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Early View

Research letter

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Treatment outcomes among childhood extensively drug-resistant tuberculosis patients in Pakistan

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Take home message: Treatment outcomes of childhood XDR-TB patients in Pakistan were better adult patients but still disappointing

To the Editor:

Extensively drug-resistant tuberculosis (XDR-TB) previously defined as "TB caused by *Mycobacterium tuberculosis* concurrently resistant to isoniazid, rifampicin, any fluoroquinolones (FQs) and at least one of the three second-line injectable (SLIs) drugs (*amikacin, kanamycin* and *capreomycin*)" is now defined as "TB caused by MTB concurrently resistant to isoniazid, rifampicin, any fluoroquinolones (FQs) and at least one additional group A drugs (levofloxacin, moxifloxacin, bedaquiline and linezolid)" [1, 2]. It is the most difficult to treat form of TB with an overall treatment success rate ranging from 4-65% [3]. Likewise other forms of TB, XDR-TB affects people irrespective of their age including children (age≤14 years). Although children suffering from DR-TB have a diverse spectrum of disease and adverse events, and different psychosocial, developmental and educational needs than adults, still they are treated with the same regimen as that of the adult DR-TB patients. The previously conducted very few studies among childhood XDR-TB patients (sample size ranged from 8-37 patients) have reported a variable rate of successful treatment outcomes (81-100%) [4, 5]. Despite a DR-TB high burden country, initiation of programmatic management of DR-TB (PMDT) back in 2010 [6] and >30 PMDT units all over the country [3], there was a lack of information about treatment outcomes of childhood XDR-TB patients from Pakistan. Thus, this study is conducted to evaluate the treatment outcomes among childhood XDR-TB patients in Pakistan.

Each PMDT unit in the country shares its monthly data with National TB Control Program through Electronic Nominal Recording and Reporting System (ENRS). We used a standardized data collection form to abstract the patients' socio-demographic, microbiological and clinical data from ENRS. The diagnosis, drug susceptibility testing (DST) and treatment of XDR-TB

patients at these centers have already been discussed in our previously published paper [3]. World Health Organization (WHO) guidelines were used to categorize treatment outcomes. The outcomes of "Cured" and "Treatment completed" were collectively grouped as "Successful outcomes", whereas, "Death", "Treatment failed" and "Lost to follow up (LTFU)" were collectively grouped as "Unsuccessful outcomes" [1, 3]. SPSS 20 was used for data analysis.

From October 2010 to June 2019, a total of 42 culture confirmed childhood pulmonary XDR-TB patients were enrolled for treatment at 13 PMDT units all over Pakistan and were included in this study. The patients' characteristics and their cross-tabulation with treatment outcomes are presented in table 1. A total of 31/42 (77.8%) patients had a previous history of TB treatment. Among them, 11 had previous history of multidrug resistant-TB (MDR-TB) treatment. In the current cohort, the notable proportion of XDR-TB patients (N= 11, 26.2%) with no history of previous TB treatment is in compliance with the recent reports stating that transmission has become an "elephant in the room" of DR-TB epidemic and call for better infection control measures. Screening of close contacts of an index TB case and referring the suspected DR-TB cases to PMDT sites for DST could help in reducing the transmission of XDR-TB [7-9]. The current study participants were resistant to a median of 7 drugs (range: 4-9). In addition to concurrent resistant to rifampicin, isoniazid, any FQ and SLI, 73.8% were resistant to pyrazinamide, 71.4% to ethambutol and 64.3% to streptomycin. Among SLIs, resistance was highest for kanamycin (73.8%), followed by capreomycin (71.4%) and amikacin (61.9%). A total of 9.5% patients were also resistant to ethionamide. Patients were treated with a median of 9 drugs (range: 6-12). The most commonly used drugs were pyrazinamide and cycloserine (95.2%), followed by ethionamide (85.7%), para-amino salicylic acid (83.3%), linezolid (73.8%), moxifloxacin (59.5%), capreomycin (54.8%), co-amoxiclav (52.4%), clofazimine

(47.6%), levofloxacin (38.1%), clarithromycin (35.7%), amikacin (31%), bedaquiline (11.9%), high dose isoniazid (11.9%) and kanamycin (2.4%). A total 29 patients (69%) achieved sputum culture conversion (SCC) defined [10] as "two successive negative cultures taken one month apart following a positive culture" with a median SCC time of 2 months (Interquartile range [IQR]: 2-4.5) . Time to SCC in the current cohort was comparatively shorter than that observed among XDR-TB patients in Pakistan (3 months, IQR: 2-5) [3]. However, it was relatively longer than the time to SCC (median: 1.1 months, IQR: 0.9-1.6) observed among childhood and adolescent MDR and XDR-TB patients observed in Belarus [5]. The relatively shorter time to SCC in the later study could be due to the fact that majority of its participants were suffering from MDR-TB rather than the most difficult to treat XDR-TB [5]. Moreover, its treatment regimen contained bedaquiline which is reported to be associated with achieving early SCC among DR-TB patients [11, 12]. A total of 21 patients (50%) achieved successful treatment outcomes (19 cured and 2 treatment completed). The median duration of treatment in patients with successful outcomes was 25 months (range: 22-37). Of the remaining 21 patients (50%) with unsuccessful outcomes, 12 (28.6%) died, four (9.5%) were declared treatment failure and five (11.9%) were lost to follow up (LTFU). Median time to death was 6 months (range: 1-19). Of the five patients who were LTFU, three were lost prior to achieving SCC. The current treatment success rate (50%) was above the treatment success rate of XDR-TB patients (adults and children combined) globally (39%) [13] and in Pakistan (40.6%) [3]. However, comparatively high treatment success rate among childhood XDR-TB patients has been reported by a meta-analysis (N=37, treatment success rate=81%) [4]and a study from Belarus (N=20 [children + adolescents], treatment success rate=100%) [5]. Proportion of deaths (28.6%) in the current cohort was lower than that reported among XDR-TB patients (children + adults) from

Pakistan (36.9%) [3] but higher than that reported by a meta-analysis of childhood XDR-TB patients (11%) [4] and a study from Belarus (children + adolescents) where no patient died, no failed the treatment and no one was LTFU [5]. Comparatively better treatment success rate in study from Belarus could be due to the use of bedaquiline- or delamanid containing regimen in all patients and inclusion of both children and adolescents in the study [5]. The use of bedaquiline containing regimen in MDR and XDR-TB patients has been reported to be associated with early SCC and better treatment outcomes [5, 11, 12] and has been recommended by WHO latest guidelines for the treatment of DR-TB [1]. Cross-tabulation in the current study could not yield any significant association between the patients' variables and treatment outcomes possibly due to limited sample size.

In conclusion, we report the treatment outcomes among 42 childhood XDR-TB patients who received PMDT between 2010 and 2019 in Pakistan. Although the treatment success rate was above the global and national treatment success rates (39% and 40.6% respectively) of XDR-TB patients (children and adults combined) [3, 13], but it was still disappointing. Although to the best of our information, it is the largest data set of individual cohort of childhood XDR-TB patients published till date and the inclusion of nationwide cohort of childhood XDR-TB patients was the major strength of the study, but limited sample size, lack of information about the adverse events, chest radiographs and their impact on treatment outcomes are the major limitations of this study. Shifting from the conventional treatment regimen containing SLIs to the WHO recently recommended all oral regimens [1] and individual patients data meta-analysis of treatment outcomes among large number of childhood XDR-TB patients are urgently needed.

Table 1: Distribution of treatment outcome among childhood XDR-TB patients (N= 42)

Characteristics	Treatment outcomes		p-value
	Successful	Unsuccessful	
Age (years)			0.537
< 10	9 (45)	11 (55)	
10-14	12 (54.5)	10 (45.5)	
Baseline weight (kilogram)			0.525
≤35	7 (43.8)	9 (56.2)	
>35	14 (53.8)	12 (46.2)	
Gender			0.495
Female	14 (46.7)	16 (53.3)	
Male	7 (58.3)	5 (41.7)	
History of TB treatment			0.726
No	5 (45.5)	6 (54.5)	
Yes	16 (51.6)	15 (48.4)	
History of SLD used			0.095
No	17 (58.6)	12 (41.4)	
Yes	4 (30.8)	9 (69.2)	
History of MDR-TB treatment			0.079
No	18 (58.1)	13 (41.9)	
Yes	3 (27.3)	8 (72.7)	
Co-morbidities			1.000
No	21 (52.5)	19 (47.5)	
Yes	0 (0.0)	2 (100)	
Baselines sputum smear grading			Not measure
Negative	3 (37.5)	5 (62.5)	
Scanty(1-9) *	1 (100)	0 (0.0)	
+1†	11 (64.7)	6 (35.3)	
+2‡	1 (16.7)	5 (83.3)	
+3§	5 (50)	5 (50)	
Sputum culture conversion month			0.976
≤ 2	13 (72.2)	5 (27.8)	
> 2	8 (72.7)	3 (27.3)	
Used of Linezolid			0.726
No	5 (45.5)	6 (54.6)	
Yes	16 (51.6)	15 (48.4)	
Used of Clofazimine			0.064
No	14 (63.6)	8 (36.4)	
Yes	7 (35)	13 (65)	
Used of Bedaquiline			0.634
No	18 (48.6)	19 (51.4)	
Yes	3 (60)	2 (40)	

*Scanty=1–9 AFB (Acid fast bacilli)/100 HPF (High power field); †+1=10–99 AFB/100 HPF); ‡+2= 1–9AFB/HPF; §+3 > 9 AFB/HPF

Conflict of interest

None declared

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