International Journal of Research and Review
Vol. 9; Issue: 11; November 2022
Website: www.ijrrjournal.com
Case Report *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

A Case Report of Drug Resistant Tuberculosis Involving Brain

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DOI: https://doi.org/10.52403/ijrr.20221154

ABSTRACT

We report a 21 year old male resident of Tasgaon, Maharashtra who was diagnosed with drug resistant tuberculosis affecting his lungs and brain, resistant to first line antitubercular drug Rifampicin. Initially he was diagnosed as a case of extrapulmonary tuberculosis, left sided tubercular pleural effusion. Later during course of treatment, he developed central nervous system tuberculosis confirmed on magnetic resonance imaging brain contrast study and Cerebrospinal fluid study. Cerebrospinal fluid catridge based nucleic acid amplification test showed Rifampicin resistance. He was started on Modified longer oral Multidrug/extensively drug resistant tuberculosis regimen according to Programmatic management of drug resistant tuberculosis in India, 2021 guidelines.

KEY WORDS: Tuberculosis, Extra pulmonary, Programmatic management of drug resistance, Oral regimen, Central nervous system tuberculosis

INTRODUCTION

The emergence of drug resistant TB is one of the major public health concerns. Despite a complex treatment regimens and longer treatment periods, second line anti TB drugs are overall less effective than first line drugs [1,2]. The recent guidelines on the programmatic management of drug resistant TB in India have been released in March 2021 on world TB day. The new guidelines have given importance to emerging diagnostic trends including TrueNat, Xpert Mtb/XDR, NGS (Next generation sequencing) and evaluation for resistance and more focus on newer oral drugs including bedaquiline and delamanid. The emerging therapeutic trends include focus on Oral shorter Bdq based regimen with phasing out of injectables drugs. The replacement sequence of drugs for DRTB have also been updated.

CASE REPORT

A 21 year old male brought to the emergency room with history of headache since 1 month and altered sensorium since morning.

Patient looked pale and malnourished (BMI 21 kg/m2) and had a temperature of 38 °C, heart rate 104/min, BP 110/78mmhg, respiratory rate of 24/min, coarse crackles were present over left lung lower zone. He was having GCS 10/15 with spontaneous eye movements, incomprehensible sound production and localisation of pain. Pupils were bilaterally equal and reactive to light, both plantars were mute, signs of meningeal irritation were present.

On history taking it was found that he was having wet cough and breathlessness 3 months back. He visited a local physician, chest Xray showed left sided moderate pleural effusion which was confirmed with HRCT chest report. Pleural fluid analysis showed tubercular in nature, he was labelled as a case of extrapulmonary TB, left sided tubercular pleural effusion. He Took antitubercular treatment for 2 months and later discontinued himself.

Laboratory evaluation revealed following values : Hb 8.8 g/dL, TLC 9960/microL, platelet count 2.9 lakh/micorL, serum creat 0.8 mg/dL, BUL 30 mg/dL, RBSL 90 mg/dL, bilirubin total 0.7 mg/dL, direct 0.2 mg/dL, indirect 0.5 mg/dL, ALT 29 IU/L, AST 30 IU/L, ALP 111 IU/L, proteins Total 6.8 g/dL, Albumin 4.1 g/dL, Globulin 2.7 g/dL, prothrombin time 12 sec (control 12), INR 1, aPTT 22 sec, ESR 40 mm/hr, CRP 1.4 g/dL, HIV negative, HbsAg negative, anti Hbc IgG negative, PS for MP and MP card test negative, urine routine normal, USG abdomen pelvis showed grade 1 fatty liver. Chest Xray showed mild left sided pleural effusion. Fundoscopy was normal. Next day we conducted MRI brain plain plus contrast imaging which showed multiple ring enhancing focal lesions of 3-5mm, scattered in supratentorium as well as posterior fossa involving bilateral cerebral hemispheres, brainstem and cerebellar hemispheres with basal exudates. No hydrocephalus. Guarded lumbar puncture was done, CSF analysis showed WBC count 340/cubmm with 90% Lymphocytes and 10% neutrophils, RBC 22/cubmm, protein 152 mg/dL, glucose 42 mg/dL, ADA 68 IU/L. CSF CBNAAT came positive with resistance to rifampicin.

Figure 1 – chest Xray PA view on day 1 of admission showing left sided mild pleural effusion.

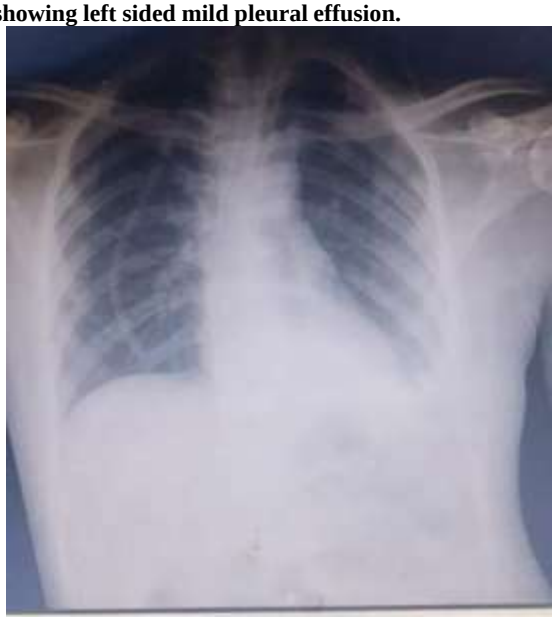
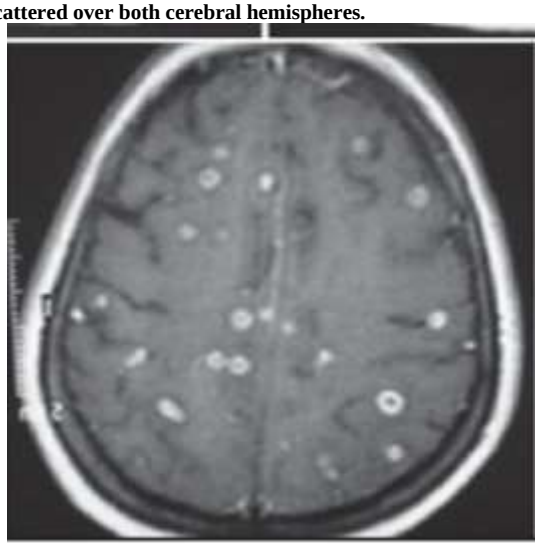


Figure 2 – MRI brain plain plus contrast imaging on 2nd day showing multiple ring enhancing focal lesions of 3-5mm scattered over both cerebral hemispheres.



We started him on IV Injection Dexamethasone 8mg, three times daily (dose of 0.4mg/kg/day and patient weight being 59 kg), Inj Mannitol 100cc iv, three times daily, Inj Phenytoin sodium 600mg loading dose followed by 100mg, three times daily. We started him on Longer Oral M/XDR TB Regimen as recommended by PMDT India 2021, which has total of 18 months duration with intensive phase of 6 months followed by continuation phase of 12 months. The regimen included following oral drugs.

1. Bedaquiline 400mg once daily for first 2 weeks followed by 200mg, 3 times per week (Monday, Wednesday, Friday) for next 22 weeks.
2. Levofloxacine 1 gram, once daily
3. Linezolid, 600mg, once daily for 6 months then tapered to 300mg for remaining period.
4. Cycloserine, 750mg, once daily
5. Clofazimine, 100mg, once daily
6. Pyridoxine, 100mg, once daily.

Patient responded to the treatment and gradually regained his consciousness. He was discharged on 28th day with further follow up instructions.

After 2 months, patient started complaining of diminished vision in both eyes. Fundoscopy showed bilateral optic atrophy. Vision in right eye – counting fingers up to

1 foot and right eye 6/18. Repeat MRI brain plain plus contrast showed gliotic changes, no tuberculoma, no hydrocephalus. Linezolid was stopped which is the main culprit for optic neuritis and was replaced by Injectable Pyrazinamide 1750mg, once weekly and advised to continue remaining drugs. This is The Modified Longer Oral M/XDR Regimen. On follow up it was found that there was no further worsening of vision.

DISCUSSION

EPIDEMIOLOGY [1]

Indian has the highest burden of TB in world, having an estimated incidence of 2.7 million cases in 2019. Global estimates indicate that about a half million new cases of Rifampicin resistant TB (RR TB) occurred in 2019 with 78% of them having confirmed MDR TB. Estimated number of MDR/RR TB in India is 124000 (9.1/lakh population). The first National Anti Tuberculosis Drug Resistance Survey (NDRS) revealed that 28% of TB patients were resistant to any drugs and 6.19% had MDR TB.

The latest PMDT guidelines incorporate emerging diagnostic and therapeutic trends, while focusing on elimination if TB under the National TB Elimination Program, NTEP [1]. These guidelines are a welcome step, with the updated recommendations backed by evolving evidence and are in coherence with WHO technical report [2].

PATHOPHYSIOLOGY

CAUSES OF DRUG RESISTANCE [1]

1. From bacteriological perspective,- genetic mutation.
2. Inadequate or poorly administered treatment regimen.
3. Clinical characteristics of patients.
4. Weak TB services leading to delay in detection and effective treatment of drug resistance.

DIAGNOSIS OF DRUG RESISTANCE – NEWER TECHNIQUES IN DRUG SENSITIVITY TESTING [1]

Mainly there are 2 types tests, Genotypic tests and Phenotypic tests. Genotypes testing mainly has 2 methods, first one is NAAT (Nucleic Acid Amplification Test) like CBNAAT (Xpert Mtb) and newer TrueNat which mainly detect only resistance to rifampicin. Second method is LPA (line probe assay) which detects resistance to Rifampicin, Isoniazid, fluoroquinolones, and second line injectables. 2nd test is phenotypic drug sensitivity testing (pDST) using MGIT (mycobacterial growth indicator tube).

PMDT 202Q, now explicitly recommends resolving discordant on Rifampicin resistance (RR) between NAAT and first line LPA with a successively repeated NAAT [3]. Another new update has added for NGS (Next Generation Sequencing) which can help in detection of genomic sequence variants to predict TB drug resistance phenotypes [3].

Figure 1 – Drug resistance and their target lesions.

Drug resistance	Target region
Isoniazid	inhA promotor, katG,fabG1, oxyR- ahpC intergenic region
Ethionamide	inhA promotor
Fluoroquinolone	gyrA, gyrB
Amikacin, Kanamycin, Capreomycin	rrs, eis promotor

Figure 2 – Line probe assay and it's interpretation.

Drug	Gene	Test results	Clinical interpretation
Rifampicin	rpoB	Resistance inferred or detected	R is not effective
Isoniazid	katG	Resistance to high level H inferred or detected	H is unlikely to be effective even at high dose
	InhA	Resistance to low level H inferred or detected	H at high dose is likely effective. Eto/Pto are not effective
Fluoroquinolones	gyrA	Resistance to Lfx and low level Mfx inferred Resistance to Lfx and low level Mfx detected	Lfx is not effective. Mfx could be used at higher dose. The regimen should be reevaluated based on phenotypic DST results to Mfx at clinical breakpoint
		Resistance Lfx and high level Mfx detected (MUT 3B, MUT 3C, MUT 3D)	Lfx / Mfx is not effective
	gyrB	Resistance to Lfx and low level Mfx inferred Resistance to Lfx and low level Mfx detected	Lfx is not effective. Mfx could be used at higher dose. The regimen should be re-evaluated based on phenotypic DST results to Mfx at clinical breakpoint.
Second-line injectable drugs	rrs	Resistance inferred or detected	Am, Km and Cm are not effective
		Resistance to Am inferred (mutation at 1402)	Km and Cm are likely not effective. Phenotypic DST result should guide the choice to use Am in the treatment regimen
	eis	Resistance inferred or detected	Am and Cm are likely effective. Km is not effective

TREATMENT – NEWER GUIDELINES FOR MANAGEMENT OF DR TB IN INDIA [1]

Newer treatment regimens – Shorter oral Bedaquiline containing MDR/RR TB regimen and Longer oral M/XDR TB regimen are now mainly used. Gradual phasing out of Injectable second line drugs with above fully oral regimens is going on. The BPaL regimen (Bdq, pretomanid, linezolid) can also be used as a last resort in individualized settings since the evidence for this combination is still evolving [4].

COVID 19 Pandemic has created big hurdles in DR TB program at all levels, but intensive implementation of the updated PMDT guidelines must be ensured and continued [5]. Fearing risk of increased morbidity and mortality, COVID 19 and TB coinfection also needs to be timely evaluated in all suspected cases for effective therapy and best outcome [6,7].

Grouping of DR TB drugs as recommended by WHO [2] – done based on efficacy, experience of use and drug class. Mainly divided into 3 groups A,B,C. While preparing drug regimen following rules are to be followed. Group A – include all 3 drugs, group B – add one or both medicines, group C – added to complete the regimens and when medicines from group A and B cannot be used.

Image 3 – WHO grouping of drugs and principles of forming oral longer regimen. [1,2]

GROUPS & STEPS	MEDICINE	ABBREVIATION
Group A	Levofloxacin or	Lfx
Include all three medicines	Moxifloxacin	Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B	Clofazimine	Cfz
Add one or both medicines	Cycloserine or	Cs
	Terizidone	Trd
Group C	Ethambutol	E
Add to complete the regimen and when medicines from Group A and B cannot be used	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin or	Ipm-Cln
	Meropenem	Mpm
	Amikacin	Am
	(OR Streptomycin)	(S)
	Ethionamide or	Eto
	Prothionamide	Pto
	p-aminosalicylic acid	PAS

VARIOUS DRUG REGIMENS ACCORDING TO DIFFERENT CASE SCENARIOS [1]

A. Shorter oral Bdq containing MDR/RR TB regimen

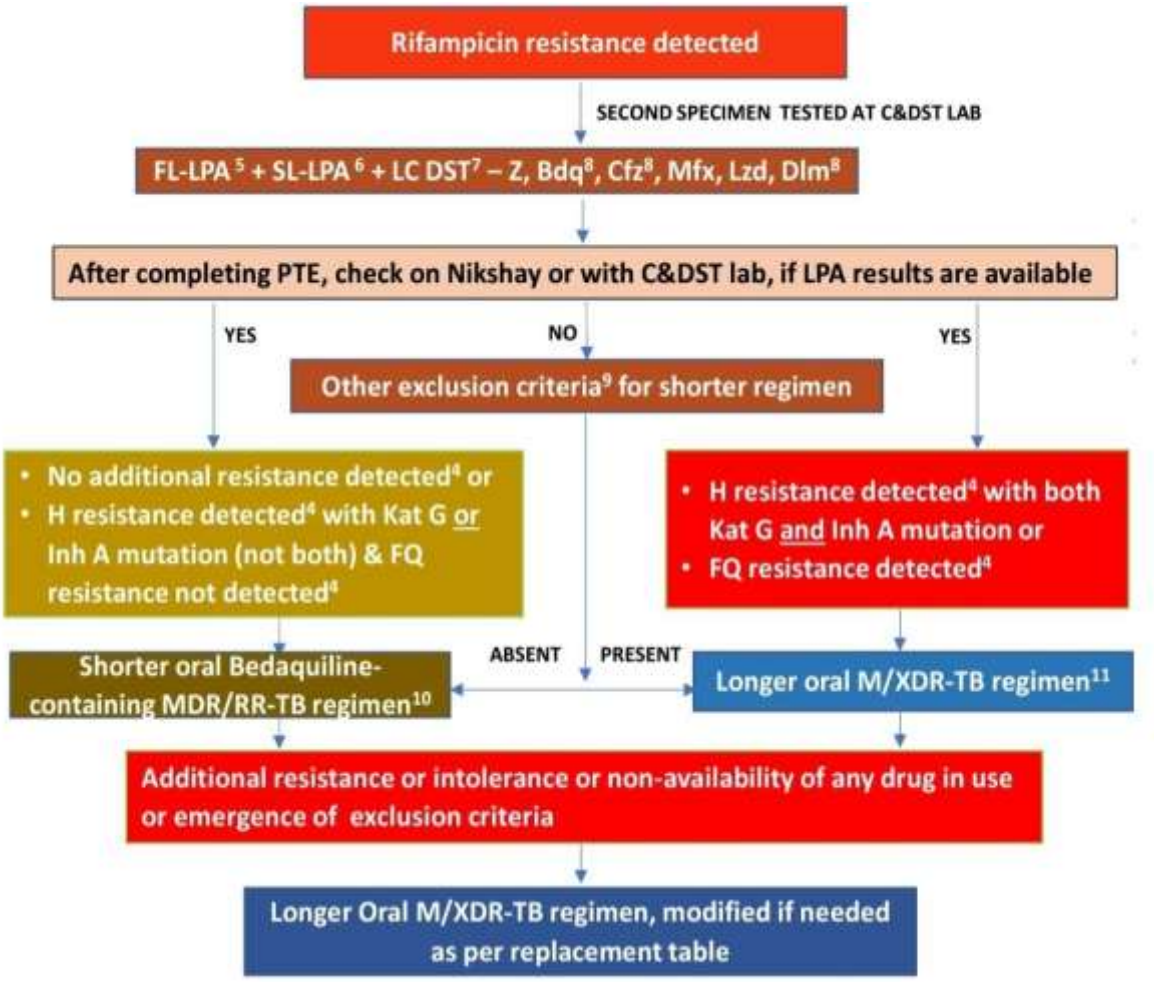
Indication – rifampicin resistance present, isoniazid resistance detected in either Kat G or Inh A (but not both), no fluoroquinolone resistance

Regimen – Bdq for total 6 months, Levofloxacine, pyrazinamide, ethambutol, clofazimine, high dose isoniazid and ethionamide for first 4 months (can be extended upto 6 months). Followed by next 5 months Levofloxacine, pyrazinamide, ethambutol and clofazimine

Figure 4 – Drugs used in short oral regimen.

SN	Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
1	High dose H (H^n)	300 mg	600 mg	900 mg	900 mg
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
5	Bedaquiline (Bdq)	Week 0–2: Bdq 400 mg daily Week 3–24: Bdq 200 mg 3 times per week			
6	Clofazimine (Cfz)	50 mg	100 mg	100 mg	200 mg
7	Ethionamide (Eto)*	375 mg	500 mg	750 mg	1000 mg
8	Pyridoxine (Pdx)	50 mg	100 mg	100 mg	100 mg

Figure 5 – Treatment algorithm for management of rifampicin resistance.



Inclusion criteria for the regimen – rifampicin resistance, fluoroquinolones sensitivity, only 1 of 2 isoniazid mutation, children with age more than 5 years, all PLHIV, Pregnant mother of more than 32 weeks [5].

Exclusion criteria for the regimen – presence of both types of INH mutation, presence if fluoroquinolone resistance, Disseminated TB, military TB, CNS TB, meningitis.

B. Longer oral M/XDR regimen [1]

Indication – resistance to rifampicin, isoniazid (both types), fluoroquinolones but sensitive to second line injectables.

Inclusion criteria- for MDR/RR patients who are excluded from shorter oral Bdq regimen.

Regimen – duration of 18-20 months. Levofloxacine, bedaquiline (6months or longer), Linezolid (600mg for 6 months then tapered to 300mg), clofazimine, cycloserine.

Figure 6 – drugs of longer oral regimen.

SN	Drugs	16-29 kg	30-45 kg	46-70 kg	>70 kg
1	Levofloxacin (Lfx)	250 mg	750 mg	1000 mg	1000 mg
2	Moxifloxacin (Mfx)	200 mg	400 mg	400 mg	400 mg
3	High dose Mfx (Mfx^{h})	400mg	600mg	800mg	800mg
4	Bedaquiline (Bdq)	Week 0–2: Bdq 400 mg daily Week 3–24: Bdq 200 mg 3 times per week			
5	Clofazimine (Cfz)	50 mg	100 mg	100 mg	200 mg
6	Cycloserine (Cs)[3]	250 mg	500 mg	750 mg	1000 mg
7	Linezolid (Lzd)	300 mg	600 mg	600 mg	600 mg
8	Delamanid (Dlm)	50 mg twice daily (100 mg) for 24 weeks in 6-11 years of age 100 mg twice daily (200 mg) for 24 weeks for ≥12 years of age			
9	Amikacin (Am)[1]	500 mg	750 mg	750 mg	1000 mg
10	Pyrazinamide (Z)	750 mg	1250 mg	1750 mg	2000 mg
11	Ethionamide (Eto)[3]	375 mg	500 mg	750 mg	1000 mg
12	Na - PAS (60% weight/vol)[2,3]	10 gm	14 gm	16 gm	22 gm
13	Ethambutol (E)	400 mg	800 mg	1200 mg	1600 mg
14	Imipenem-Cilastatin (Imp-Cln)[3]	2 vials (1g + 1g) bd (to be used with Clavulanic acid)			
15	Meropenems (Mpm)[3]	1000 mg three times daily (alternative dosing is 2000 mg twice daily) (to be used with Clavulanic acid)			
16	Amoxicillin-Clavulanate (Amx-Clv) (to be given with carbapenems only)	875/125 mg bd	875/125 mg bd	875/125 mg bd	875/125 mg bd
17	Pyridoxine (Pdx)	50 mg	100 mg	100 mg	100 mg

Figure 7 – Replacement sequence for drugs in oral longer regimen.

Sr. No	Drugs to be replaced	No. of drugs to include from			Final Regimen after replacement
		Group A (3 drugs)	Group B (2 drugs)	Group C (7 drugs)	
1	None[$]	3	2	-	6-8 Lfx, Bdq, Lzd, Cfz, Cs / 12 Lfx, Lzd, Cfz, Cs
2	1 group A drug[@]	2	2	1	**No FQ,** then 6-8 Bdq, Lzd, Cfz, Cs, Dlm / 12 Lzd, Cfz, Cs [$] **No Bdq[$],** then 6-8 Lfx*, Lzd, Cfz, Cs, Dlm / 12 Lfx*, Lzd, Cfz, Cs **No Lzd,** then 6-8 Lfx*, Bdq, Cfz, Cs, Dlm / 12 Lfx* Cfz, Cs
3	1 group B drug	3	1	1	**No Cfz,** then 6-8 Lfx* Bdq, Lzd, Cs Dlm / 12 Lfx* Lzd, Cs **No Cs,** then 6-8 Lfx* Bdq, Lzd, Cfz, Dlm / 12 Lfx* Lzd, Cfz
4	1 group A drug[@] & 1 group B drug	2	1	2	**No FQ & Cfz** then 6-8 Bdq, Lzd, Cs, Dlm, Am[#] / 12 Lzd, Cs, Z[#], Eto[#] **No FQ & Cs** then 6-8 Bdq, Lzd, Cfz, Dlm, Am[#] / 12 Lzd, Cfz, Z[#], Eto[#] **No Bdq & Cfz** then 6-8 Lfx* Lzd, Cs, Dlm, Am[#] / 12 Lfx* Lzd, Cs **No Bdq & Cs** then 6-8 Lfx* Lzd, Cfz, Dlm, Am[#] / 12 Lfx* Lzd, Cfz **No Lzd & Cfz** then 6-8 Lfx* Bdq, Cs, Dlm, Am[#] / 12 Lfx*, Cs, Z[#], Eto[#] **No Lzd & Cs** then 6-8 Lfx* Bdq, Cfz, Dlm, Am[#] / 12 Lfx*, Cfz, Z[#], Eto[#]

5	2 group A drugs@	1	2	2	**No FQ & Bdq** then 6-8 Lzd, Cfz, Cs, Dlm, Am# / 12 Lzd, Cfz, Cs, Z# **No FQ & Lzd** then 6-8 Bdq, Cfz, Cs, Dlm, Am# / 12 Cfz, Cs, Z#, Eto# **No Bdq & Lzd** then 6-8 Lfx*, Cfz, Cs, Dlm, Am# / 12 Lfx*, Cfz, Cs, Z#
6	2 group B drugs	3	0	2	**No Cfz & Cs** then 6-8 Lfx* Bdq, Lzd, Dlm, Am# / 12 Lfx*, Lzd, Z#, Eto#
7	3 or more from group A drugs@& group B drugs	Use the remaining drugs		3 or more	Remaining drugs from Group A and B plus 3-5 drugs from Group C using the conditions/sequence# below to make a regime with at least 5-6 drugs known to be effective. If Bdq and Dlm can be used, their combined use in the regimen with at least 4 -5 drugs or its extended use beyond 6 months till clinical and bacteriological conversion is achieved. If Bdq and Lzd can be used, explore the possibility of using BPaL regimen under prevailing ethical conditions.

C. Isoniazid mono/poly DRTB

Duration - 6 months in all cases except, 9 months if extensive lung involvement and 12 months if CNS TB, military TB, skeletal TB.

Regimen- Levofloxacine, rifampicin, pyrazinamide, ethambutol.

Figure 8 – drugs used for treatment of H resistance

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

Figure 9 – treatment algorithm of isoniazid resistant TB

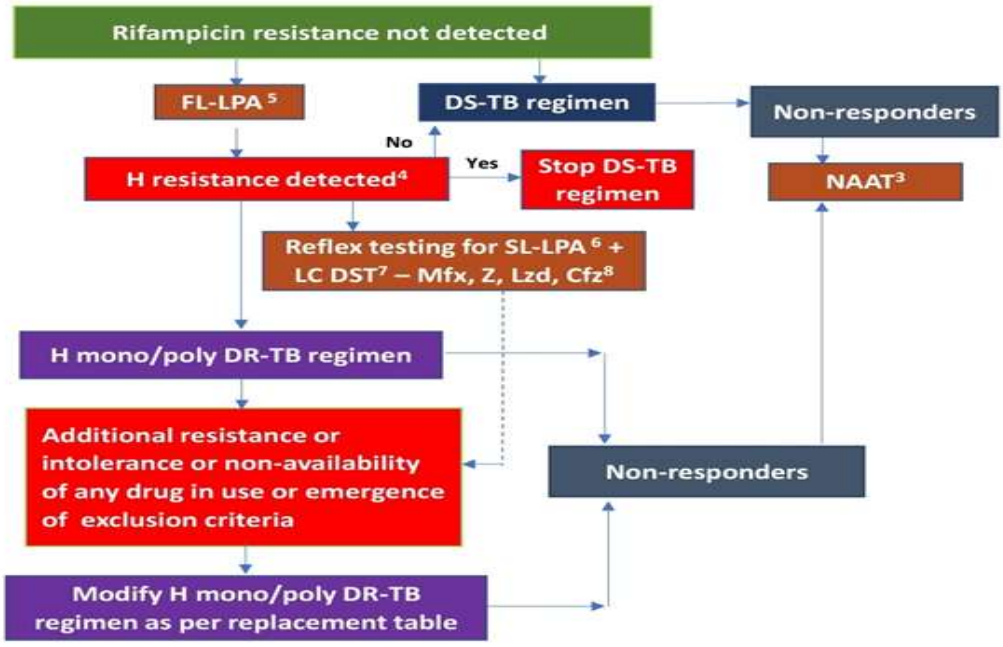
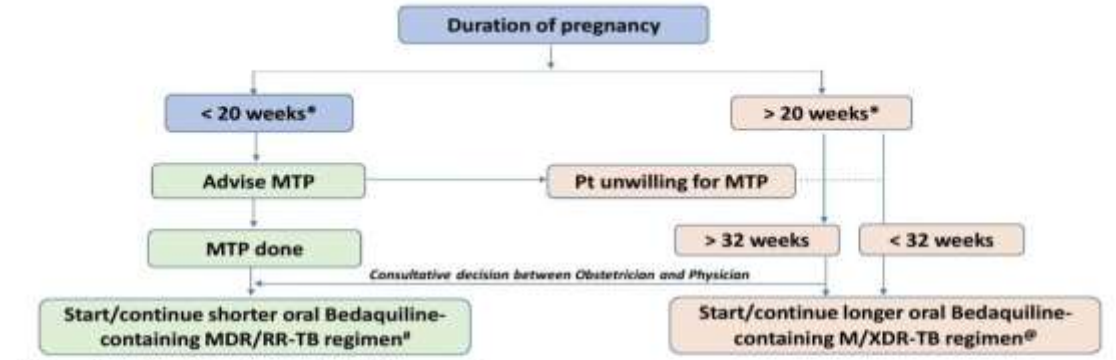


Figure 10 – sequence of drug replacement in regimen for isoniazid resistant Tb

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

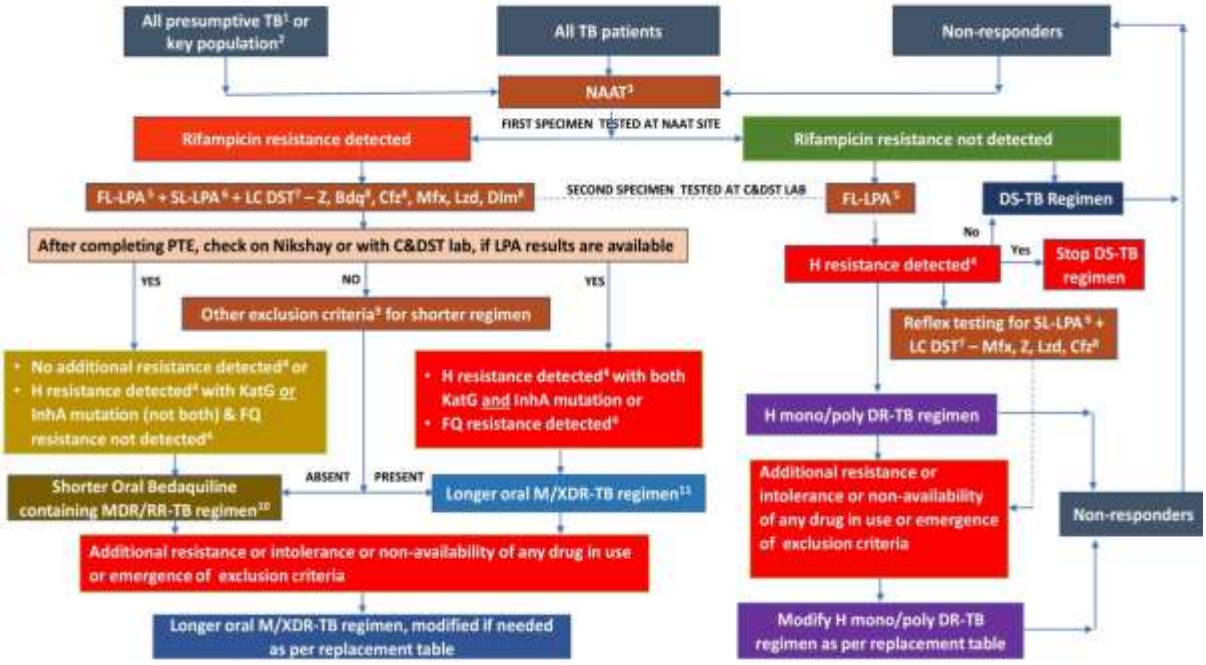
D. MDR TB management during pregnancy [1,8]



* 24 weeks will apply wherever the bill is passed.
# Regimen: 4-6 Bdq (6m) Lfx, Cfz, Eto, Hh, Z, E / 5 Lfx, Cfz, Z, E. No modifications allowed.
@ Regimen:18-20 Lfx, Bdq(6m or longer) Lzd#, Cfz, Cs. Lzd dose to be tapered to half after 6-8 months based on bacteriological response. Modify regimen if one or more drug cannot be used due to reasons of resistance, tolerability, contraindication, availability etc.

- in the order of Z E PAS.
- Eto may be considered after 32 weeks' gestation.
- Am may be considered in post-partum period only. Am will not be started in the final 12 months of treatment.

Figure 10 – Integrated drug resistant TB management algorithm [1].



CONCLUSION

Delayed detection of resistance, inadequate or poorly administered treatment regimen are the most important reasons for drug resistance. To prevent this PMDT, India has rolled out newer expansions like checking rifampicin resistance in all diagnosed TB cases. Newer drug sensitivity testings like CBNAAT, TrueNat, LPA are developed. Gradual phasing out of injectable second line drugs with short and long oral regimens is being done. Injectable SLDs are now used only to substitute oral SLDs in case of resistance or adverse drug reaction.

Declaration by Authors

Ethical Approval: Not Applicable

Acknowledgements:
Department of Pathology, GMC miraj
Department of Radiology, GMC miraj

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

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How to cite this article: Anita Basavaraj, Naveen Kannur. A case report of drug resistant tuberculosis involving brain. *International Journal of Research and Review*. 2022; 9(11): 399-408.
DOI: *https://doi.org/10.52403/ijrr.20221154*

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