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STUDY OF INCIDENCE, OUTCOME AND SIDE-EFFECT PROFILE OF INH MONORESISTANT TB TREATED WITH H MONO POLY DR REGIMEN

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ABSTRACT

BACKGROUND - INH is an important first line Anti TB drug and unexpectedly, Mono resistance to INH has been found to be as high as 17.3% in India as per the India TB Report, 2023. This reduces treatment success rates and increases incidence of MDR-TB. The regimen used in these patients as per guidelines is 6LRZE (6 months of Levofloxacin, Rifamycin, Ethambutol and Pyrazinamide)

AIM AND OBJECTIVE -To study the incidence, outcome and side effect profile of INH mono resistant TB when treated with H Mono Poly DR Regimen and to study the side effects of long term usage of Levofloxacin and Pyrazinamide.

METHODOLOGY- 78 INH Mono resistant patients were diagnosed at the Designated Microscopy centre attached to the Respiratory Medicine OP, ACSR Govt. Medical College between 1st January 2023 and 1st July 2023 (6 months) and H Mono Poly DR regimen started.

RESULTS: Out of the 78 INH MONO resistant patients, 30% belonged to 41-50 year age group (23 patients). 75% were males (57 patients), 10% developed side effects (8 patients) and about 23 % had comorbidities (18 patients). At the end of 6 months, 88.5% were declared cured (69 pts) and the Treatment Failure rate was 6.41% (5 patients). 3 deaths due to unrelated causes occurred during treatment

KEYWORDS – INH Monoreistance, Incidence, Outcome, Side effects

INTRODUCTION:-

Isoniazid, also known as Isonicotinic acid hydrazide and INH, used to treat active and latent Tuberculosis infection, has extremely good bactericidal activity and is responsible for the "early kill'' of actively multiplying Mycobacteria[1] It is also known as a Sterilising Anti-TB drug because within 20 days of starting of an Isoniazid containing regimen, 50% and more Mycobacteria are killed. However in patients with INH resistant Mycobacterium tuberculosis infection, drug regimens based on INH have a high rate of failure[2]. Resistance to INH is caused by mutations in gene coding for a bacterial catalase-peroxidase enzyme or enol-acyl carrier protein reductase inhA, katG gene.

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The India TB report of 2023 , however shows that Isoniazid mono resistance is on the rise and after MDR-TB , it is the commonest type of TB drug Resistance seen

INDIAN TB REPORT 2023[3]

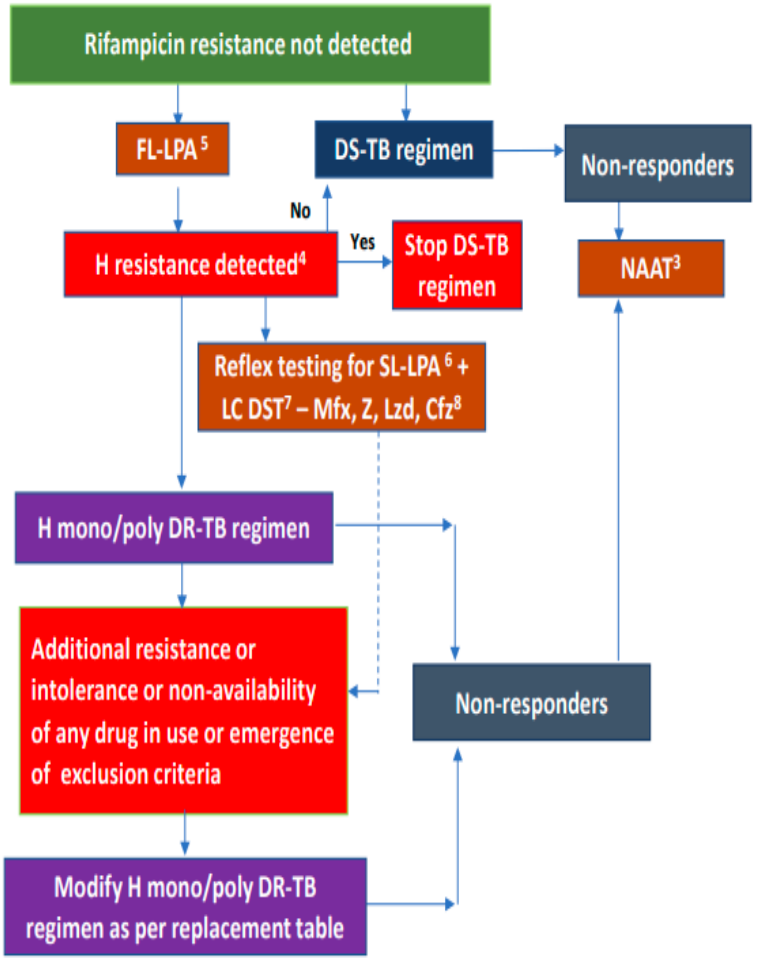
TABLE 1 :

TYPE OF RESISTANCE (IN 2022)	NO.OF PATIENTS DIAGNOSED
MDR/RR-TB	63,801 PATIENTS (69%)
PRE XDR-TB	12002 PATIENTS (13%)
XDR – TB	85 PATIENTS (0.09%)
H MONO/POLY DRUG RESISTANT TB	15953 PATIENTS (17.3%)

Once CBNAAT report shows Rifamycin sensitivity, the sputum / body sample is sent for First line Line probe assay and if H Resistance is detected, H Mono / Poly DR-TB regimen (6 months of Levofloxacin, Rifamycin , Ethambutol and Pyrazinamide) is started.

Reflexly, Second line Line probe assay is also done to test for resistance to Moxifloxacin, Pyrazinamide , Linezolid and Clofazimine[4].

FIGURE 1 :



The dosages of Drugs in the 6LREZ regimen are as follows

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TABLE 2 : **PMDT GUIDELINES 2021**

S.N	Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
1	Rifampicin (R)	300mg	450mg	600mg	750mg
2	Ethambutol (E)	400 mg	800 mg	1200 mg	1600 mg
3	Pyrazinamide (Z)	750 mg	1250 mg	1750 mg	2000 mg
4	Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg

If any of the drugs in the regimen cannot be used, the Replacement sequence is as follows

TABLE 3 : **PMDT GUIDELINES 2021**

Situation	Sequence of using replacement drugs
If Lfx can't be used	Replace with Mfx^{h} if SL LPA pattern suggests. Do LC DST for detection of resistance to Mfx^{h}, Z, Lzd & Cfz*
If Mfx^{h} or Z can't be used	Replace with Lzd. If Lzd also cannot be given, replace with Cfz* + Cs
If both Mfx^{h} and Z can't be used	Add 2 drugs of the 3 – Lzd, Cfz*, Cs in order of preference based on resistance, tolerability & availability
If R resistance	Switch to appropriate shorter or longer regimen

Commonest side effects expected from the H mono poly Drug regimen are Pruritis, rash , Gastritis and Hepatitis from Rifamycin , severe Gastritis from Levofloxacin, Joint pains and Arthralgia from Pyrazinamide and Visual defects from Ethambutol[5]

METHODOLOGY

Between Jan 1st 2023 and July 1st 2023 (6 months), all patients whose results were ''MTB Detected--Rifamycin Sensitive" and who presented to Respiratory Medicine OP, ACSR Government Medical college, Nellore were considered. There were 600 such patients. First line Line probe assay was done at Damien Foundation Hospital at Nellore, and out of these 600 patients, 78 were INH Mono resistant TB, all of them were Pulmonary TB only. All of them were explained about the study, their medical records and co morbidity details were collected. All base line investigations were done and H mono poly drug regimen (6LREZ) was started. The patients were regularly followed up.

RESULTS

1. Among 600 MTB detected patients , 78 were Isoniazid Monoresistant (13%)

2. TABLE 4 : Age distribution

AGE DISTRIBUTION	NO.OF PATIENTS (n=78)
<20 YRS	2

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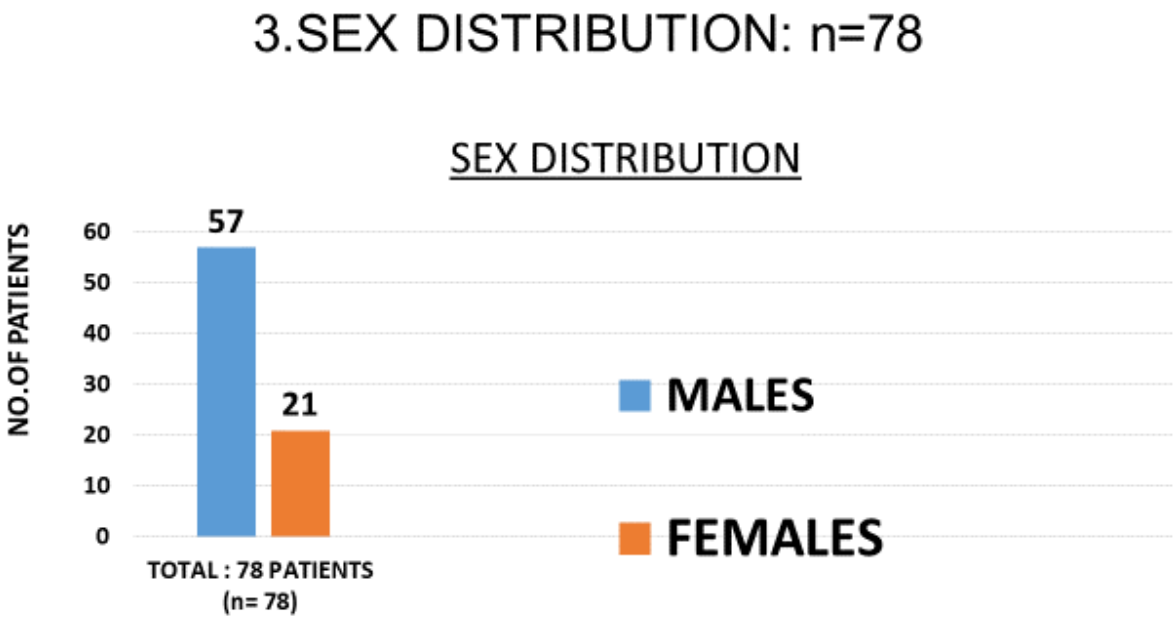
21 - 30 YRS	15
31 - 40 YRS	7
41 - 50 YRS	23
51 - 60 YRS	16
>75 YRS	9

3. **FIGURE 2 : Sex distribution** (n=78)



Male -57
Female – 21

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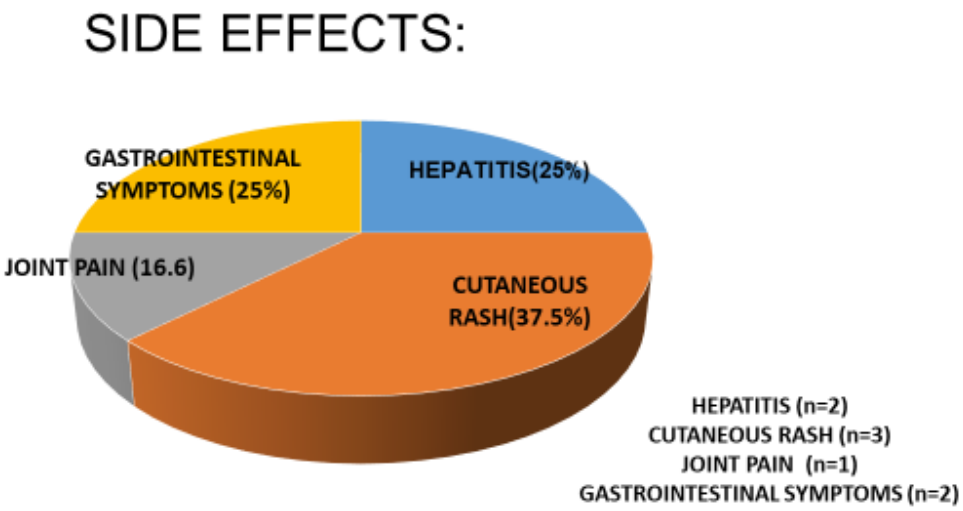
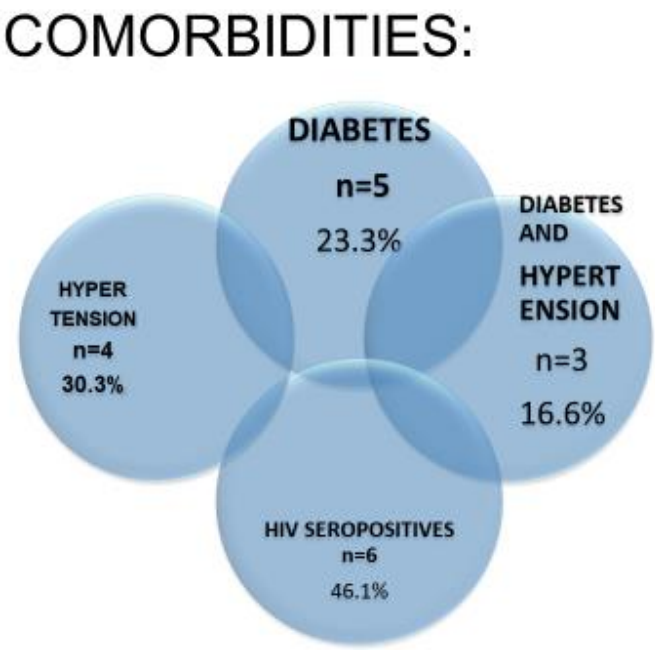
4. **FIGURE 3 : Side effects – 8 patients**



5.

HEPATITIS (n=2)
CUTANEOUS RASH (n=3)
JOINT PAIN (n=1)
GASTROINTESTINAL SYMPTOMS (n=2)

6. **FIGURE 4 : Co morbidities – 18 patients**



Diabetes -5 (23.3%)

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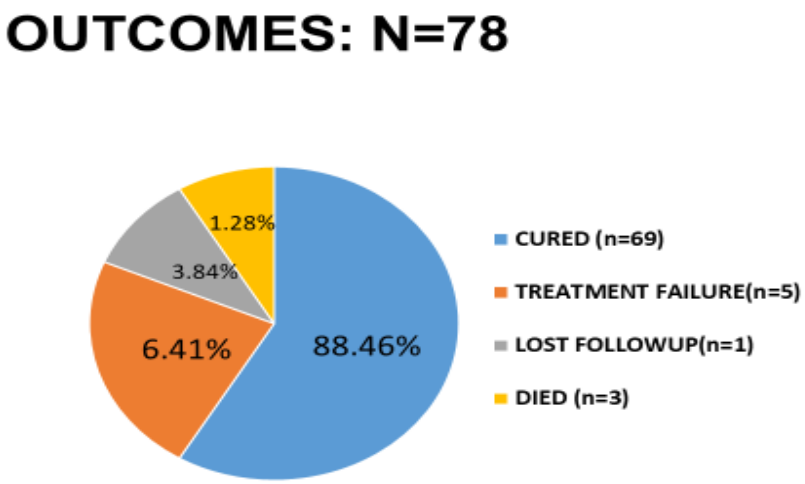
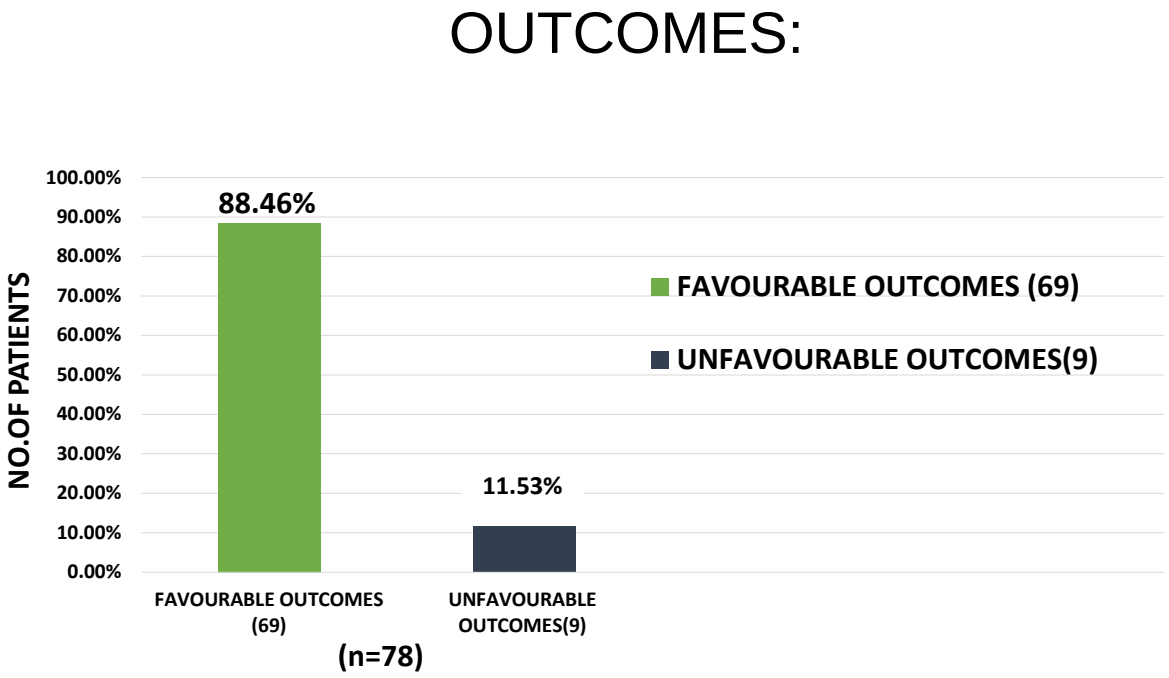
DM & HTN – 3 (16.65)
HIV seropositive – 6 (46.1%)
HTN – 4 (30.3%)

7. FIGURE 5 : Outcomes



Cured -69
Treatment failure – 5
Lost follow up – 1
Died – 3

FIGURE 6:



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DISCUSSION

Recent TB genomic studies done in Europe and the US suggest that INH mono resistance predates Multi drug Resistance in the same patient. This came to be known by the Genetic clock analysis where in timing of occurrence of resistance of each drug can be made out. Thus INH mono resistance seems to be a precursor of Multi drug resistance[6].
As early as 1986, the British Research Council Report of TB Research Trials conducted in the late 1960s and 1970s, in Africa , Singapore and Hong Kong said that cure was 100% in patients having INH mono resistant TB. Our study also shows a high cure rate 88.5%

A recent study in San Fransisco, says the outcome of INH monoresistant TB is the same as Drug Sensitive TB when any 4 first line drugs are used[7]. Salindri and Colleagues in a study in Georgia, in 2018 had similar excellent results in patients with INH mono resistance with no relative side effects in their study population[8]. Even in our study population, less than 10% developed side effects.

STRENGTHS AND LIMITATIONS: Our study is one of the few studies done on INH monoresistance in India in recent times. Because the Department of Respiratory Medicine has Designated Microscopy Centre attached to it and is a part of a well staffed TB unit, follow up was easy and efficient. However, it will be better if the patients declared cured are followed up for a longer time, say 1-2 years, to know if a relapse occurs.

CONCLUSIONS: In our study, INH mono-resistant patients formed a significant fraction of the total detected TB cases (13%). Our study shows the H mono poly Drug Resistant -TB regimen which is easy to tolerate gives good compliance and good cure rate. Pyrazinamide and Levofloxacin when given for longer periods (6 months) do not show increased side effects

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