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STUDY OF SPUTUM SMEAR AND CULTURE CONVERSION IN DRUG RESISTANT TUBERCULOSIS PATIENTS TREATED UNDER PROGRAMMATIC MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS AT ACHARYA VINOBHA BHAVE RURAL HOSPITAL

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ABSTRACT

Introduction: Drug resistant tuberculosis in patients requires treatment for long term and has a high fatality rate. Early detection of treatment failure through sputum conversion is required to predict the outcome of the therapy. Early culture conversion is a predictor of successful treatment outcomes. **Aim and Objectives:** To study the maintenance of bacterial quiescence (culture negativity) with duration of treatment and effectiveness of DOTS PLUS therapy by observing sputum smear and culture conversion. **Materials and methods:** All the diagnosed patients of Drug Resistant Tuberculosis referred by District tuberculosis centre Wardha to Drug resistant tuberculosis link centre at Acharya Vinobha Bhave rural hospital Wardha were included In the study during the period from 01/09/2016 to 31/08/2018. Sample size of 26 patients was taken. Treatment was given as per PMDT guidelines and these patients were discharged from our hospital. Through DTO and associated staff concerned sputum culture and smear reports were followed for 3rd,4th,6th,9th and 12th months. **Results:** Sputum smear and culture conversion was found out to be 57.7 % after the duration of our study, in which we could follow up all the patients for one year of treatment. The default rate observed was 19.23 %. Highest default rate was observed within the first 3 months of treatment initiation (7.69 %). The main cause of the treatment default was Adverse drug reactions, most common among them was Hepatotoxicity. Diabetes mellitus and Low BMI were associated with poorer outcomes in terms of sputum conversion. **Conclusion**: The sputum conversion rate in our study dropped significantly when comparing the results from 3rd month and 12th month of follow up respectively. This was partly due to treatment default, mainly to Adverse drug reactions. We also found out that patients who had low BMI and Uncontrolled Diabetes mellitus were more likely to be sputum smear and culture positive during follow up. So, if the proper dietary and medical management of patients with low BMI and DM is done, treatment outcomes would be better.

KEYWORDS: Tuberculosis, Drug Resistant Tuberculosis, Sputum conversion

INTRODUCTION

Tuberculosis is a bacterial infection caused by *Mycobacterium tuberculosis*. Although most commonly encountered in the lungs, it could infect any part of the body.[1] Tuberculosis (TB) ranks among the top ten causes of mortality worldwide. Since the last five years, it has been the leading cause of death from a single infectious agent, ranking above HIV/AIDS.[2] An estimated 10.4 million new cases of TB disease were detected in 2016 and 10% of these patients had an HIV infection. Out of the total, seven countries shared 64 % burden of the disease, with India dominating, followed by Indonesia, China, Philippines, Pakistan, Nigeria, and South Africa.[3] Global TB report 2017 estimated the incidence of TB in India was approximately 27,90,000 reckoning for about a quarter of the world's TB cases.[3] The rise of resistance to Anti tubercular drugs, has become an important public health issue and it remains a big reason for ineffective TB control in India.

Drug resistance is manifested as a selective growth of resistant mutants among the actively multiplying mycobacterium colonies which are acted upon by the anti-tubercular drugs. Size of the active bacillary population in the pulmonary lesions and the quality of anti-tubercular drugs used contribute individually to the emergence of drug resistance. Drug resistance in patients who have been treated for tuberculosis for 1 month or

more is defined as "Acquired drug resistance", while that of patients who have never been treated previously or treated for less than 1 month is called "Primary drug resistance". Resistance to a single drug is defined as "mono resistance" while the resistance to two or more drugs is defined as "poly resistance."[4]

"Multidrug-resistant tuberculosis" (MDR-TB) is defined as TB that is resistant isoniazid (INH) and rifampicin.[3] Globally in 2016, an estimated 4.1% (95% confidence interval [CI]: 2.8–5.3%) of new cases and 19% (95% CI: 9.8–27%) of previously treated cases had MDR/RR-TB.[5] India had the second highest total number of estimated MDR TB cases (99,000) in 2008, after China (100,000 cases).[6] "Extensive drug resistant tuberculosis" (XDR-TB) is defined as those TB cases with documented resistance to isoniazid (H) and rifampicin (R) and at least three of the six main classes of Second line drugs [aminoglycosides, polypeptides, fluoroquinolones (FQs), thioamides, Cycloserine (Cs) and para-aminosalicylic acid (PAS).[7] More recently, since March 2006, XDR-TB has become the most alarming issue in the international effort to control TB in view of the poor treatment options and poor outcomes in those who are affected in both developing countries as well as in the developed world.[8] Data from India suggests that the incidence of XDR-TB varied from 0.3 to 60 percent of the total MDR-TB cases.[7]

Potent management of drug-resistant tuberculosis (DR-TB) requires prevention, case detection, care and treatment, surveillance, drug management, and monitoring and assessment of program performance. All of such activities are coordinated by Tuberculosis control programs in India and are referred collectively as "Programmatic management of drug-resistant tuberculosis" (PMDT).[9] The PMDT services were introduced in 2007 and it took 6 years for it to become pan-India. In the beginning, DR-TB services were offered to the those known TB patients who were at a high risk of developing drug resistance i.e. treatment failures. It was followed by a scale-up approach. Fixed criteria were set to assess the risk as well as eligibility for the drug susceptibility test (DST). DST was offered to TB patients who remained smear positive during follow-up, to the previously treated patients of TB, those who were HIV positive and people who had contact with a known DR-TB patient.[10] To conduct this, huge laboratory capacity in terms of geographic coverage, DST technology, trained laboratory personnel, quality assurance and certification were required. From a few national reference laboratories (NRL), and state level Intermediate reference laboratories (IRL) with solid or liquid culture and DST facilities, the country expanded its capacity to a wide network of state and regional level intermediate reference laboratories with solid and liquid culture DST and Line Probe Assay (LPA) and district level network of Cartridge Based Nucleic Acid Tests (CBNAAT).[10]

Detection of DR-TB through Revised National Tuberculosis programme (RNTCP) has been progressively rising with increased access to various forms of DST. In 2016, RNTCP was detected and treatment initiated in about 34016 patients of MDR-TB and 2476 patients of XDR-TB.[10] The treatment outcomes of DR-TB patients according to the "PMDT" guidelines have been discussed below.[11]

Cured: A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear or culture-negative in the last month of treatment and on at least one previous occasion.

Treatment completed: A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.

Treatment failed: A TB patient whose sputum smear or culture is positive at the 5th month or later during the treatment.

Died: A TB patient who dies for any reason before starting or during the course of treatment.

Lost to follow-up: A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

Treatment default: A TB patient whose treatment was interrupted for 2 months or more.

Not evaluated: A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.

Treatment Success: The sum of cured and treatment completed.

"Sputum culture conversion" is defined as two consecutive negative cultures, collected at least 30 days apart.[12] Conversion of sputum smear and culture plays a vital role when comes to monitoring of the treatment response in patients with DR-TB, it is a clinical tool used to predict therapeutic potency. Monthly culture monitoring is crucial for earlier detection of treatment failure in patients with DR-TB.[12] For the duration of treatment with injectable agents, also the intensive phase of the treatment, sputum culture and smear conversion are proved to be important determinants.[13] Conforming to the PMDT guidelines, sputum culture conversion reports after the completion of 6 months of treatment decide the duration of the intensive phase of treatment.[13] Anticipating the initial time to culture and smear conversion is also important for planning the isolation of the patients.[11] Time to sputum culture

conversion and conversion status can be considered as proxy markers of end-of treatment outcomes in DR-TB patients.[13] From the public health point of view, reducing the time to sputum culture conversion is an important infection control measure.[14] Anticipating the initial time to sputum conversion is important when comes to isolation of patients suffering from DR-TB.

Here we did a study to evaluate sputum smear and culture conversion of DR-TB patients admitted in our hospital.

AIM AND OBJECTIVES

Aim: To study the smear and culture conversion in drug resistant tuberculosis cases treated under pragmatic management of drug resistant tuberculosis.

Objectives

1. To study maintenance of bacterial quiescence (culture negativity) with duration of treatment.
2. To study effectiveness of DOTS PLUS therapy by observing sputum conversion.
3. To evaluate any factors brought out during the research study.

MATERIALS AND METHODS

Study design and period: A prospective observational study was done to find out sputum smear and culture conversion in drug resistant tuberculosis patients treat under Pragmatic management of Drug resistant tuberculosis was conducted at Department of Respiratory Medicine, Acharya Vinobha Bhave Rural Hospital, Sawangi (Meghe) Wardha from 01/09/2016 to 31/08/2018. All the consenting diagnosed cases of Drug resistant tuberculosis coming as Indoor patients were enrolled. A total of 26 patients met the inclusion criteria were included in the study.

A Structured Standard Questionnaire (SSQ) was framed and patients enrolled in the study were interviewed. Demographic information, BMI (Body mass index in kg/m square, history of present and past illnesses including history of tuberculosis and/or anti-TB treatment, history of contact with known tuberculosis cases, history of Diabetes, Hypertension, COPD, HIV, alcohol use, smoking and other relevant data were collected. ELISA for HIV1 and HIV2 was done of all the patients with no records. Informed written consent was taken from all the participants. BMI was graded using the criteria by Obesity foundation India.[15]

Underweight- <18.5 kg/m^2
Normal- 18.5-25 kg/m^2
Overweight- 25- 30 kg/m^2
Obese- 30-35 kg/m^2
Severely obese- >35 kg/m^2

Anaemia was assessed by using the WHO criteria[16]
Sample size: 26

Inclusion criteria: All the diagnosed patients of drug resistant tuberculosis (MDR/XDR) admitted to our hospital for treatment.

Exclusion criteria: Patients who are not willing to give their consent to participate in the study**.**

All of the 26 patients were admitted in our hospital and treatment was initiated after doing a pre-treatment evaluation. Pre-treatment assessment is systematically conducted on all patients to identify those at a greatest risk of adverse effects and poor outcomes and to establish a baseline. The required initial pre-treatment clinical investigation includes a thorough medical history and physical examination. The conditions we screened for an initial medical evaluation are enlisted.[17]

Table No. 1: Conditions which are screened for in DR-TB patients.

• HIV infection (option of HIV testing)	• Acute or chronic liver disease	• Pregnancy
• Diabetes mellitus	• Mental illness	• Breast feeding
• Hypertension	• Drug or alcohol dependency	• Seizures
• Renal insufficiency		• Malnutrition
		• Thyroid disease

All patients starting drug resistant tuberculosis treatment underwent the following tests.

- Acid-fast smear, mycobacterial cultures and DST.
- Baseline potassium, creatinine, serum glucose and serum glutamic-pyruvic transaminase (SGPT; alanine transaminase (ALT)).
- HIV rapid testing
- Baseline complete blood count.
- Pregnancy test for women of childbearing age.
- Thyroid function tests
- Ultrasonography of Abdomen and Pelvis
- Chest Radiograph
- Ophthalmic, Psychiatric and ENT examination

The patients in our study were treated under PMDT regimen for MDR-TB.[18] The drugs used were

- Kanamycin- 15-20 mg/kg
- Levofloxacin- 750 mg once daily
- Ethionamide- 10 mg/kg
- Ethambutol- 14.5–20.0 mg/kg
- Pyrazinamide- 8.2–25.0 mg/kg
- Cycloserine- 500 mg once daily
- Pyridoxine- 100 mg once daily

Sputum examination

- After 7 days of pre-treatment evaluation and starting of the treatment regimen, the patients were discharged.

- With the help of DTO and concerned staff, sputum smear and culture follow up was done on the 3rd, 6th, 9th and 12th month of treatment.
- The processing of sputum samples was carried out by IRL (Intermediate research lab) at Nagpur.
- Smear and culture reports were collected from the District Tuberculosis centre as per the time schedule.
- Monitoring of smear/culture conversion was assessed as per the time schedule.
- Effectiveness of the treatment was assessed by monitoring the bacteriological conversion.

Sputum smear examination was done by Fluorescence microscopy. Fluorescence staining utilizes basically the same approach as Z-N staining, but carbol fuchsin is replaced by a fluorescent dye (auramine-O, rhodamine, auramine-rhodamine, acridine orange etc), the acid for decolourization is milder and the counter stain, though not essential, is useful to quench background fluorescence. Both sensitivity and specificity of fluorescence microscopy are comparable to the characteristics of the Z-N technique. The most important advantage of the fluorescence technique is that slides can be examined at a lower magnification, thus allowing the examination of a much larger area per unit of time. In fluorescence microscopy, the same area that needs examination for 10 minutes with a light microscope can be examined in 2 minutes.[19] In the fluorescent staining, smears are examined at much lower magnifications (typically 250x) than used for ZN-stained smears (1000x). Each field examined under fluorescence microscopy, therefore, has a larger area than that seen with bright field microscopy. Thus, a report based on a fluorochrome-stained smear examined at 250x may contain much larger numbers of bacilli than a similar report from the same specimen stained with carbol fuchsin and examined at 1000x. For the purpose of uniformity for examination and quantitative reporting of results, a method has been suggested whereby the number of acid-fast bacilli observed under fluorochrome staining could be divided by a "magnification correction factor" to yield an approximate number that might be observed if the same smear were examined under 1000x after carbol fuchsin stain. To adjust for altered magnification of fluorescent microscope, when using objectives of x20 or x25 powers, divide the number of organisms seen under FM by the factor of 10. Similarly, if one using a 40 x objective the magnification correction factor is 5, and if one using a 45 x objective it is.[19] Comparative grading of Zn stain and Fluorescent staining (2)

Table No. 2: Shows the comparison between Zn stain and fluorescent microscopy.

RNTCP ZN staining grading (using 100x oil immersion objective and 10x eye piece)	Auramine O fluorescent staining grading (using 20 or 25x objective and 10x eye piece)	Reporting /Grading
>10 AFB/field after examination of 20 fields	>100 AFB/field after examination of 20 fields	Positive, 3+
1-10 AFB/field after examination of 50 fields	11-100 AFB/field after examination of 50 fields	Positive, 2+
10-99 AFB/100 field	1-10 AFB/ field after examination of 100 fields	Positive, 1+
1-9 AFB/100 field	1-3 AFB/100 fields	doubtful positive /repeat
No AFB per 100 fields	No AFB per 100 fields	Negative

Sputum culture and DST examination was done using liquid culture method. Rapid form of liquid tuberculosis culture is also known as MGIT. MGIT contains modified Middlebrook 7H9broth base. When supplemented with MGIT Growth Supplement and PANTA, it provides an optimum medium for growth of a majority of mycobacterial species. All types of specimens, pulmonary as well as extra-pulmonary (except blood), can be inoculated into MGIT for primary isolation of mycobacteria. Urine specimens have not been evaluated but other investigators have reported successful isolation of mycobacteria from urine specimens. Mucoid specimens are expected to contain contaminating bacteria as normal flora and must be digested (liquefaction) and decontaminated before inoculation. On the other hand, aseptically collected body fluids or tissue biopsies do not need to be decontaminated. However, since it is difficult to maintain sterile conditions throughout the collection of specimens, it is recommended that all specimens be decontaminated. Aseptically collected specimens need only light decontamination. Clinical specimens collected in large volumes more than 10 ml) require centrifugation before decontamination to reduce the overall volume and to concentrate mycobacteria present in the specimens into a smaller volume. After decontamination, the specimen should be centrifuged again and the sediment used for preparation of smear and inoculation for culture.[20] Drug resistance was found out using Sputum CBNAAT also called as Xpert MTB/RIF assay. It is an automated cartridge-based molecular technique which not only detects Mycobacterium Tuberculosis but also rifampicin resistance within two hours.[21] The assay utilizes single-use plastic cartridges with multiple chambers that are preloaded with liquid buffers and lyophilized reagent beads necessary for sample processing, DNA extraction and hemi nested rt-PCR. Clinical sputum samples (or decontaminated sputum pellets) are treated with a sodium hydroxide and isopropanol-containing sample reagent (SR). The SR is added to the sample (currently recommended at a 3:1 ratio for sputum pellets and a 2:1 ratio for unprocessed sputum samples) and incubated at room temperature for 15 min. This step is designed to reduce the viability of M. tuberculosis in sputum at least 106-fold to reduce biohazard risk. The treated sample is

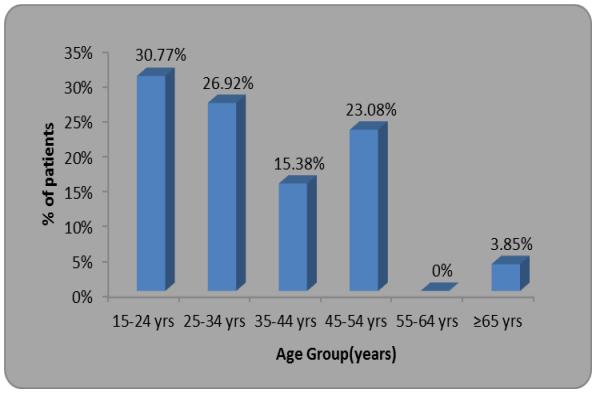
then manually transferred to the cartridge which is loaded into the Gene Xpert instrument. Subsequent processing is fully automated.[22] The cartridge incorporates a syringe drive, a rotary drive and a filter upon which M. tuberculosis bacilli are deposited after being liberated from the clinical material. The test platform employs a sonic horn that inserts into the cartridge base to cause ultrasonic lysis of the bacilli and release of the genetic material. The assay then amplifies a 192 bp segment of the rpoB gene using a hemi-nested rt-PCR reaction. The assay also contains lyophilized Bacillus globigii spores which serve as an internal sample processing and PCR control. The B. globigii PCR assay is multiplexed with the M. tuberculosis assay. Mycobacterium tuberculosis is detected by the five overlapping molecular probes (probes A–E) that collectively are complementary to the entire 81 bp rpoB core region. M. tuberculosis is identified when at least two of the five probes give positive signals with a cycle threshold (CT) of ≤38 cycles and that differ by no more than a prespecified number of cycles.

OBSERVATION AND RESULTS

Age wise distribution revealed most of the patients (30.77 %) were in the range of 15-24 years with the mean age being 32.73±13 (table 3, graph 1).

Table. 3: Distribution of patients according to age in years.

Age Group(yrs)	No of patients	Percentage (%)
15-24 yrs	8	30.77
25-34 yrs	7	26.92
35-44 yrs	4	15.38
45-54 yrs	6	23.08
55-64 yrs	0	0.00
≥65 yrs	1	3.85
Total	26	100
Mean ± SD	32.73±13(17-65 years)	

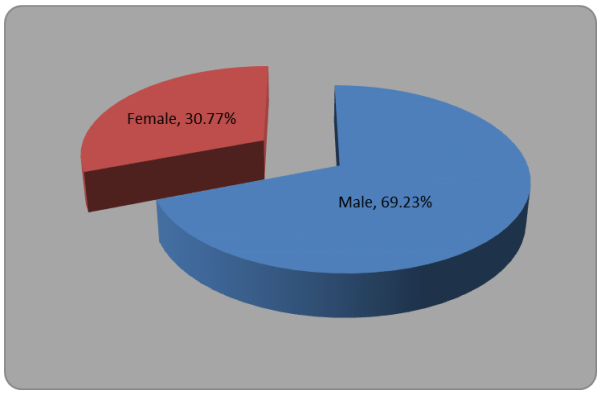


Graph. 1: Distribution of patients according to age in years.

Gender wise distribution revealed most the patients (18 out of 26: 69.23 %) were males (table 4, graph 2).

Table. 4: Distribution of patients according to gender.

Gender	No of patients	Percentage (%)
Male	18	69.23
Female	8	30.77
Total	26	100



Graph. 2: Distribution of patients according to gender.

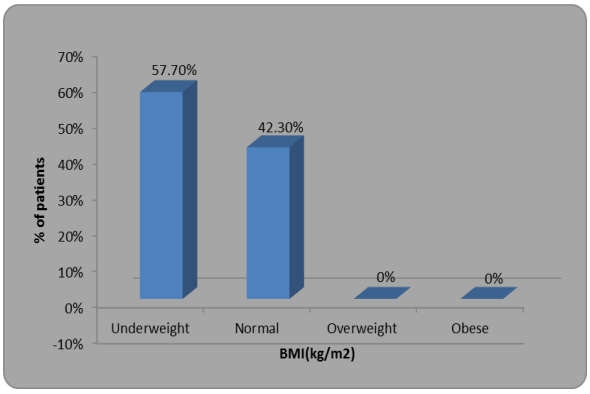
BMI wise grading revealed that most of the patients 15(57.70%) were underweight while 11(42.3 %) were in the normal range. None of our patients was in the Overweight and Obese BMI range (table 5, graph 3).

Considering the past medical history, previous history of Tuberculosis was the most common history which was present in 84.62 % (22 out of 26 patients), Alcoholism and Smoking were 15.38 % respectively while History of Tuberculosis contact was present in 3.85 % of the patients (table 6, graph 4).

Coming to the associated co-morbidities, Type 2 Diabetes mellitus (7 out of 26) was present in 26.92 % of the patients while Hypertension was seen in 3.85 %(1 out of 26) patients. No patients in our study had COPD, Bronchial Asthma, Chronic Liver disease or Thyroid disorder (table 7, graph 5).

Table. 5: Distribution of patients according to BMI(kg/m2).

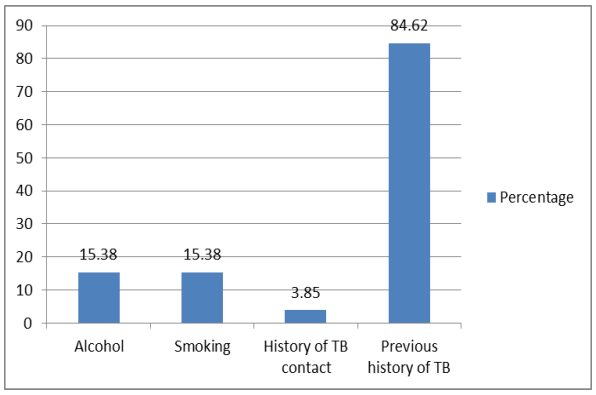
BMI(kg/m^2)	No of patients	Percentage (%)
Underweight	15	57.7
Normal	11	42.3
Overweight	0	0
Obese	0	0
Total	26	100
Mean ± SD	16.25 ± 2.61(11 – 20.20 kg/m2)	



Graph. 3: Distribution of patients according to BMI(kg/m^2).

Table. 6: Distribution of patients according to past medical history.

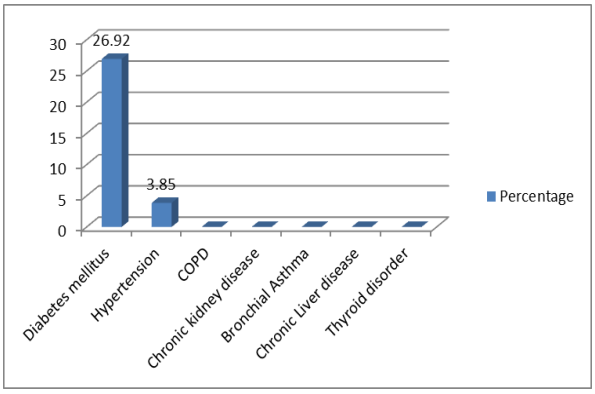
Past History	No of patients	Percentage (%)
Alcohol	4	15.38
Smoking	4	15.38
History of TB contact	1	3.85
Previous history of tuberculosis	22	84.62



Graph. 4: Distribution of patients according to past history.

Table 7: Distribution of patients according to comorbidities.

Comorbidity	No of patients	Percentage
Diabetes Mellitus	7	26.92
Hypertension	1	3.85
COPD	0	0
Chronic Kidney disease	0	0
Bronchial Asthma	0	0
Thyroid disorder	0	0

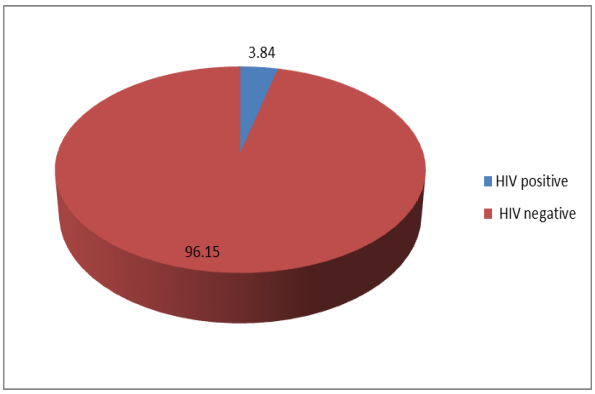


Graph. 5: Distribution of patients according to comorbidities.

The results here depict that 3.84(1 out of 26) patients was a known case of HIV infection (table 8, graph 6).

Table. 8: Distribution of patients according to HIV status.

HIV Status	No of patients	Percentage (%)
Positive	1	3.84
Negative	25	96.15

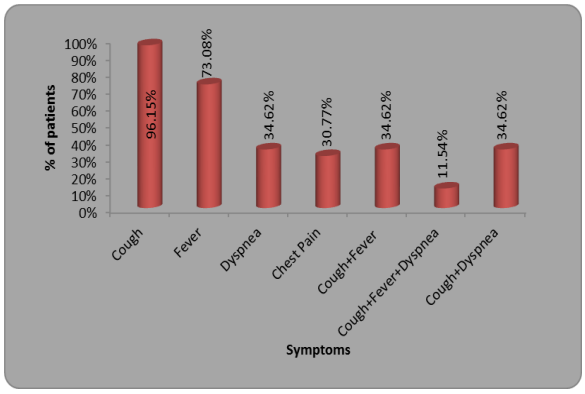


Graph. 6: Distribution of patients according to HIV status.

In symptomatology, cough was the most common symptom present in 96.15 % (25 out of 26) of the patients, followed by fever in 73.08 % (19 out of 26) of the patients and Dyspnea in 34.62 % (9 out of 26) of the patients (table 9, graph 7).

Table. 9: Distribution of patients according to symptoms.

Symptoms	No of patients	Percentage (%)
Cough	25	96.15
Fever	19	73.08
Dyspnea	9	34.62
Chest Pain	8	30.77
Cough + Fever	9	34.62
Cough + Fever + Dyspnea	3	11.54
Cough + Dyspnea	9	34.62



Graph. 7: Distribution of patients according to symptoms.

The mean complete blood count observed was 10557.69 with a standard deviation of 10557.69 +/- 6471.61 (table 10).

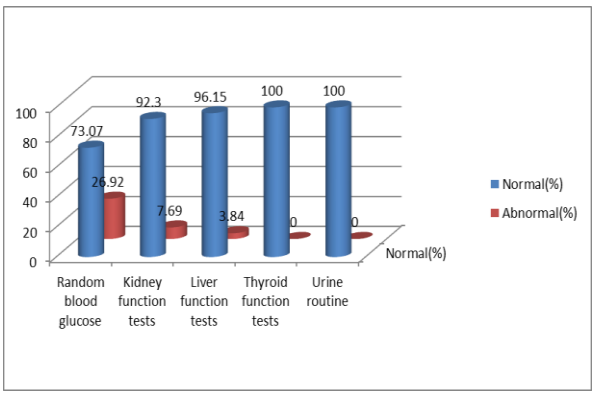
Table. 10: Distribution of patients according to complete blood count.

Minimum	Maximum	Mean	Std. Deviation
3500	36000	10557.69	6471.61

Coming to the biochemical tests, Random blood glucose levels were abnormal in 26.92 % of the patients, kidney function tests in 7.69 % of the patients while liver function tests in 3.84 % of the patients. Thyroid function tests and urine routine microscopy were normal in all the patients. (table 18, graph 9)

Table. 18: Distribution of patients according to biochemical tests.

Biochemical test	Normal (%)	Abnormal(%)
Random blood glucose	73.07	26.92
Kidney function tests	92.3	7.69
Liver function tests	96.15	3.84
Thyroid function tests	100	0
Urine routine	100	0

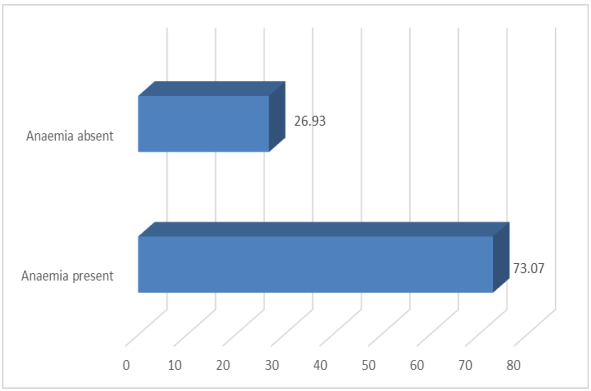


Graph. 9: Distribution of patients according to biochemical tests.

Results showed that 73.07 % (19 out of 26) had Anaemia. (table 19, graph 10)

Table No. 19: Distribution of patients according to Hemoglobin levels.

Anaemia	No of patients	Percentage
Present	19	73.07
Absent	6	26.93

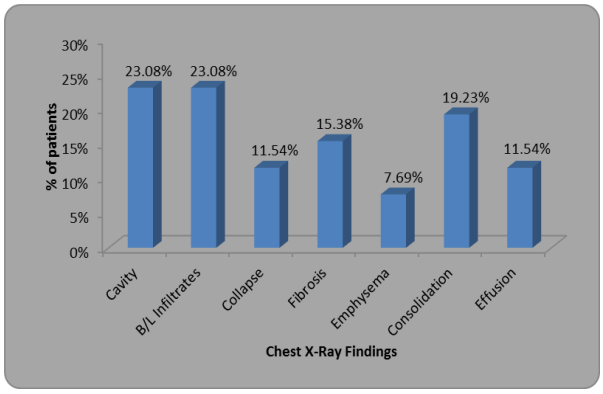


Graph. 10: Distribution of patients according to presence/absence of Anaemia.

In the chest radiology findings, Cavitatory lesions in the lungs and Bilateral lung infiltrates were the most common present in 23.08 % of the patients, followed by Consolidatory lesions (19.23 %), lung fibrosis (15.38 %), lung collapse/pleural effusion (11.54%) and Emphysematous changes (7.69 %). (table 20, graph 11)

Table. 20: Distribution of patients according to chest x-ray findings.

Chest X-Ray findings	No of patients	Percentage (%)
Cavity	6	23.08
B/L Infiltrates	6	23.08
Collapse	3	11.54
Fibrosis	4	15.38
Emphysema	2	7.69
Consolidation	5	19.23
Effusion	3	11.54

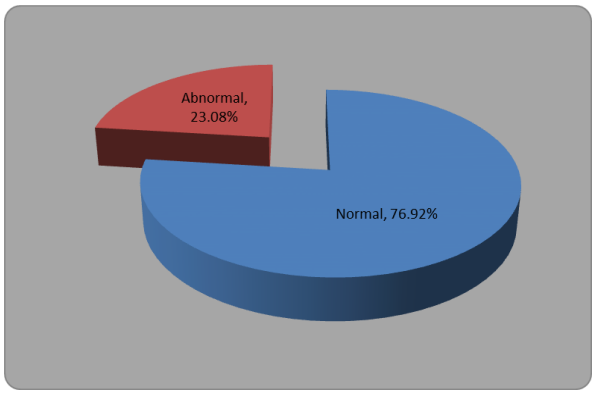


Graph. 11: Distribution of patients according to chest x-ray findings.

USG abdomen and pelvis were abnormal in 23.08 % (20 out of 26) of the patients.
(Table 21, Graph12)

Table. 21: Distribution of patients according to USG abdomen and pelvis.

USG abdomen and pelvis	No of patients	Percentage (%)
Normal	20	76.92
Abnormal	6	23.08
Total	26	100

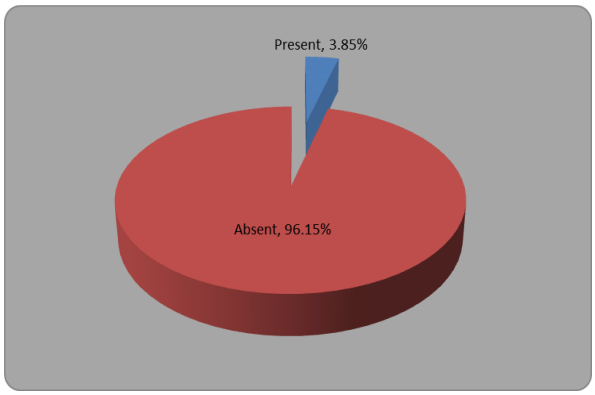


Graph. 12: Distribution of patients according to USG abdomen and pelvis.

ENT complaints were present in 3.85 % (1 out of 26) of the patients. (Table 22, Graph 13)

Table. 22: Distribution of patients according to ENT complaints.

ENT complaints	No of patients	Percentage (%)
Present	1	3.85
Absent	25	96.15
Total	26	100

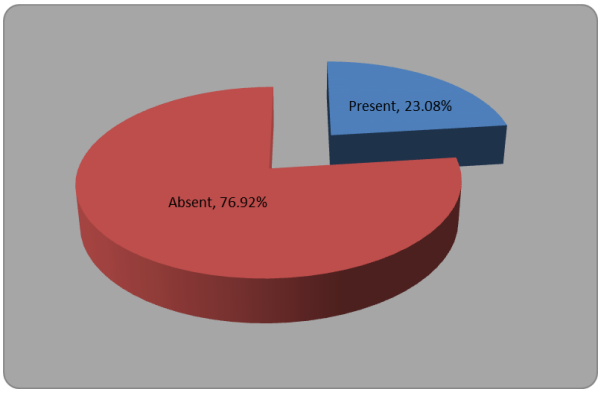


Graph. 13: Distribution of patients according to ENT complaints.

Psychiatric symptoms were present in 23.08 % (6 out of 26) of the patients.

Table. 23: Distribution of patients according to psychiatric complaints.

Psychiatric complaints	No of patients	Percentage (%)
Present	6	23.08
Absent	20	76.92
Total	26	100

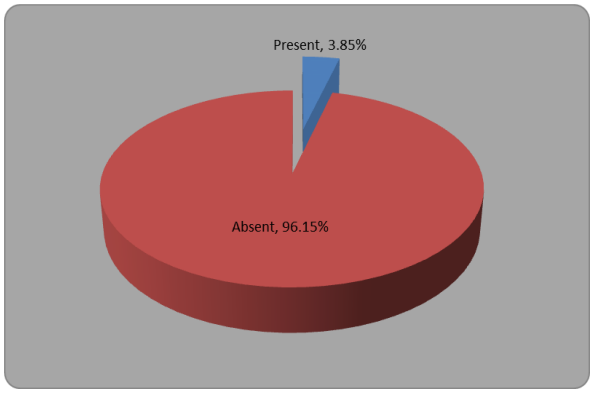


Graph. 14: Distribution of patients according to psychiatric complaints.

Ophthalmic complaints were present in 3.85 % (1 out of 26) of the patients.

Table. 24: Distribution of patients according to ophthalmic complaints.

Ophthalmic complaints	No of patients	Percentage (%)
Present	1	3.85
Absent	25	96.15
Total	26	100



Graph. 15: Distribution of patients according to ophthalmic complaints.

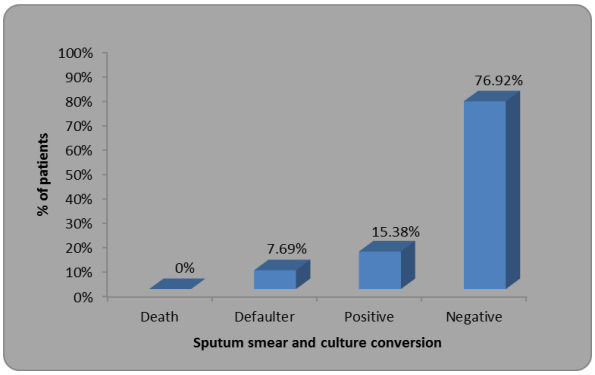
After 3 months of follow up, we found out that 76.92 %(20 out of 26) were sputum smear and culture negative while 15.38 % (4 out of 26) were smear and culture positive, 7.6 % (2 out of 26) defaulted and none of the patients died. (table 25, graph 16.1).

After 6 months of follow up, we found out that 65.38 %(17 out of 26) were sputum smear and culture negative while 23.08 % (6 out of 26) were smear and culture positive, 11.54 % (3 out of 26) defaulted and none of the

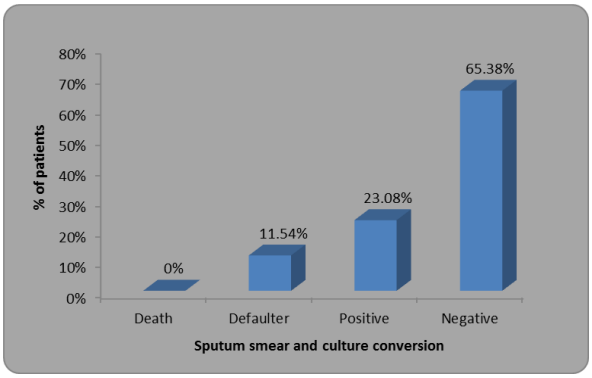
patients died. (table 25, graph 16.2). After 9 months of follow up, we found out that 57.7 %(15 out of 26) were sputum smear and culture negative while 26.92 % (6 out of 26) were smear and culture positive, 15.38 % (4 out of 26) defaulted and one of the patients died during the course of treatment. (table 25, graph 16.3). After 12 months of follow up, we found out that 57.70 %(15 out of 26) were sputum smear and culture negative while 19.23 % (5 out of 26) were smear and culture positive, 19.23% (5 out of 26) defaulted and one of the patients died during the course of treatment. (table 25, graph 16.4).

Table 25: Distribution of patients according to sputum smear and culture conversion

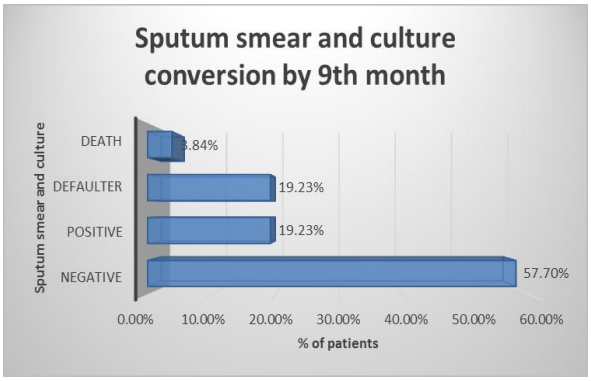
Sputum Smear and culture conversion	3rd month	6th month	9th month	12th month
Negative	20(76.92%)	17(65.38%)	15(57.7%)	15(57.7%)
Positive	4(15.38%)	6(23.08%)	6(23.08%)	5(19.23%)
Defaulter	2(7.69%)	3(11.54%)	4(15.38%)	5(19.23%)
Death	0(0%)	0(0%)	1(3.85%)	1(3.85%)



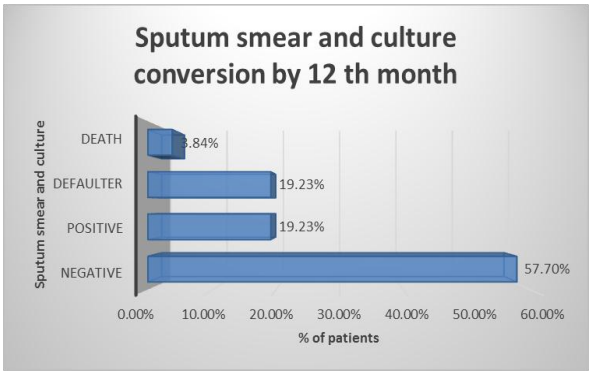
Graph. 16.1: Distribution of patients according to sputum smear and culture conversion at 3rd month



Graph. 16.2: Distribution of patients according to sputum smear and culture conversion at 6t month



Graph. 16.3: Distribution of patients according to sputum smear and culture conversion at 9th months.



Graph. 16.4: Distribution of patients according to sputum smear and culture conversion at 12thmonth.

DISCUSSION

Drug resistant tuberculosis is a growing problem in India. The common reason for this is either noncompliance of the patient or resistant strain spread. It is still one of the major challenges for the RNTCP. Sputum smear and culture is an important indicator for assessing treatment effectiveness. The present study was done to observe the sputum smear and culture conversion in DR-TB patients who are treated with the PMDT regimen as prescribed by the RNTCP. Our study, although had a small sample size, found out the regimen recommended by RNTCP for DR-TB is effective in terms of good culture conversion rates (76.92 % in the 3rd month, 65.38 % in the 6th month, 57.7 % in the 9th month and 57.7 % after 1 year) with a low death rate of 3.84 % during the one yearly duration of our study. Challenges that came were, treatment default and missed doses by the patients due to ADRs.

Sociodemographic characteristics: The gender wise distribution in our study showed a male preponderance in DR-TB patients consisting of 69.23 % males and 30.77 % females which resonated with similar studies done in India in which the male percentages were 68 %, 62 % and 71.8 % respectively by Velayutham et al, Jain et al and Patel et al[13,23,14] This data of ours was also in line with 3 similar studies done internationally, Liu et al, Farley et al, Geerlings et al[12,24,25] By this data we can

say that there could be a male preponderance for developing DR-TB.

The mean age of the patients in our study was 32.73±13 years which was similar to a study done by Jain et al[23] in India where the mean age was 31.42 ± 12.29. This was different from two other similar studies done in India by Velayutham et al and Patel et al[13,14] and one similar study done by Liu et al in China where it was 51 ± 10 years[26] Our data shows that mostly youth are affected by DR-TB which is an alarming issue for the progress of a country as a whole. DR-TB is a big cause of morbidity as well as mortality.

BMI wise grading revealed that most of the patients, 15 (57.70%) were underweight. This is higher than a similar study done in India by Velayutham et al in which 37.9 % patients were underweight.[13]

60% of our patients who were culture positive at the end of one year of treatment were in the underweight BMI range. This shows than low BMI adversely affects sputum culture conversion. This finding was also consistent with the study done by Velayutham et al in India where they also found out that low BMI adversely affects sputum culture conversion.[13] Several second line drugs such as FQs and PAS cause significant anorexia, further worsening the nutritional status. Good nutritional support is the key to better treatment outcomes in DR-TB patients.

Past history and comorbidities

In past medical history, 15.38 % of the patients had a history of smoking, 15.38 % had a history of chronic alcoholism and 3.85 % of the patients had a history of contact with a TB patient. Treatment outcomes didn't vary in the patients who had a history of alcoholism, smoking or a history of TB contact.

In our study only 3.84 % (1 out of 26) patients had concomitant **HIV** infection, this data was coherent to a similar study done in India[13] in which there were 4 % patients with HIV infection. Our data is different from 3 international studies which have a higher percentage of HIV positive patients 26%, 38 % and 12 % respectively.[18,24,27] Sputum culture conversion was not affected in the patient with HIV infection. This is important because DR-TB with concomitant HIV infection generally results in poor treatment outcomes, if both the diseases are not treated aggressively.

Type 2 Diabetes mellitus was found in 26.92 % of the patients in our study which was in coherence to a similar Indian study done by Velayutham et al[13] wherein they had 30 % patients of Type 2 Diabetes mellitus. Our findings were in contrast to 3 international studies by Kurbatova et al, Magee et al and Palomino et al who had lesser percentage of patients with DM type 2, the percentages were 0.02, 4.6 and 3.1 respectively[28,29] (21) In our study out of the patients who were culture positive at the end of 1 year 60 % (3/5) had Type 2 Diabetes mellitus. In all of these patients the diabetes control was not efficient. Hence we may say that uncontrolled DM type 2 can lead to poorer outcomes in the treatment of DR-TB patients.

3.85 % of our patients had Hypertension, none of them had COPD, CKD, Bronchial Asthma or Thyroid disorder.

Assessing the treatment history in our study **84.61 % of the patients were Category 2 treatment failure, while 15.38% were new cases** while none of our patient was Category 1 treatment failure. This data of ours was in contrast to a similar Indian study by Velayutham et al[13] in which the patients in the Category 2 treatment failure, new cases and Category 1 treatment failure were 78.65 %, 15.88 % and 0.01 % respectively. Our findings were coherent to a similar study done in India by Jain et al[23] in which like our study, they had most of the patients in the Category 2 treatment failure group (94 %). Our findings were similar to one international study in which they found 89 % patients in the Category 2 treatment failure regimen while it was in contrast with 2 international studies by Linshuang et al and Long et al which had lesser percentage of Category 2 treatment failure cases i.e. 41.3 % and 38.7 % respectively.[30,22] The percentage of new cases in our study was more than majority of similar studies done in India and worldwide. **There was no significant difference between culture conversion in New cases and in the patients with a previous history of Tb**. This was in contrast to a study done by Telzak et al[31] where they had found that patients with a previous history of TB had a poor treatment outcome.

Clinical features and biochemical parameters

Cough was the most common symptom which was present in 96.15 % of the patients, followed by Fever, Dyspnoea and Chest pain. While weakness and loss of appetite were not a symptom in any of our patient. This data was in coherence with the facts of Centres for disease control and prevention.[32]

Considering the routine biochemical investigations, most common abnormality was an increased RBS in 26.92 % followed by deranged KFT (7.69%) and deranged LFT (3.84 %). Urine routine microscopy as well as Thyroid function tests were normal in all the patients. Urine pregnancy test was negative in all the patients. **Anaemia was present in 73.07 %** of the patients.

The most **common chest radiographic findings in our study were Cavitatory lesions** (23.08 %), Bilateral infiltrates (23.08 %) and Consolidatory lesions (19.23 %). This data of ours was different than a study done by Kurbatova et al, Akalu et al and Leimane et al[28,33] in which they found Cavitatory lesions on the chest radiograph in 66.2 %, 40.82 % and 68.1 % respectively. Our finding was in line with a study done by Magee et

al[29] in which they found Cavitatory lesions in 26.9 % of the patients.

USG abdomen and pelvis was done in all the patients. 6 patients had an abnormal USG in which the most common abnormality was Hepatomegaly (50%), followed by Ascites and lymphadenopathy.

As a part of pre-treatment evaluation ENT, Psychiatric and Ophthalmic check-up was done, Psychiatric complaints were the most common which were present in 23.08 % of the patients followed by ENT (3.85 %) and ophthalmic (3.85 %). Depression was the most common psychiatric complaint which was present in 66.6 % of the patients, followed by Psychosis. One patient who had drug induced psychosis, who ended up defaulting the treatment.

Treatment default, death, median time of sputum conversion and sputum culture conversion rate:
The default rate observed in our study was 19.23 %. This was identical to similar studies done in India by Joseph et al, Patel et al and Jain et al who found a default rate of 13 %, 15.2 % and 23 % respectively.[34,14,23]

This data was similar to an international study done by Farley et al in South Africa[24] where they found the default rate to be 20.9 %. Our finding was in contrast to a study by Kurbatova et al which was done in multiple centres at various countries[28] where they found the default rate to be only 1%.

The main cause for treatment default in our patients were Adverse drug reactions. 5 out of 26 patients who defaulted had developed ADRs. 3 out of 5 (60 %) patients had Hepatotoxicity, one had drug induced psychosis and one had ototoxicity. Though symptomatic management and appropriate drug omission was done but still the patient discontinued the treatment even after proper counselling and missed the follow-up visits. This could be due to illiteracy and less patient education.

In our study we observed only one death was observed, which was 3.84 % of the patients. This was in contrast to three Indian studies by Joseph et al, Jain et al and Velayutham et al who observed greater death rates of 7.87 %, 19 %, 17 % respectively.[34,23,13] Greater death rates were also observed in various international studies by Akalu et al, Kakchapati et al, Geerligs et al that is 11 %, 7 % and 20 % respectively.[33,35,25] This could be due to the fact that we had lesser patients enrolled in our study. The median time for culture conversion in our study was 60 days which was lesser than two of the similar Indian studies by Velayutham et and Patel et al which had the median time of 91.3 days and 125.02 days respectively.[13,14] This shows that over all response and adherence to the treatment was good.

The sputum smear and culture conversion rate in our study was 76.92 % in the 3rd month, 65.38 % in the 6th month, 57.7 % in the 9th month and 57.7 % after 1 year. Velayutham et al[13] did a study in Chennai where the 3rd monthly sputum conversion rate was lesser than in our study that is 57 %, the 6th monthly sputum conversion rate was more that is 79 %, a similar comparison was found with another study done in Gujarat by Jain et al[23] in which they found the sputum conversion rates to be 56.1 %, 64.61 % and 68.4 % respectively. Our 3rd monthly and 6th monthly sputum conversion rate was very less than another study done in Chennai by Joseph et al[34] in which they found out the 3rd monthly and 6th monthly sputum conversion rates to be 84 % and 87 % respectively. This may be due to the fact that, as this study was done in a National Tuberculosis research centre so, the monitoring and surveillance of the patients would have been better. Our 6th monthly and 12th monthly sputum conversion rates were more than a study done in Patel et al[14] where they found the rates to be 43.4 % and 52 % respectively. Most common reasons behind sputum smear and culture positivity in our study was the missed scheduled drug doses by the patients, this may be attributed to many factors such as ADRs, symptomatic relief, long term treatment and a need to take up their monetary responsibilities for their families specially in the case of male patients.

CONCLUSION

The sputum conversion rate in our study dropped significantly when comparing the results from 3rd month and 12th month of follow up respectively. This is partly due to treatment default which may be contributed mainly to Adverse drug reactions. It is important to regularly monitor patients for these ADRs, explain to them that it is the part of the treatment course, treat them symptomatically and make sure that they don't discontinue the treatment. Second reason behind the drop in the sputum conversion rate are the "missed doses" by the patients during the course of treatment. Along with ADRs the reason behind this is that the patients feel symptomatically better and hence don't feel requirement to continue the regimen. They need to be educated well about the course of the disease, treatment and importance of not missing the daily doses.

Also, in our study we found out that patients who had low BMI and Uncontrolled Diabetes mellitus were more likely to be sputum smear and culture positive during follow up, So, if patients who have a low BMI are advised to take proper diet, preferably protein rich, the chances of their treatment success would be more and they will more likely to sputum convert. In patients having Diabetes mellitus if the sugar levels are controlled with proper medical and dietary management, the treatment outcomes would be better.

Limitations and Recommendations

Limitations

- The first limitation of our study is that the time period of our evaluation is only 2 years. So, the data of sputum

smear and culture remains incomplete for the patients whose treatment duration exceed our period of study.

- Secondly, to perform an analysis we needed a common time factor and so we could follow up all 26 patients only up to 1 year of treatment. Treatment outcome of the patients couldn't be evaluated because of this reason.

- Finally, our sample size was taken only from a single centre of a district of the country. Multicentric studies with a larger sample size with appropriate time duration are required to adequately assess bacteriological conversion in DR-TB patients of the country.

Recommendations/Suggestions

- We would like to recommend studies with a larger cohort of patients in Maharashtra involving multiple districts, this would give the idea of sputum conversion in DR-TB patients treated under PMDT in the state as a whole.

- As stated earlier, our study period was only 2 years and so we couldn't follow up all our patients throughout the course of the treatment and so the treatment outcomes couldn't be assessed. It is suggested that the study period could be prolonged for a better evaluation of treatment cure and treatment failure.

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