

Effectiveness of directly observed treatment short course (DOTS) in tuberculosis –A patient-centered case management approach

Amina Talib¹, Shagufta Iram², Muhammad Saeed³, Mehwish Akhtar⁴, Aamir Hanif⁵, Ambereen Anwar⁶

ABSTRACT

Objective: To assess the treatment outcome and follow-up status of newly diagnosed Tuberculosis (TB) patients registered in Directly Observed Treatment Short course (DOTS).

Study Design: Descriptive case series study

Place and Duration: Department of Pathology TB Laboratory, Allama Iqbal Medical College (AIMC) during the period of 12th May 2016 to 25th March 2017.

Methodology: Study was carried out among Patients referred to TB laboratory, from DOTS clinic Jinnah Hospital Lahore Pakistan for ZN smear microscopy. Sputum samples were collected at 2nd, 4th and 6th months and processed for Ziehl Nelson (ZN) smear microscopy and Löwenstein–Jensen (LJ) culture. All cases that were positive on LJ culture on follow up were also processed for GeneXpert Mycobacterium tuberculosis /Rifampicin (MTB/RIF) Assay. If any cases were diagnosed as multi drug resistant (MDR) they were referred to MDR clinic for further management. Outcome were evaluated in accordance with World Health Organization (WHO) recommendation and classified as: cured, treatment completed, defaulted, treatment failure, death or other.

Results: Among 109 ZN smears positive patients 100% were also positive for MTB on LJ culture at the time of diagnosis. Male and females were 55.9%, 44.0% respectively, mean age was 38.40 ± 18.55 years. Overall mortality rate was 6.4%, completely cured 76.1%, treatment failure and MDR 1.8%, defaulted 13.7%. ZN smear conversion rate was 96.1%, 97.8% and 97.6% at 2nd, 4th and 6th month respectively.

Conclusion: The results of the present study concluded that DOTS is an effective therapy for treatment of TB patients. It not only keeps patients to cure completely by completing treatment but also identifies the MDR-TB cases which can be referred to MDR clinic immediately for purpose of treatment.

Keywords: DOTS, Effectiveness, Tuberculosis, TB management ZN Smear, GeneXpert,

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INTRODUCTION

Tuberculosis (TB) aptly earned such morbid nicknames like the "White Plague", and "Captain of the Men of Death¹. TB was declared a national emergency by the ministry of health Pakistan in 2011. In spite of maximum efforts and multiple strategies to control TB, diagnosis and management of the disease is still a major challenge for microbiologists and clinicians^{2, 3}. Moreover emergence of multidrug resistance (MDR-TB) aggravated the seriousness of situation⁴. From day first several guidelines, policies were made to fight against this deadly infectious disease caused by Mycobacterium Tuberculosis (MTB). Now a days TB have terror among society, as it has become a significant reason of morbidity and mortality⁵. Unfortunately Pakistan stands 5th with TB and 4th with MDR-TB among high burden countries⁶. The resurgence of TB is may be due to its mismanagement, delayed diagnosis, improper treatment, non-compliance of patients, unawareness of prevention and its treatment among the community⁷. Timely treatment and management of newly diagnosed patients is single and easiest way to control TB^{8,9}. Mismanagement in treatment is usually observed from the patient side because of self-medication without any expert

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supervision, non-compliance to anti-tuberculosis drugs due to its side effects i.e. nausea, vomiting, nervous symptoms, and diarrhea¹⁰.

To overcome this issue, World Health Organization (WHO) introduced Directly Observed Treatment, Short-course (DOTS) therapy also called TB-DOTS, as a major policy for patients treatment and follow up all over the world in 1993¹¹. DOTS depends on five main components, Government commitment, Case detection by sputum smear microscopy, Standardized treatment regimen directly of six to nine months observed by a healthcare worker for at least the first two months, Free drug supply and standardized recording and reporting system that allows assessment of treatment results^{12,13}. So it will provide a glimpse of the effectiveness and compliance of patients towards DOTS.

Although many studies are available on patients follow up but very few studies are available on effectiveness of DOTS, outcomes microbiologically like by ZN smear microscopy and LJ culture. Paucity of literature is available from Pakistan, therefore present study was planned, and the objective of present study was to assess the treatment outcome and follow-up status of newly diagnosed Tuberculosis (TB) patients registered in Directly Observed Treatment Short course (DOTS).

METHODOLOGY

This descriptive case series study was carried out among the patients referred for ZN microscopy to TB laboratory of pathology department Allama Iqbal Medical College (AIMC) from DOTS clinic Jinnah hospital Lahore, from 12th May 2016 to 25th March 2017. DOTS clinic serves to huge population at Lahore, Pakistan. Study was conducted after approval of Ethical review board of institute. Non probability sampling technique was used and a total of 109 patients (ZN smear positive and LJ culture positive at the time of diagnosis) were selected from DOTS clinic and were followed up during their course of treatment to assess treatment outcome. From May 2016 to March 2017 both genders, the patient included in this study were confirmed cases of pulmonary tuberculosis (PTB), aged 15 years and above, diagnosed by detection of acid Fast bacilli (AFB) by ZN smear microscopy were included. Patients having co-existing HIV infection, the previous history of anti-tuberculosis treatment and samples which were collected in open and leaky container or containing volume less than 01ml were excluded.

Two sputum specimens of each patient (109 x2=218) were collected at the time of diagnosis i.e. first-morning sample and spot sample. Every sample was collected in a sterile leak-proof, tightly capped and labeled container. Appropriate smears were made for ZN smear microscopy. Löwenstein–Jensen (LJ) culture was put on LJ media after decontaminating the sputum according to WHO protocol.

All these patients were registered and followed up during their DOTS treatment and sputum samples were collected at 2nd, 4th and 6th months, and again processed for ZN smear microscopy and LJ culture. All those cases that were positive on LJ culture on follow up were also processed for GeneXpert

MTB/RIF Assay. If any cases were diagnosed as MDR that was referred to MDR clinic for further management. Patients were provided with free TB medications for a period of 6 months by the tertiary care Hospital DOTS clinic. Every Patient was followed up regularly until completion of treatment and treatment outcome were evaluated in accordance with WHO recommendation and classified as: cure, treatment completed, defaulted, treatment failure, death or other.

Different treatment outcomes were observed according to WHO guidelines¹⁴ (i) Cured: Who had accomplished treatment and had sputum smears negative on at minimum two instances, one of which was at the completion of treatment. (ii) Treatment completed: treatment completed, smear negative at the completion of Intensive Phase (IP), but then again none at the end of treatment. (iii) Defaulted: after starting treatment who has not taken anti-TB drugs for 2 months or more consecutively, (iv) Died: patient who died during treatment (v) Treatment failure: treatment result (outcome) is not known.

For quality assurance and quality control of ZN smear Microscopy, positive and negative slides for AFB were stained with each set, and examined by laboratory technologists, every undecided slide was rechecked by consultant microbiologist.⁴ For LJ culture: American type culture collection (ATCC) strains of H37rv was used for quality assurance purpose against quality of culture medium and growth of mycobacterium. Sterile water inoculated LJ medium bottle was used as negative control.⁴ For GeneXpert Technology: this technique is multiplexed with MTB assay, *Bacillus globigii* spores oblige as control for PCR and internal sample processing⁴

Data Analysis: Data analysis was done with the use of SPSS version 21.0 Frequency and percentages were presented for quantitative variables like cured, Treatment failure, MDR, Defaulted and Mortality.

RESULTS

Out of 109 clinically diagnosed newly-detected ZN smears positive patients, 55.9% (n=61) were male, 44.0% (n=48) were females, mean (SD) age was 38.40 ±18.55 years. Overall among total 109 cases, mortality rate was 6.4% (n=7), 76.1% (n=83) were completely cured while treatment failure and MDR were 1.8% (n=2). Unfortunately a very high rate of 13.7% (n=15) cases were defaulted due to any unknown reason. (Table-I)

Table-I: Gender based frequency distribution of treatment outcomes of DOTS therapy (N=109)

Gender	Cured	Treatment failure	Defaulted	Mortality	MDR	Total
Male	45 (73.8%)	1 (1.6%)	9 (14.8%)	5 (8.2%)	1 (1.6%)	61 (100%)
Female	38 (79.2%)	1 (2.0%)	6 (12.5%)	2 (4.1%)	1 (2.0%)	48 (100%)
Total	83 (76.1%)	2 (1.8%)	15 (13.7%)	7 (6.4%)	2 (1.8%)	109 (100%)

Table-II: Frequency distribution showing outcomes of cases on smear microscopy and culture at the end of 2nd 4th and 6th month. (N=109)

Variable	2 nd month	4 th month	6 th month
Remaining cases	106 (97.2%)	91 (83.4%)	85 (77.9%)
Mortality	3(2.8%)	2 (2.1%)	2 (2.3%)
Defaulted	0 (0%)	11 (12.0%)	4 (4.7%)
Zn Smear(+ve)	4 (3.7%)	2 (2.1%)	2 (2.3%)
Zn Smear (–ve)	100 (96.1%)	89 (97.8%)	83 (97.6%)
LJ Culture (+ve)	5 (4.7%)	3 (3.2%)	2 (2.3%)
LJ Culture (–ve)	101 (95.2%)	86 (94.5%)	81 (95.2%)
GeneXpert MTB Detected	5 (4.7%)	3 (3.2%)	2 (2.3%)
GeneXpert MDR Detected	2 (1.8%)	0 (0%)	0 (0%)

109 patients underwent ZN smear microscopy and LJ culture at the time of enrollment in DOTS program. Among these 109 newly detected ZN smear-positive cases 100% (n=109) were also positive for MTB on LJ culture while GeneXpert was not processed on at the time of diagnosis as per WHO guidelines. All these cases were referred to DOTS clinic for TB treatment.

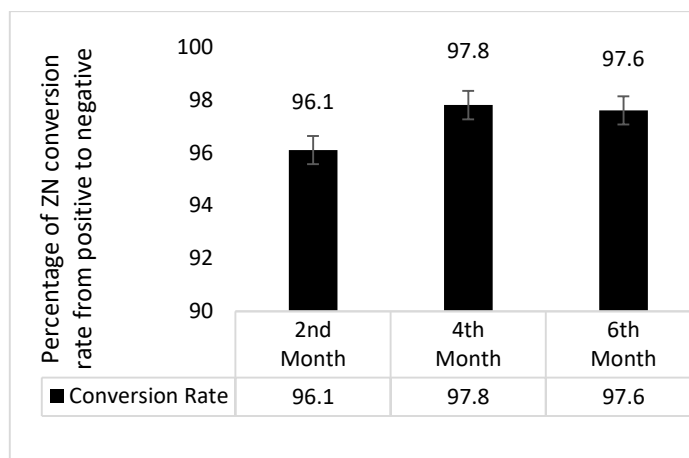
At 2nd month of follow up of total 109 cases, 2.8% (n=3) died and 97.2% (n=106) were returned to DOTS clinic of which 4.7% (n=5) were LJ culture as well as GeneXpert positive, among these rifampicin resistance (MDR) was detected in 1.8% (n=2) cases. Furthermore, 3.7% (n=4) were ZN smear positivity. MDR cases were referred to MDR clinic for further management. ZN smear conversion rate was 96.1% (n=100).

At 4th month of follow up of total 106 cases, MDR 1.8% (n=2) were already removed and among remaining 104 cases 2.1% (n=2) were died, 12.0% (n=11) were defaulted and 83.4% (n=91) were resumed to DOTS clinic, of them 3.2% (n=3) were LJ and GeneXpert Positive, no one MDR was detected, 2.1% (n=2) were ZN smear positive, ZN smear conversion rate was 97.8% (n=89).

Table-III: Age group wise distribution of treatment outcomes among patients under DOTS therapy (N=109)

Age Group Years	Cured	Treatment failure	Defaulted	Mortality	MDR	Total
15-24	32 (86.5%)	1 (2.7%)	2 (5.4%)	-	2 (5.4%)	37 (100%)
25-34	10 (76.9%)	-	1 (7.7%)	2 (15.4%)	-	13 (100%)
35-44	11 (84.6%)	-	1 (7.7%)	1 (7.7%)	-	13 (100%)
45-54	17 (77.3%)	-	4 (18.2%)	1 (4.5%)	-	22 (100%)
55-64	6 (50%)	1 (8.3%)	5 (41.7%)	-	-	12 (100%)
> 64	7 (58.3%)	-	2 (16.7%)	3 (25%)	-	12 (100%)
Total	83 (76.1%)	2 (1.8%)	15 (13.7%)	7 (6.4%)	2 (1.8%)	109 (100%)

At 6th month of follow up, of total 83.4% (n=91) cases, 2.3% (n=2) were died, 4.7% (n=4) were defaulted and only 77.9% (n=85) were attended at DOTS clinic among which 2.3% (n=2) were still positive on LJ, GeneXpert and ZN smear microscopy. ZN smear conversion rate was 97.6% (n=83). Fig-1

**Fig-1: ZN smear Conversion rate from positive to negative (N=109)**

It was observed that every smear-positive case was also positive on LJ culture as well as GeneXpert, and every LJ culture positive cases were also GeneXpert Positive. All cases which were both smear and culture negative at the end of the treatment were referred as cured 83(76.1%). Those cases which were smear, culture or GeneXpert positive at the end of the treatment were termed as treatment failure 2(1.8%) and those who left the treatment termed as a defaulter 15(13.7%). Those who were GeneXpert rifampicin resistant detected were MDR 2(1.8%).

DISCUSSION

Latest diagnostic techniques and new drugs were used to diagnose and treat tuberculosis for last few decades. In spite of extra efforts and multiple improved policies and strategies to control TB. The disease is still prevailing¹⁵. Even MDR-TB has emerged as a new challenge to the clinicians, not only late diagnosis, but also non-compliance of patients, due to many other reasons WHO started the DOTS for patient management, which proved to be very effective^{16,17}.

In DOTS therapy a trained health care worker (HCW) or another individual (excluding a family member) provides the prescribed TB drugs and watches the patient swallow every dose so certifying that patient takes the correct drugs in the accurate doses at the exact intervals for the right extent¹⁸. But in remote areas where availability of health care personnel is difficult, any accountable family member of the patient takes the responsibility to supervise the patient daily when he or she swallows medicine^{18,19}. A high cure rate after DOTS therapy has been observed because of improved drug compliance owing to strict supervision which is the core element of this strategy. Almost 60% patients were benefitted from DOTS in 1990, later on, in 1993, World Development Report claimed DOTS strategies as one of the most cost-effective public health investments for the TB control. Since 1995, 41 million people have been successfully treated and up to 6 million lives saved through DOTS and the Stop TB Strategy. Almost 5.8 million TB cases were recovered through DOTS programs in 2009²⁰. Since 2001 health policy of Pakistan makes a direct reference for controlling the disease by using the WHO-recommended strategy DOTS. The National Tuberculosis Control Program (NTP) is responsible for overall TB control activities in the country. karanjekar et al from India revealed death rate 3.2%, high mortality observed in males patients which may attributed to high default rate in male 23% then female 14.9% and 76.1% were completely cured, while treatment failure were 1.8% and MDR were also 1.8%. Unfortunately 13.7% cases were defaulted due to any unknown reason. Unfortunately cure rate was very stumpy in age group above 55 years. Our results are in the favor of previous study conducted by Chennaveerappa et al²¹, from south India reported 84.2% were cure, 2.2% failure and 8.2% defaulter, the total death rate was 6.1% and total success rate was 83.4%.

In case of treatment failure our results are high 1.8% as compare previous study reported 0.7% failure rate in hadia zone²². Therefore MDR-TB should be considered as an upcoming threat, but a small frequency indicated that first line treatment is playing an encouraging role in breaking the chain of spread. Treatment failure to DOTS includes many reasons like non-compliance of patients to treatment or resistance to any other drug instead of Rifampin, which can't be detected at GeneXpert. Therefore through more advanced technical instruments and by performing GeneXpert at the start of treatment will be helpful to seek out the reason of treatment failure. Regrettably present study exposed high rate of defaulters 13.7% especially in male patients 14.8% then female 2.55%. Very high rate of treatment discontinuation was observed among old age group, behind this not feeling well was major problem for treatment discontinuation. This Attrition (loss of follow up) rate demands a better and focused follow up of patients to reduce the defaulter rate. Effective counseling for importance of regular treatment and side-effects is key point. One of the reasons of loss of follow up of patients is the report giving to patients at 2nd, or 4th month when the patients came to know about the negative report, they don't take medicine. To overcome this problem end report of treatment should be issued to patients by DOTS clinic

staff. The present study reported 76.1% were completely cured, very low rate as compare to Verma et al²³. Revealed a DOTS treatment success rate of 89.8%. Another south Indian study reported 88% smear conversion rate at 2nd month and 100 % cure rate at the end of treatment²⁴. Acquah et al reported 8.1% smear positivity at the follow up of the 2nd month²⁵. From Delhi²⁶ 91.0% treatment success reported in Category I patients. VD karanjekar et al from India revealed treatment success rate as 78.3%. Results of this study are very close to our study which indicates a cure rate of about (76.1%) as cure rate and very good sputum conversation are inspiring. Therefore DOTS is an effective approach in treating Tb patients.

Conversion frequency from positive ZN smear to smear negative at 2nd, 4th and 6th month was 96.1%, 97.8%, and 97.6% respectively. It is very encouraging not only for policy makers but also for clinicians. Low cure rate and high mortality among old age group is may credited to recurrence of endogenous infection. This dilemma is attributed atypical clinical and radiological features poor nutritional position and other misleading symptoms, From the present study frequency of mortality was recorded about 6.4%, but we were not assured that either reason of patient's death was tuberculosis or any other disease like heart attack, diabetes, or hepatitis, so there should be a complete profile of all tests in record of TB control program.

The treatment of TB infected patients is well-thought-out solitary as the concern of DOTS, but TB patient is also accountable for his/her individual health by initial diagnosis and treatment adherence of TB. Operative counseling is major key point to enhance attentiveness. As inappropriate management during treatment additional generates the problematic situation like multi-drug resistant TB. Therefore, missionary enthusiasm of self-care by patient, public contribution, and proper policy formulation in health care system can certainly tackle this subject.

CONCLUSION

The results of the present study concluded that DOTS is an effective therapy for treatment of TB patients. It not only keeps patients to cure completely by completing treatment but also identifies the MDR-TB cases which can be referred to MDR clinic immediately for purpose of treatment.

RECOMMENDATIONS

A high defaulter rate indicated that there are some loopholes or faults in implementing this Programme which can be rectified by more focused approach along with educating the patients and society.

CONTRIBUTION OF AUTHORS

Talib A: Data collection, Lab work, Results compilation

Iram S: Conceived idea, Designed methodology, Results interpretation, Final approval

Saeed M: Manuscript writing, Data interpretation

Akhtar M: Statistical analysis

Hanif A: Data collection

Anwar A: Critical review, Literature search

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