Which agents should we use for the treatment of multidrug-resistant Mycobacterium tuberculosis?

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The inappropriate treatment of drug-susceptible tuberculosis can lead to the selection and transmission of multidrug-resistant tuberculosis (MDR-TB), indicating resistance to at least isoniazid and rifampicin. In the treatment of MDR-TB, residual first-line drugs, such as ethambutol, pyrazinamide and streptomycin must be appropriately combined with additional second-line drugs, guided by individual susceptibility patterns. The clinical pharmacology of these second-line antituberculous drugs is reviewed. Fluoroquinolones represent the only substantial therapeutic advance in the last 20 years. Many factors potentially affect the outcome of MDR-TB. Treatment adherence, prior exposure to antituberculous drugs, the number of drugs to which the infection is still susceptible and the time since the first diagnosis of tuberculosis are the most relevant. The management of MDR-TB requires considerable expertise. When initiating or revising therapy for MDR-TB, the process of selecting drugs should rely on prior treatment history, results of susceptibility testing and an evaluation of the patient’s adherence. In making drug selection, we propose to follow a hierarchy based on the intrinsic activity against Mycobacterium tuberculosis and the clinical evidence of efficacy of the available active compounds.

Keywords: M. tuberculosis, multidrug-resistant tuberculosis, therapy, second-line agents

Introduction

Infection by Mycobacterium tuberculosis remains a leading cause of death. It is estimated that nearly $9 \times 10^6$ new cases of active disease occur each year. The vast majority of the world burden of tuberculosis (TB) is in developing countries, which is one of the main reasons why only 23% of the prevalent active cases are currently estimated to receive an appropriate antituberculous treatment.

Inappropriate treatment of drug-susceptible tuberculosis and its consequences on the susceptibility of M. tuberculosis to existing medications

Along with unacceptably low cure rates and the continued spread of tuberculosis in the community, a major consequence of inappropriate treatment is the selection of M. tuberculosis isolates that are resistant to antituberculous drugs. Basically two broad categories of inappropriate therapy may be identified: the wrong treatment prescribed (drugs, dosing intervals, duration) or an inadequate intake by patient. Although treatment of drug-susceptible TB has changed little over the last 30 years, the incorrect initial prescription of an antituberculous regimen still represents a frequent occurrence. A shortage of drugs has been one of the most common reasons accounting for the inadequacy of the initial anti-TB regimen, especially in resource-poor settings, but an ignorance of basic principles of TB management is also a factor. More forgivable but equally harmful errors are made in the choice of drugs for the treatment of drug-resistant TB, often on the basis of an unreliable past medical history and/or in vitro testing of M. tuberculosis drug-susceptibility. However, taking into consideration the high success rate of TB treatment under the DOT policy (Directly Observed Treatment), the principal cause for the generation of drug-resistant TB generally appears to lie in the low degree of patient compliance with treatment. Thus, inappropriate treatment here refers to the patient’s decision to interrupt an otherwise effective regimen or to take just part of the regimen prescribed, the latter being the worst situation in terms of probability of promoting the development of resistance.

How multidrug resistance is defined in tuberculosis

The widely adopted acronym MDR-TB (multidrug-resistant tuberculosis) indicates the presence of M. tuberculosis resistance to, at least, isoniazid and rifampicin, the two fundamental
components of any regimen for the treatment of drug-susceptible TB. Amongst the existing antituberculous drugs, isoniazid has the strongest early bactericidal action and thus significantly contributes to rapidly making patients non-infectious, whilst rifampicin has unique antibacterial properties against bacilli that are no longer in the active phase of replication.2 The definition of MDR works as a sort of operational threshold in this setting, due to the major consequences that resistance to isoniazid and rifampicin has on the treatment of TB.10

How resistance to antituberculous drugs is generated

The suboptimal use of antituberculous medications creates a selective milieu in the host’s tissues where the initially scanty drug-resistant mutants are able to replicate, eventually replacing the initially drug-susceptible M. tuberculosis population.14 A predictable clinical consequence of these events is disease recrudescence due to drug-resistant bacteria and, unless properly treated, the likely evolution of such a case is towards chronicity.7

The selection of drug-resistant M. tuberculosis depends on the frequency of the specific drug-resistant mutants in the initially drug-susceptible bacterial population. As a consequence, the chance of selecting such mutants is the highest in the case of monotherapy.2 Whilst mutants resistant to a single drug may be fairly easily selected by monotherapy, the probability of selecting mutants that are resistant to multiple drugs decreases exponentially by increasing the number of drugs to which M. tuberculosis is simultaneously exposed.2 The rationale for combination therapy was proven by a series of clinical demonstrations that provided unambiguous evidence of how the administration of multiple drugs bears a significantly lower chance of both disease recrudescence and selection of drug-resistant strains compared with monotherapy.2,4 Such clinical research eventually gave the current therapeutic strategy, which consists of three or four drugs in the initial phase of therapy, followed by a consolidation two-drug phase once the initial bacterial biomass has been reduced to such an extent that the chance of selecting residual drug-resistant mutants is exceedingly low.2

Major differences between the treatment of drug-susceptible and drug-resistant tuberculosis

Unlike most bacterial infections, for which several options of comparable efficacy are often available when drug resistance occurs, the cure rate of drug-resistant TB is almost invariably decreased compared with the standard treatment of drug-susceptible disease.10 Furthermore, MDR-TB requires a two- to fourfold longer period of treatment compared with drug-susceptible TB.2,12 Since with even the shortest treatment course (6 months) so far validated for drug-susceptible TB,12 most of the problems from which drug-resistance originates are related to the length of treatment (especially considering tolerability and adherence), the longer time that is required to treat MDR-TB clearly implies an additional risk of poor treatment adherence and, consequently, of treatment failure.13 Two other major issues significantly contribute to the higher complexity of the treatment of MDR-TB compared to drug-susceptible disease: the increased cost (up to 100 times higher) and the higher frequency of adverse reactions.10,12

In terms of treatment duration, the greatest difference between drug-susceptible and MDR-TB is the lack of a real substitute for rifampicin, the crucial drug in short-course TB chemotherapy.1 The introduction of rifampicin allowed the duration of the length of antituberculous treatment to be reduced from 18–24 months down to the currently accepted standard of 6–9 months.4 A major property that has been attributed to rifampicin is its ability to affect dormant bacilli.2,4 Whilst at the outset of anti-TB treatment, the vast majority of organisms are actively replicating and are therefore susceptible to anti-mycobacterial agents, in the subsequent phases of therapy, the residual M. tuberculosis population switches to a virtually inactive metabolic status which makes these organisms poorly susceptible to drugs.2,4 It is thought that these inactive bacilli undergo periodic metabolic reactivation and that during these short periods of activity rifampicin is able to exert its action on the bacterial RNA polymerase, whilst these brief periods of time are insufficient for the other otherwise equally effective bactericidal agents to produce any appreciable effect.15

Treating MDR-TB: essential clinical pharmacology of second-line antituberculous drugs

By definition, chemotherapy of MDR-TB cannot rely upon isoniazid and rifampicin, the two most powerful drugs for the treatment of tuberculosis. Depending on the individual susceptibility pattern, residual first-line drugs must be appropriately combined with additional second-line drugs (Table 1).

**Streptomycin, other aminoglycosides and capreomycin**

In clinical practice, an important feature of aminoglycosides and capreomycin is the need for parenteral administration.16,17 Aminoglycosides exert their effects by binding to the 30S subunit of bacterial ribosomes, thus leading to reduced mRNA reading and impaired protein synthesis.18 These drugs must penetrate into mycobacteria in order to reach their molecular targets. At low pH values, as in cavities or abscesses,19 drug penetration through bacterial porins is limited and this could be one of the reasons accounting for the clinical ineffectiveness of aminoglycosides as single anti-TB agents.19 Moreover, these molecules do not penetrate mammalian cells and therefore lack efficacy against intracellular bacteria.18,19 Aminoglycosides are bactericidal only against rapidly dividing mycobacteria, and have little or no activity against bacilli which are not replicating,18,19 such as those persisting for long periods in the stationary phase of growth. This is the pharmacodynamic rationale of using aminoglycosides only in the induction phase, when a large number of rapidly multiplying bacilli at the extracellular level are present, whilst in the maintenance phase agents active against intraplagocytic and slowly dividing mycobacteria are needed.2

Another crucial issue related to long-term administration of aminoglycosides is toxicity. Ototoxicity and nephrotoxicity are well recognized as dose-related adverse effects of aminoglycosides.2,20 Amikacin is reputed to be less vestibulotoxic and nephrotoxic than streptomycin and kanamycin and this could be advantageous in clinical practice, especially for long treatment periods.22 The toxicity profile of capreomycin is similar to that of aminoglycosides, including nephrotoxicity.23 A distinct clinical entity associated with capreomycin is a form of renal tubulopathy characterized by ion losses with resultant alkalosis.23

Resistance to streptomycin is more common in those areas where the drug has been more widely used.24 Ribosomal
Table 1. Formulations, dosing, type of activity and evidence of clinical evaluation of agents available for MDR-TB treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Average daily dose</th>
<th>Type of antimycobacterial activity</th>
<th>Evaluation in clinical studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazinamide</td>
<td>tablet (500 mg)</td>
<td>15–30 mg/g</td>
<td>bactericidal at acid pH</td>
<td>+</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>tablet (100, 400 mg)</td>
<td>15–30 mg/kg</td>
<td>bacteriostatic</td>
<td>+</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>1 g vial, iv or im injection</td>
<td>20–40 mg/kg (1 g)</td>
<td>bactericidal against exponential phase bacilli</td>
<td>+</td>
</tr>
<tr>
<td>Amikacin/kanamycin</td>
<td>500 mg and 1 g vial, iv or im injection</td>
<td>15–30 mg/kg (1 g)</td>
<td>bactericidal against exponential phase bacilli</td>
<td>+</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>1 g vial, iv or im injection</td>
<td>15–30 mg/kg (1 g)</td>
<td>bactericidal against exponential phase bacilli</td>
<td>+</td>
</tr>
<tr>
<td>p-Aminosalicylic acid</td>
<td>granules (4 g packets);</td>
<td>8–12 g/day</td>
<td>bacteriostatic</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>tablet 500 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td>capsule (250 mg)</td>
<td>10–15 mg/kg</td>
<td>bacteriostatic</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>usually 500–750 mg in two doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethionamide/prothionamide</td>
<td>tablet (250 mg)</td>
<td>15–20 mg/kg</td>
<td>bactericidal</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>usually 500–750 mg/day in single daily or two divided doses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>tablet (500 and 750 mg)</td>
<td>500–1000 mg daily</td>
<td>weakly bactericidal</td>
<td>+</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>tablet (400 mg)</td>
<td>400–800 daily</td>
<td>weakly bactericidal</td>
<td>+</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>tablet (500 mg)</td>
<td>500–1000 daily</td>
<td>bactericidal</td>
<td>+</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>tablet (400 mg)</td>
<td>400 mg daily</td>
<td>bactericidal</td>
<td>-</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>tablet (400 mg)</td>
<td>400 mg daily</td>
<td>bactericidal</td>
<td>-</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>tablet (1000/250 mg)</td>
<td>3000/750 mg in three doses</td>
<td>bactericidal against exponential phase bacilli</td>
<td>+/-</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>tablet (500 mg)</td>
<td>1000 mg</td>
<td>bacteriostatic</td>
<td>-</td>
</tr>
<tr>
<td>Linezolid</td>
<td>tablet and vial (600 mg)</td>
<td>1200 mg in two doses</td>
<td>bacteriostatic</td>
<td>-</td>
</tr>
</tbody>
</table>

im, intramuscular; iv, intravenous.

Data based on Crofton et al.10 and Blumberg et al.18

Table modifications due to mutations in the region of the S12 interaction with 16S rRNA, and particularly changes of the codon 43, are probably the main mechanisms of resistance,25 although other mechanisms are not excluded. The binding site of each of the aminoglycosides may be different, therefore the ribosomal mutations that mediate resistance to aminoglycosides are likely to be drug-specific.26 Amikacin is generally active against streptomycin-resistant strains of Mycobacterium tuberculosis,27 whilst cross-resistance with kanamycin is the rule.26 On the other hand, strains resistant to amikacin are generally also resistant to streptomycin. Capreomycin, although very expensive for countries with limited resources, is also potentially active against streptomycin-resistant strains.26 Capreomycin-resistant strains are not usually resistant to amikacin, while the inverse seems to be the case for low-level, but not for high-level, amikacin resistance.26

**p-Aminosalicylic acid (PAS)**

Discovered in the 1940s, the antimycobacterial agent PAS was considered to be a first-line agent,28 in combination with isoniazid and streptomycin, until it was replaced by ethambutol in the early 1960s.29 PAS exerts a bacteriostatic effect on M. tuberculosis by competitively blocking the conversion of para-aminobenzoic acid into folic acid.30 PAS is usually given orally. The granular formulation now available is more easily administered and better tolerated than the original tablet formulation (20–24 tablets per day).31 However, side effects related to PAS are frequent and include gastrointestinal symptoms, hypersensitivity reactions (up to 10%), hypothyroidism, thrombocytopaenia and intestinal malabsorption.31

**Thioamides**

Following the discovery of isoniazid, numerous pyridine derivatives were tested, with ethionamide and prothionamide being shown to have antimycobacterial activity.32 The mechanism of action is, like isoniazid, at the level of synthesis of mycolic acids.33 Both the drugs are bactericidal in vitro but resistance can rapidly emerge.32 The usual dosage is 500–1000 mg per day in two doses. The most important adverse drug events are gastrointestinal disturbance and hepatotoxicity (hepatitis in 4.3% of patients), with ethionamide slightly less toxic than prothionamide.34,35 Other side effects include neuritis, convulsion, dizziness and gynaecomastia. Interestingly, isoniazid-resistant bacilli are usually susceptible to these thioamides, although they share the same parent compound, isonicotinic acid.33 Cross-resistance is complete between ethionamide and prothionamide.32

**Cycloserine**

Cycloserine exerts an antimycobacterial bacteriostatic effect by competitively blocking two metabolic steps of the biosynthesis of the bacterial cell wall.36,37 Clinical studies in the 1950s showed decreased efficacy compared with PAS, and severe dose-related neuropsychiatric toxicity.38 The latter is frequent (up to 50% of patients at the dose of 1 g/day) and includes convulsive seizures, psychotic episodes, slurred speech, drowsiness and coma.39,40 Smaller and divided doses reduce the frequency of adverse events.39 The oral dose used currently is 250 mg twice or three times a day, and therapeutic drug monitoring is advocated so as not to exceed plasma levels of 30 ng/mL.40
**Rifamycins other than rifampicin**

Rifabutin has considerable cross-resistance with rifampicin, with less than 15% of *M. tuberculosis* strains resistant to rifampicin retaining susceptibility to rifabutin.41 In this minor proportion of cases, some of the mutations selected by rifampicin do not modify the RNA polymerase sufficiently as to render this protein resistant to rifabutin.42 However, the proportion of discordant resistance is too low to make rifabutin a generally useful drug in rifampicin-resistant disease, and no clinical studies have addressed this issue.

The pattern and the mechanism of resistance of rifapentine is identical to that of rifampicin.43

**Fluoroquinolones**

Fluoroquinolones inhibit topoisomerase II (DNA gyrase) of *M. tuberculosis*.44 The other molecular target of fluoroquinolones, topoisomerase IV, is absent in *M. tuberculosis*.45 A notable property of fluoroquinolones relates to their ability to penetrate into macrophages and to exert intracellular mycobactericidal activity.55 Although the activity of fluoroquinolones against *M. tuberculosis* was already evident from the early pre-clinical ‘in vitro’ screening,48 their use in the treatment of TB has never been formally pursued by the manufacturers for overt commercial reasons. Most clinical experience has been accumulated with first-generation fluoroquinolones, ofloxacin and ciprofloxacin,57 which are currently approved as second-line agents for MDR-TB by the WHO, American Thoracic Society, and Centers for Disease Control.10,48 However, the number of clinical studies examining the role of fluoroquinolones for MDR-TB is limited. Further to the clinical data available on ciprofloxacin studies examining the role of fluoroquinolones for MDR-TB is very limited and no clinical data have yet been reported.

For many years, the currently accepted rule49 was to use lower doses than those achievable in serum and lung tissue of patients (MIC₉₀>128 ng/mL)74,75 In animal models, however, clarithromycin was shown to restore, by an unknown mechanism, the 50S ribosomal subunit.72 The literature currently available is very limited and no clinical data have yet been reported.

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
<th>MIC (mg/L)</th>
<th>Cₘₐₓ (mg/L)</th>
<th>Cₘₐₓ/MIC</th>
<th>AUC/MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>0.5–4.0</td>
<td>1.5</td>
<td>1–2</td>
<td>10–20</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>1.0–2.0</td>
<td>4.0</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1.0</td>
<td>6.21</td>
<td>5–7</td>
<td>40–50</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>0.2–0.5</td>
<td>1.18</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.2–0.25</td>
<td>3.42</td>
<td>8.4</td>
<td>68</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>0.12–0.15</td>
<td>4.34</td>
<td>9</td>
<td>96</td>
</tr>
</tbody>
</table>

Data based on Ginsburg et al.69 and Berning.44
against MDR strains. However, no clinical data on the use of clarithromycin in the treatment of MDR-TB are available.

**β-Lactams**

Co-amoxiclav and ampicillin/sublactam have *in vitro* activity against *M. tuberculosis*. The β-lactamase inhibitor is essential to overcome mycobacterial β-lactamase hydrolysis and to allow penetration of the aminopenicillin through the cell wall. The EBA of co-amoxiclav was reported to be comparable to that of ofloxacin, supporting a potential role in the clinical setting. However, bactericidal activity against only exponential-phase and not stationary-phase bacilli suggested a potential clinical usefulness only in the early stages of treatment or as a supportive agent to prevent the selection of resistance against companion drugs. The anecdotal efficacy of co-amoxiclav-containing regimens for treatment of MDR-TB has been described, but definitive clinical evaluation has not yet been carried out.

**Clofazimine**

Clofazimine, a riminophanazine used against *Mycobacterium leprae* and *M. avium* infections, is active against *M. tuberculosis*. Clofazimine concentrates in macrophages and was reported to be efficacious in a murine model of tuberculosis. No clinical data on its use for treating MDR-TB are currently available.

**Phenothiazines**

These compounds are currently used in the management of psychosis. Chlorpromazine has a titrable activity in the inhibition of the growth of intracellular *M. tuberculosis* *in vitro*. Thoridazine has also been shown to be active against MDR *M. tuberculosis*, although the cardiac safety profile is still under investigation. Phenothiazines have not yet been tested for their antmycobacterial activity in humans.

**Nitroimidazopyrans**

Newer compounds of this class (which includes metronidazole) were found to display a considerable activity against *M. tuberculosis* through the inhibition of both protein and lipid synthesis. They also exert a bactericidal effect against bacilli in the stationary phase. A recently synthesized nitroimidazopyran was shown to act *in vitro* against MDR *M. tuberculosis*, and its clinical development seems warranted.

**Other compounds**

A series of chemically heterogeneous molecules are undergoing *in vitro* and *in vivo* testing, but very limited information on their development is currently available. Tubactinomycin is a polypeptide active against amikacin-resistant strains that was found to be better tolerated than capreomycin in a preliminary clinical assessment in East Asia. Acetamides belong to a new class of compounds with specific and promising antimycobacterial activity. Pyrrole derivatives were shown to have bactericidal activity against MDR *M. tuberculosis* strains.

**Outcome of MDR-TB**

Most of the data concerning the therapeutic outcome of MDR-TB come from the experience of the last two decades. Following the resurgence of TB in the 1980s, most of the attention devoted to MDR-TB was initially focused on its association with HIV infection, particularly following well publicized episodes of inter-human spread among subjects with AIDS. The outcome of MDR-TB in the era before the introduction of highly active antiretroviral therapy for HIV infection was found to be very poor, with median survival times barely above 2 months. However, most of these patients were very immunosuppressed at the time of diagnosis of MDR-TB and the latter probably had a relatively minor role in determining outcome. The available knowledge on the outcome of MDR-TB therefore comes from a relatively small number of case series. Most of these studies had a retrospective design and there are virtually no randomized clinical studies comparing different regimens for the treatment of MDR-TB. As a consequence, the choice of drug regimens is still mainly based on the application at the individual level of several chemotherapeutic principles rather than upon the results of clinical trials. The heterogeneity of MDR-TB cases is a further complicating factor. Nevertheless, certain variables that influence outcome can be identified.

Two major case series of MDR-TB outside the setting of HIV infection have been reported in some detail respectively describing the outcome of 171 and 26 patients. In the study by Goble et al., 171 MDR-TB patients with a median age of 46 years who had received a median of six drugs before being retreated, and shed bacilli found to be resistant to a median of six drugs, had an overall response rate of 56%, while in the study by Telzak et al., 26 MDR-TB patients with a median age of 37 years and a prior exposure to a median of 3.5 drugs (only 35% had previously received some form of anti-TB treatment) had a 96% rate of treatment success. Taken together, these two studies give an informative picture of the major factors that determine the chances of curing MDR-TB. A lower prior exposure to anti-TB drugs, a higher number of anti-TB drugs to which the individual infection is still susceptible and a shorter time since the first TB diagnosis (indicating a less advanced disease) indicate a greater chance of successful treatment response. These findings have been confirmed by other studies, such as the French national survey by Flamant-Saillour et al. and Park et al. demonstrated that carefully selected regimens (preferably including four drugs to which the infection was proven to be fully susceptible) led to relatively high cure rates in a series of 107 Korean MDR-TB patients shedding bacilli initially resistant to a mean of four drugs. The importance of the number of antituberculous drugs to which MDR-TB isolates are still susceptible is also emphasized by the reports by Salomon et al. and Turett et al. who found that the prompt institution of appropriately selected regimens may even significantly improve the short-term outcome of MDR-TB in patients with HIV infection. In Mexico, Perez-Guzman et al. showed how in particularly favourable conditions, such as with limited baseline resistance and reliable laboratory information on drug susceptibility, MDR-TB in HIV-negative patients may even respond to regimens as short as 12 months.

**Principles and practice in the management of MDR-TB**

The current performance of anti-MDR-TB treatment worldwide falls far short of what could be achieved by the most effective use of the existing diagnostic and therapeutic weapons.
Nevertheless, MDR-TB may still be considered as a curable disease. The successful management of MDR-TB requires specialized expertise. There are three major issues to be considered: diagnostic techniques, drugs and adherence.

A basic starting point is the access to a good diagnostic service. Although most microbiology departments are able to carry out basic microscopy and isolation of mycobacteria, the expertise required to carry out dependable drug-susceptibility testing is variable. When testing for second-line drugs is considered, the number of centres able to provide reliable results on drug susceptibility of *M. tuberculosis* is reduced to just one or two per country. In these centres, rapid methods to reduce time of diagnosis of MDR-TB and of susceptibility testing could play a crucial role. The radiometric BACTEC 460 technique has been proven to be reliable for second-line drug-susceptibility testing compared with the standard proportion method with solid media, whilst newer fully automated non-radiometric culture methods (e.g. MGIT 960, MB/BACT) have been evaluated only for first-line antituberculous agents. Among tools for rapid detection of resistance, a reverse hybridization-based probe assay (INNO-LiPA Rif TB) is available for detection of mutations in the *rpoB* gene for resistance to rifampicin, whilst many other amplification-based methods have been proposed for resistance to isoniazid, aminoglycosides and fluoroquinolones.

When initiating or revising therapy, the general rule is never to add a single drug to a failing regimen: this will simply result in additional resistance. At least three, but preferably four or five, previously unused drugs whose *in vitro* activity is proven should be administered. In designing a regimen we should not aim to keep drugs in reserve: that is the way to lose the last battle. With adequate information, the choice of an anti-MDR-TB regimen becomes a stepwise process, with preference being given to the residual first-line agents shown to be still active, such as pyrazinamide, streptomycin and ethambutol. Resistance to one of the antituberculous aminoglycosides, most often streptomycin, generally still allows for the selection of another compound from this class. Depending on the local resources, a parenterally administered drug such as amikacin, capreomycin or kanamycin could potentially be included, in association with second-line oral agents (fluoroquinolones, ethionamide, PAS, cycloserine, clarithromycin, co-amoxiclav, linezolid) (Table 3).

In making the selection of the latter, we propose a hierarchy (Table 4) based on their intrinsic activity against *M. tuberculosis* and clinical evidence of efficacy.

Treatment duration has to be determined on an individual basis, but, as a general rule, it should be continued for at least 18 months after sputum conversion. Second-line drugs are typically less effective and have more side effects than first-line agents. According to baseline *M. tuberculosis* drug susceptibility, withdrawal of one or more drugs may be possible during treatment without compromising the outcome, but bacteriostatic and not bactericidal agents should be preferentially interrupted, unless intolerable side effects are the reason prompting a regimen revision (e.g. aminoglycosides, cycloserine).

Adherence is a major issue. Apart from the case of primary MDR-TB, a lack of treatment adherence in the past is typically the factor that has caused the patient to have MDR-TB. If proper action is not taken to ensure patient compliance, the chance of further treatment failure and increased resistance is high. Referral to adherence-promoting TB services is therefore important. Hospital-based treatment is advisable at least until sputum conversion occurs. After discharge, DOT should be given, particularly for cases of acquired resistance and prior evidence of non-adherence. In the bacteriological and clinical monitoring of response to therapy, it must be anticipated that improvement of MDR-TB is usually slower than with drug-susceptible TB. However, in most case series, patients who eventually became culture negative converted sputum sample after 2–3 months of therapy.

The role of surgery in the management of patients with extensive pulmonary disease has not been established in randomized studies. However, in some case series, patients with severe MDR-TB appeared to benefit from resection of damaged lung tissue, especially when extensive and longstanding fibrosis is present and treatment failure occurred with a large panel of drug resistance.

### The DOTs Plus Strategy

Based on an awareness of the multiple difficulties faced by any large-scale intervention aimed at fighting MDR-TB, a special initiative has been launched within the framework of the Global

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**Table 3. Suggested regimens for patients with different patterns of MDR-TB**

<table>
<thead>
<tr>
<th>Pattern of drug resistance</th>
<th>Suggested regimen</th>
<th>Minimum duration (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid and rifampicin (± streptomycin)</td>
<td>EMB, PZA, FQN, AMK</td>
<td>18</td>
<td>in extensive diseases, an additional agent may be added</td>
</tr>
<tr>
<td>Isoniazid, rifampicin and ethambutol (± streptomycin)</td>
<td>PZA, FQN, AMK plus 2</td>
<td>18</td>
<td>surgery should be considered</td>
</tr>
<tr>
<td>Isoniazid, rifampicin and pyrazinamide (± streptomycin)</td>
<td>EMB, FQN, AMK plus 2</td>
<td>18–24</td>
<td>surgery should be considered</td>
</tr>
<tr>
<td>Isoniazid, rifampicin, ethambutol and pyrazinamide (± streptomycin)</td>
<td>FQN, AMK plus 3</td>
<td>18–24</td>
<td>surgery should be considered</td>
</tr>
</tbody>
</table>

Data based on Crofton *et al.* and Blumberg *et al.*

EMB, ethambutol; PZA, pyrazinamide; FQN, fluoroquinolones (most experience involves ciprofloxacin, ofloxacin and levofloxacin; moxifloxacin and gatifloxacin have not been yet evaluated in clinical trials); AMK, amikacin (capreomycin may be an alternative in case of resistance).

Additional agents: ethionamide, PAS, cycloserine, β-lactams, clarithromycin, linezolid, clofazimine.

*After sputum conversion.*
TB Strategy.\textsuperscript{121} This newly conceived programme consists of a comprehensive approach including the major DOTs principles but technically devoted to the intensive diagnostic and therapeutic management of MDR-TB.\textsuperscript{121,122} DOTs Plus relies upon a working DOTs Strategy within the activities of the local TB control programme.\textsuperscript{121,122} Based on the knowledge of the prevailing resistance patterns in the community, on the individual drug history and on the availability of second-line antituberculous drugs, an initial regimen is chosen (including an injectable drug) and then the patient undergoes monthly monitoring by means of sputum microscopy and culture. Reliance on a reference laboratory able to provide appropriate information on the susceptibility of individual isolates of \textit{M. tuberculosis} is also an operational requirement, in order to allow for timely changes in the regimen initially selected and for updating the information on the resistance status of \textit{M. tuberculosis} strains in the community.

### References


