



Applicability of the World Health Organization recommended new shorter regimen in a multidrug-resistant tuberculosis high burden country

To the Editor:

In order to improve the adherence and treatment outcomes of multidrug-resistant (MDR) tuberculosis (TB) patients, the World Health Organization (WHO) has recently recommended a new, shorter and cheaper treatment regimen. The new regimen, comprised of 4–6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, ethambutol and high dose isoniazid followed by 5 months of moxifloxacin, clofazimine, pyrazinamide and ethambutol [1], has produced excellent outcomes under operational research conditions in various settings [2–4]. However, the recommendation that it should be used only for MDR-TB patients who are neither previously treated with second-line anti-TB drugs, nor resistant to fluoroquinolones or injectable second-line anti-TB drugs [1], generates concerns about its applicability in MDR-TB high burden countries [5]. In the current cross-sectional study, culture-confirmed MDR-TB patients treated at two units for programmatic management of drug-resistant TB in Pakistan were evaluated for drug resistance pattern and eligibility to be treated with the new shorter regimen.

A total of 832 culture-confirmed MDR-TB patients consecutively enrolled for treatment at Lady Reading Hospital Peshawar (Khyber-Pukhtoonkhwa) and Nishtar Hospital Multan (Punjab) from January 2012 to July 2016 met the inclusion criteria and were included in the study. Patients with drug-resistant TB other than MDR-TB (extensively drug-resistant, poly-drug-resistant and mono-drug-resistant TB) and who had a history of MDR-TB treatment were excluded. At the study sites, presumed drug-resistant TB patients were initially evaluated with two sputum samples for acid-fast bacilli by direct sputum smear microscopy using Ziehl Neelsen staining method and GeneXpert System's MTB/Rif (*Mycobacterium tuberculosis*/rifampicin). Upon positive smear microscopy and rapid drug susceptibility test (DST), sputum samples were sent to Aga Khan University Hospital Laboratory, Karachi, Pakistan, National TB reference laboratory, Islamabad, Pakistan or Provincial TB reference laboratory, Peshawar, Pakistan for sputum culture and DST. At the reference laboratories, DST was carried out by using Agar proportion method on enriched Middlebrook 7H10 medium (BBL; Beckton Dickinson, Sparks, MD, USA) at the following concentrations [6]: rifampicin ($1 \mu\text{g}\cdot\text{mL}^{-1}$), isoniazid ($0.2 \mu\text{g}\cdot\text{mL}^{-1}$), streptomycin ($2 \mu\text{g}\cdot\text{mL}^{-1}$), ethambutol ($5 \mu\text{g}\cdot\text{mL}^{-1}$), ofloxacin ($2 \mu\text{g}\cdot\text{mL}^{-1}$), amikacin ($4 \mu\text{g}\cdot\text{mL}^{-1}$), kanamycin ($5 \mu\text{g}\cdot\text{mL}^{-1}$), capreomycin ($4 \mu\text{g}\cdot\text{mL}^{-1}$), and ethionamide ($5 \mu\text{g}\cdot\text{mL}^{-1}$). DST for pyrazinamide was carried out at $100 \mu\text{g}\cdot\text{mL}^{-1}$ by using BACTEC Mycobacterial Growth Indicator Tube (MGIT) in accordance with manufacturer's instructions. A standardised data collection form was used to retrospectively abstract patient's information. This study was approved by the research and ethics committee of the Postgraduate Medical Institute, Peshawar, Pakistan.

The majority of patients were female (52.4%), 21–40 years old (47.5%) and previously been treated for TB (93.6%). A high proportion of patients (47.6%) were resistant to all five first-line anti-TB drugs, and 51.4% were resistant to second-line anti-TB drugs. Among first-line drugs, resistance was highest for pyrazinamide (79.6%), followed by ethambutol (76.2%) and streptomycin (62.6%). Of second-line drugs, resistance was highest for ofloxacin (48.6%), followed by ethionamide (5.6%) and injectable second-line drugs (0.4%). Upon taking resistance to fluoroquinolones (irrespective of generation) as one of the criteria for a patient's ineligibility to be treated with the shorter regimen, a total of 409 (49.2%) study participants

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High prevalence of ofloxacin resistance should not limit the applicability of the new shorter regimen in Pakistan <http://ow.ly/HCA306dUjU>

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were not eligible for treatment with the shorter regimen, mainly due to ofloxacin resistance (48.6%) followed by history of second-line anti-TB drug use (1.3%) and resistance to injectable second-line drugs (0.4%). However, a recently conducted multicountry study among TB patients has reported a low level of moxifloxacin resistance in Pakistan. The study reports that at $0.5 \mu\text{g}\cdot\text{mL}^{-1}$, only 7.5% of new TB cases and 13.8% of rifampicin-resistant TB cases in Pakistan were resistant to moxifloxacin, which decreased further to 0.4% and 1.4% respectively when tested at $2 \mu\text{g}\cdot\text{mL}^{-1}$. Moreover, when the minimum inhibitory concentration (MIC) for moxifloxacin was increased from $0.5 \mu\text{g}\cdot\text{mL}^{-1}$ to the clinical break point of $2 \mu\text{g}\cdot\text{mL}^{-1}$, the cross-resistance between ofloxacin and moxifloxacin drastically dropped from 72% to only 7% [7]. This suggests that resistance to ofloxacin does not necessarily preclude susceptibility to moxifloxacin/gatifloxacin and should not be a reason for depriving MDR-TB patients from the moxifloxacin/gatifloxacin-containing shorter regimen. So in an MDR-TB high burden country like Pakistan, where DST for fluoroquinolones is conducted for ofloxacin only, the applicability of the new regimen can be increased by 1) increasing the MIC for ofloxacin from $2 \mu\text{g}\cdot\text{mL}^{-1}$ to $4 \mu\text{g}\cdot\text{mL}^{-1}$, 2) administration of moxifloxacin at a higher dose of $\geq 600 \text{ mg}$ once daily and 3) clearing the ambiguity in guideline recommendations [8] by specifically mentioning “resistance to moxifloxacin/gatifloxacin” rather

TABLE 1 Predictors of ofloxacin resistance

Variables	Ofloxacin resistance		Univariate analysis	p-value	Multivariate analysis	p-value
	Yes	No				
Sex						
Female	207 (47.5)	229 (52.5)	Referent			
Male	197 (49.7)	199 (50.3)	1.095 (0.834–1.438)	0.513		
Age years						
≤20	101 (48.6)	107 (51.4)	Referent			
21–40	193 (48.9)	202 (51.1)	1.012 (0.723–1.416)	0.944		
41–60	83 (46.4)	96 (53.6)	0.916 (0.614–1.367)	0.667		
>60	27 (54)	23 (46)	1.244 (0.670–2.310)	0.490		
Weight kg						
<40	128 (50.4)	126 (49.6)	Referent			
≥40	276 (47.8)	302 (52.2)	0.900 (0.670–1.209)	0.482		
Residence						
Rural	290 (50.9)	280 (49.1)	Referent			
Urban	130 (49.6)	132 (50.4)	0.891 (0.450–1.032)	0.452		
Smear grading						
Negative	22 (44.9)	27 (55.1)	Referent			
Scanty (1–9 AFB per 100 HPF)	5 (33.3)	10 (66.7)	0.614 (0.183–2.062)	0.430	0.575 (0.168–1.693)	0.377
+1 (10–99 AFB per 100 HPF)	132 (53.2)	116 (46.8)	1.397 (0.754–2.585)	0.288	1.297 (0.695–2.421)	0.414
+2 (1–9 AFB per HPF)	102 (39.5)	156 (60.5)	0.802 (0.434–1.485)	0.484	0.772 (0.413–1.443)	0.418
+3 (>9 AFB per HPF)	143 (54.6)	119 (45.4)	1.475 (0.799–2.723)	0.214	1.378 (0.740–2.566)	0.313
Previous treatment centre						
Public	166 (43.1)	219 (56.9)	Referent		Referent	
Private	193 (55.5)	155 (44.5)	1.643 (1.227–2.200)	0.001	1.531 (1.064–2.203)	0.022
Public/private matrix	26 (57.8)	19 (42.2)	1.805 (0.966–3.373)	0.064	1.668 (0.882–3.154)	0.115
New patients	19 (35.2)	35 (64.8)	0.716 (0.395–1.297)	0.271	0.487 (0.090–2.634)	0.403
Previous TB regimen						
Category I	195 (49.9)	196 (50.1)	Referent		Referent	
Category II	161 (46.3)	187 (53.7)	0.865 (0.648–1.156)	0.327	0.910 (0.676–1.225)	0.535
New patients	16 (34.8)	30 (65.2)	0.536 (0.283–1.015)	0.056	1.051 (0.218–5.059)	0.951
Unknown	32 (68.1)	15 (31.9)	2.144 (1.126–4.085)	0.020	2.087 (1.036–4.205)	0.039
Registration category						
New	20 (36.4)	35 (63.6)	Referent		Referent	
Failure of previous TB treatment	182 (46.2)	212 (53.8)	1.502 (0.838–2.694)	0.172	0.757 (0.130–4.424)	0.757
Relapse	27 (45.8)	32 (54.2)	1.477 (0.697–3.129)	0.309	0.771 (0.123–4.813)	0.780
Defaulter of previous TB treatment	8 (53.3)	7 (46.7)	2.000 (0.631–6.339)	0.239	0.850 (0.112–6.465)	0.876
Unknown outcome of previous episode	167 (54)	142 (46)	2.058 (1.137–3.725)	0.017	0.734 (0.126–4.294)	0.732
MDR-TB treatment centre						
Lady Reading Hospital Peshawar	230 (48.3)	246 (51.7)	Referent			
Nishtar Hospital, Multan	174 (48.9)	182 (51.1)	1.023 (0.777–1.346)	0.874		

Data are presented as n (%) or odds ratios with 95% confidence intervals, unless otherwise stated. AFB: acid fast bacilli; HPF: high power field; TB: tuberculosis; MDR: multidrug-resistant.

than “resistance to fluoroquinolones” as an ineligibility criteria for treatment with the shorter regimen. Furthermore, the high prevalence of cross-resistance between ofloxacin and levofloxacin (87%) observed in five TB high burden countries [7] advocates for the use of moxifloxacin-containing regimen for MDR-TB treatment rather than the currently used levofloxacin one [9]. Although in the current study resistance to first-line anti-TB drugs which make part of the shorter regimen (pyrazinamide and ethambutol) was highly prevalent, owing to the unreliable nature of DST for these agents, it is not recommended to base decision-making on the basis of resistance to pyrazinamide and ethambutol [10]. Nevertheless, prospective case-controlled studies are required to evaluate the suitability and impact of the new shorter regimen in all geographical regions where MDR-TB is endemic [5] and the prevalence of resistance to second-line drugs is high. As a high rate of ofloxacin resistance was observed in the current study, we evaluated the study participants for the risk factors for ofloxacin resistance. In multivariate analysis, previous TB treatment with unknown regimen (OR 2.087; $p=0.039$) and episode of previous TB treatment in the private sector (OR 1.531; $p=0.022$) emerged as risk factors for ofloxacin resistance (table 1). As resistance to fluoroquinolones has widely been reported as a risk factor for unsuccessful treatment outcomes in MDR-TB patients [11, 12], the high degree of ofloxacin resistance among MDR-TB patients in Pakistan [13, 14] makes it a threatening issue that could be multifactorial. Patient’s previous exposure to fluoroquinolones due to self-medication, over the counter availability of antibiotics in the country and irrational prescription of fluoroquinolones by inadequately trained practitioners upon misdiagnosing TB with other lower respiratory tract infections are the possible reasons for high fluoroquinolone resistance among MDR-TB patients in Pakistan [13, 14]. The current finding of previous TB treatment in the private sector as a predictor of ofloxacin resistance is in compliance with a previous report from Pakistan [14]. The inadequate knowledge of private practitioners regarding TB diagnosis and management, divergence from practice guidelines, lack of supervision on patient adherence and complacency regarding patient loss to follow-up have previously been reported from Pakistan [14, 15]. In the current study, patients with unknown regimen of previous episode of TB treatment were significantly more likely to be ofloxacin resistant. All these patients with the unknown previous regimen had received treatment in the private sector. We suppose that the previous TB treatment with guideline-divergent regimens containing a fluoroquinolone resulted in the emergence of fluoroquinolone resistance in these patients. Despite availability of the free TB treatment in public health facilities through the national TB programme, previous TB treatment in the private health sector of 41.8% of the current study participants is a finding of concern, especially when there are reports of TB mismanagement in the private sector [14, 15] and its association with high incidence of ofloxacin resistance [14]. This emphasises that national TB programmes should urgently consider innovative ways to make the public health sector more appealing and trustworthy, and train private practitioners in TB management. The concerned health authorities should adopt more restrictive policies to control non-prescription sale of fluoroquinolones, scale up the efforts to improve public awareness about TB and the hazards of self-medication with antibiotics. As the present study included patients from a widely distributed geographical area of two different provinces of Pakistan, we believe that our findings reasonably reflect the drug resistance pattern of MDR-TB patients at other units for programmatic management of drug-resistant TB in the country.

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