Multidrug-resistant Tuberculosis – From Epidemiology to Treatment Design

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Abstract

Multidrug-resistant tuberculosis (MDR-TB) and extensively resistant tuberculosis (XDR-TB) are present in most regions of the world and represent a serious threat to the control of tuberculosis. They usually result from errors somewhere along the chain of management of the disease that favoured the selection of resistant mutants, progressively replacing drug-sensitive strains and transmitted to further patients. The currently recommended strategies for the control of this serious situation is the rapid identification of drug-resistant strains, careful drug management of patients with second-line drugs and prevention of the transmission of mycobacteria to contacts. Optimal selection and number of drugs and duration of treatment are not clearly defined. Prevention of the creation of additional cases of MDR-TB is crucial.

Keywords

Tuberculosis, multidrug-resistant tuberculosis (MDR-TB), extensively resistant tuberculosis (XDR-TB), treatment

Disclosure: Jean-Pierre Zellweger has no conflicts of interest to declare. No funding was received for the publication of this article.

Received: 27 May 2015 **Accepted**: 19 June 2015 **Citation**: *European Respiratory and Pulmonary Diseases*, 2015;1(1):20–24 *DOI: 10.17925/ERPD.2015.01.01.20*

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Epidemiology

Strains of *Mycobacterium tuberculosis* (*M. tbc*) are able, like other bacteria, to develop resistance against antibiotics. The first observations were published shortly after the introduction of streptomycin and were the basis of the current recommendation of combining several antibiotics for the treatment of tuberculosis (TB).[1] Rigorous application of this principle could have possibly prevented the development of drug resistance. In spite of this, drug resistance against the most active antibiotics increased progressively and is currently a widespread phenomenon. Apart from resistance against single drugs, resistance against the two most active anti-TB drugs, isoniazid and rifampicin, known as multidrug resistance (MDR-TB), has increased and new forms of resistance have emerged, like the resistance against isoniazid, rifampicin, injectable drugs and quinolones, known as extensively drug-resistant strains (XDR-TB).

The latest reports from the World Health Organization (WHO) estimate the number of MDR-TB to half a million cases, of which 10 % are XDR-TB, a large part being left untreated, with a high death burden.[2] In some regions of the world or in some at-risk populations, like gold miners in South Africa, the rate of MDR-TB is increasing rapidly, particularly in previously treated cases, in spite of the fact that the global incidence rate in the same population had decreased during the same time period.[3] Recent reports reveal alarming levels of drug-resistant TB in many Eastern European regions,[4] such as Belarus, where the rates reach 35.3 % in new patients and 76.5 % among previously treated cases[5] or in Ukraine, where the association with HIV seems to increase the problem.[6] In Russia, if the current trends continue, the incidence of drug-resistant TB could be higher than the incidence of drug-sensitive TB within the next few years.[7] Prisons seem to be places where the incidence of TB (including drug-resistant forms) is particularly high.[7,8] In China, a recent survey concluded that the proportion of MDR-TB cases among new and previously treated patients is 5.7 % and 25.6 %, respectively, and the total number of MDR-TB cases is about 110,000.[9] The increase in drug-resistant TB is also observed in children in some regions of the world.[10]

Risk Factors for MDR-TB

Most surveys report an association between previous treatment for TB and high rates of drug resistance.[11,12] The prevalence of MDR-TB is higher among patients who were already treated for TB and failed or recurred, but this group represents only a minority among all cases of TB. In absolute numbers, the majority of cases is observed in new patients, who never received a treatment before and who were contaminated by a patients harbouring a resistant strain.[13] As a consequence, in some regions of the world, new patients are at high risk of having MDR-TB even in the absence of previous treatment.

Apart from close contact with a patient with drug-resistant TB, other factors associated with the presence of MDR-TB are migration, young age and HIV.[14]

One particular cause seems to be the induction of resistance by insufficient bioavailability of some anti-TB drugs such as rifampicin.[15] Low serum levels of anti-TB drugs, which are observed in some patients,[16] may induce the development of resistance against one or several drugs. Some studies have confirmed that patients with a low serum level of the first-line anti-TB drugs have a worse outcome than patients with a level within the expected range.[17] This may also explain why some patients develop a drug-resistant form of TB in spite of full adherence to a correct treatment.[18,19] One may suspect that drugs of low quality or insufficient

bioavailability may contribute to the creation of drug resistance. How important this phenomenon may be in the progressive extension of MDR-TB in some regions is unclear. Studies are ongoing to decide if the recommended dose of rifampicin will have to be changed in the future.[20]

Why is MDR-TB Increasing in Some Regions of the World?

There are many reasons for the increase of MDR-TB and XDR-TB worldwide, but they all have one point in common: there was some error along the chain of management, inducing a mutation in a strain of sensitive mycobacteria and the selection of mycobacteria that have become resistant to one or several antituberculous drugs, which will progressively replace the sensitive bacteria.[21] Among the usual causes are inappropriate treatment of mycobacteria with an undetected resistance against a single drug, use of drugs of bad quality, insufficient drug dosage, changes in drug schedule or dosage and addition of a single drug to a failing regimen. Retreatment of patients with a recurrent episode of tuberculosis with the same drugs as for the first episode, without appropriate drug susceptibility testing (DST), is a possible cause of amplification of the drug-resistance pattern and transformation of a strain with single drug resistance to MDR-TB. This can happen even under normal programmatic conditions, if the drug sensitivity testing is not performed in suspect cases.[22,23] Patients with an unsuspected drug resistance who are not cured at the first treatment attempt have a high risk of developing further resistance and harbour an MDR-TB strain.[24–26] This is the reason why the ancient recommendation of WHO to use a retreatment regimen containing the same first-line drugs in addition to streptomycine, which has proven successful in settings with a low frequency of drug resistance,[27] has been put into question[28] and is now no more valid.[29] Furthermore, some strains, like the Beijing genotype, seem to mutate more rapidly and be more virulent so that in some regions they progressively replace the other strains.[30]

The practical issue is that in many settings, if the DST of the strain are not performed rapidly (which is the norm in many regions lacking proper laboratory equipment), patients with MDR-TB will receive inadequate treatment for several weeks or months before the correct diagnosis is made and an appropriate treatment is started. The consequence is that many MDR-TB patients will have a prolonged period of infectiousness and be a danger to other patients and to the staff. Furthermore, as the cure rate of patients with MDR-TB strains is lower than the cure rate in patients with sensitive strains, some patients with MDR-TB can become chronic excretors (the author has observed a case surviving 27 years with a smear-positive pulmonary TB resistant to all anti-TB drugs known in the 1970s).

Infectiousness and Transmission of MDR-TB Strains

The problem of the duration of the infectious period of patients with drug-resistant forms of TB is debated.[31] Animal models do not confirm the impression of a higher risk of transmission from drug-resistant TB cases[32] and the sputum positivity is not always correlated with the infectiousness.[33] In spite of this, many MDR-TB cases seem to have been acquired in a hospital[9] and infection-control measures should be considered with special attention in all settings where patients with MDR-TB are treated, in order to decrease the risk of transmission to other patients, visitors or healthcare workers.[34] A recent survey has demonstrated that, even in Europe, the current management of MDR-TB and XDR-TB, and in particular the infection-control measures, is far from optimal.[35] Active case finding among the contacts of patients with MDR-TB should be performed to detect the presence of other cases in the same social group. It is particularly important to assess if children with MDR-TB have been in contact with relatives with a similar form of TB.

Once the strain has become resistant to one or several drugs, it can be transmitted to contacts who may develop a similar disease without having been submitted to any previous error in management.[36] MDR-TB can be observed in patients who were never treated before and were infected by another case of MDR-TB (primary forms) or in patients who already received some form of drug treatment for tuberculosis and interrupted, relapsed or failed the first treatment attempt (secondary forms). The proportion of primary forms in a population reflect the current deficiencies of the programme to prevent the transmission of tuberculosis, whereas the secondary forms result from prior errors during the management of cases who received an incomplete or inappropriate treatment schedule.

The clinical forms of MDR-TB are similar to the forms due to drug-sensitive strains. The clinical presentation may be more severe, with extensive lesions, if the correct diagnosis and initiation of an appropriate treatment was delayed.

Treatment of MDR-TB

The emergence of *M. tbc* strains resistant to anti-TB drugs has been described as occurring rapidly after the introduction of streptomycin[37] and led to the concept of drug combination for the treatment of tuberculosis.[1] Until the 1990s and the rapid emergence of MDR-TB in New York,[38] the treatment was mainly empirical, with unsatisfactory results (44 % death or failure in the report by Goble in 1993[39]), until some attempts in standardisation were published, mostly relying on expert opinion.[40] Then, some of the basic principles of management of drug-resistant tuberculosis, like the rule of not adding a single drug to a failing regimen, have been defined, but were largely ignored by physicians in many regions of the world.

The first Guidelines on the management of drug-resistant tuberculosis, including MDR-TB, were published by the WHO in 1996.[41] The proposal was to administer 3 months of a combination of five drugs, always containing at least one injectable drug and a quinolone, followed by three oral drugs administered during 18 months. The Guidelines were revised in 2006 and 2008,[42] followed by a field guide in 2009.[43] A complete revision was published in 2011[44,45] and a new companion handbook in 2014.[46] Other Guidelines or recommendations have been published by the International Union against TB[47] and by the Tuberculosis Network European Study Group TBnet.[14] The rationale behind the new recommendations of WHO, which are more or less similar to other proposals from the recent literature,[48] is to treat the patient with the drugs that offer the highest possible prospect of rapid bactericidal action and to treat long enough to be certain to eradicate the last existing mycobacteria.

The current recommendations of WHO[2,44] for the treatment of MDR-TB include the following points:

- Rapid DST for isoniazid and rifampicin or at least of rifampicin alone, as a proxy for MDR-TB, in all cases suspect of MDR-TB (this may be all cases in some regions of the world).
- The treatment regimen should include four drugs with proven or likely effectiveness in the intensive phase, including an injectable drug, later-generation fluoroquinolone (no ciprofloxacine), ethionamide

Table 1: WHO Recommended Grouping of Anti-tuberculosis Drugs

Group Name	Anti-TB Agent	Abbreviation
Group 1: first-line oral agents	Isoniazid	H
	Rifampicin	R
	Ethambutol	E
	Pyrazinamide	Z
	Rifabutin	Rfb
	Rifapentine	Rpt
Group 2: injectable anti-TB drugs (injectable agents or parenteral agents)	Streptomycin	S
	Kanamycin	Km
	Amikacin	Am
	Capreomycin	Cm
Group 3: fluoroquinolones	Levofloxacin	Lfx
	Moxifloxacin	Mfx
	Gatifloxacin	Gfx
Group 4: oral bacteriostatic second-line anti-TB drugs	Ethionamide	Eto
	Prothionamide	Pto
	Cycloserine	Cs
	Terizidone	Trd
	Para-aminosalicylic acid	PAS
	Para-aminosalicylate sodium	PAS-Na
Group 5: anti-TB drugs with limited data on efficacy and/or long-term safety in the treatment of drug-resistant TB (this group includes new anti-TB agents)	Bedaquiline	Bdq
	Delamanid	Dlm
	Linezolid	Lzd
	Clofazimine	Cfz
	Amoxycilline/clavulanate	Amx/Clv
	Imipenem/cilastin	Ipm/Cln
	Meropenem	Mpm
	High-dose isoniazid	High-dose H
	Thioacetazone	T
	Clarithmycin	Clr

TB = tuberculosis; WHO = World Health Organization. From: Companion Handbook to the WHO Guidelines for the programmatic management of drug-resistant tuberculosis.[46]

or prothionamide, and either cycloserine or para-aminosalicylic acid (PAS).

- The recommended duration of the intensive phase is now 8 months, followed with at least 12 months of continuation therapy (after termination of the use of the injectable drug).
- Monitoring the response to MDR-TB treatment with smear and cultures.
- Addition of antiretrovirals in patients co-infected with HIV.
- The management of MDR-TB should be based mainly on ambulatory care and not hospitalisation, in order to limit the possible transmission to other patients, healthcare staff and visitors. Outpatient management needs the implementation of a well-functioning network of community workers and decentralisation of care close to the patient's residence.

The recommendations from WHO are based on the existing evidence, but there are still very few studies comparing different regimens and treatment options. The outcome of treatment as reported in observational studies and in the last WHO report is currently unsatisfactory,[49,50] with a success rate of about 50 % (documented cure or treatment completion), below the success rate for drug-sensitive TB. Interestingly, one of the only studies comparing several treatment options demonstrated that a high success rate (89.7 %) can be obtained by a 9-month regimen, including gatifloxacin, clofazimine, ethambutol and pyrazinamide throughout the treatment period supplemented by prothionamide, kanamycin and high-dose isoniazid during the intensive phase.[51] These results were confirmed by a large study of more than 500 patients in Bangladesh and by several studies in Africa.[52–54] Omitting the quinolone or the high-dose isoniazid or presence of a resistance to quinolones gave a lower rate of success. Although these results may not apply to other settings, particularly Eastern Europe with high rates of additional resistance, and gatifloxacine is not authorised in many countries, the results are interesting and demonstrate that the cure rate may be high, even with a shorter regimen. Further studies are currently ongoing to confirm these findings.

The list of second-line drugs, which may be used for the treatment of MDR-TB and XDR-TB, is presented in *Table 1* (after WHO).[2] Among the first-line drugs, isoniazid and rifampicin are considered inactive by definition and will not be used, but some experts recommend the use of isoniazid in higher doses, due to the fact that the resistance to isoniazid may not be complete.[55] The results from the study in Bangladesh seems to confirm this option.[51] The latest recommendations from WHO also propose to keep pyrazinamide in the treatment schedule, considering that the DST for pyrazinamide is not fully reliable and is not available in many laboratories.

Administering moxifloxacine in a normal or increased dose, in spite of resistance to quinolones, seems to improve the outcome, if the strain has retained an intermediate sensitivity.[56]

Several studies have demonstrated that linezolid is a potent antituberculous drug with good efficacy against most MDR-TB strains, but the use is limited by high costs and high frequency of adverse events.[57,58] Clofazimine, an anti-leprosy drug, is another drug with a potential efficacy against drug-resistant TB strains, and has been used in a 9-month regimen in Bangladesh, but the experience is still limited, the drug is not available in all countries and has not been approved for the treatment of TB.[59,60]

Other drugs with weak activity, such as meropenem, co-trimoxazole, clarithromycine, co-amoxycilline and thioridazide, may be considered in cases where the number of available drugs with proven activity is limited, particularly in cases with XDR-TB.[61]

The treatment of MDR-TB and XDR-TB is long, difficult, expensive and associated with a high rate of adverse events (up to 79 % in some reports).[62,63] The correct use of second-line drugs requires experience and a good knowledge of their effect and interactions.[64] Some adverse events will necessitate the addition of other drugs, increasing the number of drugs to be used and the cost of treatment. The costs of treatment of MDR-TB are much higher than the costs of treatment for drug-sensitive TB. In countries with limited resources or in regions where MDR-TB are a large proportion of all cases, the costs to a national TB programme may not be affordable.[65]

Surgery, which was one of the only options for cure before the antibiobic era, is again mentioned as one option in the framework of the treatment of drug-resistant TB. Its place has recently been revised.[66–68] In patients with a new episode of MDR-TB, unilateral lung involvement and good general condition, surgery seems to improve the outcome whereas in patients in retreatment, with XDR-TB, bilateral disease or low body mass index, the outcome is poor.

Drug-resistant stains can be transmitted to contacts. The evidence of the benefit of a preventive treatment for infected contacts is limited, but some studies seem to support a policy of preventive treatment according to the pattern of drug resistance of the index case.[69,70]

New Options

The current treatment options for MDR-TB are far from satisfactory, but are presently the best hope for a cure. New, more efficient, drugs have been recently introduced and may allow in the future an increase of the cure rate and a decrease of the duration of treatment. Recently, encouraging reports were published on the efficacy of delamanide (OPC67683),[71,72] bedaquiline (TMC207)[73] and pretonamid (PA-824),[74] which all have the potential of shortening the time to culture conversion and to improve the outcome. The WHO has issued policy documents on the use of bedaquiline[75] and delamanid,[76] but the new drugs have been approved in few countries only and the experience with them is still limited. QT prolongation induced by the new anti-TB drugs and by the combination with several other drugs, like quinolones and clofazimine, is a matter of concern and makes regular monitoring mandatory.[77] Errors in the use of the new drugs may increase the size of the problem in the populations, like the improper use of rifampicine after its introduction, which probably led to the development of MDR-TB. Therefore, the new drugs will have to be used under strict conditions, bearing in mind the potential negative consequences of further errors in management.

Prevention of MDR-TB

As long as there is no rapid, cheap and efficient treatment for MDR-TB, the best hope for the control of the problem is the prevention of the transmission of resistant strains in the population and the correction of errors, which may induce an increase or an extension of the MDR-TB strains.[78,79] The conditions for this, as detailed in a recent report from WHO,[80,81] are:

- The rapid detection of drug-resistant strains among all cases of tuberculosis, particularly among patients with relapse, failure or risk factors for resistance or among patients exposed to MDR-TB in their environment. This needs a well-functioning network of laboratories with the capacity for performing rapid DSTs. The use of the new molecular genotyping analysis (like MTB-RIF assays) have demonstrated a potential for shortening the delay of detection of drug resistance,[82-84] but there are financial obstacles to the broad implementation of such devices, particularly in places where they would be most needed. In the meantime and in the places where rapid technologies are not in place, it is the responsibility of the local TB programme managers (and the health authorities) to ensure that the more traditional methods are used in an efficient way, avoiding interruption in consumables delivery, use of inappropriate procedures and long delays in the transmission of the results to the clinicians.
- The appropriate treatment of all cases with proven or suspect drug resistance, in order to avoid the creation of further drug resistance (amplification phenomenon) and reduce the period of infectiousness and the duration of possible transmission to a minimum.
- Infection control measures, to limit the transmission of *M. tbc* strains to healthcare workers, other patients and visitors.
- The availability of quality-controlled second-line drugs, without interruption in drug delivery, stock-outs, administrative or financial obstacles.
- Proper case management until the cure of the patients, particularly for patients with risk of treatment interruption for any reason (deportation, imprisonment, travel, refusal, conflicts with local managers). If needed, decentralisation of care to facilitate the adherence has to be considered.[85] As stressed by members of the International Union against TB, *"a poor drug-resistant programme is probably worse than no programme at all"*.[86]

The Future

MDR-TB and XDR-TB are serious threats to the control of tuberculosis in many regions of the world, apart from HIV, and frequently simultaneously with it. They are an obstacle to the intended policy of TB elimination.[87,88] New drugs[89] may improve the outcome in the future, but need to be approved and available in the countries that need them most. New vaccines[90] may help to control the situation, but there is no real prospect for them in the near future.[91] Therefore, the best current option is an improvement of preventive measures, by a proper implementation and use of the diagnostic methods, careful selection of the appropriate treatment, efforts to obtain the cure of all new cases and infection control to avoid the further extension of the disease in the population.[92] If we fail, there may be a return to ancient times, where the cure of tuberculosis was mainly left to chance, sunlight, cod liver oil and bed rest in sanatoria.[93] ■

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