

Sharing Five Years Experience of Delivering DRTB Services from a Tertiary Care Setting- A Descriptive Study

Sunny George, Rajagopal TP, Annamma P C, PT James, Ravindran Chetambath

Department of Pulmonary Medicine, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala

ABSTRACT

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Background: The estimated global annual mortality from Tuberculosis (TB) is close to 2 million. Although management of TB has faced many challenges in the past, the emergence of multidrug resistant (MDR) and extremely drug resistant (XDR) tuberculosis has taken the role of adding oil to fire phenomenon jeopardising the efforts of a proper tuberculosis control programme. In a country like India where the prevalence of the disease as well as the population density are factors aiding the maintenance of a constant pool of Tuberculosis patients, Programmatic Management of Drug resistant Tuberculosis (PMDT) is projected as the only solution for managing MDR & XDR patients. Five years of our experience in dealing with these patients has been really rewarding. This paper aims to share the experience we had in managing these challenging cases which were a constant threat to the community.

Aim: To analyze the profile and management aspects of multidrug resistant and extremely drug resistant tuberculosis started on second line medications from the DOTs plus site at Kozhikode Government Medical College over a period of five years.

Methodology: The study was a descriptive analysis conducted in the Department of Pulmonary Medicine in 512 MDR-TB patients and 24 XDR patients enrolled under DOTs Plus programme during the period between February 2009 and June 2014 and analysing the profile and management aspects of patient care under the Drug resistant TB (DRTB) services offered from our DOTs plus site to patients coming from the northern seven districts of Kerala.

Results: The pattern of patient inflow from all the northern districts was uniform except Wynad and Lakshadweep where the total population is much lower than the other districts. Males accounted for 78.9% cases registered. There were 34% cases of diabetics amongst the MDR-TB patients. Only 1.8% cases had co existent HIV infection. 56.4% cases belonged to the more than 45 kg weight band. Only 1.6% cases had proven extra pulmonary MDR TB. 5.7% cases registered had definite contact history. 41.4% cases amongst the contact positive group belonged to the category of health care worker. The success rates in outcomes were to the tune of 64.2% and no patients waiting for treatment initiation after instituting decentralisation of DRTB services which is a first time initiative at the Kozhikode DRTB site and the results are well in accordance with international standards of care in managing MDR-Tuberculosis.

Conclusion: This study showed that despite implementing DOTs programme throughout the state, there was a uniform rate of emergence noted in the number of multi drug resistant tuberculosis. There were a high proportion of diabetics among these patients and pulmonary form of drug resistance was much more common than extra pulmonary. In a properly functioning DRTB centre decentralising the services to its peripheral centres has not compromised in the standards of care as evidenced by the success rate reported. However 5.3% cases developed XDR-TB which poses a major threat to the community as well as the policy makers as we are not left with newer potent molecules to curtail this menace.

Keywords: "MDR-TB" (multi drug resistant tuberculosis); XDR-TB (extensively drug resistant "PMDT" (Programmatic management of Drug resistant Tuberculosis; "DOTs Plus"; "DRTB (Drug resistant tuberculosis) centre", "Kozhikode model".

*See End Note for complete author details

INTRODUCTION

Programmatic management of drug resistance (PMDT) has given definite guidelines for pre-treatment evaluation and initiation of second line medications to MDR & XDR TB patients. Worldwide the reported proportion of MDR-TB was 3.5% among new cases in 2013. Kerala being a linear strip of land along the

Arabian coast with 14 districts and estimated 32 million population, DOTs plus services were instituted for the southern 7 districts with the DOTs plus site at Thiruvananthapuram in December 2008. The northern 7 districts have their DOTs plus site located at Kozhikode which started functioning in February 2009. Five years of experience in managing these patients gave us insights in to the practical problems faced at the field

Corresponding Author:

Dr. Sunny George, Associate Professor, Department of Pulmonary Medicine, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala, India-673008. Phone: 09847283847, Email: sunsuna1@gmail.com

level which could very well be tackled by appropriate and timely modifications in the current guidelines. To adopt these proposed modifications, as policy changes, there should be proper evidences or clues towards the trends in the disease pattern.

RNTCP always had room for operational research and allowed subsequent strategic modification in the programme to adapt to the prevailing health system of the particular geographic area. Hence this paper is aimed to bring out the various trends noted while managing this dreaded disease with the operational modifications in place applied to the current PMDT guidelines with the intention of offering better care to these patients.

MATERIAL AND METHODS

Aim of the Study

This paper is aimed to analyse the various trends noted while managing this dreaded disease and the effect of operational modifications applied to the current PMDT guidelines with the intention of offering better care to these patients. This could be of benefit to the policy makers in adopting patient and community friendly modifications to the existing guidelines.

Study Methodology

Design: Observational study

Setting: DRTB centre, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala, India.

Interval: February 2009 - June 2014

Protocol

Inclusion criteria

All patients who got enrolled for the CAT-IV regime as per RNTCP for multidrug resistant tuberculosis in this DRTB centre between February 2009 - June 2014 were included in the study group. None were excluded.

Study Proper

Patient data was recorded in structured format that included the demographic data, co morbidities, contact history and other relevant details including HIV screening from a VCTC. Most of the Medical officers working in District Tuberculosis centers and peripheral health centers coming under the DRTB centre were either Chest specialists or those who have had proper DOTs Plus training. Hence arranging for a pre-treatment evaluation as per the novel idea of decentralizing

DRTB services could be an operational modification which could avoid a lot of diagnosed patients waiting in the periphery for treatment initiation as well as limit the unnecessary travel of the patient from faraway place to the DRTB centre in a public conveyance system just for the sake of treatment initiation. The check list for investigations should include, blood routine, urine routine, Chest X-ray PA view, LFT, RFT, FBS/PPBS, HbA₁C (optional), TFT, ECG, uric acid (Optional), Pregnancy test in females in the reproductive age group. As per operational modification adopted, after decentralization of DRTB services, all these data are made available to the DRTB centre utilising the internet services. The Chest X-ray could be sent either via courier (preferably) or as photo images. Accordingly decisions were taken by the DRTB site on treatment initiation for patients from periphery who were not sick enough to warrant an admission and in those patients in whom the pre treatment evaluation were acceptable. All the patients who were diagnosed as multidrug resistant tuberculosis based on the culture report provided from the Intermediate reference laboratory (IRL) at Thiruvananthapuram was started on a standardised weight based regime, category IV, which included six months of intensive phase involving six drugs which comprised of Kanamycin, Ofloxacin which later was replaced by Levofloxacin, Ethionamide, Cycloserine, Ethambutol and Pyrazinamide. The intensive phase could be extended up to 9 months for culture conversion. This was followed by four drugs excluding kanamycin and pyrazinamide for the next 18 -27 months till the last five consecutive cultures becomes negative to declare the patient as cured. The recommended follow up investigations were performed as per protocol. Recording and reporting of the data was done on a regular basis with separate quarterly reports on the success of the programme was performed as per PMDT guidelines. We analysed the data available to us on 20.06.2014 and trends in the various aspects of management of these patients were picked up.

OBSERVATIONS

There were a total of 512 patients enrolled in CAT-IV regime during the period Feb 2009 to June 2014 who was referred from the seven respective northern District TB centre's of Kerala. Initially all the patients were started on medications after admitting for a period of seven days as per the PMDT guidelines which created a major backlog of patients at the periphery and many of these patients expired even before treatment could be started. This was identified as due to the space constraints for admitting all these patients, which was mandatory, as

per guidelines. However as an operational modification it was decided to start these patients on CAT-IV regime from the periphery if they were not too sick or if their pre-treatment evaluation didn't reveal any major abnormality requiring further expert evaluation from the DRTB centre. This strategy which we referred as the, "Kozhikode Model" was made possible with the expertise of the properly trained medical officers at the peripheral health centre who could contact the DRTB centre utilising the internet as a virtual consultancy medium for directions in treatment initiation and to pick up and refer any major adverse events related to treatment for admission and expert care at the DRTB centre at any point of time. This strategy drastically reduced the unnecessary delay in starting treatment for patient diagnosed with MDR-TB and was hence a community and resource friendly modification. This idea was appreciated by the scientific community from India and abroad alike and was selected as one of the community preventive strategy for excellence in health care by the British Medical Journal Awards-India for 2014.⁸

TB Centre	No of patients
Kasargode	69
Kannur	82
Kozhikode	91
Wyanad	8
Malappuram	75
Palakkad	76
Thrissur	109
Lakshadweep	2
Total	512

It was observed that all the districts had a uniform pattern of referral to the DRTB centre in the descending order of number of patients coming from Trichur, Kozhikode, Kannur, Palakkad, Malappuram, Kasargode (Table 1). Wyanad and Lakshadweep,

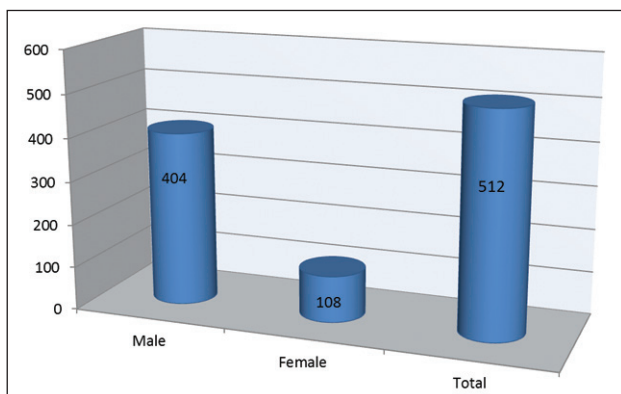


Figure 1. Gender profile

TB Centre	Population	Per lakh population
Kasargode	13,00,000	5.3
Kannur	25,00,000	3.7
Thrissur	32,00,000	3.6
Kozhikode	31,00,000	3.3
Lakshadweep	65,000	3.1
Palakkad	28,00,000	3
Malappuram	41,00,000	1.9
Wyanad	8,00,000	1.4

owing to the low population as compared to the other districts reported only very few numbers of MDR TB cases but could be significant if compared on a case per lakh population basis (Table 2). The order of frequency changed and Kasargode, Kannur and Thrissur topped the charts which should invite a more rigorous evaluation of proper DOTs services in these districts as the potential for community transmission in these

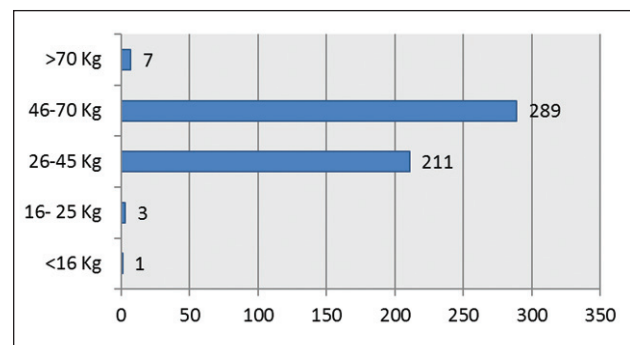


Figure 2. Weight band of patients

places are definitely more than the rest of the places.

Males predominated the group with the M: F ratio being 2.7:1 which means males are about three times more at risk of developing the disease as compared to their female counterparts (Figure 1). The prevalence among males warrants undertaking more research towards possible specific male oriented risk factor evaluation including social behaviour, travel, more chance for community exposure to open cases related to occupation, smoking, alcoholism, drug abuse etc which may often be otherwise overlooked. When the weight band of these patients was analysed, it was seen that 57.8% patients belonged to the >45 Kg wt band group, a similar observation, which was also reported earlier amongst the MDR-TB patients of Kerala by Sanjeev Nair et al in the journal Pulmon in 2009.⁶ (Figure 2).

One of the alarming situations which put the policy makers as well as the health care workers at unease is the occurrence of a sizeable number of contacts

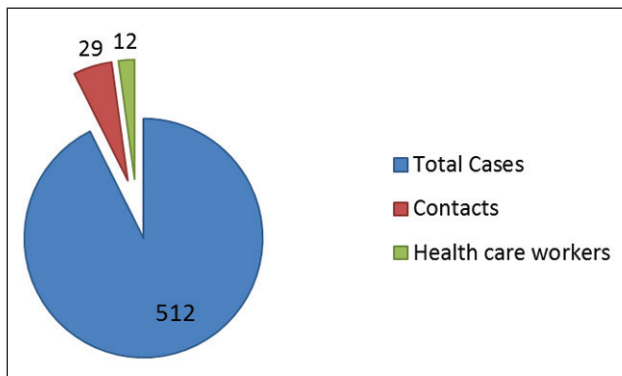


Figure 3. MDR among contacts

developing this dreaded disease. A total of 5.7% (29/512) cases among our series turned out to be contacts of current or previously treated MDR TB cases. Of these 41.4% (12/29) cases turned out to be health care workers which calls for greater stress for proper use of personal protection equipments (PPE) while doing aerosol generating procedures or closely interacting with the patients. PMDT provides generous supply of disposable PPE as well as N-95 masks for

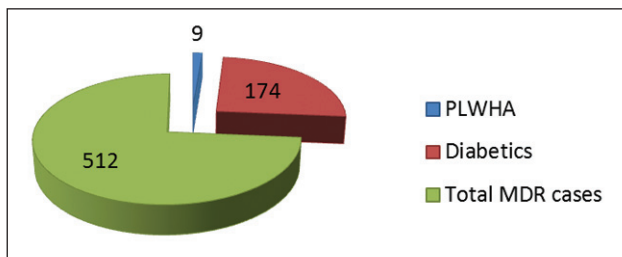


Figure 4. Diabetes and HIV amongst MDR TB cases

the prevention of health care based transmission of this disease.

The author has observed an increasing trend of Diabetic patients amongst the MDR-TB patients getting enrolled for CAT-IV regime as early as 2011.⁹ Kerala being projected as the diabetic capital of the country has reported about 17% prevalence of diabetes amongst the general population. It was seen that 34 %

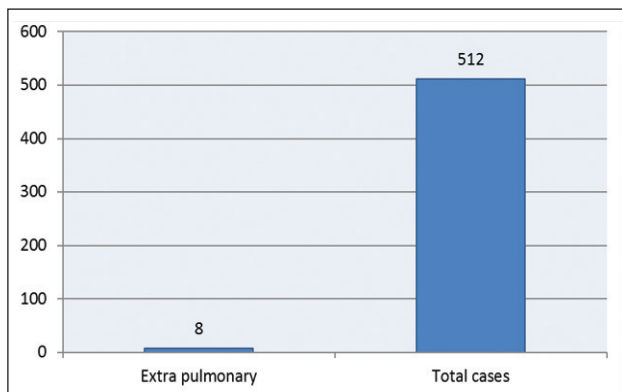


Figure 5. Extra pulmonary MDR TB Cases

cases of MDR TB patients were diabetics which means double the prevalence reported in general population. This proposes diabetes as a significant co-morbid risk factor contributing to the emergence of more and more drug resistant cases. Interestingly, it was noted that only 1.8% cases had co existent HIV infection making it a less likely contributory risk factor as against what was reported in the early 1990's, when HIV was observed as a strong risk for acquiring drug resistant tuberculosis and resulted in very high mortality rates as compared to those without HIV residing in a closed community.^{2,3}

Only 1.6% cases (8/512) were diagnosed to have extra pulmonary MDR tuberculosis. (Figure 5)

Adverse reactions (ADR)	Number of patients	Percentage	Admission
Gastritis	44	8.5%	none
Arthralgia	33	6.4%	none
Auditory disturbance	30	5.9%	none
Psychiatric disturbance	21	4.1%	9
Renal derangement	19	3.7%	12
Hypothyroidism	7	1.4%	none
Neurological ADR	5	0.97%	5
Liver dysfunction	3	0.6%	1
Dermatology	2	0.39%	2
Ophthalmic ADR	1	0.19%	none
Total recorded ADR	165/512	32.2%	17.6% (29/165)

The major concern about the implementation of any programme handling the reserve drugs for drug resistant tuberculosis is the possible adverse drug reactions (ADR) one has to anticipate and tackle in a timely manner. It was noted that there were 165 events reported during the study period which required an intervention either in the form of dose modification, temporary cessation and specific management of the adverse events as in arthralgia related to hyperuricemia. The most frequently reported adverse event was gastrointestinal side effects like gastritis, belching, vomiting and abdominal bloating. These could easily be managed with symptomatic measures and reassurance (Table 3). It was quite interesting to note that the common side effects associated with first line medications like hepatitis and dermatological side effects were much less with these drugs. However those few patients who developed dermatological as well as neurological side effects had severe ADR in the form of crippling peripheral neuropathy despite high doses of pyridoxine and exuberant seborrheic dermatitis for which culprit drug could not be recognised as stopping the drugs and challenging the drugs one by one was not possible as these patients were otherwise stable and continued

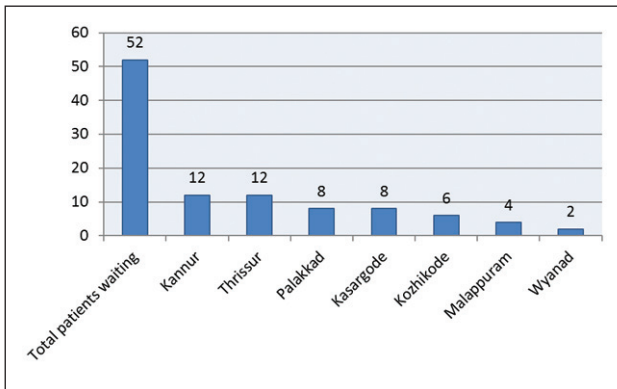


Figure 6. Technical pit fall

to be culture positive. Only 17.6 % cases of reported adverse reactions required admission for management of the same and all the rest could be managed from the periphery in a successful manner.

PMDT guidelines recommend one week admission for all diagnosed cases of MDR TB at the DRTB centre for pre treatment evaluation and initiation of CAT-IV regime. This caused considerable delay in initiating medications for large number of diagnosed patients waiting for their turn as there were only limited inpatient facilities at the DRTB centre (Figure 5). This was viewed by the DRTB centre committee as a technical pit fall as there were mortality amongst the diagnosed patients even before they could be started on CAT-IV. Hence decentralisation of DRTB centre services was proposed as an operational modification to the existing properly functioning programme which was designated as the, “Kozhikode model” and it basically involved three stages, initial stage comprised of giving regular and proper PMDT training to the medical officers under each District TB centres followed by the next stage of ensuring web based transmission of pre treatment evaluation data of each patients to the DRTB centre as and when it is available and the last stage of virtual consultancy in segregating those patients who were otherwise healthy and had no contraindication for starting medication from the periphery. The Pre treatment Chest X-ray was sent as a courier to the DRTB centre for evaluation and archiving. Thus following decentralisation it was observed that there were no diagnosed patients waiting without being initiated on treatment which was due to the successful mitigation of any technical time delay that might have prevailed earlier in the system while PMDT guidelines were strictly followed.

Kozhikode model proved to be a logical solution for mitigating the delay in CAT-IV enrolment as well as in its unique role in serving as a community and patient friendly strategy, minimizing unnecessary long distance

travel of these patients utilizing the public transport system (Figure 6). However this model should only be attempted in a properly functioning DRTB centre as per the PMDT guideline so that there are no dilutions of the existing policies or compromise in standards of patient care at any point of time. It was however observed that only a minority of patients were really sick at the time of treatment initiation that required inpatient care or specialist consultations. However all the adverse drug reactions which could not be managed from the periphery and patients at the end of treatment had to attend the DRTB centre.

When the outcome status of these patients was evaluated it was seen that the overall success rate was 64.2% (79 + 34 / 176). The success rate attained at our DRTB centre was at par with published data on MDR TB treatment success by WHO. (Figure7)

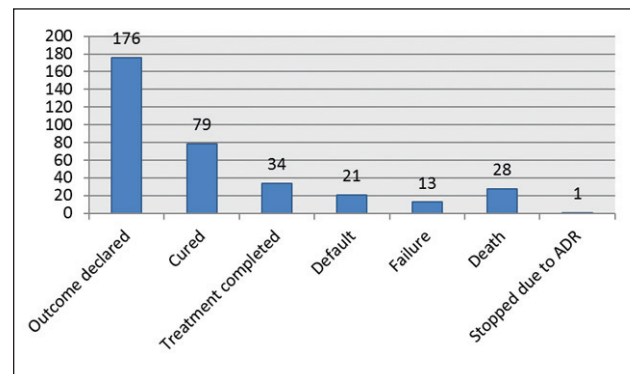


Figure 7. Outcome status

One of the growing issues of concern was the emergence of substantial numbers of XDR-TB cases (27 patients), who are INH and Rifampicin resistant strain developing resistance to any quinolone and resistance to one of the injectable amino glycosides Kanamycin, Amikacin or Capreomycin as per the WHO task force definition laid down in October 2006 (Figure 8). The treatment of XDR TB is even more complex involving several drugs and extended duration as compared to CAT-IV. The drugs coming

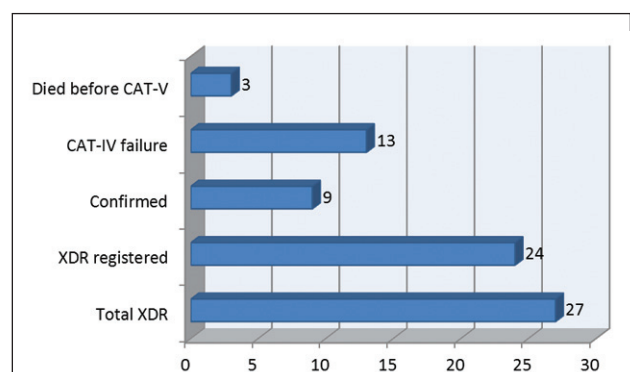


Figure 8. XDR statistics

under CAT-V (treatment for XDR TB) include moxifloxacin, clofazimine, linezolid amoxycillin clavulanate, capreomycin, PAS and high dose INH for initial 6-12 months and continuation phase for 18 months without capreomycin. Clarithromycin and Thiacetazone are kept as substitute drugs for any of the second line drug which may be withdrawn in case of a serious adverse event or intolerance.

DISCUSSION

In 2010, WHO estimated that there were globally 290,000 cases of MDR-TB among those cases of reported pulmonary TB. It was also estimated that in total there were 650,000 cases of MDR TB among the 12 million prevalent cases of TB. In 2012, new TB cases were 8.6 million and the mortality was 15.1%. Whereas there were about 0.45 million new cases of MDR TB cases reported during this year and the mortality rose to the tune of 37.8% and the death toll reported for XDR TB is even worse. Globally in 2013, there were an estimated 480 000 (range: 350 000–610 000) new cases of MDR-TB. There were approximately 210 000 (range: 130 000-290 000) deaths (43.8%) from MDR-TB in 2013.¹

Though tuberculosis management was effectively functioning under the Revised National Tuberculosis Control Programme (RNTCP) throughout the country for last several years, the growing concern amongst the policy makers, programme managers as well as the treating physicians were the existence of a large number of MDR TB cases with increasing mortality trends and a considerable proportion of emerging XDR TB cases.

To tackle this problem RNTCP has adopted a standardized regimen (CAT IV) based on the drug resistance surveillance pattern reported for our country and devising specialized centers, designated as DRTB centers, for monitoring the pre treatment evaluation, drug initiation and management of sick as well as those patients requiring specific measures for adverse event management or dose modification during the course of the disease. Due to the wide variation in factors like social, cultural, economic and geographic peculiarities which are unique to each country, along with differing literacy rates, varying levels of health awareness among public and non uniformity of health care facility existent in different states of the country, delivering standard regime for MDR & XDR TB case obviously face several challenges. Hence operational modifications acceptable to the prevailing health care delivery system utilizing the available resources in a community and patient friendly manner is of utmost importance

for the success of the programme.

Our intention for performing this analysis was to evaluate our DRTB centre performance as well as to pick up any specific trends noted amongst our patients and to share our experience in managing these patients over the last five years. We found that though there were uniform referrals of cases from all the districts except those places like Wyanad and Lakshwadeep which have less population as compared to other districts. However when patients per population of districts number of MDR TB were taken in to account it was seen that most of the districts had 3 or more patients per lakh population. This calls for rigorous scrutiny of basic DOTs activities in these districts.

Approximately three out of every four MDR TB patient being a male, puts male gender as an unexplored risk factor for the emergence of MDR TB or on the contrary poses the question whether there are female specific protective factors against MDR TB as opposed to males. If either of these exists then there could be a modifiable element which could retard the rate of occurrence of this disease. Undernutrition has been projected as a major causal factor for the high burden of tuberculosis in the underprivileged regions like some of the African and Asian countries.⁴ Researchers like Anurag bhargava et al have stressed on providing proper nutritious diet along with anti tuberculous medication for bringing down the prevalence of the disease in the country.⁵ In our series we found that 58% of our patients belonged to >45 Kg weight band and whether the nutritional aspects have a pivotal role in the development of MDR tuberculosis is a questionable issue. However beyond body mass index, immunomodulatory elements like Vit.D3, the levels of which were estimated to be extremely low in those with active tuberculosis, as suggested by researchers like PK Sasidharan et al recommends Vit. D3 fortified food for effective prevention of this disease.⁷ Whether this holds good in established MDR TB cases in aiding better sputum conversion and cure requires well structured randomized controlled trials.

Around 6% cases turned out to be contacts of MDR TB and about 42% of those developing MDR TB amongst the contact positive groups were unfortunately health care workers.¹⁰ Hence stress should be laid on proper cough etiquette, sputum disposal, judicious use of personal protection equipments and social distancing by proper counselling of the patients and family members rather than creating fear and stigma which will otherwise hinder the smooth functioning of the DOTs Plus programme. There should be policy

decisions regarding protecting the interests and gaining the confidence of those unfortunate health care workers who develop the disease during the course of their job by granting incentives and paid leave during the treatment period till they are culture negative and in a position to resume their routine work.

A high proportion of diabetic patients developed MDR TB, a trend reported by the author in 2011 about two years after starting the DRTB centre services at Kozhikode and the reported occurrence was an alarming 41%. This was thought to be an improperly addressed crucial risk factor for the development of MDR TB in patients already on DOTs and there has been a policy decision to incorporate diabetic control along with TB care by offering medications free of cost to these patients. Currently the percentage though still high has shown a decreasing trend as evidenced by the current level of 34% which is much higher than the prevalence of diabetes in Kerala which is reported to be 17%. Fortunately, only less than 2% of cases were either co infected with HIV or had extra pulmonary MDR TB making situations much more manageable as per the programme conditions.

The major concern in starting a complex regime for MDR & XDR TB, especially from the periphery is the possible occurrence of adverse reactions and their timely management. It was observed that though around one third patients developed adverse reactions to the drugs, only 17.5% cases required admission to the DRTB centre, all the rest could be managed from the periphery. Surprisingly the side effect profile was slightly different from what was usually observed with first line anti tuberculous medications. Here hepatic dysfunction and skin reactions were extremely rare. It was noted that apart from easily manageable side effects like gastritis others adverse events like, hyperuricaemia related arthralgia, auditory disturbance, psychiatric disturbance, renal dysfunction and hypothyroidism were amongst the major adverse drug reactions reported in the decreasing order of frequency. Psychiatric illness, neurological side effects, renal and hepatic derangements required admission to the DRTB site for proper management. The proportion of cases requiring admission to DRTB centre was only about one fifth of total adverse events reported which means that a major share of adverse events could be effectively managed from the local health care facility under guidance of DRTB centre utilising the Kozhikode model.

The Kozhikode model was started as a trial process to circumvent the technical delay observed in initiating treatment for diagnosed cases of MDR TB due to

limited inpatient care facilities at the isolation ward of DRTB centre. This operational modification proved itself as a breakthrough novel concept in preventive health care strategy in MDR/XDR TB management and came to be known as the, "Kozhikode Model". This is under consideration of the central TB division of India to be adapted as a policy change in PMDT guidelines on a nationwide basis. This model is a web based virtual consultancy from the DRTB centre to its feeding District TB centres. The web space being impermeable to the dreaded bacilli limits the spread of the disease by avoiding travel of those patients who are otherwise healthy and when given a choice, prefers initiation of medications from a place nearer to their residence. The experts at the periphery were given national level training in PMDT. WHO recommends that, wherever possible, patients with MDR-TB should be treated in ambulatory or community based settings rather than relying upon hospital-based models of care.^{11,12}

Dedicated team effort and specific roles played by the field staff, data entry operators, expert microbiologists at the Intermediate Reference Laboratory (IRL), other trained laboratory staff, trained medical officers at peripheral health centres as well as at the DRTB centre, efficient District TB officers, experts from all major medical specialties incorporated in to the DOTs Plus core committee for adverse event management, Nodal officer, Pulmonology experts at the DRTB centre committee, DRTB centre chair person, WHO consultants and the State TB officer together join hand in hand in easing out the complex treatment strategy of DOTs plus in to a much simpler patient friendly format. Still, extensively drug-resistant TB (XDR-TB) has been already reported by 100 countries. On an average, 9.0% (95% CI: 6.5–11.5%) of people with MDR-TB have XDR-TB. Despite all organised efforts, there are emerging cases of XDR and even TDR (Total drug resistance) which poses a major threat to the smooth and successful functioning of TB control endeavours of the country.

CONCLUSION

Five years of our experience at the DRTB centre in managing MDR TB cases showed specific trends in terms of gender, diabetic status, body weight and general health status of a major group of patients at the time of treatment initiation which lead on to the novel idea of decentralised management in appropriate cases and avoiding unnecessary technical delay in starting the treatment of already diagnosed cases. Stress has to be laid in creating proper awareness in

patients and ensuring proper cough etiquette which will definitely go a long way in minimising the spread of the disease among contacts, especially health care workers. Though the second line drugs are potentially toxic, proper follow up at the periphery as per guidelines will help the clinician to judiciously manage these cases and restricting admissions to the really indicated ones. In our study only 17.5% cases of total adverse events reported required admission, which is a resource friendly approach. Observing these trends will surely open up newer avenues for research as well as give us the courage to effectively decentralise the DRTB services in a phased manner throughout the country.

END NOTE

Author Information

1. Dr. Sunny George, Associate Professor, Department of Pulmonary Medicine, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala
2. Dr. Rajagopal T P, Professor, Department of Pulmonary Medicine, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala
3. Dr. Annamma P C, Medical officer, Department of Pulmonary Medicine, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala
4. Dr. P T James, Professor, Department of Pulmonary Medicine, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala
5. Dr. Ravindran Chetambath, Professor, Department of Pulmonary Medicine, Institute of Chest Diseases, Government Medical College, Kozhikode, Kerala

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Mrs. Anju K, Data entry operator, DRTB Center, Kozhikode; Mr. Rajamurali.K.P, TB Health Visitor, DRTB center, Kozhikode.

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