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

Received: 13 Sept 2021
Accepted: 25 Oct 2021

To the Editor:

Extensively drug-resistant (XDR) tuberculosis (TB), previously defined as that caused by *Mycobacterium tuberculosis* concurrently resistant to isoniazid, rifampicin, any fluoroquinolone (FQ) and at least one of the three second-line injectable (SLI) drugs (amikacin, kanamycin and capreomycin), is now defined as TB caused by *M. tuberculosis* concurrently resistant to isoniazid, rifampicin, any FQ and at least one additional group A drug (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% to 65% [3]. Like other forms of TB, XDR-TB affects people irrespective of their age, including children (age≤14 years). Although children suffering from drug-resistant (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 eight to 37 patients) have reported a variable rate of successful treatment outcomes (81–100%) [4, 5]. Despite Pakistan being a high DR-TB 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 that country. Thus, this study was 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 the Electronic Nominal Recording and Reporting System (ENRS). We used a standardised data collection form to abstract the patients' sociodemographic, microbiological and clinical data from ENRS. The diagnosis, drug susceptibility testing (DST) and treatment of XDR-TB patients at these centres have already been discussed in our previously published paper [3]. World Health Organization (WHO) guidelines were used to categorise treatment outcomes. The outcomes "cured" and "treatment completed" were grouped as "successful outcomes", whereas "death", "treatment failed" and "lost to follow up" (LTFU) were 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 (77.8%) out of 42 patients had a previous history of TB treatment. Among them, 11 had previous history of multidrug-resistant (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 the DR-TB epidemic and a 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 seven drugs (range 4–9). In addition to concurrent resistance 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 nine drugs (range 6–12). The most commonly used drugs were pyrazinamide and cycloserine (95.2%), followed by ethionamide (85.7%), para-aminosalicylic acid (83.3%), linezolid (73.8%), moxifloxacin (59.5%), capreomycin (54.8%), co-amoxiclav (52.4%), clofazimine (47.6%),

Shareable abstract (@ERSpublications)
Treatment outcomes of childhood XDR-TB patients in Pakistan are better than in adult patients but still disappointing https://bit.ly/3rkQ9sw

Cite this article as: Abubakar M, Ahmad N, Atif M, *et al*. Treatment outcomes among childhood extensively drug-resistant tuberculosis patients in Pakistan. *ERJ Open Res* 2022; 8: 00551-2021 [DOI: 10.1183/23120541.00551-2021].

TABLE 1 Distribution of treatment outcome among childhood extensively drug-resistant tuberculosis patients (N=42)

Characteristics	Treatment outcome		p-value
	Successful	Unsuccessful	
Age			0.537
<10 years	9 (45%)	11 (55%)	
10–14 years	12 (54.5%)	10 (45.5%)	
Baseline weight			0.525
⩽35 kg	7 (43.8%)	9 (56.2%)	
>35 kg	14 (53.8%)	12 (46.2%)	
Sex			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 use of SLD			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%)	
Comorbidities			1.000
No	21 (52.5%)	19 (47.5%)	
Yes	0 (0.0%)	2 (100%)	
Baseline sputum smear grading			Not measured
Negative	3 (37.5%)	5 (62.5%)	
Scanty[#]	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			0.976
⩽2 months	13 (72.2%)	5 (27.8%)	
>2 months	8 (72.7%)	3 (27.3%)	
Use of linezolid			0.726
No	5 (45.5%)	6 (54.6%)	
Yes	16 (51.6%)	15 (48.4%)	
Use of clofazimine			0.064
No	14 (63.6%)	8 (36.4%)	
Yes	7 (35%)	13 (65%)	
Use of bedaquiline			0.634
No	18 (48.6%)	19 (51.4%)	
Yes	3 (60%)	2 (40%)	

TB: tuberculosis; SLD: second-line drug; MDR: multidrug-resistant. [#]: 1–9 acid-fast bacilli (AFB) per 100 high-power fields (HPFs); [¶]: 10–99 AFB per 100 HPFs; [+]: 1–9 AFB per HPF; [§]: >9 AFB per HPF.

levofloxacin (38.1%), clarithromycin (35.7%), amikacin (31%), bedaquiline (11.9%), high-dose isoniazid (11.9%) and kanamycin (2.4%). A total of 29 patients (69%) achieved sputum culture conversion (SCC), defined [10] as "two successive negative cultures taken 1 month apart following a positive culture", with a median SCC time of 2 months (interquartile range (IQR) 2–4.5 months). Time to SCC in the current cohort was comparatively shorter than that observed among XDR-TB patients in Pakistan (3 months, IQR 2–5 months) [3]. However, it was longer than the time to SCC (median 1.1 months, IQR 0.9–1.6 months) observed among childhood and adolescent MDR- and XDR-TB patients in Belarus [5]. The relatively shorter time to SCC in the later study could be due to the fact that the 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 two treatment completed). The median duration of treatment in patients with successful outcomes was 25 months (range 22–37 months). 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 LTFU. Median time to death was 6 months (range 1–19 months). 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 and 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 and 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 and adolescents) where no patient died, none failed the treatment and no one was LTFU [5]. The comparatively better treatment success rate in the study from Belarus could be due to the use of bedaquiline- or delamanid-containing regimens in all patients and inclusion of both children and adolescents in the study [5]. The use of a 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 the latest WHO 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], 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 to date and the inclusion of nationwide cohort of childhood XDR-TB patients was the major strength of the study, limited sample size, and lack of information about 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 recently WHO-recommended all-oral regimens [1] and individual patient data meta-analysis of treatment outcomes among large number of childhood XDR-TB patients are urgently needed.

Muhammad Abubakar[1], Nafees Ahmad[1], Muhammad Atif[2], Amer Hayat Khan[3] and Abdul Ghafoor[4]

[1]Dept of Pharmacy Practice, Faculty of Pharmacy and Health Sciences, University of Balochistan, Quetta, Pakistan. [2]Dept of Pharmacy Practice, Faculty of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur, Pakistan. [3]Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia. [4]National TB Control Program, Islamabad, Pakistan.

Corresponding author: Nafees Ahmad (nafeesuob@gmail.com)

Acknowledgments: The authors are thankful to the National TB Control Program, Islamabad for their help in data collection.

Provenance: Submitted article, peer reviewed.

Conflict of interest: None declared

References

1 World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva, World Health Organization, 2019.
2 World Health Organization. WHO announces updated definitions of extensively drug-resistant tuberculosis. www.who.int/news/item/27-01-2021-who-announces-updated-definitions-of-extensively-drug-resistant-tuberculosis Date last updated: 27 January 2021.
3 Abubakar M, Ahmad N, Ghafoor A, *et al.* Treatment outcomes of extensively drug-resistant tuberculosis in Pakistan: a countrywide retrospective record review. *Front Pharmacol* 2021; 12: 499.
4 Osman M, Harausz EP, Garcia-Prats AJ, *et al.* Treatment outcomes in global systematic review and patient meta-analysis of children with extensively drug-resistant tuberculosis. *Emerg Infect Dis* 2019; 25: 441–450.
5 Solodovnikova V, Kumar AM, Hurevich H, *et al.* Effectiveness and safety of delamanid-or bedaquiline-containing regimens among children and adolescents with multidrug resistant or extensively drug resistant tuberculosis: a nationwide study from Belarus, 2015–19. *Monaldi Arch Chest Dis* 2021; 91: 1646.

6 Ahmad N, Javaid A, Basit A, *et al.* Management and treatment outcomes of MDR-TB: results from a setting with high rates of drug resistance. *Int J Tuberc Lung Dis* 2015; 19: 1109–1114.

7 Wahid A, Ahmad N, Ghafoor A, *et al.* Effectiveness of shorter treatment regimen in multidrug-resistant tuberculosis patients in Pakistan: a multicenter retrospective record review. *Am J Trop Med Hyg* 2021; 104: 1784–1791.

8 Leung ECC, Leung CC, Kam KM, *et al.* Transmission of multidrug-resistant and extensively drug-resistant tuberculosis in a metropolitan city. *Eur Respir J* 2013; 41: 901–908.

9 Shah NS, Auld SC, Brust JC, *et al.* Transmission of extensively drug-resistant tuberculosis in South Africa. *N Engl J Med* 2017; 376: 243–253.

10 Javaid A, Ahmad N, Afridi AK, *et al.* Validity of time to sputum culture conversion to predict cure in patients with multidrug-resistant tuberculosis: a retrospective single-center study. *Am J Trop Med Hyg* 2018; 98: 1629–1636.

11 Koirala S, Borisov S, Danila E, *et al.* Outcome of treatment of MDR-TB or drug-resistant patients treated with bedaquiline and delamanid: results from a large global cohort. *Pulmonology* 2021; 27: 403–412.

12 Borisov SE, Dheda K, Enwerem M, *et al.* Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR-and XDR-TB: a multicentre study. *Eur Respir J* 2017; 49: 1700387.

13 World Health Organization. Global tuberculosis report 2018. Geneva, World Health Organization, 2018.