THE AGA KHAN UNIVERSITY

eCommons@AKU

Section of Pulmonary & Critical Care

Department of Medicine

July 2011

Treatment Outcome of Multi-Drug Resistant Tuberculosis Treated As Outpatient in a Tertiary Care Center

Zeeshan Waheed
Aga Khan University

Muhammad Irfan
Aga Khan University

Ahmed Suleman Haque
Aga Khan University

Muhammad Owais Khan
Aga Khan University

Atif Zubairi
Aga Khan University

See next page for additional authors

Follow this and additional works at: http://ecommons.aku.edu/pakistan_fhs_mc_med_pulm_critcare

 Part of the Critical Care Commons, and the Respiratory Tract Diseases Commons

Recommended Citation

Waheed, Z., Irfan, M., Haque, A. S., Khan, M. O., Zubairi, A., Ain, N., Khan, J. A. (2011). Treatment Outcome of Multi-Drug Resistant Tuberculosis Treated As Outpatient in a Tertiary Care Center. *Pakistan Journal of Chest Medicine, 17*(3).
Available at: http://ecommons.aku.edu/pakistan_fhs_mc_med_pulm_critcare/31

Authors
Zeeshan Waheed, Muhammad Irfan, Ahmed Suleman Haque, Muhammad Owais Khan, Atif Zubairi, Noor ul Ain, and Javaid A. Khan

This article is available at eCommons@AKU: http://ecommons.aku.edu/pakistan_fhs_mc_med_pulm_critcare/31

Original Article

Treatment Outcome of Multi-Drug Resistant Tuberculosis Treated As Outpatient in a Tertiary Care Center

Zeeshan Waheed, Muhammad Irfan, Ahmed Suleman Haque, Muhammad Owais Khan, Atif Zubairi, Noor ul Ain, Javaid A Khan*

ABSTRACT

INTRODUCTION: Community-based out-patient treatment for multidrug-resistant tuberculosis (MDR TB) is relatively new concept with reported successful outcomes.

OBJECTIVE: To assess the treatment outcomes of HIV negative multidrug-resistant tuberculosis (MDR TB) patients treated as outpatient at a tertiary care center in Karachi, Pakistan.

METHODS: A retrospective observational study of 53 consecutive, culture proven HIV negative MDR TB patients (resistant at least to both Isoniazid (H) and Rifampin(R) treated at Aga Khan University Hospital, Karachi between August 1999 and March 2007. Data were collected on predesigned performa regarding patient's demography, clinical features, radiological findings, drug sensitivity, treatment and outcome.

RESULTS: A total of 53 HIV negative patients (27 males), with mean age of 37±15 years (range 15-76 years), received treatment as outpatient for culture proven MDR TB. 51 patients (96.2%) had pulmonary while 3 patients (5.6%) had extra-pulmonary TB. History of exposure to tuberculosis patients was found in 36 (67.9%) patients. Treatment regimen with 2nd line drugs was decided on individual basis according to DST on sputum culture results. The mean duration of treatment was 18 months. Successful outcome was seen in 25 patients (47.2%), 25 patients (47.2%) were loss to follow up and defaulted while 3 (5.6%) patients remain smear positive at the end of treatment. Success rate was 89 .2% in those who completed the treatment.

CONCLUSION: Community-based out-patient treatment strategy is both feasible and safe for the treatment of MDR-TB patients in resource limited country like Pakistan and this strategy should be integrated into the routine approach to treatment of MDR-TB patients in the country where the expertise are available. High default rate is this strategy is the main challenge which should be addressed.

**Section of Pulmonary & Critical Care Medicine, Department of Medicine, The Aga Khan University Hospital, Karachi-74800, Pakistan*

INTRODUCTION:

Multi drug resistant Tuberculosis (MDR TB) is a growing problem around the world especially in countries where the prevalence of TB is high. Ever since the start of chemotherapy for tuberculosis, drug resistance has kept on increasing[1]. There are various different factors which play a role in the development of tuberculous drug resistance. Among them, the significant contributors include poor patient compliance, incorrect dosing and time duration of drug treatment[2]. Tuberculous organisms that achieve resistance preserve their infectivity better and have thus increased chances of survival[3]. MDR TB is more difficult to manage and costs more than its regular drug sensitive counterpart[4].

MDR-TB is an increasing health problem in Pakistan. According to World Health Organization (WHO) [5], the estimated cases of MDR tuberculosis in Pakistan are 3.4% and 36% in new and previously treated cases of tuberculosis respectively. Globally, Pakistan is ranked 8th in terms of estimated number of tuberculosis (TB) cases, with an incidence of 181/100,000 persons.[5]

Treatment of MDR-TB is resource intensive and lasts for 24 months or more, requiring a combination of second-line drugs that are more expensive, less effective and more toxic than those used in standard first-line treatment regimens [6, 7]. The cure including response rate of MDR-TB without human immunodeficiency virus (HIV) infection using individual tailored regimens was reported from 39% to 96 % in initially hospitalized patients.[8-11]

The rationale for initial hospitalization has been to monitor complex drug regimens, optimize adherence and limit community transmission. However, there is no evidence that hospitalization actually limits community transmission.[12] in fact the risk of nosocomial transmission, both to other patients and to health care workers becomes high.[13-15] There are also economic and social costs involved in keeping patients isolated in hospitals, often far from home, and this can lead to default from treatment programmes.[16]

Community-based treatment for MDR TB is not a new concept, and successful outcomes have been reported from Peru, [17] Korea [18] and Nepal.[19]

The present study is a retrospective cohort analysis of individualized treatment outcomes of MDR TB cases treated in out-patient chest clinic at Aga Khan University hospital, Karachi Pakistan.

METHODS:

This is an observational study which includes 53 consecutive patients of MDR T.B. All cases were culture proven and resistant at least to both Isoniazid (H) and Rifampin(R). All cases were HIV infection negative and treated at the outpatient chest clinic of Aga Khan University Hospital, Karachi between the duration of August 1999 and March 2007. Data was collected on predesigned structured Performa regarding patient's demography, clinical features, past medical history, radiological findings, drug sensitivity, Duration, type and effects of treatment and outcome.

Drug susceptibility testing (DST) and drugs that had not been used in the past guided the therapy. The sputum cultures and susceptibility testing were done at Aga Khan Laboratory (AKL). AKL is the recognized laboratory for AFB culture in Pakistan. We administered minimum five drugs (range 5 to 7 drugs; median 5 drugs) during the intensive phase including one injectable aminoglycoside (mostly Kanamycin) and Quinolone (Ofloxacin and levofloxacin in most of the patients) from the 2^{nd} line and also include the sensitive drug if any from the first line according to the sensitivity results on individual basis. During the continuation phase we used 3 to 4 oral drugs according to the sensitivity from the first and 2^{nd} line drugs. In total, 20 tailored regimens with different drug combinations were prescribed according DST results.

Patients were followed in outpatient chest clinic initially fortnightly during first month and then monthly. The patients were evaluated on each visit for clinical, microbiological and radiological response regularly. They were also evaluated for side effects of the medications. They were followed by sputum microscopy and chest X-ray every three-month. Treatment was completed when the chemotherapy regimen had been taken for more than 18 months, usually 24 months for those who had attained negative sputum cultures toward the end of treatment.

Outcome definitions

We used the MDR TB treatment outcome definitions as follows:

Successful outcome: Patient who completed treatment and consistently had negative smear **Treatment default:** Patients who did not receive treatment for $\geq$ 2 consecutive months were defined as having defaulted treatment.

Treatment failure: Patients whose smear was positive at the end of six month or whose

$\geq$ 2 smears were positive during final 12 months.

Death: Patients who died due to any cause during treatment.

Statistical analysis:

The statistical package for social science SPSS (Release 16, standard version, copyright © SPSS) was used to analyze the data. The descriptive analysis was done for demographic, clinical and laboratory data. The results are presented as mean with standard deviation (SD) and numbers (percentages).

RESULTS:

A total of 53 HIV negative patients were treated for culture proven MDR TB as outpatient during study period out of which 27 (51.9%) patients were male and 26 (49.1%) were female; with mean age of 37±15 years (range 15-76 years). Their base line characteristics are presented in Table I.

Fifty one patients (96.2%) had pulmonary while 3 patients (5.6%) had extra-pulmonary TB. 5 (9.4%) had primary MDR TB while 48 (90.6%) had secondary MDR TB. History of exposure to tuberculosis patients was found in 36 (67.9%) patients. 37 (69.8%) patients had a history of taking two or more courses of antitubeculous treatment (ATT).

All the patients were resistant to both Isoniazid (H) and Rifampicin (R). Resistance against Pyrazinamide (Z) was highest (77.4%) among the other first line drugs followed by ethambutol and streptomycin. Drug resistant pattern against the first and second line drugs are presented in Table II. Treatment regimen with 2^{nd} line drugs was decided on individual basis according to DST and previous history of drugs usage. The mean duration of treatment was 18 months.

Successful outcome was seen in 25 patients (47.2%). 25 patients (47.2%) were loss to follow up and defaulted. 3 (5.6%) patients remain smear positive at the end of treatment. No death occurs in patients who continue treatments and we do not know the outcome of defaulted patients. Patients came to our clinic from all over the country as our hospital is the one of the best tertiary care hospital of the country. We tried to contact defaulted patients whom phone number was available. We were unsuccessful in most of the cases due either their phone number was incorrect or the patient deliberately did not attend the call. Due to non-availability of physical facilities for follow up of defaulted patients we could not traced the defaulters.

Twenty eighty (52.8%) developed some side effects due to medications. They were mainly minor and managed accordingly. Among the minor side effects gastro-Intestinal symptoms (like nausea, vomiting, constipation) were the most common side effects seen in 22 patients (41.5%) followed by drug induced hepatitis, neuropathy, arthralgias

and depression. 2 (3.8%) developed ototoxicity, 2 (3.8%) optic neuritis and 1(1.9%) developed seizures that require discontinuation of responsible drugs.

DISCUSSION:

It is estimated 390 000–510 000 cases of MDRTB emerged globally (best estimate, 440 000 cases).[20] Pakistan ranks eighth among the list of 22 high TB burden countries with a TB related death rate of 43/100,000 population annually.[21] The growth of the drug-resistant TB epidemic in Pakistan is presented as challenges for the National Tuberculosis treatment Plan (NTP).

In a developing country like Pakistan the infra structure of hospitals which is designed to deal with these drug-resistant TB patients is intended to deal with relatively small numbers of MDR cases thus the need for consideration for the treatment of these MDR patients as out patients is stretched and Community-based treatment strategies have come into existence.

Community-based treatment for drug-resistant TB is not a new concept, and successful outcomes have been reported elsewhere in the world[17]. There have been certain public-private partnerships and non-governmental organizations that has developed community-based treatment projects in parts of Southern Africa. [22, 23]

The main opinion in favor of in-patient treatment for drug-resistant TB relate to the need to administer and monitor complex, toxic drug regimens and to limit the community spread of drug-resistant TB. However there is no proof that hospitalization actually limits community transmission and it is likely that most patients have been infectious for several months before hospitalization,[12] Moreover, the risk of hospital acquired infection transmission, both to other patients and to health care workers, is also high.[14,15] More importantly there are also economic and social costs involved in keeping patients isolated in hospitals, often away from their residence, and this can lead to default from treatment programs.[16] and therefore there is a salient need to build up community-based strategy for the treatment of drug resistant TB patients.[24]

In our study successful outcome was seen in 25 patients i.e. around half of our study population 47.2% and only 3 (5.6%) patients remain smear positive at the end of treatment. These results support the evidence that it is feasible to develop a community based treatment program for the patients who had MDR- TB. The major drawback of this strategy found to be is the high defaulter rate although we could not identify the exact cause of the defaulters was not known but most likely is the lack of education and cost of medications are the major hindrance. If the above two major hurdles are overcome than these MDR-TB patients can be safely managed within the existing

infrastructure of the TB program where the expertise is available on an out-patient basis.

Regarding the side effects 52.8% developed some side effects due to medications but all are mainly minor in nature, they did not required to discontinue the therapy and are managed accordingly as out-patient. This again favors that hospitalization is not usually necessary for the management of the side effects. [25]

One interesting finding of our study is the presence of high resistance pattern of other first line drugs including Pyrazinamide (77.4%), Ethambutol (73.6%), and Streptomycin (69.4%). This is likely because of the fact that majority of our patient had got secondary MDR TB (90.6%) in which around one third (69.8%) had been treated with anti-tuberculous drugs multiple times which is a risk factor for developing MDR TB.

WHO recommends sequential sputum for AFB culture for the follow up of the MDR TB patients' treatment, as cultures are more sensitive than AFB smear results but due to limited resources facility for sputum AFB culture was not available freely in our country and therefore the definition of the successful treatment is confined to smear results only. It is quite possible that our results of treatment success would have been lower if we had used the criteria of culture in follow up. Other limitations of the study includes; firstly; the study design i.e., a retrospective observational study involving individualized regimens, without any controls; secondly; the small number of patient population of the study as well.

In conclusion, it is shown that a comprehensive outpatient therapeutic approach, the negative sputum conversion rate among MDR-TB patients who completed treatment was fairly high, despite of the limited resources. The results of the study here suggest that community-based treatment strategy is both feasible and safe in resource limited country and also that, this community based treatment strategy should be integrated into the routine approach to treatment of MDR-TB patients in the country where the expertise are available.

REFERENCES:

1. Paramasivan CN. An overview on drug resistant tuberculosis in India. Lung India 1998; 16:21-8.

2. Jacobs R F. Multiple drug resistant tuberculosis. Clini Infect. Dis 1994; 19:1-10.

3. Chandrasekaran S, Jagota P, Chaudhuri K. Initial drug resistance to anti-tuberculosis drugs in urban and rural district tuberculosis programme. Ind J Tub 1992; 39:171-5.

4. Kailash Chand, Tiwary S C, Varghese SJ. Prevalence of drug resistance tuberculosis in armed forces – a study from tertiary referral chest diseases hospital at Pune. MJAFI 2000; 56:130

5. Global tuberculosis control: surveillance, planning, financing. WHO report 2008. Geneva, World Health Organization.

6. World Health Organization (2008) Guidelines for the programmatic management of drug resistant tuberculosis. Emergency Update (WHO/HTM/TB/ 2008.402). Geneva, Switzerland.

7. Nathanson E, Lambregts-van Wezenbeek C, Rich ML, Gupta R, Bayona J, et al. Multidrug resistant tuberculosis in resource-limited settings. Emerg Infect Dis 2006; 12(9): 1389–97.

8. Rao NA, Irfan M, Mahfooz Z. Treatment outcome of multi drug resistant tuberculosis in a tertiary care hospital in Karachi. J Pak Med Assoc. 2009 ;59(10):694-98

9. Goble M, Iseman M, Madsen L A, et al. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N Engl J Med 1993; 328: 527–532.

10. Flament-Saillour M, Robert J, Jarlier V, Grosset J. Outcome of multidrug-resistant tuberculosis in France. Am J Respir Crit Care Med 1999; 160: 587–593.

11. Telzak E E, Sepkowitz K, Alpert P, et al. Multidrug-resistant tuberculosis in patients without HIV infection. N Eng J Med 1995; 333: 907–911.

12. Yagui M, Perales M T, Asencios L, et al. Timely diagnosis of MDR-TB under program conditions: is rapid drug susceptibility testing suffi cient? Int J Tuberc Lung Dis 2006; 10: 838–843.

13. Heller T, Lessells RJ, Wallrauch CG, Bärnighausen T, Cooke GS, Mhlongo L, et al. Community-based treatment for multidrug-resistant tuberculosis in rural KwaZulu-Natal, South Africa. Int J Tuberc Lung Dis. 2010 Apr; 14(4):420-6.

14. Andrews J R, Gandhi N R, Moodley P, et al. Exogenous re infection as a cause of multidrug-resistant and extensively drug-resistant tuberculosis in rural South Africa. J Infect Dis 2008; 198: 1582–1589.

15. Escombe A R, Moore D A J, Gilman R H, et al. The infectiousness of tuberculosis patients co-infected with HIV. PLoS Med 2008; 5: e188.

16. Baleta A. Forced isolation of tuberculosis patients in South Africa. Lancet Infect Dis 2007; 7: 771.

17. Mitnick C, Bayona J, Palacios E, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. N Engl J Med 2003; 348: 119–128.

18. Kim HJ, Hong YP, Kim SJ, Lew WJ, Lee EG. Ambulatory treatment of multidrug-resistant pulmonary tuberculosis patients at a chest clinic. Int J Tuberc Lung Dis. 2001;5(12):1129-36.

19. Malla P, Kanitz EE, Akhtar M, Falzon D, Feldmann K, Gunneberg C et al Ambulatory-based standardized therapy for multi-drug resistant tuberculosis: experience from Nepal, 2005-2006. PLoS One. 2009 Dec 23;4(12):e8313.

20. Multidrug and extensively drug-resistant TB (M/XDR-TB) 2010 GLOBAL REPORT ON SURVEILLANCE AND RESPONSE. WHO Report 2010.

21. Seema Irfan, Qaiser Hassan, Rumina Hasan. Assessment of Resistance in Multi Drug Resistant Tuberculosis Patients. J Pak Med Assoc, Sept 2006: 56(9);397-400

22. Médicins Sans Frontières, Provincial Government of the Western Cape Department of Health. A patient-centred approach to drug-resistant TB treatment in the community: a pilot project in Khayelitsha, South Africa. Johannesburg, South Africa: Médecins Sans Frontières, 2009. http://www.msf.org.za/viewnews. php?n=261 Accessed December 2009.

23. Seung K J, Omatayo D B, Keshavjee S, Furin J J, Farmer P E, Satti H. Early outcomes of MDR-TB treatment in a high HIVprevalence setting in Southern Africa. PLoS ONE 2009; 4: E7186.

24. Padayatchi N, Friedland G. Decentralised management of drug resistant tuberculosis (MDR- and XDR-TB) in South Africa: an alternative model of care. Int J Tuberc Lung Dis 2008; 12: 978–980.

25. Nathanson E, Gupta R, Huamani P, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis 2004; 8: 1382–1384.

Table 1: Characteristics of MDR TB patients

Characteristics	**Numbers n (%)**
Gender	
Male	27 (50.9)
Female	26 (49.1)
Age	37 ± 15 years
15 – 19 yrs	4 (7.5)
20 – 39 yrs	30 (56.6)
40 - 60 yrs	14 (26.4)
>60 yrs	5 (9.4)
Tobacco Usage	11 (20.8)
H/O homelessness within 1 year prior to diagnosis of TB	7 (13.2)
Previous Exposure to TB patients	36 (67.9)
Diabetes Mellitus	11 (20.8)
Immunocompromised	3 (5.3)
Steroid Use	2 (3.8)

Table 2: Resistance pattern of first and second line drugs

Drugs	**Numbers n (%)**
Rifampicin	53 (100)
Isoniazid	53 (100)
Pyrazinamide	41 (77.4)
Ethambutol 5 micro gram	39 (73.6)
Streptomycin 2/10 micro gram	37 (69.8)
Ofloxacin	12 (22.6)
Ethionamide	0 (0%)
Capreomycin	1 (1.9)
Cycloserine	6 (11.3)