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RESEARCH ARTICLE

STUDY OF 537 CASES OF DRUG RESISTANT TUBERCULOSIS (DR TB).

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Abstract

Aims:- To study outcome of 537 DR TB patients.
Settings and Design:- Prospective study (June 2011 to March 2016).
Introduction:- Multidrug-resistant tuberculosis (MDR-TB) is an increasing global problem. Though therapy of DR TB is much longer and costlier than drug sensitive TB, injectable have to be taken for six months, incidence of adverse reactions is more, thus decreasing compliance, patients do improve and even are cured if the health care personnel and caregivers encourage them to adhere to treatment.
Methods and Material:- All cases were confirmed to have drug resistance to INH and Rifampicin or Rifampicin alone before admission. After starting treatment in DR TB ward, they were referred to their respective TB Units. Follow up was kept through District Tuberculosis and City Tuberculosis Office, and patients who came for treatment or adverse drug reaction.
Results:- Males (79.41%) outnumbered females (20.59%). 388 patients (72.25%) belonged to the age group of 15 to 44 years, 81 (16.01%) were cured, 43 (8.50%) completed treatment, 88 (17.39%) died, 80 (15.81%) defaulted, 23 were HIV positive. 34 patients (6.331%) were subsequently found to have XDR TB.
Conclusions:- In this prospective study of 537 DR TB cases, 124 (24.54%) patients recovered. However 80 patients (15.81%) is a matter of serious concern. Improved compliance in sensitive cases will help to prevent drug resistance. CB NAAT has grossly decreased the time needed for diagnosing DR TB helping early initiation of treatment which can be lifesaving.

Introduction:-

Multidrug-resistant tuberculosis (MDR-TB) is an increasing global problem, with most cases arising from a mixture of physician error and patient non-compliance during treatment of susceptible TB.

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Tuberculosis (TB) remains a major health problem in India accounting for more than 20 per cent of the global incident cases. Since 1997, the Government of India has implemented {under the Revised National TB Control Programme (RNTCP)} the DOTS strategy, and covered the entire country by March 2006[2].

Having achieved the global targets for cure rates among new smear-positive pulmonary TB cases detected under the programme RNTCP, RNTCP has implemented the programmatic management of multidrug-resistant TB[2].

Multidrug-resistant tuberculosis (MDR-TB) is defined as resistance to at least isoniazid and rifampicin,[2] the two drugs that are considered as the backbone of anti TB therapy.

As per WHO's "Global Tuberculosis Report , 2012", India account for an estimated 64000 patients out of 310000 cases of Drug Resistant TB estimated to have occurred amongst the notified cases of TB across the globe in a year. India is one of the high burden countries for tuberculosis as well as drug-resistant tuberculosis.

The third global report of anti-tuberculosis drug resistance reported the prevalence of MDR-TB among new tuberculosis (TB) cases from 75 settings ranging from 0 percent to 14.2 percent[3].

Directly observed treatment, short-course (DOTS) strategy with standardized short course chemotherapy using first-line drugs is currently the mainstay of TB control globally. In terms of population coverage, India now has the second largest DOTS programs in the world. However, India's DOTS programme is the fastest expanding programme and the largest in the world in terms of patients initiated or treatment, placing more than 100,000 patients on treatment every month. However, in MDR-TB patients DOTS strategy does not provide acceptable cure rates[4, 5].

We studied 537 cases of DR admitted in DRTB centre of Aurangabad and we found that male patients were affected more than female, also maximum number of patients affected was of age group 15 to 34 age group. Also cure rate was improved 81 (16.01%) and total no of deaths were decreased 88 (17.39%). 23 patients were HIV- MDR TB co infected out of whom 16 patients are still on treatment.

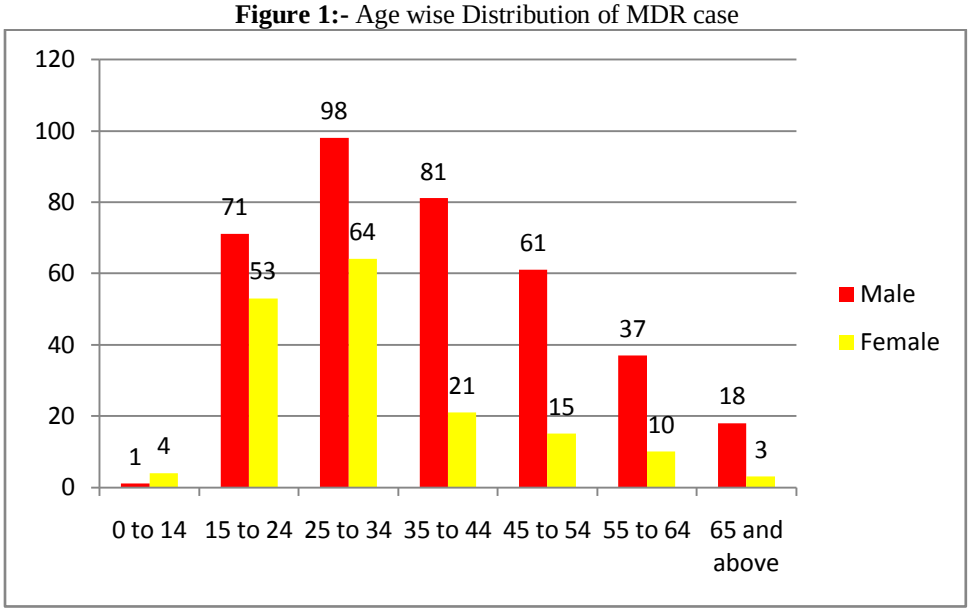
Subjects and Methods:
This was a prospective study that included patients diagnosed to have Drug Resistant TB (Isoniazid and Rifampicin resistance by solid or liquid culture) & rifampicin resistance only (by CB NAAT) who were admitted to the Drug Resistance Tuberculosis ward of our institute from June 2011 to March 2016 (Four years and nine months). All these cases were already confirmed to have drug resistance to INH and Rifampicin or Rifampicin alone before admission.

All the study subjects were evaluated after written informed consent. A thorough history was taken regarding the demographic profile, presenting complaints, past and family history of Tuberculosis. Detailed general and systemic examination was done and investigations including thyroid function tests were carried out. A week after starting treatment, the patients were discharged and referred to their respective TB Units for continuation of therapy. Follow-up was kept through District Tuberculosis Office and City Tuberculosis Office, as well as those patients who visited our institute for treatment or if they had any adverse drug reaction.

Results:-

We found maximum no of patients of age group 15 to 34 years of age (286 patients) (53.26%) followed by age group of 35 years to 54 years. (178 patients) (33.14%). (Figure 1).

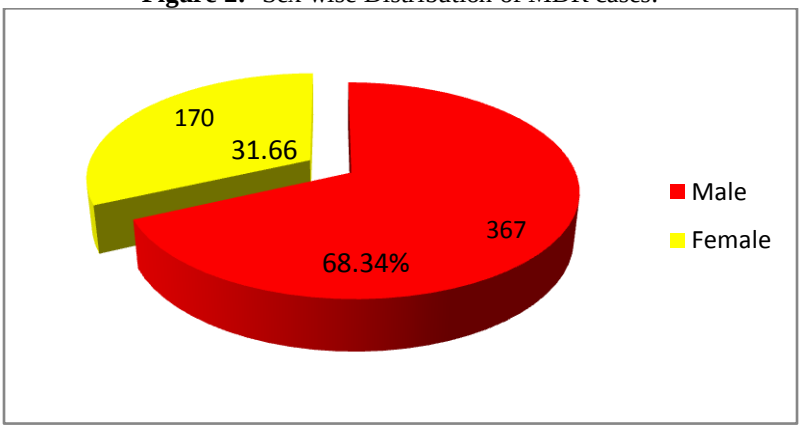
Figure 1:- Age wise Distribution of MDR case



Source: DR TB Ward.
***388 patients (72.25%) belonged to the age group of 15 to 44 years**

We found male patients more than female both in total and age specified distribution. Male population was significantly higher in age group between 25 to 44 years of age. (179 male vs. 85 females). Overall male patient 367 (68.34%) was significantly higher than female patients (170) (31.66%) (Figure 2).

Figure 2:- Sex wise Distribution of MDR cases.



Source: DR TB Ward.
***No of male patients are more than double the females.**

Most patients were belonging to weight bands 26 to 45 Kg (382) (71.14%) followed by 46 to 70 Kg (148) (27.56%) both contributing to about 530 patients (98.81%). Other weight bands were least (Table I).

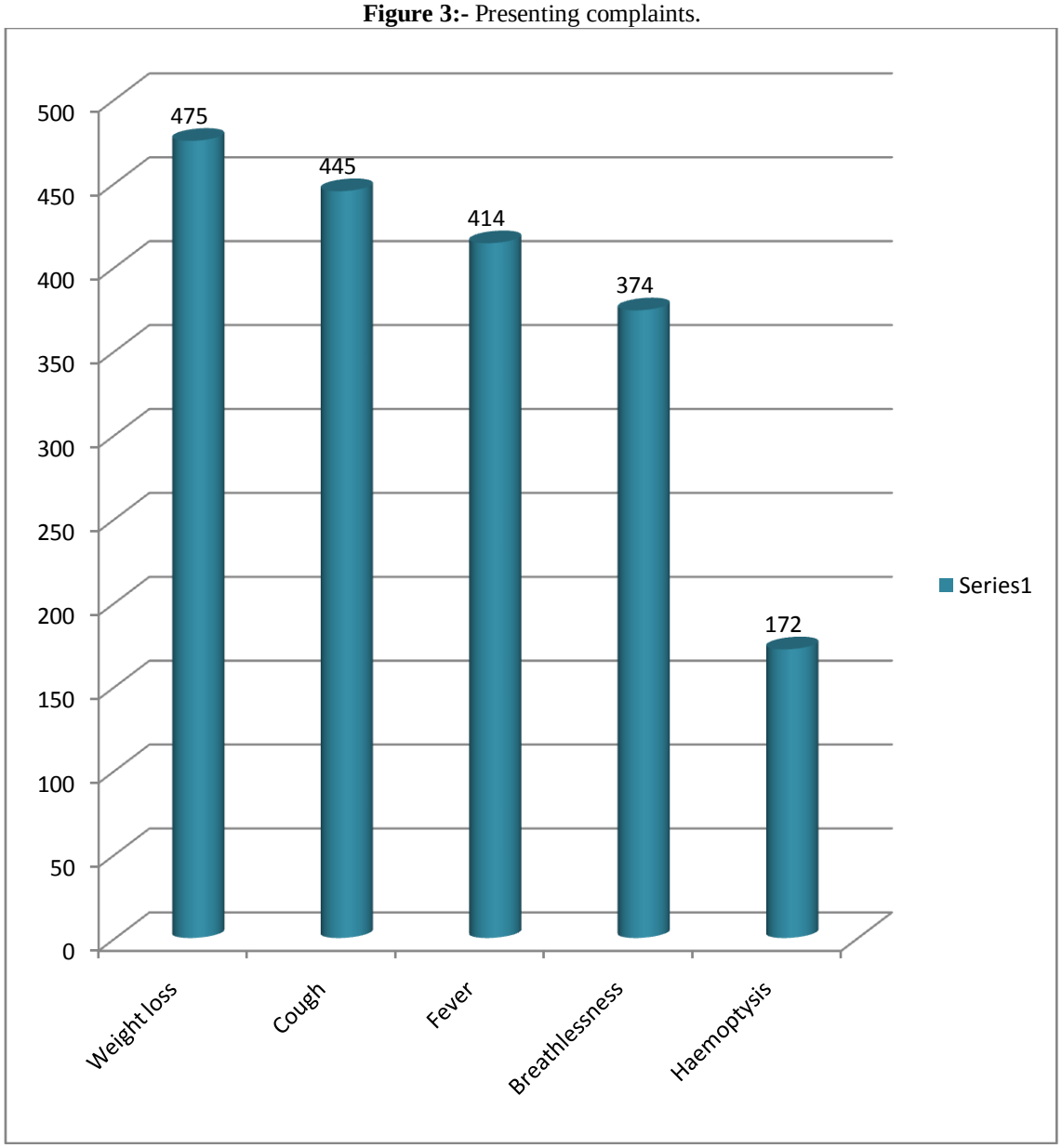
Table I:- Distribution of MDR cases as per weight bands.

Weight Bands	Total	%
<16 Kg	0	0%
16 to 25 Kg	1	0.19%
26 to 45 Kg	382	71.14%
46 to 70 Kg	148	27.56%
> 70 Kg	6	1.12%
Total	537	100%

Source: DR TB Ward.
*** Maximum (71.14%) patients were in weight band 26 to 45 Kg.**

Patients of drug resistance tuberculosis presented with weight loss (475) (94%), cough (445) (88%), fever (414) (82 %), breathlessness (374) (74 %), haemoptysis (172) (34 %). (Figure 3).

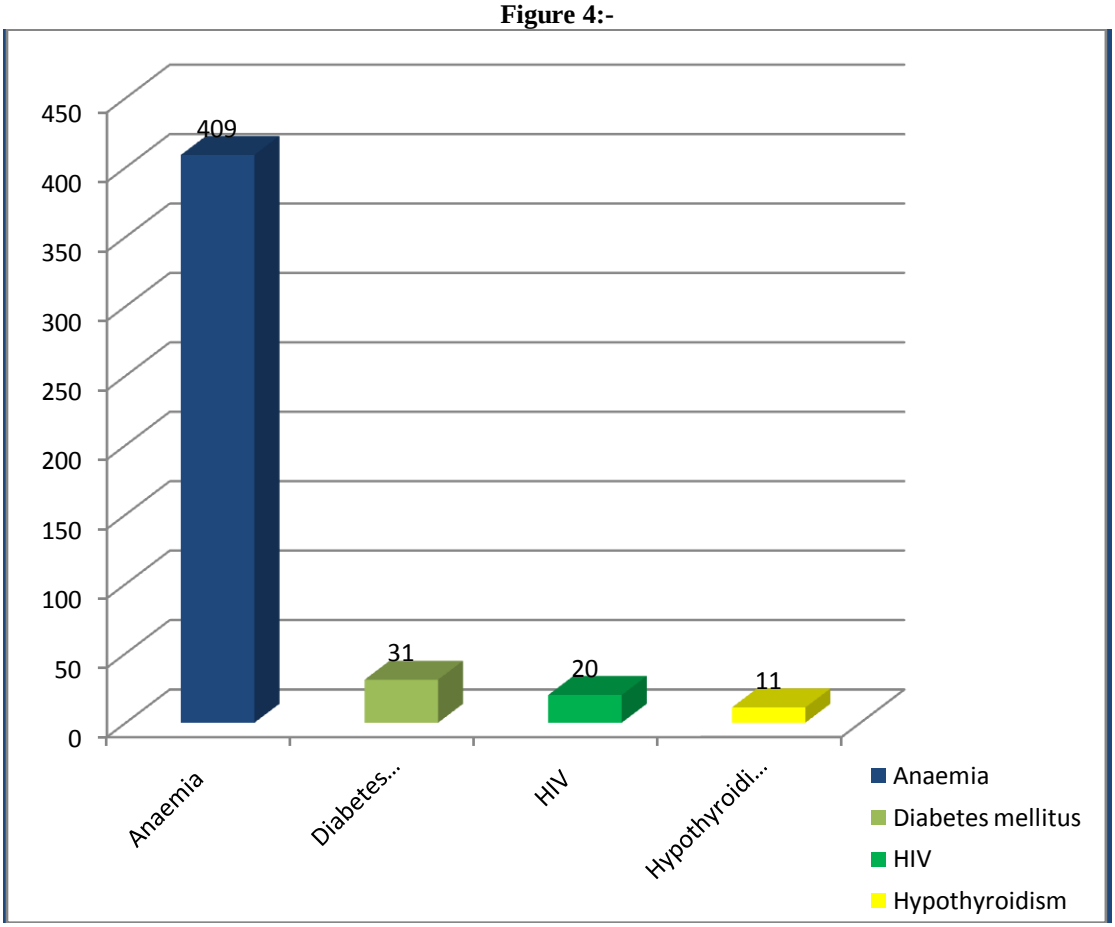
Figure 3:- Presenting complaints.



Source: DR TB Ward.

We found 409 patients (79.99%) of anaemia, 31 patients (6.03%) of Diabetes Mellitus, 23 patients (4.28%) of HIV and 11 patients (2.26%) of Hypothyroidism co-infected with MDR Tuberculosis. (Figure 4).

Figure 4:-



Source: DR TB Ward.

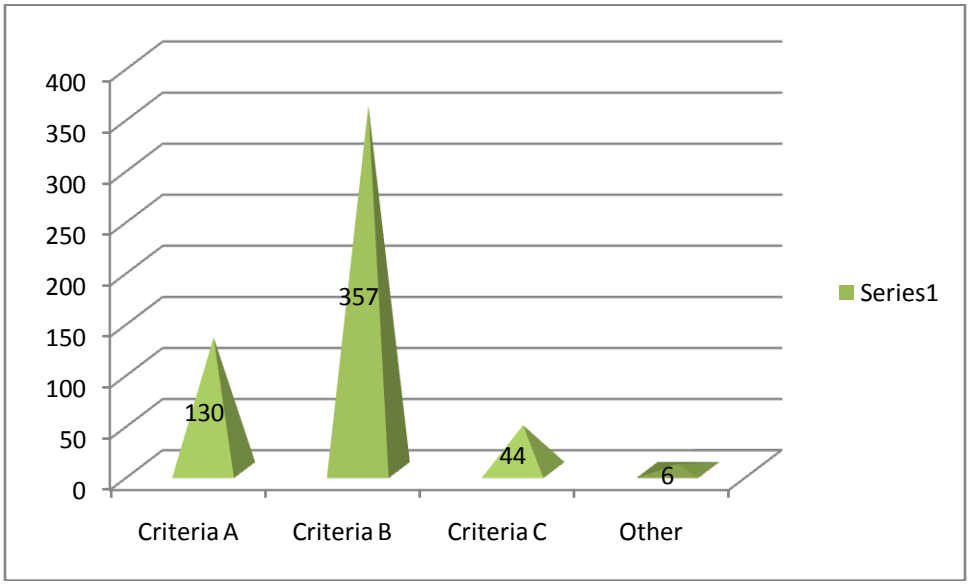
Initially our DR TB centre came under criteria A (up to May 2012)- 130 patients, from May 2012, we were in criteria B-357 patients, from May 2013 we were in criteria C- 44 patients.(Table II)

Table II:- Criteria of MDR .

Criteria A	
• Cat I Failure	= 47 (8.75%)
• Cat II Pos at 4 months or later	= 67 (12.48%)
• Cat III Failure	= 0 (0%)
• MDR TB Contact	= 16 (2.98%)
Criteria B	
• Smear Pos retreatment at diagnosis	=237 (44.13%)
• Any Follow up positive	=120 (22.35%)
Criteria C	
• Smear Neg Re. T/t at diagnosis	=28 (5.21%)
• HIV- TB Case	= 10 (1.86%)
Other	= 6 (1.12%)
• Cat IV Defaulters (Rediagnosed)	= 6 (1.12%)
• Suspected Cat IV failure	= 0 (0%)

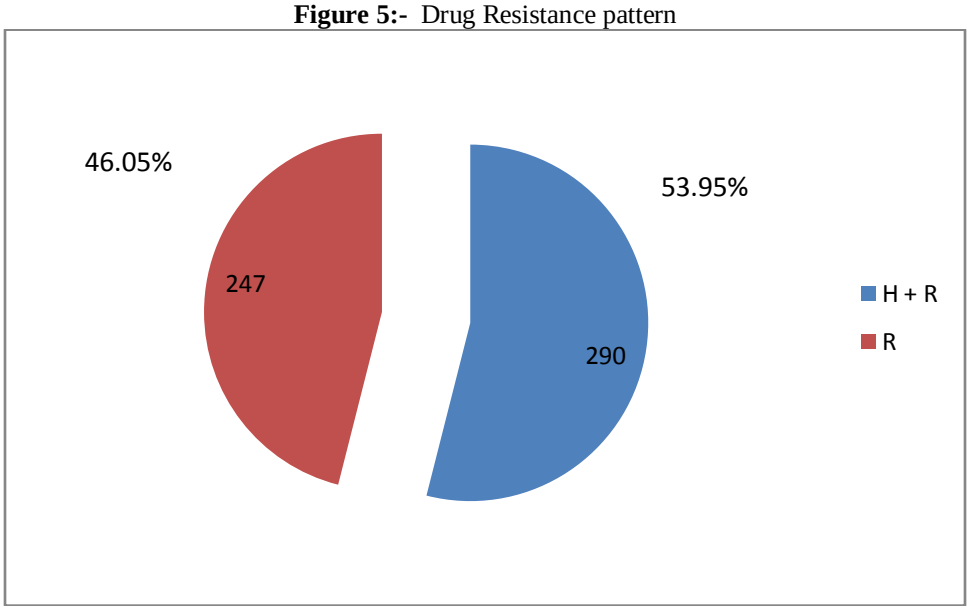
Total= 537(100%)

Of the 537 drug resistance tuberculosis patients whose drug sensitivity test was analysed, it was found that: 247/537 (46.05%) patients had Rifampicin mono-resistance (CB-NAAT-GENE Expert), 290/537 (53.95%) patients had Isoniazid and Rifampicin resistance. (Both)(LPA-Line probe assay) (Figure 5).



Source: DR TB Ward, Aurangabad

Figure 5:- Drug Resistance pattern



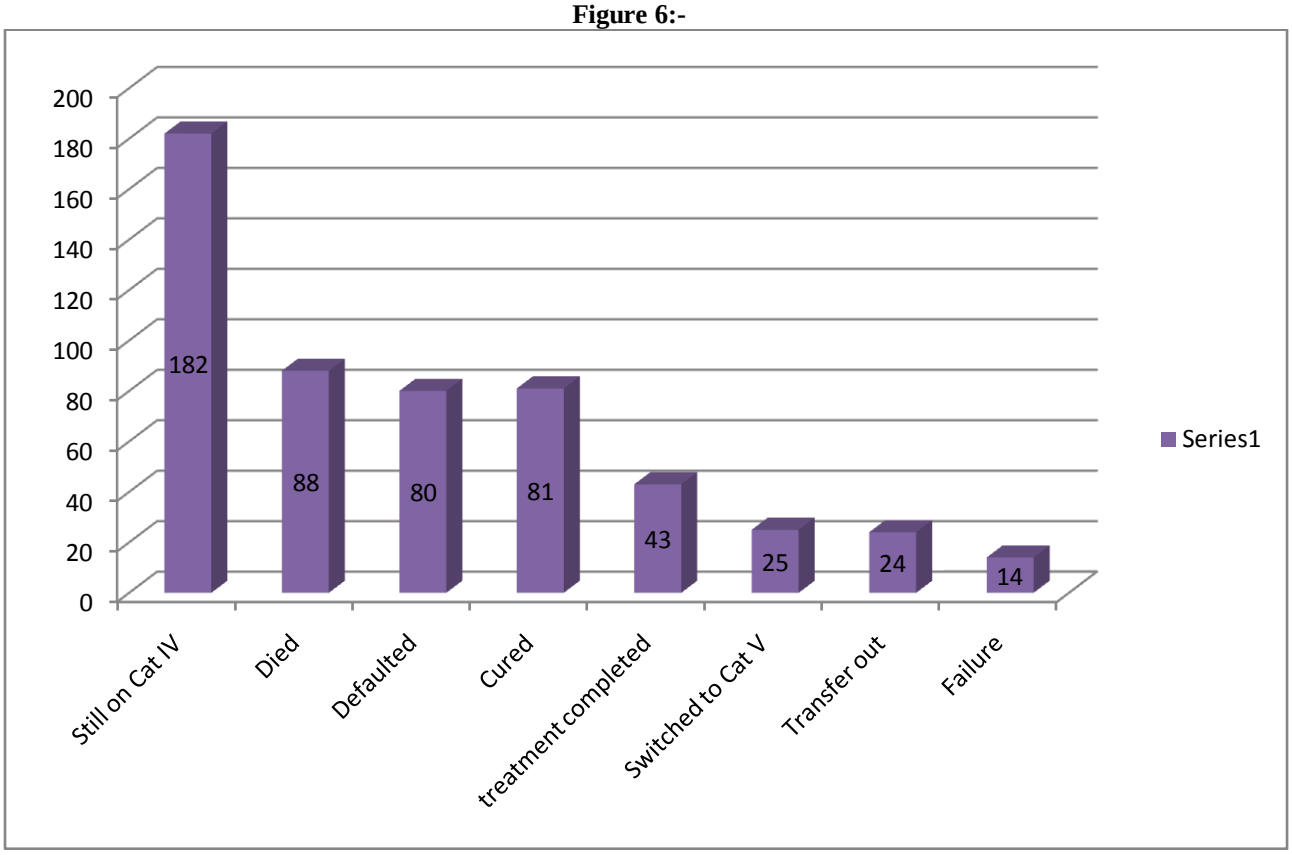
Source: DR TB Ward.

In this on-going study we found 88 patients (17.39%) died, 80 patients (15.81%) defaulted, 81 patients (16.01%) cured, 43 patients (8.50%) completed treatment, 24 patients (4.74%) transferred out, 25 patients (4.94%) were switched to cat V and 182 patients (35.97%) are still on treatment (Table III& Figure 6).

Table III:- Treatment outcomes

Started on Cat IV t/t	Died	Defaulted	Cured	Failure	Treatment Completed	Transfer out	Switched to Cat V	Still on Cat IV
537	88	80	81	14	43	24	25	182
100%	17.39%	15.81%	16.01%	2.77%	8.50%	4.74%	4.94%	35.97%

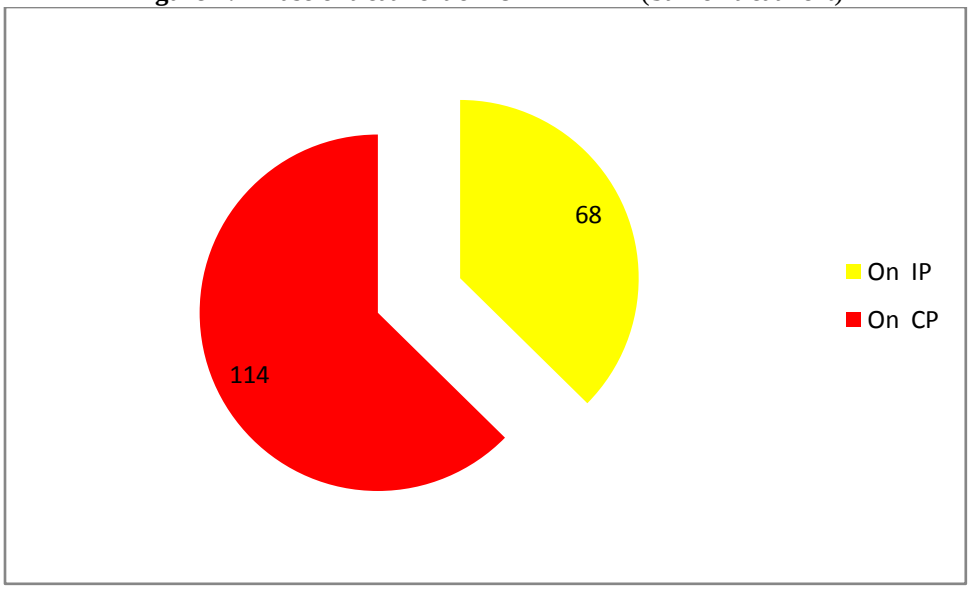
Figure 6:-



Source: DR TB Ward, Aurangabad

Currently 68 patients (37.36%) are on Intensive phase (IP) and 114 patients (62.63%) are on Continuation phase (CP) (Figure 7).

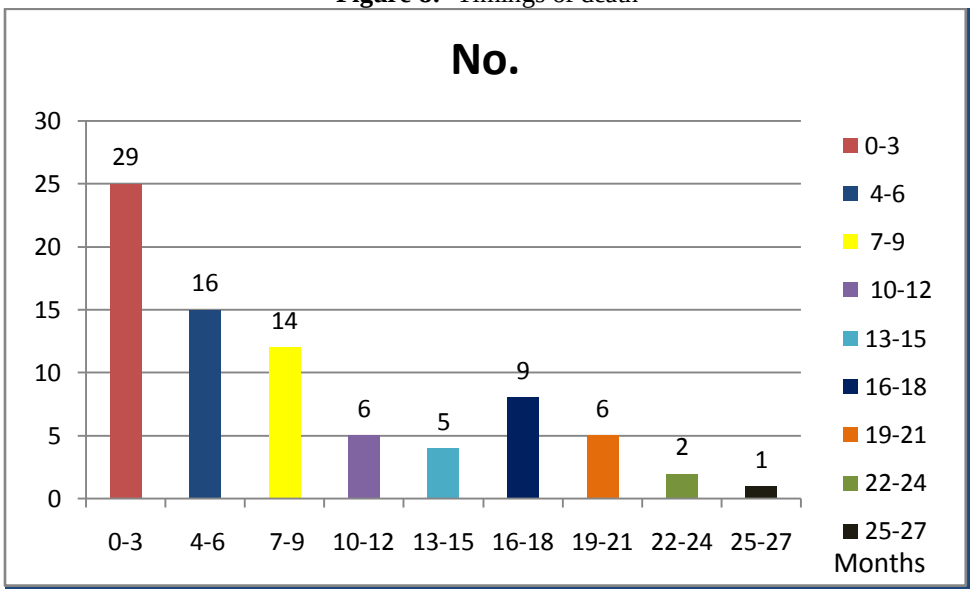
Figure 7:- Phase of treatment of 182 MDR TB (Still on treatment)



Source: DR TB Ward.

We found total 88 patients died during the study period, of which maximum no. (45 patients, 51.95%) died during first 6 months of treatment (Figure 8).

Figure 8:- Timings of death



Source: DR TB Ward.

In this study, out of 23 MDR TB patients co-infected with HIV, 6 patients (26.08%) died during treatment. 16 patients (69.56%) are still on treatment and 1 patient (4.34%) completed treatment (Cat IV). (Table IV)

Table IV:- HIV MDR TB outcomes

Started on Cat IV t/t	Died	Treatment Completed	On Treatment
23	**6**	**1**	**16**
100%	**26.08%**	**4.34%**	**69.56%**

Source: DR TB Ward.

Discussion:-

In India DR-TB in new cases has generally been reported to be less than or equal to 2-3% and DR-TB in previously treated patients has been reported to be 17%[1].

MDR TB implies resistance to INH and Rifampicin. Besidesisoniazid and rifampicin, XDR TB cases are resistant to fluoroquinolone (levofloxacin) and to at least one of the three injectable TB drugs, capreomycin, kanamycin and amikacin.[3]

Drug-resistant TB (MDR-TB and XDR-TB) has microbial, clinical, and programmatic causes. An inadequate or poorly administered treatment regimen when the patient is first diagnosed to have TB allows drug-resistant mutants to become the dominant strain in a patient infected with TB[1].

On-going transmission of established drug-resistant strains in health care facilities is also believed to be a major source of new drug resistant cases[1]. The resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli which is aggravated by an inadequate or poorly administered treatment regimen that allows drug-resistant mutants to become the dominant strain in a patient infected with TB[1, 2].

Drug-resistant TB may be either primary or acquired. Primary drug resistance is that which develops in a strain infecting a patient who has not previously been treated. Acquired resistance develops during treatment with an inappropriate regimen. In North America and Western Europe, rates of primary resistance are generally low, and isoniazid resistance is most common. In the United States, while rates of primary isoniazid resistance have been stable at 7–8%, the rate of primary MDR-TB has declined from 2.5% in 1993 to 1% since 2000.[4]

MDR TB Treatment Outcome definitions[1]

Cure: A patient who has completed treatment and has been consistently culture negative (with at least 5 consecutive negative results in the last 12 to 15 months). If one follow-up positive culture is reported during the last three quarters, patient will still be considered cured provided this positive culture is followed by at least 3 consecutive negative cultures, taken at least 30 days apart, provided that there is clinical evidence of Improvement.
Treatment completed: A patient who has completed treatment but does not meet the definition for cure or treatment failure due to lack of bacteriological results.
Treatment failure: If two or more of the five cultures recorded in the final 12-15 months are positive, or if any of the final three Cultures are positive.
Death: A patient who dies for any reason during the course of M/XDR-TB treatment
Treatment default: A patient whose treatment was interrupted for two or more consecutive months for any reason.

(Revised national tuberculosis control programme guidelines may 2014)

RNTCP Regimen for MDR TB: 6 months { Kanamycin, Levofloxacin, Ethionamide, Cycloserin, Pyrizinamide, Ethambutol }

: 18 months {Levofloxacin, Ethionamide, Cycloserin, Ethambutol}

[Reserve/Substitute drugs: PAS (Para amino salicylic acid), Moxifloxacin, Capreomycin]

Regimen for MDR TB dosage and weight band recommendations.

S.No	Drugs	16-25 Kgs	26-45 Kgs	46-70 Kgs	>70kg
1	Kanamycin	500mg	500mg	750mg	1gm
2	Levofloxacin	250mg	750mg	1000mg	1000gm
3	Ethionamide	375mg	500mg	750mg	1000gm
4	Ethambutol	400mg	800mg	1200mg	1600gm
5	Pyrazinamide	500mg	1250mg	1500mg	2000gm
6	Cycloserine	250mg	500mg	750mg	1000gm
7	Pyridoxine	50mg	100mg	100mg	100mg
	Na-PAS (80% weight/vol) Moxifloxacin (Mfx) Capreomycin (Cm)	5 gm 200 mg 500 mg	10 gm 400 mg 750 mg	12 gm 400 mg 1000 mg	16gm 400 mg 1000mg

Treatment of MDR-TB is difficult, complicated, much costlier, has to be given for 24 to 27 months. The drugs are frequently associated with high rates of adverse drug reactions, needing interruption and change of regimen[7] and also leads to defaulting. Therefore, it is imperative to monitor and treat adverse drug reactions immediately to ensure better compliance.

All efforts should be taken encourage patients to take regular treatment despite all its discomfort so as to prevent morbidity, mortality and transmission of MDR-TB[7].

In this large observational study of 537 cases, seen over four years and nine months, the maximum number of cases was in the age group of 15 to 44 years (388, 72.25%). Males (367, 68.34%) were more than twice the number of females (170, 31.66%). Majority (382, 71.14%) belonged to the weight band 26-45 years.

The plus side of the results in this study is that in spite of prolonged and difficult treatment, 124 patients (24.51%) have recovered, of whom 81 (16.01%)are cured and 43 (8.50%) have completed treatment. 182 (35.97%) are currently on treatment, of whom are in the intensive and are in the continuation phase. Our observation is that patients and caregivers, if adequately motivated, supervised and mentored, do comply with the complete therapy. 88 of the 537 patients (17.39%) died. Most of them died (29, 32.47%) within the first three months, of diagnosis. In a study of MDR TB by Sangita V Patel et al, out of 142 patients, 48 (33.10%) were cured, 5.50% completed treatment, 29.7% died and 21.10% defaulted.[13] Similarly in the study of ‘ Outcome of standardized treatment for

patients with MDR from Tamil Nadu, India', 32 patients were studied out of which, 19 patients (66%) cured, 5 (15.6%) defaulted and 3 died.[14]

Initially, when diagnosis could only be confirmed by solid culture, it took about 3 months to start treatment after resistance was suspected. Now, with the introduction of CBNAAT, it is possible to diagnose drug resistance in 2 hours. This will have a significant impact on survival, as the outcome is expected to be better if treatment is started early.

Of the twenty three HIV–DR TB confected cases, one patient has completed treatment, 16 (69.56%) are still on therapy and six (26.08%) died. None defaulted, though the pill burden in confected patients is larger and they are likely to be sicker, because of the very efficient supervision and counselling system that is embedded in ART program.

Of the 537, 34 (6.33%) patients were later diagnosed to have XDR and switched to CAT V (under RNTCP).
It is of concern that the number of patients who defaulted is 80 out of 537(15.81%).[15] In a study of 'Outcome of multi drug resistant tuberculosis cases treated by individualized regimens at a tertiary care clinic' by Dhingra V K,[16] 10 out of 27 patients defaulted (37%) but in our study, the rate of defaulters was 15.81%. In a study of defaulters by Vinitha Jayachandran et al in the private set up, financial constraints were the main reason for the defaulters.[17] However in various studies of Government Sector, the most important reason for defaulting has been adverse drug reactions that were not handled properly, poor counselling about the method of taking the drugs, importance of completing treatment and counselling of relatives/caregivers.

Difficulties in procuring drugs, distance that the sick patient had to travel, regular availability of DOT provider were other factors.

Patients who are not motivated or counselled adequately tend to stop treatment after a few weeks when they feel better. Others are discouraged if they do not improve fast enough and drop out.

Thorough and sustained counselling and sustained supervision will go a long way in improving compliance of patients, as otherwise, not only will morbidity and mortality increase, as far as the patients are concerned, but this dangerous form of the disease will spread in the community and may even replace the more benign sensitive form of tuberculosis.

All drugs should be given in a single daily dosage under directly observed treatment (DOT) by a DOT Provider six days of the week. On Sunday, the oral drugs are administered unsupervised whereas injection Kanamycin is omitted. The empty blister packs of the self-administered doses will be checked the next morning during DOT.

The cartridge based nucleic acid amplification test (CB-NAAT, e.g. the Expert MTB/RIF assay) is available at district, sub-district, medical colleges or private sector. This highly-automated system requires only a minimally trained staff, can be applied to any specimen and results are available within 2 hours.

Follow up examination the required number of sputum specimens are collected and examined by smear and culture at least 30 days apart from the 3rd to 7th month of treatment (i.e. at the end of the months 3, 4, 5, 6 and 7) and at 3-monthly intervals from the 9th month onwards till the completion of treatment (i.e. at the end of the months 9, 12, 15, 18, 21 and 24)[1]. If the 4th or 5th month culture result remains positive, the IP treatment is extended by 1 month. Also along with sputum culture, repeat chest radiograph, serum creatinine and thyroid testing is carried out.

If after the start of treatment, if patient defaults and returns within 3 months, then he is re-registered with new TB no. If he has defaulted after 3 months then sputum culture is done and if it comes positive again, he is re-registered. If culture is negative then treatment is continued with same TB number.

Acknowledgement:-
We would like to acknowledge State TB Officer and RNTCP for maintaining the DR TB centre.

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