УДК 616-002.5

Current options for the management of multidrug-resistant tuberculosis (review)

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Современные возможности контроля за туберкулезом с множественной лекарственной устойчивостью (обзор)

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Summary

Multidrug-resistant tuberculosis (MDR-TB) is a major threat to tuberculosis control in many parts of the world. The current options for managing this form of the disease are an optimal use of existing drugs, use of re-purposed or new drugs and some non-antibiotic therapeutic options. The prevention of the creation and transmission of drug-resistant strains will be crucial for the global management of tuberculosis in the future.

Keywords: tuberculosis, drug-resistant tuberculosis, MDR-TB

Резюме

Туберкулез с множественной лекарственной устойчивостью (МЛУ-ТБ) представляет серьезную угрозу для системы контроля распространения инфекции во многих частях света. Современными мерами управления этой формой заболевания являются: оптимальное использование существующих препаратов, применение новых и потенциальных (использовавшихся ранее, но по иным показаниям) лекарственных средств и некоторых иных терапевтических возможностей, не связанных с назначением антибиотиков. Предотвращение формирования и распространения лекарственно-устойчивых штаммов будет иметь решающее значение для глобального контроля туберкулеза в будущем.

Ключевые слова: туберкулез, лекарственно-устойчивый туберкулез, МЛУ-ТБ

Multidrug-resistant tuberculosis, defined as the resistance of *M. Tuberculosis* against isoniazid and rifampicin, usually under the acronym of MDR-TB, represents currently one of the major problems for the control of tuberculosis and a serious obstacle to the elimination of the disease in many parts of the world [1, 2]. If the mycobacteria have additional resistance, for instance against the two best reserve drugs which are the injectable second-line drugs (amikacine, kanamycin and capreomycin) and the fluoroquinolones (a form called extremely drug-resistant tuberculosis or XDR-TB), the problem is even more serious.

Drug-resistant strains of *M. Tuberculosis* have been observed shortly after the introduction of the first antituberculous drugs [3]. The tendency of mycobacteria, like all bacteria, to mutate and develop resistance to antibiotics is common and has been the reason for the recommendation of combined treatment with at least three drugs in order to reduce the risk of development of resistance to several drugs simultaneously. Unfortunately, due to many reasons, this may still happen. Once the mycobacteria have become resistant to one or more drugs, they tend to develop resistance to addi-

tional drugs, particularly of the resistance pattern is not discovered in due time and an inappropriate treatment is used instead of an efficient treatment. Inappropriate treatment of tuberculosis, particularly in cases where the treatment was initiated without testing the drug sensitivity, is a major cause of development of drug resistance [4]. Underdosing of first-line drugs, for instance rifampicin, may also be one of the causes of emergence of resistant strains [5, 6]. Interestingly, it has been demonstrated that some antituberculous drugs do not penetrate in sufficient amounts in the locations where the mycobacteria are present and this could create permanent or temporary periods of underdosing and gradual creation of drug resistance [7].

Drug-resistant tuberculosis was a rare event in the last half of the 20th century, and it was assumed that the vast majority of cases of tuberculosis could be cured with a standard drug treatment. For that reason, it was not considered a priority to perform a drug sensitivity test for all mycobacterial strains before the initiation of therapy. Over the last decade, the situation has changed and the number of drug-resistant strains, particularly MDR-TB and XDR-TB, seems to increase dramatically, reaching half a million cases each year [8]. The consequences are a very high burden to the local management programmes, as the treatment of drug-resistant TB is usually much more costly, long and difficult than the treatment of drug-sensitive TB. Furthermore, the results of treatment are less favourable than expected, with high rates of failure, death and recurrence [9]. One of the worrying points is the fact that, contrary to the ancient opinion that most patients with drug-resistant TB had a relapse of a prior, uncorrectly treated episode of TB (and could be suspected from the history), a large proportion of cases is now observed among new patients, who were contaminated by a resistant strain and remain unsuspected if no drug sensitivity test are performed at initiation of treatment [10]. In some regions of the world, it can be expected that in a near future the number of cases of MDR-TB may be superior to the number of drug-sensitive cases, with major consequences on the selection of initial treatment and costs for the programme [11]. The emergence of drug-resistant tuberculosis is one of the main reasons for the current recommendation to perform a drug sensitivity test at the time of diagnosis of TB, if possible by a rapid method allowing for the initiation of an adequate treatment in case of resistance to one of the main anti-TB drugs [12]. The recent introduction of rapid genetic methods for the detection of mycobacterial DNA and mutations associated with rifampicin resistance has been an important progress [13].

Facing the magnitude of the problems and the unsatisfactory results obtained in many settings, specific guidelines and recommendations for the management of M/XDR-TB have been issued [12, 14]. Several options have been proposed and will be discussed in this short review:

1. Optimal use of existing drug treatment.
2. Use of re-purposed drugs.
3. Use of new drugs.
4. Non-pharmacological treatment.

Optimal use of existing drug treatment

Antituberculous drugs are not very numerous and, if isoniazid and rifampicin cannot be used because of drug resistance, the remaining options are few. If the resistance pattern is limited to isoniazid and rifampicin, it is still possible to obtain satisfactory results with the use of the remaining available drugs. In case of associated resistance to other drugs, the choice is limited and recourse to second-line drugs is mandatory. It is important to remember that the level of resistance to some main drugs, for instance isoniazid, is variable, depending which genetic mutation is present [5, 15]. For instance, in mutations involving *inhA*, the mycobacteria may still exhibit partial sensitivity to isoniazid, and the drug may be of use, particularly if prescribed in dose higher than usual. This confirms that drug sensitivity testing is necessary in all cases with suspected or proven drug resistance and that obtaining a genotyping of the strain with determination of the precise mutations involved may be of great value for the selection of an appropriate drug treatment [16].

Use of re-purposed drugs

Several drugs now used for the treatment of drug-resistant tuberculosis were developed for the treatment of infections others than tuberculosis, like leprosy or severe, life-threatening bacterial infections. Among the drugs which were not developed initially as antituberculous drugs but demonstrated activity against *M. tuberculosis*, fluoroquinolones, clofazimin, carbapenems and linezolid are the most important ones.

Recently, the WHO proposed that all drugs active against drug-resistant strains may be re-classified according to their potency [12]. Rifampicin is absent from this list but high-dose isoniazid (as mentioned before) is included.

Fluoroquinolones (moxifloxacine, levofloxacin) are now classified as the first group of second-line antituberculous agents, due to their potency, good tissue penetration and satisfactory tolerance (although some adverse events need consideration) [17]. To note, some quinolones are also no more recommended (ciprofloxacin and ofloxacin) due to their lower efficacy. Fluoroquinolones are readily available and cheap. In some regions of the world, due to widespread use of quinolones for diverse infectious diseases unrelated to tuberculosis, the rate of

mycobacterial resistance to quinolones is high and may be an obstacle to their use as antituberculous agents [18].

Among the second-line injectable agents, streptomycine is mentioned conditionally, depending on the local rate of resistance, which may be high.

Linezolid, now classified among the core second-line agents, has a potent bactericidal action but is associated with frequent and severe haematological and neurological adverse events [19]. Sutezolid, a parent drug, may have a similar potenmcy but less adverse events.

Clofazimin, initially developed as an antituberculous drug but then used as an anti-leprosy drug, may contribute to the elimination of persistant mycobacteria and was a core complnent of the short «Bangladesh regimen». It is cheap but provoques frequent cutaneous side effects [20].

Carbapenems (imipenem, meropenem, ertapenem) are potent bactericidal drugs which have also demonstrated very good activity against *M. Tuberculosis* [21]. Their efficacy is increased by the combination with clavulanate (only available as amoxycillin/clavulanate). They have to be injected but new oral formulation (tebipenem) will be much easier to administer.

Some of the main problems associated with the prescription of second-line drugs is their high price, limited availability and frequent intolerance [22]. If available, affordable and tolerated, some second-line drugs demonstrate a high efficacy. All current guidelines recommend the use of one fluoroquinolone (cat A) combined with one of the second-line injectable agents (cat B), two other core second-line agents (cat C) with add-on agents (cat D) depending the drug sensitivity of the strain. The recommendations are to use at least 5 drugs likely or documented to be effective during the intensive phase, including pyrazinamid (except if the resistance has been unequivocally documented). The recommended duration of treatment with this combination is 8 months. After this intensive phase, the injectable drug is usually omitted from further treatment and the regimen is continued for a total duration of 20 months on average. The total duration of the treatment depend of the evolution of bacteriology,

Table

Drugs[1] recommended for the treatment of rifampicin-resistant or multidrug-resistant tuberculosis (from ref 7)

A. Fluoroquinolones[2]		Levofloxacin Moxifloxacin Gatfloxacin	Lfx Mfx Gfx
B. Second-line injectable agents		Amikacin Capreomycin Karamycin (Streptomycin)[3]	Am Cm Km (S)
C. Other core second-line agents[2]		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide Ethambutol High-dose isoniazid	Z E H^h
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	p-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin-clavulanate[4] (Thioacetazone)[5]	Pas Ipm Mpm Amx-Clv (T)

[1] This regrouping is intended to guide the design of conventional regimens; for shorter regimens lasting 9–12 month the composition is usually standardised (See Section A).

[2] Medicines is Froups A and Care shown by decreasing order of usual preference for use (subject to other considerations; see text).

[3] Refer to the text for the conditions under wich streptomycin may substitute other injectable agents. Resistance to streptomycin alone does not qualify for the definition of extensively drug-resistent TB (XDR-TB) (26).

[4] Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin.

[5] HIV-status must be tested and confirmed to be negative before thiocetazone is started.

therefore the performance of monthly cultures is recommended as a monitoring tool during the follow-up and for the assessment of the outcome of treatment.

Recently, several publications have reported high rates of successful outcome in patients with MDR-TB treated with a shorter regimen associating 7 drugs during the intensive phase of 4 to 6 months and 5 drugs during the continuation phase [23–25]. This so-called «Bangladesh regimen» has attracted attention because of its reduced duration and costs compared to the standard recommended regimen of 18 to 24 months advocated by WHO and most National Guidelines, and is now included in the latest Guidelines from WHO [12]. It should be noted that this regimen cannot be used in patients with resistance against several additional drugs, particularly fluoroquinolones. In case of resistance against fluoroquinolones, the rate of cure drops from 87,4% to 51% [24]. Therefore, the latest Guidelines from WHO and some recent publications insist that the short-course regimen can only be used under specific conditions [26]. If used indiscriminately, without careful monitoring of drug resistance before the initiation of treatment, the short regimen may create further resistance and foster relapse or the development of XDR-TB [27].

New drugs

Two new drugs, bedaquilin and delamanid, have recently been released into the market, nearly 60 years after the last release of an active antituberculous drug (rifampicin). Both have been approved by some (but not all) regulatory agencies and should be soon available in most countries affected with MDR-TB. Both drugs seem to be very active against *M. Tuberculosis* and have a satisfactory safety profile, although a close monitoring of ECG is recommended, because of possible prolongation of the QT interval, particularly if used in combination with other drugs demonstrating similar adverse events (moxifloxacin, clofazimin).Recently, the WHO issued recommendations about their use [28, 29]. Currently, bedaquilin and delamanid should be used only in patients with M/XDR-TB for whom an efficient regimen with 5 active drugs cannot be designed, due to additional resistances or intolerance to existing drugs. Many trials are ongoing and it is quite possible that the recommendations for the use of the new drugs may change in the future. There is currently no evidence that one of the new drugs is preferable to other one, although their mode of action is quite different.

The current limitations to the use of bedaquiline and delamanid are the very high price of the drugs and their limited availability in many regions of the world. Both factors may change in the future with adaptation of the commercial price, introduction of generics and widespread distribution of the drugs after approval by the regulatory authorities. One potential problem in the future will be the expected emergence of resistance against one or both the new drugs, which unfortunately has already been observed [30].

The simulatenous use of bedaquiline and delamanid is not recommended, mainly because of lack of evidence and concern about the risk of QT prolongation, but there are individual case reports of such use without adverse events and with a satisfactory outcome [31, 32].

According to a recent estimation, if the use of bedaquiline and delamanid is considered for patients with risk factors for unfavourable outcome with the currently available drugs, like resistance to fluoroquinolones, XDR-TB, history of previous treatment with second-line drugs, high bacillary load, low BMI or past incarceration, there could be an indication for one or both new drugs in nearly two-thirds of patients with MDR-TB [33]. The financial and logistical consequences or this fact may be immense.

Perchlozone, a close parent drug to thiacetazone, has recently been introduced on the Russian market [34]. According to preliminary studies, the drug seems to improve the rate and timing of bacterial negativation in drug-sensitive and drug-resistant TB, but there is up to now no large-scale controlled study to support these preliminary results and the drug is not available outside Russia. Therefore, it has not been included in the current recommendations by WHO.

Non-antibiotic treatment of MDR-TB

Many attempts have been undertaken to improve the outcome of patients with tuberculosis, even long before the introduction of antibiotics. Globally, the attempts can be classified in different categories:

a) Interventions to restore deficient immune response or increase the natural defence mechanisms;
b) Interventions to decrease the formation of granulomas and the escape of infectious agents from immune system and antituberculous drugs;
c) Interventions do decrease the bacterial burden.

Many interventions aim at improving failing defence mechanisms or increasing the natural immune defence capacity. The best known of these interventions is the use of antiretroviral therapy (ART) in patients with HIV infection, to restore the capacity of the immune system to control bacterial infections. Rapid initiation of ART in patients with TB/HIV coinfection improves survival [35] and extended availability of ART decreases the transmission of tuberculosis in high-risk populations [36]. Other interventions, targeting patients with intact immune system, like immunostimulation or supplementation with IFNgamma or diverse cytokines, yielded conflicting results and seem

to be little effective [37, 38]. Vaccination with BCG has some efficacy in protecting small children exposed to tuberculosis from severe and disseminated forms of the disease but its protective role in adults is much less convincing. Unfortunately, trials with new vaccines have not yet been successful [39].

As the granulomas seem to protect the mycobacteria from the immune system and from the action of antibiotics, some studies have tried to disrupt granulomas or inhibit their formation with immunosuppressive drugs (anti-TNF and steroids) and have demonstrated an acceleration of the bacteriological response or a decrease of the risk of relapse [40]. None of these attempts has gained general acceptance or conducted to firm recommendations. Another approach is the administration of drugs by inhalation, in order to obtain high concentrations close to the location of granulomas. This approach has been used experimentally for the administration of isoniazid, rifampicin, amikacin, pyrazinamid and levofloxacin and seems promising, but no drug (apart from amikacin) is currently available for generalized use for the treatment of tuberculosis [41, 42].

Interventions to decrease the bacterial burden have been used long before the introduction of antibiotics, based on the assumption that the immune system of the patient can cope more easily with a limited bacterial population than with an overwhelming infection. Collapse therapy, in form of thoracoplasty or artificial pneumothorax and surgical removal of affected lung tissue, have been used extensively, with controversial results. Recently, attempts have been made to reintroduce collapse therapy by the placement of intrabronchial valves in the airways of patients with intractable forms of M/XDR-TB [43]. Recent reviews of the evidence supporting surgical intervention in cases where the pharmacologic treatment is inefficient, have been published [44] and recommendations have been issued by the Regional Office for Europe of WHO [45]. The consensus is that the role of surgery is limited to the cases of M/XDR-TB for whom the possibilities of pharmacological treatment are limited and in whom surgery is still possible.

Conclusions

The management of M/XDR-TB is difficult, long, expensive and associated with high rates of adverse events, human suffering, failure, and death. It is cost-effective but extension of effective treatment to large populations may need substantial additional investmentstg [46]. Furthermore, in spite of all recommendations and the recent introduction of new drugs — which are still very expensive and not available everywhere — the number of cases is increasing. There is also a serious concern that the number of cases may increase because transmission of drug-resistant strains to bystanders is progressing without obstacle, particularly in family circle, hospitals, prisons and congregate settings, and that the preventive treatment of infected contacts is not standardized. If things progress in the same rate, the price to pay for the management of drug-resistant tuberculosis may soon overburden the capacity of many national programmes [47]. In spite of this, attention to M/XDR-TB should not divert resources from the correct management of drug-sensitive TB.

Apart from improvements in the pharmacological management of drug-resistant cases, a place has to be made for all measures which could contribute to the decrease in this huge burden. Prevention of the creation and transmission of drug-resistant strains is too neglected and has to be addressed adequately [48]. MDR-TB exists in large part because drug-sensitive cases have not been treated adequately and mycobacteria have been allowed to develop resistance against the best first-line drugs. Drug resistance does not fall from heaven and is not the result of some unavoidable curse. Avoidance of failure and relapse of new cases of tuberculosis, by ensuring the cure of drug-sensitive cases, is probably one of the main issues for the prevention of drug resistance.

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Поступила в редакцию 01.01.2017 г.

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