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Adverse Drug Reactions in Management of Multi Drug Resistant Tuberculosis, in Tertiary Chest Institute

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Abstract

Background: Multidrug resistant tuberculosis is a global threat. Effective treatment is implemented as per RNTCP guidelines. But the drugs used have great potential to develop adverse drug reactions. Such drug reactions if not managed optimally can lead to unfavourable treatment outcome. Hence, the study is to know the occurrence of adverse drug reactions. Aims: To study the occurrence of adverse drug reactions in treatment of multidrug resistant tuberculosis and hence the factors affecting the treatment. Settings and Design: Retrospective analysis of patients treated with standardised regimen for MDR-TB, as per RNTCP guidelines at a tertiary chest institute between august 2011 and December 2014. Methods and Material: Retrospective analysis of 607 patients' records reviewed for the occurrence of adverse drug reactions. All adverse reactions are noted and diagnosed either clinically or by laboratory evidence. Results: Among the 607 patients included in the study, majority had one or more adverse drug reactions. The most common was gastritis (71.7%), which was easily treatable, and the least common was visual impairment (0.2%). Only 1.7% discontinued the treatment citing adverse drug reactions and 10.5% required permanent discontinuation of the offending drug. Conclusion: Treatment of MDR-TB is challenging mainly due to the long duration of treatment and the potential adverse reactions of the drugs used. These reactions are frequent but majority of them can be successfully managed without treatment interruption. Training the peripheral health centre workers to identify and refer the patients with adverse reaction bears a major impact on treatment outcome.

Keywords

MDR-TB, ADR, Adherence, Outcome

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1. Introduction

Multidrug resistant tuberculosis (MDR-TB), defined as resistance to at least rifampicin and isoniazid, is a growing concern throughout the world. As per recent global tuberculosis report of WHOm the incidence of MDR-TB is 3.5% among new cases and 20.5% among previously treated for tuberculosis cases [1]. India along with China & Russian Federation contributes to about half the load of MDR-TB cases [1].

Programmatic management of drug resistant tuberculosis (PMDT) services in India were initiated from August-2007. A standardised Cat IV regimen has been implemented by the Revised National Tuberculosis Control Programme (RNTCP) [2]. The duration of MDR-TB treatment is 24 - 27 months and multiple drugs are used in the regimen which has a great potential for adverse drug reactions. Adverse drug reactions associated with the second line anti-tuberculosis drugs used has a severe impact on adherence [3] [4] to treatment. As adherence to treatment is the key to successful outcome, identification and early management of adverse drug reactions plays a major role in MDR-TB management. Several studies have contributed to the knowledge of these adverse reactions [5]-[7]. In this study we report the occurrence of adverse drug reactions encountered during MDR-TB treatment.

Material & Methods: Retrospective cohort study was done in SDSTRC & Rajiv Gandhi institute of Chest Diseases, a tertiary chest institute.

Inclusion criteria: Sputum culture confirmed MDR-TB patients who received at least 3 months of MDR-TB treatment during August 2011 to December 2014 were included in this analysis.

All confirmed cases were admitted for pre-treatment evaluation as per National guidelines. Baseline investigation included clinical examination, chest X-ray, complete haemogram, liver function test, blood urea, serum creatinine, blood sugar-fasting, post prandial, HIV (ELISA), thyroid profile, urine pregnancy test for women of child bearing age group.

Patients were initiated on standardised Cat IV regimen which includes kanamycin, levofloxacin, ethionamide, pyrizanamide, ethambutol, cyclosereinefor 6 - 9 months and levofloxacin, ethionamide, ethambutol, cyclosereine for 18 months. Para-Aminosalicylic acid was used as a reserve/substitute drug .Dosage of the drugs was as per weight bands recommended. After 10 - 15 days of initiation of treatment, patients were discharged from hospital and continued treatment from pre-identified peripheral units. As per national guidelines, patients were clinically monitored regularly. Serum creatinine was repeated every month for first 3 months and every 3 months thereafter in patients receiving kanamycin. Symptomatic patients were evaluated by chest physicians and appropriate laboratory investigations were done on advice. Specialist consultation (psychiatric, audiometric, ophthalmic, dermatologist) was taken whenever indicated.

Retrospective data was collected by reviewing patient case files, treatment cards, registers maintained at DOTS-Plus site and reports from peripheral units submitted on line. For adverse drug reactions defined by laboratory values, at least one documented abnormal value was considered. For those not defined by laboratory values, event was considered if the chest physician/pharmacovigilence team documented the reaction in the patient case file according to his/her clinical criteria (**Table 1**).

Management of these adverse reactions symptomatically with/without modification of the MDR-TB regimen was noted if documented in the case file/treatment card.

Exclusion criteria:

1) Patients who received less than 3 months' treatment at the time of this study.

2) Patients with abnormal laboratory value at baseline evaluation were excluded while analysing for that particular adverse effect.

The study was approved by the institutional DOTS plus and ethical committee.

2. Results

607out of 675 patients had received at least 3 months' treatment at the time of this study and only those were included in the study.

Majority of the cohort experienced adverse drug reactions. Many patients experienced more than one adverse reaction. Adverse drug reaction ranged from minor (gastritis, rash, nausea, diarrhoea, arthralgia) to major life threatening events (renal failure, hepatotoxicity). **Table 2** shows the clinical and demographic data of 607 patients in study.

The most common of adverse drug reactions was related to gastrointestinal system. 435 (71.7%) patients of 607 complained of mild gastritis, nausea, vomiting. Other five commonly occurring adverse reactions were ar-

Table 1. Definition of adverse effects: [5] [6].

Side Effects	Definition
Gastro-intestinal	Nausea, vomiting or pain abdomen
Diarrhoea arthralgia	Documented by physician Joint pains with or without arthritis
Nephrotoxicity	Elevation of Serum creatinine levels above the normal values*
Oto-vestibular toxicity	1) Hearing loss confirmed by physical examination or audiometry 2) Vestibular side effects like dizziness/vertigo/tinnitus.
Dermatologic	Any drug reaction felt to be related to anti-tuberulous medication, as documented by TB physician/dermatologist
Peripheral neuropathy	Symptoms & findings consistent with neuropathy eg: numbness, tingling or burning in trunks or extremities, diagnosed by physician or nerve conduction studies
Seizure	Seizure activities witnessed or unwitnessed
Hypothyroidism	Serum TSH levels >10 micro IU/ml
Hepatotoxicity	Elevation of transaminases thrice the upper normal limit or/and bilirubin twice the upper normal limit*
Ocular	Visual changes suggestive of optic neuritis or loss of color vision confirmed by an ophthalmologist
Psychiatric	Presence of one or more of the following Depression, adjustment disorders, anxiety/psychosis suicidal tendencies as diagnosed by psychiatrist

*Normal range: AST (0 - 45 U/L); ALT (0 - 45 U/L); bilirubin (0.1 - 1 mg/dl); creatinine (0.6 - 1.2 mg/dl).

Table 2. Clinical and demographic data of MDR-TB patients.

Sex Ratio	
Male	402
Female	205
Age	
<30 yrs	231
>30 yrs	376
Weight	
<25 kgs	8
>25 kgs	599
Disease	
New (cat I-failure)	159
Re-Treatment (Cat II-failure)	448
Demography	
Urban	430
Rural	177

thralgia (14%), depression (13%), diarrhoea (8.6%), peripheral neuropathy (5.8%) and skin rash (4.3%). The least occurring were nephrotoxicity (0.5%) & ocular (0.2%) (**Table 3**). Although majority of the patients had an adverse drug reaction, only 1.7% stopped the treatment. Only 64 (10.5%) patients required permanent discontinuation of the offending drug from the regimen due to adverse drug reaction.

Most of the adverse drug reactions were managed on outpatient basis with symptomatic treatment. **Figure 1** shows the flow of treatment in the study population. Offending drugs were either reduced in dose or temporarily suspended. Re-introduction of the drug was generally attempted after improvement of symptoms.

3. Discussion

Adverse drug reactions during MDR-TB treatment reported by Indian studies varied from 57.14% to 94.3% [3]

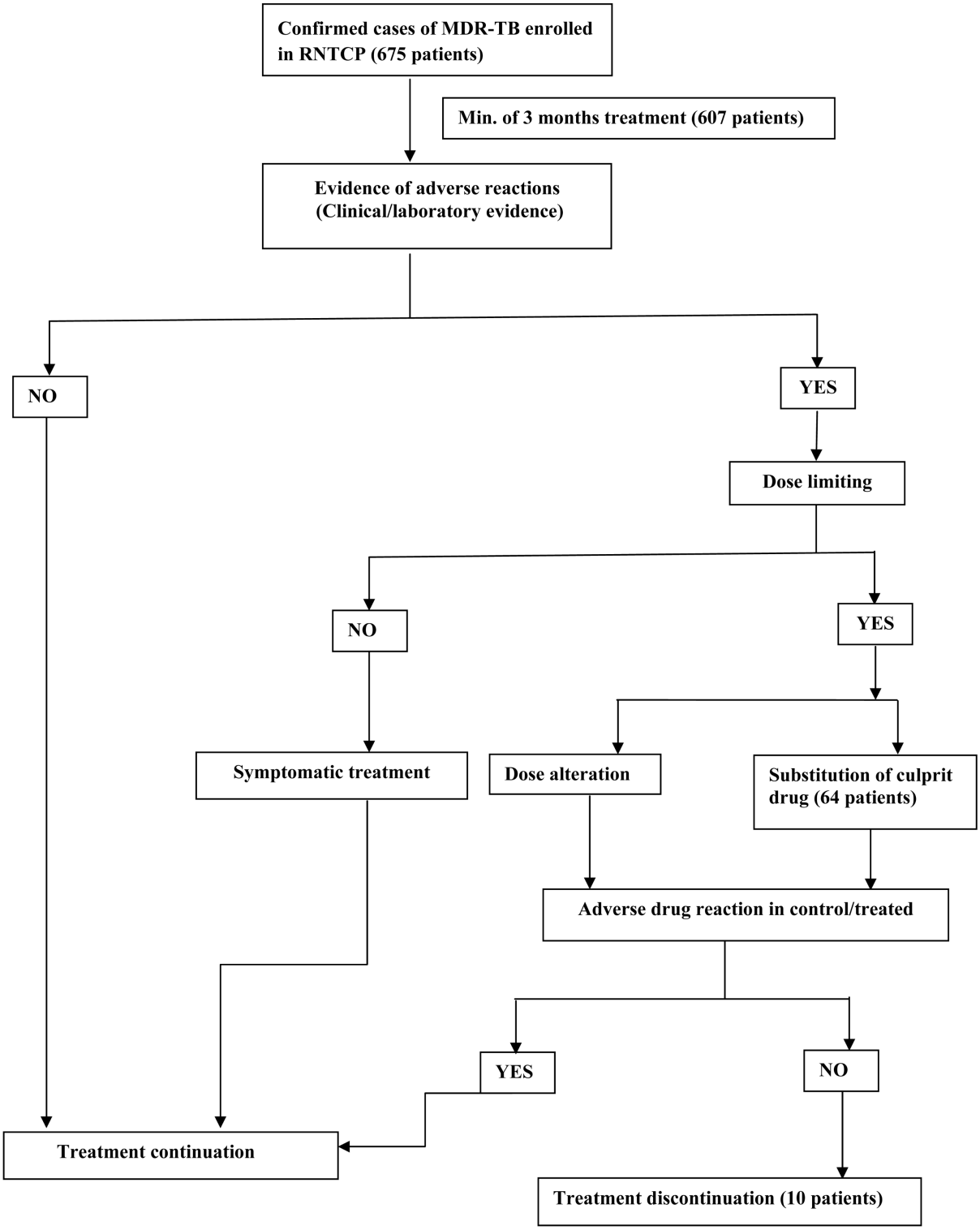

Figure 1. Treatment pattern in patients of MDR-TB.

[4]. In our cohort of 607 patients treated with standardised Cat IV regimen, majority experienced one or more adverse drug reactions.73.3% of 244 patients, consecutively enrolled into the DOTS-Plus program in Tomsk, Russia reported adverse drug reactions. Though the study involved individualised regimen, it generally included

Table 3. Frequency of adverse drug reactions.

Adverse reactions	No.	%
Gastrointestinal (nausea, vomiting, pain abdomen)	435	71.1
Nephrotoxicity	3	0.5
Hepatotoxicity	7	1.2
Hypothyroidism	19	3.1
Depression	78	13
Psychosis	10	1.6
Seizures	15	2.5
Oto-vestibular toxicity	18	3
Arthralgia	85	14
dermatologic	26	4.3
Neuropathy	35	5.8
Opthalmic	1	0.2
Diarrhoea	52	8.6

a parenteral aminoglycosides, PAS, thioamides & cycloserine [5].

Although majority of our cohort explained adverse drug reactions, only 1.7% discontinued the treatment. These findings are similar to the experience reported from five DOTS plus pilot projects, where only 2.1% stopped the treatment due to adverse drug reactions [7]. Other studies done in Tomsk, Russia &Lima, Peru reported that none of the patient required discontinuation of the entire treatment due to adverse reaction alone [5] [6].

But 10.5% of the patients required permanent discontinuation of the offending drug. This was comparable to study from Lima, Peru which reported 11.7% required discontinuation of offending drug [6]. But this was significantly less compared to other studies reporting 28.7% and 30% [5] [7] (**Table 4**).

Gastrointestinal adverse reactions were the commonest (71.7%) in our study which was similar to other studies reported in India & outside [3]-[7] (**Table 5**).

Depression was noted in 78 (13%) patients of our cohort which ranged from mild to severe suicidal tendencies. Other studies reported depression between 6.2% - 18.3% [5]-[7]. A study from Egypt showed that 26.5% MDR-TB patients had depression [8]. Cycloserine being the culprit drug was discontinued in few severe cases and in majority it was continued along with anti-depressant therapy. Socio-economic problems, chronicity of the disease may have added to depression in many cases.

Hypothyroidism was reported less frequently (3.1%) in our study. In comparison few studies reported hypothyroidism ranging from 10% - 39.5% [5] [6] [8]. In our study, as per the guidelines TSH was done at baseline and was repeated on clinical suspicion. The subtle symptoms of hypothyroidism may be either missed by the clinicians or attributed to unpleasant effect of drugs, so may be under-diagnosed. Also the other studies used combination of both PAS and thioamides as frequent drugs in the regimen as compared to our study where ethionamide was the only drug. PAS was used as a substitute drug, in our study for only the life threatening adverse drug reaction or an initial resistance to any second line drugs [5] [6] [8].

Ototoxicity, hepatotoxicity and nephrotoxicity were observed less frequently in our study. Nephrotoxicity was documented in only 0.5%, in spite of regular monitoring of serum creatinine levels every month during first 3 months and every 3 months thereafter till kanamycin was administered. Liver function tests were also frequently repeated in most of the patients who presented with GI disturbance/loss of appetite. Frequent monitoring for these potential adverse reactions, not only clinically but also by well-defined laboratory criteria, may be the reason for appropriate management and thus minimizing the life threatening impact of these.

Our study has certain limitations. It being a retrospective study, adverse drug reactions may be under-reported/over-reported, which is there may be documentation errors. Adverse reactions which lacked definite laboratory criteria were relied on physicians' documentation leading to reporting bias. Few adverse drug reactions

Table 4. Rate of complete cessation and discontinuation of offending drug.

	Tomsk, Russia [5]	DOTS Plus pilot projects [7]	Lima, Peru [6]	Present
Regimen type	Individualised	Individualised	Individualised	Standardised
Permanent discontinuation of offending drug	28.70%	30%	11.70%	10.50%
Complete stop of treatment	Nil	2.10%	Nil	2%

Table 5. Adverse drug reactions in different studies.

	Tomsk, Russia [5]	DOTS Plus pilot projects [7]	Lima, Peru [6]	Present Study
Study type	Retrospective	Retrospective	Retrospective	Retrospective
No of cohort	244	818	60	607
Adverse reactions				
	%	%	%	%
Gastrointestinal (nausea, vomiting, pain abdomen)	75.4	61.2	100	71.1
Nephrotoxicity	9.8	1.2	3.3	0.5
Hepatotoxicity	16.8	2.2	1.7	1.2
Hypothyroidism	17.2	3.5	10	3.1
Depression	8.6	6.2	18.3	13
Psychosis	11.9	3.4	10	1.6
Seizures	11.5	4	8.3	2.5
Oto-vestibular toxicity	15.6	12	6.7	3
Arthralgia	47.1	16.4	6.7	14
Dermatologic	16	4.6	43.3	4.3
Neuropathy	4.1	7.9	20	5.8
Opthalmic	_	4.4	_	0.2
Diarrhoea	46.3	21.1	_	8.6

may have been missed by the treating physician. Regular clinical monitoring of the patients as per programmatic guidelines was difficult in some non co-operative, non adherent cases. Some laboratory parameters like liver function tests and TSH were not repeated at regular intervals. They were done as and when required if clinician suspected symptoms.

4. Conclusion

MDR-TB treatment is a major challenge given the chronic nature of disease, long duration of treatment and multiple drugs used in the regimen. The wide spectrum of potential adverse drug reactions further escalates this challenge. As we could see in our study, though adverse drug reactions were frequently reported, majority continued the treatment with either supportive treatment or discontinuation of offending drugs. Non adherence to treatment due to any reason can negatively impact the treatment outcome. Prompt identification and management of adverse drug reactions holds the key to successful outcome. Under programmatic conditions, training of primary health care workers to detect adverse drug reactions, development of management protocols feasible at peripheral centres and prompt referral to higher centres if required, can have a major impact on treating the adverse reactions and hence the management of MDR-TB.

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