment regimens,
5. Duration of treatment must be optimal and effective. It is vital that the physicians of 21st century must understand the basic principles of anti TB chemotherapy to ensure efficient use of available drugs to postpone or even reverse the impending epidemic of drug resistant tuberculosis.

CONCLUSIONS

Proportion of MDR-TB was high among the TB patients of young age group of 21 to 40 years, which is economically most productive group, patients with high bacillary load, male-married individuals, persons with low educational status, rural dwellers, patients who took anti TB treatment multiple times with inadequate regimen and or dose. From this study we also found that no improvement of symptoms, early improvement of symptoms, side effects of drugs and financial burden, were the determinants of treatment interruption, with subsequent adverse consequences.

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