ORIGINAL ARTICLE

Culture conversion and six months interim outcomes in retreatment cases of pulmonary MDRTB — a six month interim analysis

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Abstract

Objectives: To estimate the time to culture conversion and factors associated with failure to culture conversion, six-month interim outcomes and associated risk factors with poor interim outcomes in multi-drug resistant tuberculosis patients previously treated with second-line drugs.

Method: The prospective clinical case series study was conducted from March 2016 to January 2017 at the Indus Hospital Tuberculosis Clinic and seven other sites that are part of the hospital's Programmatic Management of Drug Resistant Tuberculosis initiative. All bacteriologically confirmed multi-drug resistant tuberculosis retreatment patients were enrolled. Data was collected on age, gender, site of enrollment, detailed history of previous treatment with anti-tuberculosis drugs, medical history, history of first-line drugs, history of second-line drugs, treatment outcomes, baseline sputum smear microscopy and monthly follow-up sputum smear microscopy and culture results. Data was subjected to univariate and multiple logistic regression analyses, and risk factors for failure to culture conversion were assessed using Cox Proportional Hazards Model.

Results: Out of 266 patients, 143(53.8%) were males, the overall largest age group was 5-24 years 97(36.5%), and 250 (94%) patients had previous history of treatment with first-line drugs. Overall, 101(40.1%) patients experienced poor interim outcome. Poor interim outcomes were significantly associated with higher number of drugs on the regimen, (odds ratio: 1.27; 95% confidence interval: 1.03-1.58) and high sputum smear grading (odds ratio: 4.56; 95% confidence interval: 3.30-18.71). Besides, 186(70.3%) patients experienced culture conversion within the initial six months of treatment.

Conclusion: The success rate of re-treatment of multi-drug resistant tuberculosis with conventional regimen was found to be unacceptably low.

Keywords: Multi-drug resistant tuberculosis, Second-line drugs, Culture conversion, Interim outcomes, Sputum smear microscopy. (JPMA 71: 2710; 2021)

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Introduction

Multi-drug resistant tuberculosis (MDRTB) is a more difficult-to-treat form of TB that requires prolonged and extensive chemotherapy with second-line drugs (SLDs) which are least effective and are associated with adverse effects and poor outcomes.[1-4]

The global incidence for MDRTB in 2015 was 480,000, and 190,000 deaths were reported.[5] Globally, the incidence of MDRTB is 3.3% in new cases and 20% in previously-treated cases.[6]

Pakistan is listed fourth among the 22 high-burden countries in the world for MDRTB.[5] The results of a recent drug resistance surveillance carried out in Pakistan showed that the estimated percentage of MDRTB in new notified TB cases is 3.7% while in the cases previously treated for TB it is 18.1%.[7]

MDRTB treatment is widely available in Pakistan through the programmes implemented by the National TB Control Programme (NTP) and the Global Fund. The management of MDRTB is difficult and has lower success rates compared to susceptible TB.[8,9]

Retreatment of MDRTB is a major challenge as these cases have been previously treated on MDRTB regimen and declared as 'cured', 'treatment completed', 'lost to follow-up', 'treatment failed' and 'not evaluated' which includes patients for whom treatment outcome is not assigned, the cases 'transferred out' to another treatment unit and for whom treatment outcome is unknown.[6] If the patient is lost to follow-up or has not taken the drugs, uninterrupted treatment, though 'completed' or 'cured', the chances of retreatment relapse with amplified drug sensitivity test (DST) are higher i.e. the patient develops resistance with more drugs.[10,11] Hence, designing a regimen becomes complicated for physicians as the choice shrinks and they have to prescribe more drugs to intricate the four effective drugs on the

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regimen, which means higher number of less effective drugs with more adverse effects and lower success rate.[12-14]

The current study was planned to find the predictors of time to culture conversion and unfavourable interim outcomes in MDRTB retreatment cases to identify the patients at the risk of treatment failure or death and those who do not benefit from the retreatment while taking the six-month interim outcome as predictor of the final outcome.[13]

Materials and Methods

The prospective longitudinal study was conducted from March 2016 to January 2017 at the Indus Hospital TB Clinic and seven other sites that are part of the hospital's Programmatic Management of Drug Resistant Tuberculosis (PMDT) initiative. These sites are Ghulam Muhammad Mahar Medical College Hospital, Sukkur, Jinnah Postgraduate Medical College, Karachi, Chandka Medical College Hospital, Larkana, Fatima Jinnah Chest Hospital, Quetta, Institute of Chest Diseases, Kotri, People's University of Medical and Health Science, Nawabshah, and Civil Hospital, Mirpurkhas. Approval for the study was obtained from the ethics review board of the Dow University of Health Sciences (DUHS), Karachi. Separate consent was unnecessary as it was a non-experimental and prospective clinical case series, and direct patient contact was not made at any point. Only patients' medical records and laboratory reports were reviewed from the hospital's health management information system and laboratory records.

The sample was raised using non-probability purposive sampling technique, and data of all bacteriologically-confirmed MDRTB patients was included who had previous history of SLDs for one month or more, were culture-positive at baseline, and were being treated under NTP guidelines[15] and who had completed at least 3 months on the treatment. Extra pulmonary TB cases were excluded, and so were those who were transferred out to other facilities before six months of their treatment as the six-month interim outcome and time to culture conversion could not be assessed for such patients. Patients' sputum smear microscopy and culture results were reviewed prospectively till 6 months of their treatment and later till their 6-month interim outcome was available and sputum smear testing and culture results of the sputum sample taken at the 6th month became available.

Data was collected on age, gender, site of enrolment for each patient, detailed history of previous treatment with anti-TB drugs, medical history, history of first-line drugs (FLDs), history of SLD patients exposed to for a month or more, treatment outcome of SLDs, baseline sputum smear microscopy and DST, monthly follow-up sputum smear microscopy and culture results which were obtained from the hospital management information system records using medical record numbers. Number of the drugs a patient took on previous SLD treatment was noted. Time to culture conversion was calculated from the start of treatment till the patient had 2 consecutive negative cultures. The results of sputum smear microscopy results were graded as negative, scanty (1-9 Acid Fast Bacilli [AFB]/100 High Power Fields [HPF]), Positive 1+ (10-99 AFB/100 HPF), Positive 2+ (1-9 AFB/HPF) and Positive 3+ (>9 AFB/HPF).

To determine the risk factors of poor interim outcomes, univariate and multiple logistic regression analyses were done. To determine the effects of continuous variables on interim outcomes independent t test was performed. Risk factors for failure to culture conversion were assessed using the Cox Proportional Hazards Model. Only variables with $p<0.25$ were included in the final multivariate analysis except age and gender. Confidence interval (CI) was set at 95% and $p<0.05$ was considered statistically significant.

Results

Out of 266 patients, 143(53.8%) were males, the overall largest age group was 5-24 years 97(36.5%), and 250

Table-1: Demographic characteristics and previous history of study participants (n= 266).

Demographics	n (%)
Age Groups (years)	
5 - 24	97 (36.5)
25 - 34	77 (28.9)
35 - 44	43 (16.2)
45- 54	30 (11.3)
55+	19 (7.1)
Gender	
Male	143 (53.8)
Female	123 (46.2)
Previous history of FLD	
Yes	250 (94.0)
No/Unknown	16 (6.0)
Outcome of previous FLD treatment (n=250)	
Cured	15 (6.0)
Complete	29 (11.6)
Failed	130 (52.0)
Lost to follow up	11 (4.4)
Not Evaluated	65 (26.0)
Number of SLDs patient is exposed to	
Mean ± SD	4.4 ± 13.4
Inter Quartile Range	4 - 5
Outcome of previous SLD treatment	
Cured	3 (1.1)
Complete	6 (2.3)
Failed	67 (25.2)
Lost to follow up	45 (16.9)
Treatment not evaluated	145 (54.5)

*Outcome with previous second line drugs treatment. FLD: First-line drugs, SD: Standard deviation.SLD: Second Line Drugs

Table-2: Current clinical characteristics of study participants (n= 266).

Patient's characteristics	n (%)
Registration Groups	
Previously Treated after Relapse	9 (3.4)
Previously Treated after Failure	67 (25.2)
Previously Treated after Lost To Follow Up	45 (16.9)
Others Previously Treated	143 (53.8)
Unknown	2 (0.8)
Presence of comorbid diseases	
Yes	35 (13.2)
No	231 (86.8)
Comorbid Diseases (n=35)	
Diabetes	22 (8.3)
Hepatitis B	3 (1.1)
Hepatitis C	6 (2.3)
Depression	1 (0.4)
Deep Vein Thrombosis	1 (0.4)
Renal Disease	1 (0.4)
Epilepsy	1 (0.4)
Number of FLDs patient is resistant to	
Mean ± SD	4.2 ± 0.84
Range	4 - 5
Number of SLDs patient is resistant to	
Mean ± SD	0.72 ± 0.63
Range	0 - 2
Number of Drugs on the Regimen	
Mean ± SD	7.2 ± 1.86
Range	5 - 12
Baseline Sputum Smear Grading Results (n=255)	
Negative	73 (27.4)
Scanty	21 (7.9)
Positive 1+	42 (15.8)
Positive 2+	40 (15.0)
Positive 3+	79 (29.7)
Injectable	
Amikacin	175 (65.8)
Capreomycin	91 (34.2)
Resistance to Flouroquinolone	
Yes	144 (54.1)
No	122 (45.9)

FLD: First-line drugs, SLD: Second-line drugs, SD: Standard deviation, DVT: Deep vein thrombosis.

(94%) patients had previous history of FDL treatment. Interim results of 14(5.2%) patients could not be evaluated due to either sample contamination or non-expectorant sputum at month 6. Hence, for interim outcome analysis, the sample was cropped to 252(94.7%). Out of patients with previous FLD treatment, 15(6%) were cured at the end of the treatment, 29(11.6%) completed the treatment, 130(52%) failed, 11(4.4%) were lost to follow-up and the treatment outcome of 65(26%) was not evaluated, unknown or documentary evidence was not available. The mean number of SLDs patients were previously exposed to was 4.4±13.4 (range: 4-5). In terms of outcomes of previous SLD treatment, 3(1.1%) patients

Table-3: Mean time to culture and interim outcome.

Time to Culture Conversion (days)*	
Mean	62.17 ± 35.51
Inter Quartile Range	30.0-69.0
Interim Outcomes†	
Negative	151 (59.9)
Positive	59 (23.4)
Died	32 (12.7)
Lost to follow up	10 (4.0)
Interim Outcome Categories‡	
Favourable	151 (59.9)
Poor	101 (40.1)

* n for this category is 187 i.e, patient who experienced culture conversion within 6 months.
† n for this category is 252 as interim outcomes are available for 252 patients, the reason for the missing values are either sample contamination or non-expectorant sputum on month 6.
‡ Negative interim outcomes recoded as favourable, and others were recoded as poor.

Table-4: Association of patient's clinical characteristics with Interim Outcomes, n= 252.

	Interim Outcome		
	Favourable Outcome 151 (59.9%)	Poor Outcome 101 (40.1%)	
	Mean ± SD	**Mean ± SD**	**p-value***
Time to culture conversion (in days)	52.15 ± 30.75	72.97 ± 42.25	<0.001
Number of SLDs patient is exposed to	4.16 ± 1.49	4.74 ± 1.52	0.003
Number of SLDs patient is resistant to	0.66 ± 0.62	0.78 ± 0.64	0.139
Number of Drugs on the Regimen	6.92 ± 1.84	7.79 ± 1.76	<0.001

*p-value calculated using Independent t-test. SLD: Second-line drugs, SD: Standard deviation.

were cured, 6(2.3%) competed the treatment, 67(25.2%) failed, 45(16.9%) were lost to follow-up, treatment outcome of 145(54.5) was not evaluated, unknown or documentary evidence was not available (Table-1).

The mean number of FLDs patients were resistant to was 4.2±0.84 (range: 4-5). The mean number of SLDs patients were resistant to was 0.72±0.63 (range: 0-2). The mean number of drugs on the current regimen was 7.2±1.86 (range: 5-12). Besides, 175(65.8%) patients were treated with injection amikacin and 91(34.2%) were treated with injection capreomycin. Resistance to flouroquinolones was identified in 144(54.1%) patients (Table-2).

Overall, 187(70.3%) patients experienced culture conversion within the initial 6 months of treatment. The mean time to culture conversion was 62.17± 35.51 days (range: 30-69 days). Out of 151(60%) patients who had favourable outcome, 142(94%) experienced culture conversion. The patients who had poor interim outcomes, 41(40.6%) had culture conversion but later on had poor outcomes at the end of the follow-up, 30(50%) died, 9(15%) defaulted and 21(35%) reverted.

Table-5: Factors associated with poor interim outcome using logistic regression (n=252).

Characteristics	Poor Interim Outcome OR* (95% CI)	p-value	aOR** (95% CI)	p-value
Age (years)				
	1.02 (1.00-1.04)	0.01	1.01 (0.99-1.03)	0.22
Gender				
Male	Ref		Ref	
Female	0.87 (0.52 - 1.44)	0.59	1.19 (0.61-2.33)	0.61
Outcome of previous FLD treatment				
Cured	Ref			
Complete	0.36 (0.09-1.43)	0.15	0.29 (0.04-1.79)	0.19
Failed	0.66 (0.21-2.00)	0.47	0.87 (0.18-4.08)	0.87
Lost to follow up	0.37 (0.06-2.03)	0.26	0.15 (0.01-1.29)	0.09
Not Evaluated	0.80 (0.25-2.55)	0.71	0.50 (0.10-2.54)	0.41
Number of SLDs patient is exposed to	1.30 (1.09-1.55)	0.00	1.25 (0.98-1.61)	0.07
Outcome of previous SLD treatment				
Cured/Complete	Ref		Ref	
Failed	0.94 (0.23 - 3.85)	0.94	1.32 (0.23-7.50)	0.75
Lost to follow up	0.60 (0.14 - 2.57)	0.50	0.80 (0.13-4.69)	0.81
Treatment not evaluated	0.37 (0.09 - 1.46)	0.16	1.02 (0.18--5.64)	0.98
Number of SLDs patient is resistant to	1.35 (0.90-2.02)	0.14	0.86 (0.39-1.92)	0.73
Number of Drugs on the Regimen	1.27 (1.10-1.46)	<0.01	1.27 (1.03-1.58)	0.02
Baseline Sputum Smear Grading Categories				
Negative	Ref		Ref	
Scanty	2.55 (0.84-7.76)	0.10	1.70 (0.32-9.01)	0.53
Positive 1/Positive 2/Positive 3	4.56 (2.30-9.00)	<0.01	7.86 (3.30-18.71)	<0.01
Injectable				
Amikacin	Ref			
Capreomycin	3.01 (1.75-5.16)	<0.01	1.34 (0.63-2.83)	0.44
Resistance to Flouroquinolone				
Yes	Ref		Ref	
No	0.65 (0.39 - 1.09)	0.10	0.75 (0.28-2.02)	0.57

*OR: Crude Odds Ratio, CI: Confidence Intervals. FLD: First-line drugs, SLD: Second-line drugs.
**aOR: Adjusted Odds Ratio, adjusted for all including study Variables.

In terms of interim outcomes on month 6 of treatment, 152(60.3%) patients were sputum smear and culture negative, 59(23.4%) were sputum smear or culture positive, 32(12.7%) died before completing 6 months of treatment, and 10(4%) did not complete the 6-month treatment and were lost to follow-up (Table-3).

Delayed culture conversion was associated with poor interim outcome (p<0.001). The number of SLDs a patient was previously exposed to was significantly higher for those who had poor interim outcomes (p=0.003) and the higher number of drugs on the regimen was significantly associated with poor interim outcome (p<0.001) (Table-4).

Univariate logistic regression showed that older age (OR: 1.02, 95% CI: 1.00-1.04) patients who had previous exposure to higher number of SLDs were at higher risk of poor interim outcome (OR: 1.30, 95% CI: 1.09-1.55), while with the higher number of drugs on the regimen, the odds of poor interim outcomes increased (OR: 1.27, 95% CI: 1.10-1.46). Patients who were treated with capreomycin were had increased odds of poor interim outcome compared to those who were treated with amikacin, (OR: 3.01, 95% CI: 1.75-5.16). Patients with higher sputum smear grading at the baseline were also at increased risk of poor interim outcome, and patients with baseline sputum smear grading Positive 3+ / Positive 2+ / Positive 1+ were more likely to have poor interim outcome than those who were sputum smear-negative at the baseline (OR: 4.56, 95% CI: 2.30-9.00).

However, after adjustment in multiple logistic regression, poor interim outcomes were significant with higher number of drugs on the regimen (OR: 1.27, 95% CI: 1.03-1.58) and the higher sputum smear grading was significantly associated with poor interim outcomes compared to those who had negative smear grading results at the baseline, and patients with sputum smear

Table-6: Associated factors with time to culture conversion using Cox Regression (n=266).

Characteristics	Culture Conversion HR* (95% CI)	p-value	aHR** (95% CI)	p-value
Age (years)	0.98 (0.97-0.99)	0.04	0.99 (0.98-1.00)	0.32
Gender				
Male	Ref		Ref	
Female	1.15 (0.86-1.54)	0.32	0.92 (0.64-1.31)	0.64
Outcome of previous FLD treatment				
Cured	Ref		Ref	
Complete	1.60 (0.71-3.58)	0.25	1.34 (0.53-3.39)	0.53
Failed	1.41 (0.68-2.92)	0.35	0.92 (0.38-2.22)	0.87
Lost to follow up	2.35 (0.92-5.97)	0.07	2.51 (0.87-7.20)	0.09
Not Evaluated	1.95 (0.92-4.14)	0.08	2.07 (0.85-5.05)	0.11
Number of SLDs patient is exposed to	0.90 (0.83-0.99)	0.04	0.99 (0.89-1.11)	0.96
Outcome of previous SLD treatment				
Cured/Complete	Ref		Ref	
Failed	0.98 (0.38-2.50)	0.97	1.12 (0.38-3.28)	0.83
Lost to follow up	1.35 (0.52-3.49)	0.53	1.45 (0.48-4.34)	0.50
Treatment not evaluated	2.12 (0.86-5.20)	0.10	2.11 (0.74-5.96)	0.16
Number of FLDs patient is resistant to	1.11 (0.94-1.31)	0.20	1.07 (0.88-1.31)	0.46
Number of SLDs patient is resistant to	0.78 (0.62-0.98)	0.04	1.30 (0.89-1.90)	0.17
Number of Drugs on the Regimen	0.877 (0.80-0.95)	0.00	0.91 (0.83-1.01)	0.10
Baseline Sputum Smear Grading Categories				
Negative	Ref		Ref	
Scanty	0.61 (0.34-1.10)	0.10	0.62 (0.31-1.21)	0.16
Positive 1+/Positive 2+/Positive 3+	0.56 (0.40-0.77)	<0.01	0.46 (0.31-0.67)	0.00
Injectable				
Amikacin	Ref		Ref	
Capreomycin	0.58 (0.42-0.81)	0.00	0.79 (0.53-1.17)	0.25
Resistance to Flouroquinolone				
Yes	Ref		Ref	
No	1.53 (1.15-2.05)	0.00	2.00 (1.23-3.24)	0.01

*HR: Hazard Ratio, CI: Confidence interval, FLD: First-line drugs, SLD: Second-line drugs.
**aHR: Adjusted Harzard Ratio, adjusted for all including study variables.

grading results Positive 3+ / Positive 2+ / Positive 1+ were more likely to have poor interim outcome compared to negative (OR: 7.86, 95% CI: 3.30-18.71) (Table-5).

In univariate Cox Regression, older age (OR: 0.98, 95% CI: 0.97-0.99), higher number of SLDs patient was previously exposed to (OR: 0.90, 95% CI: 0.83-0.99), more number of SLDs patient was resistant to (OR: 0.78, 95% CI: 0.62-0.98), higher number of drugs on the regimen (OR: 0.877, 95% CI: 0.80-0.95), treatment with capreomycin (OR: 0.58, 95% CI: 0.42-0.81), resistance with fluoroquilnolones (OR: 1.53, 95% CI: 1.15-2.05) and higher baseline sputum smear grading Positive 3+ / Positive 2+/ Positive 1+ (OR: 0.56, 95% CI: 0.40-0.77) were significantly associated with failure to culture conversion within the initial 6 months of treatment.

However, in multivariate Cox Regression, the patients who were not resistant to fluoroquinolones were more likely to experience culture conversion than those who were resistant to fluoroquinolones (OR: 2.00, 95% CI: 1.23-3.24). The patients with higher sputum smear grading were 54% less likely to experience culture conversion within the initial 6 months of treatment with SLDs (OR: 0.46, 95% CI: 0.31-0.67) (Table-6).

Discussion

The study showed that 40.1% of the retreatment MDRTB patients had poor interim outcomes on the completion of six months of treatment, while 23.4% patients remained culture or sputum smear positive at the end of the six-month follow-up. While higher sputum smear grading at baseline and higher number of SLDs on the regimen were associated with poor interim outcome.

The percentage of the poor interim outcomes in our cohort is higher than the percentage of poor treatment outcome reported by other studies; 40.1% versus 20.4%-21.3%.[5,16] It might have been because all of the patients in the current cohort were those who were previously

exposed to SLDs. However, the result of a study conducted in Pakistan are in agreement with the current findings.[17] The loss to follow-up rate in the cohort was quite lower compared to some studies[16,17] and higher than others.[5] The mortality rate was fairly comparable to an earlier report.[16]

Older age, previous exposure with SLDs and treatment with capreomycin were associated with poor treatment outcomes in Uzbekistan, Georgia, Armenia, Swaziland and Kenya.[16] A study from Pakistan reported older age, lower body weight, residence in rural area, fluoroquinolones resistance, previous treatment with SLDs, SLD resistance and cavitary lung disease were associated with poor outcome in MDRTB patients.[18] However, the current study found that the higher number of drugs on the regimen and higher sputum smear grading at baseline were the factors associated with poor interim outcome in both univariate and multivariate regression models.

The current study found that the mean time to culture conversion was significantly higher among the patients who had poor interim outcome compared to those who had favourable interim outcome and it increased as the number of SLDs patients were previously exposed to . Time to culture conversion was observed to be higher among patients with higher number of drugs on the regimen. Higher sputum smear grading at baseline and fluoroquinolones resistance were significantly associated with delayed culture conversion.

The findings are consistent with earlier reports.[19]

The present study found that the proportion of patients who experienced culture conversion within 6 month of treatment initiation was lower than earlier studies.[20] The reason for lower proportion of culture conversion might be the previous history of SLD as in the current cohort all patients were previously exposed to SLDs. The mean time to culture conversion was 62.17 days, or 2.06 months. It was comparable to the median time to culture conversion in Tanzania and China.[21,22] The median time to culture conversion in the current study in months was lower than that reported previously in the same setting in the cohort of patients who were treated on internationally quality assured (IQA) drugs, and comparable to those who were treated with non-IQA drugs.[23]

The MDRTB relapse rate in the current setting was lower than earlier findings.[24]

The case finding for MDRTB and extensively drug-resistant TB (XDRTB) should be enhanced as early initiation of treatment will favour better outcomes and less further resistance. Fluroquinolones resistance was high, and we recommend adding another effective drug as part of standard MDRTB regimen. Bedaquiline and delamanid should be made available across the country to be used in eligible patients to reduce mortality due to MDRTB. Pyrazinamide should be added to regimen and considered clean only if reliable DST shows susceptibility to it. Drugs with unclear efficacy, like para-aminosalicylic acid (PAS) and clarithromycin should be avoided in MDRTB regimen as such medicine cause unnecessary burden on patients with various side-effects.

Conclusion

The success rate of retreatment cases, when treated with conventional MDRTB regimen, although 60%, was not satisfactory. Conventional MDRTB regimen was not found to be adequate to treat MDRTB patients who have been previously exposed to SLDs. Improvised treatment regimen should be considered.

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