

Assessing the level of drug resistance in TB patients: what is the pattern of resistance?

José A Caminero (IUTLD) provides a step-by-step approach for TB treatment

When analysing complexity, efficacy, costs, adverse reactions of antituberculosis treatment, and prognosis, important differences become apparent if patterns of drug resistance are considered. Four levels of complexity emerge: (1) susceptibility to all drugs; (2) resistance to either isoniazid or rifampicin, but not to both; (3) multi-drug resistance (MDR-TB) resistance to at least isoniazid and rifampicin; and (4) MDR-TB plus resistance to fluoroquinolones and all the injectables. The last level does not exactly correspond to the extensive drug-resistance definition (XDR-TB; MDR-TB plus resistance to fluoroquinolones, and at least to one of the second-line injectables). This article addresses the different levels of complexity in the treatment of tuberculosis and proposes the best approach for the treatment.

Introduction

The prognosis of patients with tuberculosis (TB) significantly changed around 50 years ago with the onset of chemotherapy. The first drugs discovered with anti-tuberculous effects were para-aminosalicylic acid (PAS) and streptomycin in 1943.¹ Although PAS was the first drug investigated,¹ studies with streptomycin were much more numerous during the 1940s and 1950s, and they became crucial in the development of the bacteriological bases for the treatment of tuberculosis. Shortly after the description of streptomycin, clinical trials with streptomycin monotherapy were conducted in Great Britain² and the United States.³ The case fatality from tuberculosis in these trials was reported to be considerably reduced. However, it was also observed that patients improved over the first few months and subsequently deteriorated in many cases due to the acquisition of streptomycin resistance. Among survivors, sputum conversion did not differ much between those who had received streptomycin and those who had not.³ The unsolvable problem was the selection of resistant strains. Streptomycin trials had a considerable impact on research for the next 20 years, which predominantly focused on methods for preventing the emergence of drug resistance. Further studies demonstrated that the addition of PAS to streptomycin significantly lowered the risk of acquiring resistance.⁴ The subsequent discovery of isoniazid and its addition to the regimen including PAS and streptomycin in the 1950s resulted in a highly effective regimen which was able to cure the great majority of patients with tuberculosis.⁵ Since then, tuberculosis has been considered a curable disease in almost all the cases with low adverse reaction rates. Moreover, these reactions were significantly reduced with the discovery of ethambutol and its addition to the same regimen instead of PAS.⁶ However, ethambutol neither increased the efficacy of the treatment schedule

nor shortened its length; the treatment remained very long with duration of at least 18 months.

Since the innovation of the 18-month schedule in the mid-1950s until today, only one truly effective drug has been discovered for the treatment of tuberculosis; this is rifampicin, which embodied a revolutionary change in treatment.⁷ The actual role of the new fluoroquinolones in the initial phase of antituberculosis treatment remains to be established.⁸ The introduction of rifampicin in the place of streptomycin resulted in a earlier sputum conversion.⁹ However, this was not the main progress made with the rifampicin-containing chemotherapy. It was demonstrated that 9 months of isoniazid plus rifampicin, supplemented by either ethambutol or streptomycin during the first 3 months, was the optimum treatment duration;¹⁰ the term 'short-course chemotherapy' became the brand name of this new successful strategy.¹¹

The bacteriological rationale for the pharmacological treatment of tuberculosis was established later, between 1950 and 1970,¹² and led to the development of the best known regimen to treat new patients. This regimen, consisting of isoniazid and rifampicin for 6 months with a 2-month initial intensive phase with pyrazinamide and ethambutol (see Table 1), has a demonstrated efficacy (cured + completed treatment / cured + completed treatment + failures) of over 95% in patients with tuberculosis caused by drug-susceptible organisms; the adverse reaction rate is lower than 2–3%.¹² This is the Category I treatment regimen from the World Health Organization.¹³

Levels of complexity in the tuberculosis treatment related to the pattern of resistance

The high efficacy of the 6-month regimen with rifampicin, which made virtually all patients with tuberculosis curable, concerned only those harbouring drug-susceptible organisms. Unfortunately, although these patients still represent the great majority of cases in all countries around the world, the number of individuals carrying drug-resistant strains has considerably increased during the last 20–30 years. This phenomenon is closely related

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to the misuse of these antituberculous drugs. This situation is of great concern in some regions and countries in the world.¹⁴

The efficacy of this 6-month regimen decreases if resistance to isoniazid or rifampicin is present, and is even lower in the presence of resistance to both drugs.^{7,12,15,16} In these circumstances, resorting to other, less effective first-line (streptomycin, pyrazinamide, ethambutol) or to second-line drugs becomes necessary. Among the second-line drugs, only two groups possess bactericidal activity: the fluoroquinolones and the injectables (aminoglycosides (kanamicyne and amikacyne) and polypeptides (capreomicyne). The possibility of using one of these will give a very different chance of therapeutic success. Therefore, when analysing complexity, efficacy, costs, and adverse reactions of anti-tuberculosis treatment, important differences become apparent if patterns of drug-resistance are considered. When the activity, tolerance, adverse reactions, and costs of each of these antituberculous drugs, as well as their potential combinations, are considered, four levels of complexity and success rates of antituberculous therapy can be identified.

1. Treatment of fully susceptible tuberculosis

The most favourable situation for treatment is when all new cases (Category I) harbour strains that are susceptible to all drugs; fortunately these still represent the majority of cases in all parts of the world (although patent differences exist between zones and countries). As stated before, the Category I regimen of the World Health Organization,¹³ comprising rifampicin for 6 months, has a confirmed efficacy of over 95% in these patients, with an adverse reaction rate lower than 2-3%.¹² Even in countries with very scarce economic

Table 1 Tuberculosis treatment related to the pattern of resistance: basic recommendations

1. Treatment of fully susceptible tuberculosis - 2 (H-R-Z-E) / 4 (H-R)
2. Treatment of tuberculosis with resistance to either isoniazid or rifampicin a) Resistance to H - 2 (R-E-Fq-Z) / 7 (R-E-Fq) b) Resistance to R - 2 (H-E-Fq-Z) / 16 (HR-E-Fq)
3. Treatment of patients with multidrug-resistant tuberculosis (MDR-TB), but with susceptibility to second-line drugs - X (Kn-Fq-Eth-Cs) / XX (Fq-Eth-Cs) X: Intensive phase: at least until culture negativisation XX: Continuation phase: until 18 months after culture negativisation
4. Treatment of patients with MDR-TB and resistance to fluoroquinolones and injectables - Individualised treatment following the rules expressed in this article
Note: H: isoniazid; R: rifampicine; Z: pyrazinamide; E: ethambutol; Fq: fluoroquinolone; Kn: kanamicyne; Eth: Ethionamide; Cs: cicloserine.

resources but efficient tuberculosis control programmes, success rates higher than 85–90%, with failure rates under 1%, could be attained;^{17,18} taking into account that in programme conditions defaults are always detrimental to these figures. If tuberculosis is susceptible to all drugs and the drug intake is closely supervised, a cure is virtually always assured.^{7,12,19,20} The overall cost of drugs for this treatment could be in the order of US\$10.

2. Treatment of tuberculosis with resistance to either isoniazid or rifampicin

Within the second level of complexity are cases with resistance to either isoniazid or rifampicin, but not both, with or without resistance to other first-line drugs. Within this group, the most problematic are cases with resistance to rifampicin, given the activity of this drug against all bacillary populations and its efficacy throughout the treatment.²¹ In fact, many authors have reported the minimal or non-existent relevance of resistance to isoniazid in regard to the final outcome of treatment in new cases.²¹ In any case, the likelihood of selecting resistance to rifampicin in those patients, initially resistant to isoniazid and whose sputum smears are positive at the beginning of the second phase, is yet to be demonstrated. Consequently, treatment for patients with resistance to isoniazid should be reinforced and maintained for at least 9–12 months.^{7,15,22} In this case, the most suitable regimen would be the combination of rifampicin, ethambutol and pyrazinamide or fluoroquinolone during 9 months (see Table 1); this could also offer success rates over 95%.¹⁵ The cost of drugs for this treatment will fluctuate between US\$20 and US\$200, depending on whether fluoroquinolone is added or not.

However, as mentioned above, resistance to rifampicin even in the case of conserved susceptibility to isoniazid complicates the situation; indeed, reinforced treatment regimens of at least 12–18 months in length, which is longer than is needed for treatments with rifampicin,^{7,15,22} will be necessary to achieve similar results with other drugs. These cases are an exception in clinical practice and, for this reason, most of these patients should be treated as multi-drug-resistant tuberculosis (MDR-TB), but adding isoniazid to the regimen. In the rare situation where there was confirmed only mono-resistance the ideal treatment would include 18 months of isoniazid, ethambutol and a fluoroquinolone, with pyrazinamide during the first intensive 2-month phase (see Table 1).¹⁵ Other drugs like the injectables could be used in the case of added resistance to any of the drugs that should be given with isoniazid.¹⁵ The efficacy of this regimen could still be over 90%; its cost is slightly higher, but could be obtained for less than US\$300 or US\$400.

3. Treatment of patients with multi-drug-resistant tuberculosis

The third level of complexity corresponds to patients with resistance to, at least, isoniazid plus rifampicin (MDR-TB), whose cure rate with Category I treatment decreases to 20–50%.²³ In such cases, therapeutic success

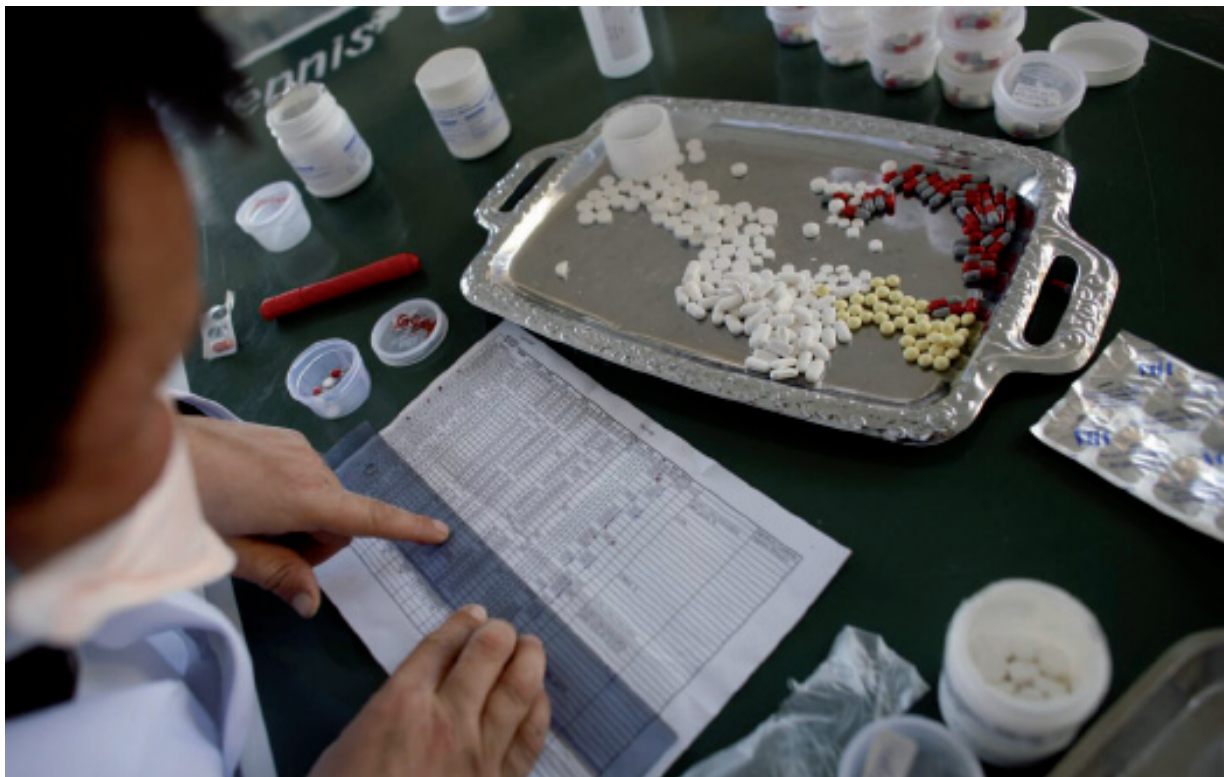
is difficult to obtain, as patients require regimens of at least 18–24 months in length using much more toxic, less effective and more expensive drugs.^{7,15,22} However, the short period (10–15 years) of thorough MDR-TB study has shown that cure rates are quite variable, with some studies reporting an efficacy over 90%^{16,24,25} while in others it is barely over 50%.^{16,26,27} The option of using other first-line drugs (ethambutol, pyrazinamide, streptomycin),²⁸ fluoroquinolones,^{2,9,30} and other injectables²⁸ clearly influenced the likelihood of success. Although in most cases of MDR-TB the rest of the first-line drugs cannot be prescribed^{26,28,30–33} because of proved or suspected resistance, the possibility of including them along with the other second-line drugs increases the efficacy of treatment; it could improve from 80% to 93% if any of these drugs can be added.²⁸ All studies consistently find that the cure rate is clearly associated with, among other factors, the opportunity to include fluoroquinolones^{29,30} and injectables¹⁶ in the treatment.

The ideal regimen for these patients is the combination of a fluoroquinolone, ethionamide, and ethambutol (cycloserine can replace ethambutol in the case of proved or suspected resistance to this drug) over 18–24 months, with reinforcement of an injectable and pyrazinamide during the first 6 months (see Table 1).^{15,16,22} The efficacy of this or a similar regimen, provided there is good care for adverse reactions, could be over 90%^{16,24,25,28,33,34} when the possibility exists of using a fluoroquinolone and an injectable and of having these patients preferably taken care of in a specialised centre. When drugs from these two groups cannot be used, the likelihood of success decreases greatly and would entail another level of complexity in the treatment of tuber-

culosis, as will be considered later. At best, the price of the drugs alone for this regimen is over US\$5000, an excessive cost for the great majority of countries with low- and middle-level economic resources, further complicating the treatment of patients from this group.

4. Treatment of patients with MDR-TB and resistance to fluoroquinolones and injectables

Among the second-line drugs only the fluoroquinolones and the injectables (aminoglycosides and polypeptides) possess bactericidal activity and could be considered very effective. Studies determining the important role of kanamycin, amikacin, and capreomycin in the treatment of tuberculosis were published between 1960 and 1980, prior to the standardisation of the current therapeutic regimen for new cases. Cases at that time (rifampicin and fluoroquinolones were not available), were resistant to isoniazid, streptomycin and PAS.¹⁶ Most of the articles report the use of fluoroquinolones as a factor associated with a favourable response in the treatment of MDR-TB.^{29,30} Therefore, among the second-line drugs, fluoroquinolones and the injectables correspond to what isoniazid and rifampicin represent among the first-line drugs. Unfortunately, these two groups are not only the most effective but in fact, the only second-line drugs that have been available in most low- and middle-income countries during the last decades. In many settings, a considerable number of MDR-TB cases have received indiscriminate prescription of these drugs. Such patients lack the possibility of receiving drugs from these two groups and thus bear a therapeutic success rate under 50–60%,^{16,28–32,35} which is very close to that observed in tuberculosis patients who do not receive



A cocktail of drugs depending on the pattern of treatment resistance

any kind of treatment.³⁶ The cases where these groups of drugs (fluoroquinolones and injectables) cannot be prescribed represent the fourth level of complexity in the treatment and cure of tuberculosis. They require an individualised treatment complying with some basic rules^{15,16,22} and having a duration of no less than 24 months, receiving much less effective (ethionamide, cycloserine, PAS, clofazimine, etc), more toxic and more expensive drugs. Even in the best case, the cost of these treatments is never under US\$10 000, to which must be added the cost of the management of the frequent adverse reactions to these and to the ancillary drugs.

However, the situation differs when the use of a fluoroquinolone or an injectable is permitted. In this sense, thinking of a possible prognosis, the current extensive drug-resistant tuberculosis (XDR-TB) definition may be inappropriate, particularly as it allows the use of one of the injectables (kanamycin, amikacin, or capreomycin), along with ethionamide, cycloserine and PAS. Cases under this definition might reach a cure rate over 80% when access to this regimen and adequate management of adverse reactions is granted; a rate which is very close to that achieved in patients with MDR-TB and without XDR-TB. If the current XDR-TB definition is maintained, we will shortly be in need of a new one for the cases referred to in this section, for which the best classification would be XXDR-TB (extra-extensive drug-resistance).³⁷

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