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Applicability of the shorter 'Bangladesh regimen' in high multidrug-resistant tuberculosis settings☆

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SUMMARY

In spite of the recent introduction of two new drugs (delamanid and bedaquiline) and a few repurposed compounds to treat multidrug-resistant and extensively drug-resistant tuberculosis (MDR- and XDR-TB), clinicians are facing increasing problems in designing effective regimens in severe cases. Recently a 9 to 12-month regimen (known as the 'Bangladesh regimen') proved to be effective in treating MDR-TB cases. It included an initial phase of 4 to 6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol, followed by 5 months of moxifloxacin, clofazimine, pyrazinamide, and ethambutol. However, recent evidence from Europe and Latin America identified prevalences of resistance to the first-line drugs in this regimen (ethambutol and pyrazinamide) exceeding 60%, and of prothionamide exceeding 50%. Furthermore, the proportions of resistance to the two most important pillars of the regimen – quinolones and kanamycin – were higher than 40%. Overall, only 14 out of 348 adult patients (4.0%) were susceptible to all of the drugs composing the regimen, and were therefore potentially suitable for the 'shorter regimen'. A shorter, cheaper, and well-tolerated MDR-TB regimen is likely to impact the number of patients treated and improve adherence if prescribed to the right patients through the systematic use of rapid MTBDRsl testing.

1. Introduction

The World Health Organization (WHO) recently published its End TB Strategy, stressing the importance of diagnosing, treating, and preventing both multidrug-resistant (MDR)- and extensively drug-resistant (XDR-) tuberculosis (TB).[1–3] MDR-TB is defined as resistance to at least rifampicin and isoniazid, the two most effective anti-TB drugs, while XDR-TB is a more severe form of MDR-TB with additional resistance to any fluoroquinolone and to injectable second-line drugs (amikacin, capreomycin, kanamycin).

The Strategy also states the possibility of eliminating TB through the implementation of specific interventions that are currently recommended for low TB incidence countries.[4,5] Among the eight core interventions, the management of MDR-TB has an important role.[4,5]

MDR- and XDR-TB represent a growing clinical and public health concern, with over 480 000 cases and 190 000 deaths estimated to have occurred globally in 2014.[1] In spite of the progress achieved,[6] only a proportion of existing MDR- and XDR-TB cases have access to quality diagnosis[1,7] and treatment, with treatment being long (up to 24 months), expensive, and complicated by severe adverse events.[2,3,6–12] Furthermore, treatment outcomes are still unsatisfactory, with treatment success

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rates remaining suboptimal, and success rates decreasing progressively from 50% in MDR-TB cases to 40% in XDR-TB cases and less than 20% in cases with resistance patterns beyond XDR-TB.[2,3,13,14]

Following more than 40 years of neglect since the launch on the market of the last TB-specific drug (rifampicin), the available armamentarium of anti-TB drugs currently includes two new drugs (delamanid and bedaquiline) and a few repurposed compounds.[9,15–25] As clinical experience with these new drugs and some of the repurposed drugs is still limited, and the number of drugs for which susceptibility is confirmed is often very limited,[20–22] clinicians face more and more difficulties in designing effective regimens as per WHO guidelines.[16]

Recent evidence suggests that a 9 to 12-month regimen (known as the 'Bangladesh regimen') may be effective in treating MDR-TB cases (Table 1).[26–28]

As part of the ALAT/ERS LATSINTB project (a research coordination project), the present article describes the rationale for the introduction of the Bangladesh or 'shorter regimen' to treat MDR-TB, the principles of the new 2016 WHO recommendations, and the main operational issues related to their implementation under programmatic conditions in high MDR-TB prevalence settings.

2. Rationale for the shorter regimen and the new WHO guidelines

The rational composition of this new regimen is similar to that of the traditional 24-month one, with a consistent number of drugs and the inclusion of a fluoroquinolone, a second-line injectable drug, and two other 'companion' drugs (e.g., drugs supporting the core drugs to prevent the selection of drug-resistant mutants).[13,15,16] However, in the new regimen moxifloxacin is 'the' fluoroquinolone, while clofazimine replaces cycloserine. The Bangladesh regimen includes an initial phase of 4 to 6 months of kanamycin, gatifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol, followed by 5 months of gatifloxacin, clofazimine, pyrazinamide, and ethambutol.[13,14,16]

Based on the available evidence, the WHO has recommended this shorter MDR-TB regimen in its new 2016 MDR-TB guidelines, with moxifloxacin replacing gatifloxacin (originally used in the Bangladesh regimen).

The new regimen, which is much cheaper than longer ones (<1000 dollars),[8,16] is indicated only for "adults and children with rifampicin-resistant and MDR-TB who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents have been excluded or considered highly unlikely".[16] The indication also includes people living with HIV/AIDS.[16] A summary of the composition of the regimen and a list of the recommended exclusion criteria for the shorter TB regimen in favour of the longer regimen are given in Table 2.

The same WHO guidelines recommend a diagnostic tool designed to speed up the detection of TB resistance – the rapid molecular MTBDRsl test.[16] The promotion of broader and quicker molecular testing will ensure the appropriate selection of patients who will benefit from the shorter MDR-TB regimen, while reducing the 'infectious period' and the subsequent transmission of resistant strains of *Mycobacterium tuberculosis* within the community. Furthermore, the rapid initiation of an adequate regimen will minimize the possible development of additional drug resistance ('super-resistance'), which is among the criteria defining 'treatment failure' in the 2015 WHO definitions.[1]

3. Operational issues and evidence of eligibility for the shorter regimen

This is a concrete demonstration of the genuine efforts being made to provide wider access to quality MDR-TB diagnostic and

Table 1
Evidence available on the efficacy and safety of the shorter regimen (known as the Bangladesh regimen) to treat multidrug-resistant tuberculosis

Study (Ref.)	Setting/number of cases	Study results	Conclusions	Comments
Piubello et al. Int J Tuberc Lung Dis 2014 (26)	Niger National Tuberculosis Programme; 65 MDR-TB patients	Cure was achieved in 58 patients (89.2%, 95% CI 81.7–96.7); 6 died and 1 defaulted; all 49 patients assessed at the 24-month follow-up after cure remained smear- and culture-negative	Standardized 12-month treatment for MDR-TB was highly effective and well tolerated in patients not previously exposed to second-line anti-TB drugs in Niger	The main adverse events were vomiting (26.2%) and hearing impairment (20%), but no treatment had to be stopped; 1 patient HIV-infected (1.7%)
Van Deun et al. Am J Respir Crit Care Med 2010 (27)	Prospective observational study conducted over a 12-year period in this large TB control program in Bangladesh; 427 MDR-TB patients	206/427 (48.2%) patients received the most effective treatment regimen; a minimum of 9 months of treatment with GFX, CFZ, EMB, and PZA throughout the treatment period, supplemented by PTO, KM, and high-dose INH during an intensive phase of a minimum of 4 months, giving a relapse-free cure of 87.9% (95% CI 82.7–91.6)	Serial regimen formulation guided by overall treatment effectiveness resulted in treatment outcomes comparable to those obtained with first-line anti-TB treatment; confirmatory formal trials in populations with high levels of HIV co-infection and in populations with a higher initial prevalence of resistance to second-line anti-TB drugs are required	Major adverse drug reactions were infrequent and manageable Compared with the 221 patients treated with regimens based on OFX and commonly PTO throughout, the hazard ratio of any adverse outcome was 0.39 (95% CI 0.26–0.59)
Aung et al. Int J Tuberc Lung Dis 2014 (28)	Bangladesh National Tuberculosis Programme; prospective, observational study of a GFX-based directly observed regimen, mainly with initial hospitalization; 515 MDR-TB patients	515 patients were recruited from 2005 to 2011, 84.4% had a bacteriologically favourable outcome; due to extensive disease with delayed sputum conversion, only half of the patients completed treatment within 9 months; 95% completed treatment within 12 months; 11 patients failed or relapsed, and 93.1% of the 435 patients who were successfully treated completed at least 12 months of post-treatment follow-up	The excellent outcome of the Bangladesh regimen was largely maintained; bacteriological treatment failures and relapses were rare, except among patients with high-level GFX resistance, notably in the presence of PZA resistance	The strongest risk factor for a bacteriologically unfavourable outcome was high-level FQ resistance, particularly when compounded by initial PZA resistance Low-level FQ resistance had no unfavourable effect on treatment outcome Amplification of drug resistance occurred only once, in a patient strain that was initially only susceptible to KM and CFZ

CFZ, clofazimine; CI, confidence interval; EMB, ethambutol; FQ, fluoroquinolone; GFX, gatifloxacin; INH, isoniazid; KM, kanamycin; MDR-TB, multidrug-resistant tuberculosis; OFX, ofloxacin; PTO, prothionamide; PZA, pyrazinamide; TB, tuberculosis.

Table 2
Composition of the shorter regimen (known as the Bangladesh regimen) to treat multidrug-resistant tuberculosis, and the main contraindications suggesting prescription of the longer regimen[a]

Composition	
4–6 Km–Mfx–Pto–Cfz–Z–$H_{high\text{-}dose}$–E/5 Mfx–Cfz–Z–E: 4 to 6 months of kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol, followed by 5 months of moxifloxacin, clofazimine, pyrazinamide, and ethambutol	
Contraindication	**Comments**
Confirmed resistance to or suspected ineffectiveness of a drug in the shorter MDR-TB regimen (except isoniazid resistance)	Evaluation of the drug resistance pattern of all patients with rapid diagnostic methods is recommended
Exposure to ≥1 second-line drugs in the shorter MDR-TB regimen for >1 month	
Intolerance to ≥1 drugs in the shorter MDR-TB regimen or risk of toxicity (e.g., drug–drug interactions)	Intolerance to a drug composing the regimen is, in practice, equivalent to resistance to the drug
At least one drug in the shorter MDR-TB regimen not available	
Pregnancy	Insufficient evidence available
Extrapulmonary disease	Insufficient evidence available

MDR-TB, multidrug-resistant tuberculosis.
[a] Note: The emergence of treatment failure, drug intolerance, return after an interruption >2 months, or emergence of any other exclusion criterion implies interruption of the shorter regimen and a move to the longer one.

treatment services in high MDR-TB prevalence countries. Following the endorsement of the shorter MDR-TB regimen, clinicians and public health experts have started posing three questions:

(1) Under programmatic conditions, what is the proportion of patients who might not be eligible for the shorter regimen in reference centres or settings concentrating on difficult-to-treat MDR-TB cases (e.g., those exposed to several previous rounds of treatment or with previous treatment failure)? In other words, what proportion of cases will be eligible for treatment with the shorter MDR-TB regimen in programmatic (non research) settings?
(2) In countries or settings with sub-optimal laboratory services, will it be possible to use the shorter regimen based on epidemiological surveillance data or periodic drug resistance surveys?
(3) In the case of resistance to one or two of the drugs in the regimen, can compromised drugs be substituted in order to maintain the efficacy of the regimen, and if so, to what extent?

In summary, the regimen is for MDR-TB cases not previously treated with second-line anti-TB drugs and, therefore, should not be used in the case of (a) previous use of any of the Bangladesh regimen drugs, and (b) documented or suspected resistance to one or more of them.[16]

Initial evidence is available only for the first question. A recent multi-centre, observational, retrospective, cohort study of the International Carbapenems Study Group (ICSG) was conducted in reference MDR-TB centres in Europe (eight countries) and Latin America (three countries).[13,14] All of the drugs in the Bangladesh regimen were routinely tested in the participating centres, except high-dose isoniazid and clofazimine. The study found that only 14 out of 348 adult patients (4.0%) were susceptible to all of the drugs, and were therefore potentially suitable for the 'shorter regimen'.[13] Interestingly, the prevalence of resistance to the first-line drugs in the regimen (ethambutol and pyrazinamide) exceeded 60% and that of prothionamide exceeded 50%. Furthermore, the proportion of resistance to the two most important pillars of the regimen – quinolones and kanamycin – exceeded 40%. The prevalence of resistance to these two drugs was higher in Latin American than in Europe. The authors concluded that the shorter MDR-TB regimen "would have an impact on only minority of patients and may have limited use in these settings where patients have more resistant forms of TB and are more treatment experienced (like in reference centres)". However, the limited sample size, non-representativeness of the data with the possibility of selection bias, and the limited reliability of drug susceptibility testing to pyrazinamide and ethambutol (even when performed in quality assured laboratories) should be considered when interpreting the results of that study. In addition, no reliable drug susceptibility testing is yet available for clofazimine and ethionamide.[13]

This study confirmed the results of previous non-representative cohorts that identified prevalence rates around 30% for fluoroquinolones, 60% for ethambutol, 70% for pyrazinamide, 45% for prothionamide and 70% for kanamycin in a sample of patients in Europe, with strong representation of MDR-TB hot spots like Romania and former Soviet Union countries.[29] As these studies were not designed to evaluate the Bangladesh regimen, they did not provide information on how many patients would potentially have benefitted from the regimen.

A final comment is that we need more information on the suitability of patients for high-dose isoniazid. The existing evidence suggests that high-dose isoniazid is effective in the presence of the *inhA* gene mutation and in absence of the *katG* mutation. This combination is estimated to be present in no more than 12% of patients globally, with lower values in Africa.

The answer to question 2 is not available, and it is the authors' opinion that caution is needed in assuming that no drug resistance exists in low MDR-TB prevalence settings; testing all cases is the best option.

As far as question 3 is concerned, it is likely that kanamycin will be replaced by capreomycin or amikacin, although these modifications will increase the cost of the regimen.[13] It is also possible that, in view of resistance to one or more drugs in the regimen, clinicians might decide to replace them with the new drugs (delamanid, bedaquiline) or with the most effective repurposed drug (although more prone to adverse events), e.g. linezolid. It is important to underline that these changes are not recommended, as no evidence currently exists regarding the possibility of modifying the regimen with these drugs while keeping the short duration profile (and ensuring tolerability, efficacy, and adherence).[13]

4. Conclusions

In conclusion, a shorter, cheaper, and well-tolerated MDR-TB regimen is likely to impact the number of patients treated and improve adherence.[13,14] The preliminary evidence available on the country- or setting-specific prevalence of resistance to the drugs in the regimen needs to be expanded, taking into account that high combined resistance to fluoroquinolones and pyrazinamide might represent the main limitation to the success of the new regimen.[28,30]

A core factor in facilitating the appropriate use of the new regimen will be the systematic use of rapid MTBDRsl testing, so that the regimen is prescribed to the correct patients.

The increasing possibility of dosing blood levels of the different drugs through therapeutic drug monitoring (TDM) will further improve the tolerability of the shorter regimen (as well as that of the longer one) in the coming future, while increasing treatment adherence.

Importantly, the role of expert discussion (cohort discussion and 'consilia') to support clinical decisions in difficult-to-treat cases needs, once more, to be emphasized.[31]

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