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Treatment Outcomes among Patients Treated With Category II Anti-tuberculosis Regimen: Short Review

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Abstract

Tuberculosis (TB) is one of the leading causes of morbidity and mortality, especially in developing and under-developed nations. To add to the burden, drug resistant TB is on the rise and India is handling the dual burden of drug sensitive TB and resistant TB. Previously treated TB cases when compared to the newly diagnosed, have poor treatment success rates and nearly seven times higher incidence of multi drug resistant TB. Proper management of patients treated with Category-II anti-tuberculous treatment (ATT) can result in decrease in emergence of drug resistant bacilli and interruption of disease transmission. Very few studies have reported the treatment outcomes of re-treatment cases and the associated factors in the literature. Favourable outcome rates are highly variable among the failure, relapse and default subgroups. There are many challenges faced by the treating physicians in diagnosis, treatment and follow-up of the re-treatment cases. This review describes the outcomes of patients treated with Category-II ATT and the challenges in managing the previously treated cases successfully. Relapse type of re-treatment cases had better success rates compared to other subgroups.

Keywords: Tuberculosis; Re-treatment cases; Success rates; Drug resistance

Introduction

Tuberculosis (TB) ranks as the leading infectious cause of death worldwide. The ultimate aim of Sustainable Development Goals (SDGs) with respect to TB is "to end the global TB epidemic by 2030" (Target 3.3). The expected decline in incidence of TB by 2030 (as compared to 2015) is 80%, which is approximately equal to <20/100,000 population. The mortality rate due to TB should reduce by 90% compared to 2015 and there should be no single TB- affected family which is facing the catastrophic costs due to TB [1]. In 2016, around 10.4 million people developed TB disease and 1.67 million people died from TB. Access to TB care has improved worldwide and TB mortality rate has shown 37% decline since 2000. Between 2000 and 2016, 53 million lives were saved through effective diagnosis and treatment of TB [2]. On the other hand, the number of people diagnosed with Multidrug-resistant TB (MDR-TB) increased three fold between 2009 and 2013. An estimated 4.9 lakhs people developed MDR-TB and 1.1 lakh were diagnosed with rifampicin resistant TB (RR-TB) in 2016. The incidence of MDR-TB/RR-TB was about 4.1% in new cases and 19% in previously treated cases. Use of new rapid diagnostics has facilitated the detection of drug resistant TB. As the number of MDR-TB cases diagnosed is increasing worldwide, the first priority action to address this crisis is to prevent the development of drug resistance through high quality treatment of drug susceptible TB [2]. Lot of research is being done in the treatment outcomes and their predictors for patients with newly diagnosed with drug sensitive TB and for patients with drug resistant TB. Re-treatment (or) previously treated TB cases are not much explored but they constitute a significant part of the TB burden and the treatment success in this group is not as high as the new cases.

TB Burden in India

India contributed to 25% of the global TB incident TB cases and about 34% of global TB-related deaths in 2015. The Revised National TB Control Programme (RNTCP) has been progressive in addressing issues related to TB control in the country. It has achieved great success in reduction of prevalence of TB and morbidity and mortality due to TB. Despite the availability of services for TB diagnosis and treatment across the country, the burden of TB is still high. RNTCP made a major revision in its technical and operational guidelines in March 2016 in which the treatment strategy is being changed from intermittent to daily regimen. This change is being implemented in a phased manner throughout the Country [3].

The first line drugs used in treatment of TB patients are Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (S). Under RNTCP, a new case of TB patient will receive 6 months of treatment with 2 months of Intensive Phase (IP) with HRZE daily and 4 months of Continuation Phase (CP) with HR daily. Re-treatment TB case will receive 8 months of daily treatment with 3 months of IP (2 month HRZES and 1 month HRZE) and 5 months of CP (HRE). The causes for re-treatment include default in treatment, treatment failure and relapse of the disease after successful completion of treatment [3]. Overall success rate of microbiologically confirmed new and retreatment TB cases is 88% and 71% respectively in the year 2015 [4].

Rise in Drug Resistant TB

India is one of the countries in the world with the highest burden of MDR-TB [5]. The estimated MDR/RR-TB cases among the notified pulmonary TB cases in 2016 were 84000. The incidence of MDR-TB was 12% among the notified retreatment pulmonary TB patients and 2.8% among the notified new pulmonary TB patients in 2016 [2]. As

the number of MDR-TB cases diagnosed is increasing in the country, it becomes essential to identify factors responsible for development of drug resistance. The main factors that contribute to DR-TB burden are inadequate treatment of drug susceptible TB and delay in diagnosis of drug resistant TB.

Re-treatment Cases and their Significance

As per RNTCP report 2017, the treatment success rate among smear positive retreatment cases has been maintained at 70% since implementation. Among the retreatment cases in 2015, 11% defaulted treatment, 8% died and treatment failure was seen in 3% of cases [3]. The outcomes are still worse among patients who failed or relapsed after their initial TB treatment [6]. WHO treatment guidelines published in 2010 recommended TB treatment guided by drug susceptibility testing for all previously treated patients using rapid diagnostic techniques [4]. However, Category II regimen is repeatedly given to patients despite differences in the outcomes of the retreatment category. Globally, in the year 2015, only 53% of the previously treated patients were reported to have undergone a drug sensitivity testing for rifampicin [2]. In India, 60% of previously treated cases are reported to have had a rifampicin sensitivity testing [3].

An operational assessment of the utility of Category II was done in 2010 in Georgia, a country with a high burden of TB especially drug resistant TB. Following this assessment, the National Tuberculosis Programme decided no longer to recommend Category II treatment because of high rates of streptomycin resistance among previously treated patients and poor outcomes among patients on Category II. The programme concluded that previously treated patients should undergo drug susceptibility testing and patients with documented resistance (including mono resistance) would receive a regimen based on drug susceptibility results [7]. A retrospective study done in West Bengal among smear positive re-treatment patients reported that unfavorable outcome was more among the treatment failure subgroup and those with high grades of sputum positivity [8]. A systematic review on DOTS for TB relapses in India reported that majority of the relapses presented within six months of treatment completion. The outcome of relapse cases put on treatment was less effective than new cases and the review concluded that DOTS category II treatment may not be adequate for re-treatment patients [9].

Treatment Outcomes among Previously Treated Cases

A precise analysis of the treatment outcomes of retreatment cases is needed to identify existing strengths and weaknesses in the management of retreatment cases. This data will help the programme to decide the measures for improving tuberculosis care in this group of patients. We performed two literature searches, a more generalized search initially regarding retreatment cases in tuberculosis in Pub Med and Google scholar followed by a focused search for specific topics such as treatment, smear grading, disease severity and outcomes. We chose the articles that were related to treatment outcomes in re-treatment cases written in the English language. We also reviewed the reference list of the identified articles for additional relevant articles. Studies have been conducted in different countries and the case definitions and treatment regimens used were as per the national guidelines which prevailed during the study period. Studies not done in re-treatment cases and articles published in language other than English were excluded.

Studies available in the literature are mostly cohort studies done retrospectively through review of records, as summarized in (Table 1), the success rates and factors associated with unfavourable outcomes among patients treated with Category-II ATT. Re-treatment cases are usually grouped into three categories before initiation of treatment- relapse, failure and treatment after default (TAD). Relapse subgroup contributes to more than half of the patients who were started on Category-II treatment. Overall, Cases which belonged to the relapse group had more success rates compared to the other groups.

Authors, Country, Year of publication	Study design, Sample size	Type of re-treatment patient	Success rates	Factors associated with the outcomes
Ottmani et al., Morocco, 2006 [10]	Retrospective cohort study, N=14635	Relapse-81.7%, Failure-5.2%, Treatment After Default (TAD)-13.1%	74.8% in relapse group, 58% in failure group, 51.4% in TAD group	Failure and default group of patients were more likely to fail and default Category-II treatment respectively.
Mukherjee et al., India, 2009 [8]	Retrospective cohort study, N=234	Relapse-63.24%, Failure-22.24%, TAD -14.52%	76.35% in relapse group, 53.85% in failure, 55.88% in TAD	Failure subgroup and patients with high grade smear positivity had more chances of unsuccessful outcomes.
Mukwaya AN et al., Uganda, 2013 [11]	Retrospective cohort study, N=331	Relapse-46%, Failure-6%, TAD-48%	54% in relapse (smear +) group, 48% in failure group, 31% in TAD group, 38% in relapse (smear -) group, 28% in relapse (no smear performed) group	Relapse smear (+) and failure cases were less likely to have favourable outcomes.
Dooley et al., Morocco, 2011 [12]	Retrospective cohort study, N=291	Relapse-80%, Failure-7%, TAD -13%	74% in relapse group, 48% in failure, 41% in TAD	Failure of sputum conversion by 3rd month of treatment and hospitalization during treatment were associated with unsuccessful outcomes.
Nabukenya M et al., Uganda, 2015 [13]	Retrospective cohort study, N=730	Relapse- 26.9%, Failure-6%, TAD-21.6%, Others-45.5%	68.4% in relapse group, 31.8% in failure, 50% in TAD, 49.7% in others group	Odds of success were less among failure and others group of patients.
Ade et al., Benin, 2016 [14]	Retrospective cohort study, N=241	Relapse-61%, Failure-32.4%, TAD-6.6%	95% in relapse group, 91.3% in failure, 80% in TAD	95% in relapse group, 91.3% in failure, 80% in TAD

Table 1: Studies on TB treatment outcomes among previously treated cases reported in the literature.

Challenges in Managing Previously Treated TB Patients

Previously treated cases, if not managed properly can contribute to more disease transmission in the community and rise in occurrence of drug resistant TB [4]. Although there is a progress in diagnosis and treatment of this group of patients, challenges still exist and they have to be addressed promptly as ending TB is one of the global research priorities [5]. All patients before starting on Category-II ATT have to undergo drug susceptibility testing. But in resource limited settings, this is not followed as a routine. Though rapid diagnostics like GeneXpert are gaining popularity in quick diagnosis of *M. tuberculosis* and rifampicin resistance, cost factor hinders the regular use of such newer methods [15].

Once the patient is initiated on treatment, regular intake of drugs for a period of eight months is crucial. Poor compliance to treatment can be due to social factors, drug side effects, sense of wellbeing after few weeks of treatment, lack of time and forgetfulness [16]. Counselling the TB patients at regular intervals is very important as it reinforces the significance of regular treatment and identifies person specific problems in maintaining the adherence. Screening of family members of TB patients is recommended as it helps in prevention of disease transmission through preventive therapy and early diagnosis of cases if any, present in the family, the challenges faced by the physicians and healthcare workers in managing the previously treated TB cases, as summarized in (Table 2).

Component	Challenges
a. Diagnosis	Lack of Drug sensitivity testing before treatment initiation
	Unavailability of rapid diagnostics
b. Treatment	Difficulty in completing the treatment due to long duration
	Non-adherence due to side effects, disappearance of symptoms, social factors
	Low success rates in case of associated co-morbidities like HIV, Diabetes mellitus
	Poor implementation of contact screening as a routine to prevent disease transmission to family members
	Non-availability of regular counseling to the patients
c. Follow-up	Missing sputum testing at the end of intensive phase and continuation phase
	Absent/improper documentation of treatment outcome

Table 2: Challenges in management of retreatment cases.

Conclusion

Information on risk factors associated with unfavourable outcomes among re-treatment patients will help the policy makers to strengthen guidelines for management of re-treatment patients. If these patients are treated effectively, this can increase the success rate of treatment and decrease the development and transmission of drug resistant TB. Prospective studies are needed for in-depth analysis of the factors associated with unsuccessful outcomes among previously treated cases, taking into account the contributing social, economic and environmental factors.

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