

Treatment of multidrug-resistant tuberculosis: evidence and controversies

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SUMMARY

In the last decade, multidrug-resistant tuberculosis (MDR-TB, defined as resistance to at least isoniazid and rifampicin) has become an epidemiological issue of first priority at the global level. Case management needs to be simplified and standardised, as in many countries MDR-TB cases cannot receive individualised attention from specialist physicians. However, before any decision can be made on standardisation, a careful analysis must first be made of the evidence and controversies behind the various published recommendations. Unfortunately, the controversies outweigh the evidence. The difficulties lie not only in the absence of controlled trials to validate specific recommendations, but also in the very different and even contradictory results found in the literature. It is therefore essential to analyse these discrepancies before developing rational, uniform recommendations. The analysis should encompass the most essential and

controversial issues regarding the management of MDR-TB patients: 1) confirmation of diagnosis in a suspected MDR-TB patient, and determination of the value of drug susceptibility testing; 2) the number of anti-tuberculosis drugs required to treat MDR-TB; 3) the most rational use of effective drugs against tuberculosis; 4) the advisable length of parenteral drug administration or of the initial phase of treatment; 5) the contribution of surgery to the management of MDR-TB patients; and 6) the optimal regimen for treating MDR-TB: standardised vs. individualised regimens. The evidence and controversies regarding each of the above questions are analysed with the aim of facilitating decision making in the treatment of these complex patients.

KEY WORDS: tuberculosis; multidrug resistance; MDR; management; treatment; standardised; individualised

AMONG THE FEW DRUGS AVAILABLE for the treatment of tuberculosis (TB), only isoniazid (INH) and rifampicin (RMP) are highly effective. Curing TB patients with resistance to at least both of these drugs, multidrug-resistant tuberculosis (MDR-TB), is therefore very difficult and presents huge challenges worldwide. MDR-TB as a global epidemiological problem is a relatively recent concern. The World Health Organization (WHO) guidelines for the treatment of tuberculosis published in 1991 contained only one paragraph concerning chronic patients and did not provide a thorough approach to the problem of multidrug resistance.¹ These guidelines advised the use of INH, aiming to reduce the bacillary burden, a practice that is clearly proscribed today. This short paragraph no longer appeared in the second edition of the guidelines (published in 1997)² and no mention whatsoever is found in the guidelines from the International Union Against Tuberculosis and Lung Disease (The Union) for TB management in low-income countries.³ None-

theless, in the middle of the 1990s, the growing concern about this problem prompted the WHO to issue specific guidelines for the management of patients with MDR-TB.⁴

Once MDR-TB had developed into a global epidemiological priority, it became clear that treatment needed to be standardised where possible. However, given the substantial differences between many MDR-TB cases, efforts to randomise patients or to group them into homogeneous groups so as to apply and compare different treatment strategies have proved virtually fruitless. As a consequence, no controlled trials have been conducted to compare the various treatment regimens or drugs, and personal experience has largely become the basis for case management. There is a great deal of expert opinion on MDR-TB and, although this is not as rigorous as clinical trials or formal observational studies, it should certainly be considered seriously when discussing how to deal with the problem. However, at the same time, personal ex-

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Table 1 Outcome of TB patients resistant to INH, SM and PAS treated with only three second-line drugs in the pre-RMP era

Reference	Country	Years	Patients <i>n</i> *	Follow-up period	Cured/ completed treatment <i>n</i> (%)	Efficacy of regimen [†] %	Died <i>n</i> (%)	Defaulted/ withdrew/ lost [‡] <i>n</i> (%)	Failures/ no response [§] <i>n</i> (%)
Tousek ¹⁴	Czechoslovakia	1959–1962	55	24 months	45 (82)	96	—	8 (14)	2 (4)
Zierski ¹⁵	Poland	1958–1962	32	9 months	31 (97)	97	—	—	1 (3)
Fischer ¹⁶	USA	1960–1962	146	4 years	122 (83) [¶]	83 [#]	27 (18)	—	37 (25) [¶]
Kass ¹⁷	USA	1960–1962	74	4 years	58 (79)	81 ^{**}	—	—	16 (21)
Pines ¹⁸	UK	1961–1963	12	24 months	9 (75)	90	2 (17)	—	1 (8)
Somner ¹⁹	UK	1960–1962	22	5 years	20 (91)	100	1 (4.5)	1 (4.5)	—
Kass ^{20,††}	USA	1962–1964	24	277 days	23 (96)	96	—	—	1 (4)

* MDR-TB patients with outcome known in the study.

[†] Cured + completed treatment/cured + completed treatment + failures + no response to treatment.

[‡] Includes patients who did not take their drugs regularly.

[§] Includes relapses known in patients cured previously.

[¶] Sputum conversion after 120 days of treatment; 30 patients (20.5%) relapsed during the observation period. Only seven failures. The final number of cured cases is not given.

[#] Of 68 living patients whose culture status was known as of January 1966, 60 (88%) remained consistently non-infectious.

^{**} By January 1964, 60 (81%) of the 74 patients were known to be still culture-negative.

^{††} The only study using EMB in the regimen.

TB = tuberculosis; INH = isoniazid; SM = streptomycin; PAS = para-aminosalicylic acid; RMP = rifampicin.

perience can also introduce considerable bias related to specific circumstances, even in the practice of the best physicians.

Experts may differ in their approach to critical issues when it comes to patient management. A good example is the norms published by the two leading thoracic societies, the American Thoracic Society (ATS) and the British Thoracic Society (BTS), which are prepared by the best experts in the field. On reviewing ATS guidelines for the treatment of patients with drug resistance published in 1965,⁵ 1966,⁶ 1994⁷ and 2003,⁸ inconsistencies can be observed regarding such important aspects as the number of drugs to be included in the regimen⁹ and the validity of drug susceptibility testing (DST). Similar inconsistencies can be observed when reviewing BTS regulations from 1990¹⁰ and 2000,¹¹ or WHO guidelines from 1996,⁴ 2003¹² and 2006.¹³

Besides the scarcity of controlled trials on MDR-TB, the results of key publications dating from the pre-RMP period (prior to 1966) (Table 1)^{14–20} and after the introduction of RMP (1966 to the present) (Table 2)^{21–34} differ greatly and are sometimes contradictory. When attempting to make reasoned, standardised recommendations, it is of fundamental importance to analyse differences and controversies. The analysis should encompass the most essential and controversial issues regarding the management of patients with MDR-TB, in order to facilitate decision making in the treatment of these patients.

CONFIRMATION OF DIAGNOSIS IN SUSPECTED MDR-TB PATIENTS: THE REAL VALUE OF DST

In the chapter advising on drug selection for the treatment of patients with drug resistance, the 1966 ATS guidelines state: ‘The selection of anti-tuberculosis agents is based upon the history of previous therapy

and the results of reliable drug susceptibility tests . . .’.⁶ The relevance of drugs employed in the past when deciding on a therapeutic regimen in patients with drug resistance and the risk of obtaining unreliable results from DST were already acknowledged here. Forty years after the publication of these guidelines very little, if any, progress has been made on the subject.

The main predictor of resistance to a particular drug is the demonstration of its prior use in monotherapy for more than one month.^{35,36} To obtain this evidence it is essential to be meticulous in obtaining the history of anti-tuberculosis treatment in all patients suspected of MDR-TB.^{36,37} This should include an accurate assessment of the dosage and combinations of drugs to obtain a precise record of drug introduction and withdrawal, which will allow any real or masked monotherapy previously received by the patient to be evaluated. Using this method, one can accurately predict resistance to specific drugs and prevent their inclusion in the retreatment plan.^{36,37} If the treatment history is taken meticulously, it can identify not only the errors that caused many of the failures, but also those drugs with potential efficacy, despite prior use, if they were prescribed in sound associations and led to culture conversion in the past. However, the treatment history can be problematic, in that it relies on the patient’s ability to remember the drugs taken in the past and/or on access to patient charts for previous episodes of TB. For these reasons, the patient’s history should be taken by a person with experience in treating MDR-TB.

Another approach to obtaining the resistance pattern is DST against first- and second-line drugs. DST has several weaknesses, including delays in obtaining the results, usually >3 months after sampling (when carried out by conventional methods on solid media), and failure due to insufficient growth of cultures. It is also important to realise that although the *in vitro* and

Table 2 Outcome of MDR-TB patients in key articles published since the introduction of RMP

Reference	Country	Years	Treatment	Drug resistant, median	Patients, n*	New MDR, n (%)	Cured/ completed treatment, n (%)	Efficacy of regimen†, %	Died, n (%)	Defaulted/ withdrew/ lost, n (%)	Failures/ no response‡, n (%)	Associated with poor outcome
Leimane ²¹	Latvia	2000	Individualised	4	204	55 (27)	135 (66)	76	14 (7)	26 (13)	29 (14)	Previous MDR treatment; ≤ 5 drugs ≥ 3 months; OFX resistance; BMI < 18.5
Mitnick ²²	Peru	1996–1999	Individualised	6	75	—	55 (73)	83	5 (7)	14 (19)	1 (1)	Low haematocrit; Low BMI
Palmero ²³	Argentina	1996–1999	Individualised	4.1	141	50 (35.5)	64 (45)	60	27 (19)	28 (20)	7 (5)	No hospitalisation; resistance to several drugs
Suarez ²⁴	Peru	1997–1999	Standardised	—	298	—	136 (46)	52	32 (11)	34 (11)	96 (32)	Resistance to ≥ 5 drugs
Goble ²⁵	USA	1973–1983	Individualised	6	171	—	75 (44)	56	8 (4.6)	22 (13)	59 (34)	High number of drugs received previously; male sex
IOM TB ²⁶	Vietnam	1990–1995	Standardised	7	130	—	107 (82)	98	6 (4.6)	14 (11)	2 (1.5)	Age > 45
Park ²⁷	Korea	1993–1996	Individualised	4	83	—	63 (76)	82.5	—	20 (24)	11 (13)	High number of drugs received previously
Geerlig ²⁸	Netherlands	1985–1998	Individualised	5	39	—	32 (82)	97	6 (14)	—	1 (2.5)	—
Tahaoglu ²⁹	Turkey	1992–1999	Individualised	4.4	158	—	121 (77)	90	7 (4)	17 (11)	13 (8)	Older age; previous OFX treatment
Narita ³⁰	USA	1994–1997	Individualised	4.8	81	—	46 (57)	100	26 (32)	9 (11)	—	Treatment on an out-patient basis
Van Deun ³¹	Bangladesh	1997–1999	Standardised	—	58	—	40 (69)	93	8 (14)	7 (12)	3 (5)	—
Chan ³³	USA	1984–1998	Individualised	6	139	—	71 (51)	64.5	16 (11) [§]	21 (15)	39 (28) [§]	No surgery; younger; no quinolones

* Number of MDR-TB patients with outcome known in the study.

† Cured + completed treatment/cured + completed treatment + failures + not responded.

‡ Including the relapses known in patients cured previously.

§ 6 patients died from TB after relapse.

MDR-TB = multidrug-resistant tuberculosis; RMP = rifampicin; MDR = multidrug resistance; BMI = body mass index; IOM = International Organization for Migration; TB = tuberculosis.

in vivo correlation of DST is very reliable for INH and RMP, this is not the case for other anti-tuberculosis drugs,^{36–40} and it should be kept in mind that although drug resistance as detected by DST reflects the inefficacy of a drug in culture media, it does not necessarily correspond to the efficacy of the drug in a new regimen.

Despite its drawbacks, however, DST should be performed systematically against first-line drugs for all patients; it is adequate for INH and RMP, but less so for streptomycin (SM) and ethambutol (EMB),^{36,38,39} for which the susceptibility results are more reliable than the resistance results,³⁸ while for pyrazinamide (PZA) the BACTEC system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD), a radiometric method that is not available in most low-income countries, is required. DST against second-line drugs should not be carried out systematically on account of its difficulty, cost and poor reliability.^{36,38,41} Even in wealthier countries, where multiple methods are available for performing DST for second-line drugs, interpretation of the results requires cautious analysis by experienced staff. Studies aiming to standardise DST results for second-line drugs are scarce and yield inconsistent results; the concentrations used for each drug and the definitions of resistance vary widely, even between the best performing laboratories.^{36,38,42} Today, it appears that the DST results for some second-line drugs, such as kanamycin (KM) and ofloxacin/ciprofloxacin, but not others, may be of great help, as long as they are carefully compared with the patient's treatment history.^{36,38,41}

Accordingly, the diagnosis of MDR-TB should be based on the patient's treatment history (failure of standard regimens, exposure to patients with MDR-TB, etc.) and on the results of DST against INH and RMP, for which reliability approaches 100%.³⁸ Under National Tuberculosis Programme (NTP) conditions, the history of drugs previously used in the country and the epidemiological surveillance of DST against INH and RMP after the failure of a standard regimen should be considered. For example, in a country where cycloserine and para-aminosalicylic acid (PAS) have never been used, it can be assumed that all patients from this country will be susceptible to these drugs.

NUMBER OF DRUGS REQUIRED TO TREAT A PATIENT WITH MDR-TB

One of the most controversial issues in the debate around MDR-TB in recent years is the number of drugs required to treat a patient with multiresistance,^{9,36,43,44} mainly because of the absence of controlled trials to compare different regimens. It is nearly impossible to gather samples of adequate numbers of patients with similar patterns of resistance to carry out clinical trials of regimens with different numbers of drugs. Moreover, the efficacy of the different anti-tuberculosis drugs varies, emphasising the need for a rational reg-

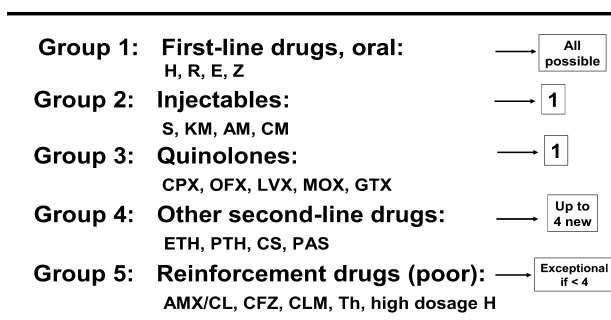


Figure Rational classification of anti-tuberculosis drugs. H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin; KM = kanamycin; AM = amikacin; CM = capreomycin; CPX = ciprofloxacin; OFX = ofloxacin; LVX = levofloxacin; MOX = moxifloxacin; GTX = gatifloxacin; ETH = ethionamide; PTH = prothionamide; CS = cycloserine; PAS = para-aminosalicylic acid; AMX/CL = amoxicillin + clavulanic acid; CFZ = clofazimine; CLM = clarithromycin; Th = thiacetazone.

imen design. Taking into account the basic activity of the drugs available, it could prove more effective to use a regimen combining three or four bactericidal drugs rather than five or six bacteriostatic agents with weak activity. It is therefore important to properly classify the available drugs and associate them rationally (Figure).

In the absence of controlled trials, expert opinion prevails and perspectives differ according to personal experience. As a result, significant discrepancies are found in the guidelines published by the scientific societies, and divergences have emerged over time. The ATS recommendations are a good example: in 1965⁵ and 1966,⁶ the ATS recommended using two or three new drugs to treat drug resistance, in 1994 at least three (no references are provided to support this change)⁷ and in 2003 four to six.⁸ As discussed later,⁹ this important change in the number of drugs recommended by the ATS⁸ for the treatment of resistant patients was based on three studies that showed acceptable results only with four to six drugs,^{25,27,28} but did not compare them to the results from groups treated with fewer drugs.⁹ Similarly, the 1990 BTS guidelines recommended at least three drugs,¹⁰ and then five or more in 1998,¹¹ with only one reference supporting this important change,⁴⁰ the same reference quoted in the ATS guidelines. The expert opinion of M Iseman^{40,44} clearly had a considerable influence on the modifications to the ATS and BTS recommendations regarding the number of drugs that were necessary. Dr Iseman and his group's work in a reference centre in Denver, CO, USA, which receives the most complex MDR-TB cases with resistance to many other drugs, is well known. Their experience is based on the management of very difficult cases with resistance to multiple drugs and dubious susceptibility to or weak activity of the few remaining available medications.^{25,32,40} In these cases, the use of five or more drugs is no doubt

justified, as are the many other heroic measures undertaken in the hope of saving patients' lives.

The 1996⁴ and 2003¹² WHO guidelines recommend at least three drugs, similar to the recommendations of the ATS in 1993⁷ and the BTS in 1990.¹⁰ This term was nevertheless changed to 'at least four drugs' in the most recent WHO guidelines for the treatment of MDR-TB patients in 2006.¹³

A comprehensive critical review of the literature highlights good studies from the pre-RMP period, showing that treatment with only three drugs may ensure very favourable clinical outcomes in patients with resistance to SM, INH and PAS (Table 1).¹⁴⁻²⁰ These studies showed success rates of 75%¹⁸ to 97%,¹⁵ three of them demonstrating success rates of more than 90%.^{15,19,20} On the other hand, other studies from the RMP period (Table 2) have demonstrated good outcomes with more than four drugs,²¹⁻³⁴ with success rates of 44-46%²³⁻²⁵ to 82%.²⁶⁻²⁸ However, only the study by Leimane et al. showing a success rate of 66%, compares the results with the number of drugs received by the patients.²¹ This excellent study, which finds a correlation between inferior results and the administration of five or fewer drugs, was performed in Latvia, a setting with very high rates of MDR-TB, where most of the patients, including those with no history of previous TB treatment, are resistant to many drugs other than INH and RMP. This situation may be very similar to that experienced by Iseman's group.^{25,32,33,40}

As expressed above, the opinions of experts are influenced by their own experience. Those confronted with patients with moderate resistance (probable resistance to a low number of drugs and treatment history of no or very few second-line drugs) tend to recommend treatments with at least three drugs,^{4-7,9,10,12,37,43} while those who derive their experience from very complex cases (resistance to multiple drugs and history of administration of multiple second-line drugs) tend to recommend five medications or more, as many drugs might have compromised efficacy (probable resistance) or weak action.^{21-23,25,27-30,32-34,45,46} The first approach may be valid for patients from countries where second-line drugs have rarely been used, i.e., many countries in Africa, Latin America, the eastern Mediterranean region and some very poor nations in Asia. However, this approach would be inadequate for patients from countries where second-line drugs have been widely used—and probably misused—in the past. For these patients, the second option therefore seems more reasonable. Additional data are necessary and are currently being collected to validate and confirm these recommendations.

Given that the main goal in making recommendations is to ensure that they are suitable for the majority of patients, it could be concluded that: 1) the use of three effective second-line drugs could be sufficient (natural resistant mutants per drug $>1 \times 10^5$) from a

bacteriological point of view; 2) in the field, however, some drugs often have compromised efficacy or very weak action; 3) for this reason, under NTP conditions, a second-line drug regimen should include at least four drugs;¹³ and 4) occasionally, when several drugs exhibit compromised efficacy or very weak action, it may be justified to prescribe more than four drugs.

MOST RATIONAL USE OF EFFECTIVE ANTI-TUBERCULOSIS DRUGS IN MDR-TB PATIENTS

As previously mentioned, not only is the number of drugs available to control TB limited, but their efficacy differs, and some of the drugs exhibit cross-resistance.²⁷⁻⁵¹ Based on the activity, efficacy, route of administration, tolerance, availability and costs of anti-tuberculosis drugs, they can be classified into five groups (see Figure).^{13,36,45,46} At least four medications¹³ should be selected to design a regimen, starting from Group 1 (first-line drugs for oral administration) and moving on to the next group when no adequate drug is left in the previous groups. It should be noted that in Groups 2 (injectable agents) and 3 (fluoroquinolones), only one drug should be selected from each group due to documented total or partial cross-resistance within groups.^{47,49,50}

Group 5 (Figure) is composed of drugs for which anti-tuberculosis action has not been documented in clinical trials (except for thiacetazone). Their high or low efficacy has been reported only in *in vitro* experiments or animal models.⁵²⁻⁵⁷ These drugs (including thiacetazone) have been designated as reserve drugs due to their low activity and high toxicity, particularly in human immunodeficiency virus (HIV) infected patients.⁵⁸

A drug that has been used to treat a patient in a failing regimen should not be included in the total four drugs in the retreatment regimen, despite an encouraging DST result. If the DST results show susceptibility to this drug, it should be added to the regimen in addition to the other four drugs.

Finally, there is a tendency to include PZA in these regimens,^{4,24,31,37} as it is almost always used along with other potent drugs in the initial phase of treatment regimens and is usually stopped before the emergence of resistance. Although this is a good argument for susceptibility to PZA, confirmation by DST is very difficult, requiring BACTEC. If PZA is added, it should therefore not be included among the four drugs.

LENGTH OF PARENTERAL DRUG ADMINISTRATION OR OF THE INITIAL PHASE OF TREATMENT

Compelling evidence is also lacking regarding the optimal length of parenteral drug administration or of the initial phase of treatment. No clinical trials

have compared the efficacy of regimens with different lengths of parenteral drug administration in patients with drug resistance. In the pre-RMP period, although many studies evaluated regimens that contained an aminoglycoside, the regular length of administration was not stated. Fischer et al. reported an 83.5% sputum conversion rate by the fourth month using only three drugs, including KM, over a period of 16–24 weeks.¹⁶

Controversy is again noted when reviewing key sets of guidelines. The WHO and The Union recommend only 2 months of SM in the standard retreatment regimen with first-line drugs.^{3,12} In the WHO guidelines for the treatment of patients with MDR-TB published in 1997,⁴ this period of parenteral administration was extended to a minimum of 3 months, or until culture conversion. However, the 2003 WHO guidelines, while maintaining the same length of treatment with SM in the Category II regimen, recommended that it be extended to a minimum of 6 months for the treatment of chronic patients.¹² In addition, the recently published 2006 guidelines suggest: 'at least six months and at least four months after the patient first becomes and remains smear or culture negative.'¹³

The 1994 and 2003 ATS guidelines merely mentioned that in the absence of another therapeutic option, the maximum cumulative dose of SM to be prescribed should be 120 g, due to its toxic effects.^{7,8} No reference was made to other injectable drugs. In 1998, the BTS recommended the use of five or more drugs for patients with MDR-TB, indicating that they should be given until cultures became negative, after which treatment with three drugs should be continued.¹¹ Although it is very likely that the injectable agent would be included among the drugs to be withdrawn when cultures become negative, this is not specifically mentioned. Experts' opinions on this subject are also contradictory:^{36,37,40,45,46} some tend to recommend 3–6 months,^{36,37,40} while others suggest a minimum of 12 months after the cultures have become negative, when the patient is likely to be susceptible to only four drugs, or even throughout administration if the patient presents with extensive lung damage or a high degree of resistance.^{45,46}

Considering that the site of action of SM may be exclusively extracellular, it would be estimated to be of low efficacy once cultures have become negative. However, Crowle et al. demonstrated that SM also has intracellular activity.⁵⁹ If these findings *in vitro* correspond also to effects *in vivo*, and if other injectable agents behave like SM, this group of drugs would be likely to remain effective even after culture conversion. For this reason, recommendations about the length of administration of injectable drugs should be decided in the context of the other drugs in the regimen, the patient's bacteriological status and close monitoring of adverse effects. If a regimen provides three

effective drugs from Groups 1, 3 and 4 (Figure) after withdrawal of the injectable agent, this agent can be safely withdrawn when the cultures become negative. On the other hand, when fewer than three effective drugs are available, or if any of them belong to Group 5, more lengthy administration of the injectable agent should be considered, depending on the efficacy of the remaining drugs and the patient's bacteriological status, and the appearance of adverse effects should be monitored very closely.

CONTRIBUTION OF SURGERY TO THE TREATMENT OF MDR-TB PATIENTS

A historical review of TB treatment during the first half of the twentieth century shows that surgery played a major role.^{37,60,61} The reduction of the bacillary burden achieved by the different surgical procedures in the pre-chemotherapy era provided a higher cure rate than did the natural evolution of the disease,⁶² but surgery failed to entirely eradicate bacilli from the lesions and it always involved high morbidity and mortality.^{60,61} After the discovery of effective drugs to fight TB, surgery was progressively abandoned until the 1970s, when it practically disappeared from case management. The question emerged again in patients with MDR-TB and resistance to multiple other drugs, when practically no available chemotherapy regimen ensured cure. Under these circumstances, many patients today confront a situation very similar to that of patients in the pre-chemotherapy era.

Despite the absence of randomised trials assessing the role of surgery in the treatment of patients with MDR-TB, virtually all available guidelines and specific recommendations on the subject include a mention of surgery,^{5-8,37,45} albeit in a very secondary role,^{5-8,37,45,63} and it is recommended only in patients who meet the three following conditions: 1) a fairly localised lesion; 2) adequate pulmonary function; and 3) a lack of sufficient available drugs (two or three with very weak action) to design a regimen potent enough to ensure cure.

The strongest advocates of surgical treatment recommend scheduling surgery at the time of the lowest possible bacillary load, preferably when sputum smears and culture have become negative, and suggest continuing chemotherapy after the procedure until completion of a predetermined pharmacological regimen of 18–24 months.^{32-34,45} It would be necessary to evaluate the clinical outcome of these patients with negative cultures if the chemotherapy were continued without surgery, considering that pharmacological treatment has demonstrated efficacy in sputum conversion and at this point the bacillary load is much lower. It should be kept in mind that surgery performed in such patients, even by the most experienced surgeons,^{33,34} still results in high morbidity and mortality.

Surgery should therefore only be considered for the management of MDR-TB for patients who fulfil the three conditions mentioned above, and it should be performed by experienced surgeons with the support of efficient postoperative care units.^{33,34} These conditions exist in only a few countries in the world, most of them industrialised.

THE OPTIMAL REGIMEN FOR MDR-TB: STANDARDISED VS. INDIVIDUALISED REGIMENS

The guidelines of scientific societies in high-income countries have always advocated individualised case management.^{5-8,10,11} With an abundance of resources at their disposal, various authors have published recommendations based on individualised criteria for the selection of the best possible regimen for each patient.^{40,45,46} The main principles of this individualisation are selection of treatment based on the DST results and elaboration of aggressive therapeutic regimens in settings that allow close follow-up of patients by skilled professionals. Several published studies have reported the efficacy of this strategy (Table 2).^{21-23,25,27-30,32-34} This is, however, a highly expensive approach that is difficult to implement in the majority of middle- and low-income countries, which bear the highest burden of MDR-TB.⁶⁴ As many countries have employed very few second-line drugs in recent years, the micro-organisms would be expected to be more susceptible to these than would be assumed from the often unreliable DST results.³⁶ For this reason, the 1996 WHO recommendations for the treatment of MDR-TB favoured the use of standardised treatment regimens in specific circumstances.⁴ Standard treatment regimens for these MDR-TB patients facilitate their management, reduce the number of specialist physicians needed and reduce the overall cost of treatment by five to ten times. In the light of these advantages, various authors have advocated standard management, but again, only under specific conditions.^{31,36,37,65} The efficacy of this strategy has been confirmed by reports in the literature.^{26,31}

To begin to resolve this controversy and simplify the management of MDR-TB cases, they could be divided into three treatment categories: 1) initial MDR-TB in patients with no history of anti-tuberculosis treatment (or who have received them for less than 1 month); 2) MDR-TB cases who have received only first-line drugs in the past; and 3) MDR-TB cases who have received both first- and second-line drugs in the past. The various possible management strategies for these patients are discussed separately.

Initial MDR-TB in patients with no history of anti-tuberculosis treatment (or who have received them for less than 1 month)

Opinions regarding the treatment of initial MDR-TB patients also differ,^{36,45} as no study has so far aimed to

validate the different treatment options. On the one hand, there are studies like that by Espinal et al., in which 95 (52%) of 184 patients diagnosed with initial MDR-TB and treated in six countries (Peru, Korea, Hong Kong, Italy, Ivanovo Oblast [Russia] and Dominican Republic) received an initial regimen with INH and RMP throughout and showed success rates of between 11% in Ivanovo Oblast and 60% in Hong Kong.⁶⁵ Other studies have shown a high rate of incident MDR-TB in patients who had previous contact with known MDR-TB cases.⁶⁶ In either case, it appears inadequate to recommend standard regimens containing INH and RMP when faced with a known initial MDR-TB situation because of the serious risk of amplifying resistance.¹³ It appears more judicious to recommend that contacts of MDR-TB cases be treated with the same regimens as their index cases.¹³

MDR-TB cases who have received only first-line drugs in the past

Even in countries with an abundance of resources, MDR-TB patients who have received only first-line anti-tuberculosis drugs could be treated with standardised regimens consisting of second-line drugs. Following the sequence described in the Figure, the regimen for these patients might include an injectable agent other than SM, a fluoroquinolone and two other drugs from Group 4 (preferably ethionamide and cycloserine, given their tolerance and efficacy). EMB should be added if the DST shows susceptibility, even if it has been used in the past. This standard regimen fulfils all the requirements previously set, and will avoid the danger of improvised treatments³⁷ and the problem of interpreting the results of DST against second-line drugs.³⁸

MDR-TB cases who have received both first- and second-line drugs in the past

The management of these patients poses the most difficult problem, as they have often suffered from a regrettably lengthy sequence of therapeutic errors, with multiple regimens and drugs administered during the past years, which are very often hard to determine. The only solution in these cases is individualised management following the premises presented in this article. However, particular situations may require standardised regimens. This is the case in many countries where only one or two second-line drugs have been available commercially. This situation is particularly frequent in middle- and low-income countries that have had access only to KM and fluoroquinolones as reserve drugs. Following the logical sequence described in the Figure, a regimen including capreomycin from Group 2 and the three drugs from Group 4 (ethionamide, cycloserine, PAS) could be recommended, while in those regions and countries that have only used KM and amikacin as reserve drugs, a fluoroquinolone would replace PAS in the above regimen.

CONCLUSION

There is little evidence and much controversy regarding the treatment of MDR-TB. Disagreements seem to stem mainly from the diverse experiences of experts in the field. A very cautious approach is therefore required regarding every aspect of the management of MDR-TB patients, as proposed in the present article. Given the significant global increase in MDR-TB in recent years, more solid evidence validating the various recommendations will certainly come to light in the near future.

References

- 1 World Health Organization. Guidelines for tuberculosis treatment in adults and children in national tuberculosis programmes. WHO/TB/91.161. Geneva, Switzerland: WHO, 1991.
- 2 World Health Organization. Treatment of tuberculosis: guidelines for national programmes. 2nd ed. WHO/TB/97.220. Geneva, Switzerland: WHO, 1997.
- 3 Enarson D A, Rieder H L, Arnadottir T, Trébuçq A. Management of tuberculosis. A guide for low income countries. Fifth Edition. Paris, France: The International Union Against Tuberculosis and Lung Disease, 2000.
- 4 Crofton J, Chaulet P, Maher D, et al. Guidelines for the management of drug-resistant tuberculosis. WHO/TB/96.210. Geneva, Switzerland: WHO, 1997.
- 5 American Thoracic Society. Chemotherapy of pulmonary tuberculosis in adults: the choice of drugs in relation to drug susceptibility. A statement of the Committee on Therapy. Am Rev Respir Dis 1965; 92: 508–512.
- 6 American Thoracic Society. Treatment of drug-resistant tuberculosis. A statement by the Committee on Therapy. Am Rev Respir Dis 1966; 94: 125–127.
- 7 American Thoracic Society, Centers for Disease Control and Prevention, American Academy of Pediatrics. Treatment of tuberculosis and tuberculosis infection in adults and children. Am J Respir Crit Care Med 1994; 149: 1359–1374.
- 8 American Thoracic Society, Centers for Disease Control and Prevention, Infectious Disease Society of America. Treatment of tuberculosis. Am J Respir Crit Care Med 2003; 167: 603–662.
- 9 Caminero J A, de March P. Statements of ATS, CDC, and IDSA on treatment of tuberculosis. Am J Respir Crit Care Med 2004; 169: 316–317.
- 10 Citron K M, Darbyshire J H, Ormerod L P, Smith M L. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations of the joint tuberculosis committee of the British Thoracic Society. Thorax 1990; 45: 403–408.
- 11 Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Thorax 1998; 53: 536–548.
- 12 World Health Organization. Treatment of tuberculosis: guidelines for national programmes. 3rd ed. WHO/CDS/TB/2003. 313. Geneva, Switzerland: WHO, 2003.
- 13 World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2006.361. Geneva, Switzerland: WHO, 2006.
- 14 Tousek J, Jancik E, Zelenka M, Jancikova-Máková M. The results of treatment in patients with cultures resistant to streptomycin, isoniazid and PAS: a five-year follow-up. Tubercle 1967; 48: 27–31.
- 15 Zierski M, Zachara A. Late results in re-treatment of patients with pulmonary tuberculosis. Tubercle 1970; 51: 172–177.
- 16 Fischer D A, Lester W, Dye W E, Moulding T S. Re-treatment

- of patients with isoniazid-resistant tuberculosis. Analysis and follow-up of 146 cases. *Am Rev Respir Dis* 1968; 97: 392–398.
- 17 Kass I. Chemotherapy regimens used in retreatment of pulmonary tuberculosis. Part I. Observations on the efficacy of combinations of kanamycin, ethionamide and either cycloserine or pyrazinamide. *Tubercle* 1965; 46: 151–165.
 - 18 Pines A. Treatment of pulmonary tuberculosis with cultures resistant to two or more drugs: a series of 44 patients. *Tubercle* 1965; 46: 131–142.
 - 19 Somner A R, Brace A A. Late results of treatment of chronic drug-resistant pulmonary tuberculosis. *BMJ* 1966; 1: 775–778.
 - 20 Kass I. Chemotherapy regimens used in retreatment of pulmonary tuberculosis. Part II. Observations on the efficacy of combinations of ethambutol, capreomycin and companion drugs, including 4-4 diisoamlyoxythiosemicarbanilide. *Tubercle* 1965; 46: 166–177.
 - 21 Leimane V, Riekstina V, Holtz T H, et al. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. *Lancet* 2005; 365: 318–326.
 - 22 Mitnick C, Bayona J, Palacios E, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. *N Engl J Med* 2003; 348: 119–128.
 - 23 Palmero D J, Ambroggi M, Brea A, et al. Treatment and follow-up of HIV-negative multidrug-resistant tuberculosis patients in an infectious diseases reference hospital, Buenos Aires, Argentina. *Int J Tuberc Lung Dis* 2004; 8: 778–784.
 - 24 Suárez P G, Floyd K, Portocarrero J, et al. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. *Lancet* 2002; 359: 1980–1989.
 - 25 Goble M, Iseman M D, Madsen L A, Waite D, Ackerson L, Horsburgh C R Jr. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med* 1993; 328: 527–532.
 - 26 International Organization for Migration Tuberculosis Working Group. Outcome of second-line tuberculosis treatment in migrants from Vietnam. *Trop Med Intern Health* 1998; 3: 975–980.
 - 27 Park S K, Kim C T, Song S D. Outcome of chemotherapy in 107 patients with pulmonary tuberculosis resistant to isoniazid and rifampicin. *Int J Tuberc Lung Dis* 1998; 2: 877–884.
 - 28 Geerligs W A, van Altena R, de Lange W C M, van Soolingen D, van der Werf T S. Multidrug-resistant tuberculosis: long-term treatment outcome in the Netherlands. *Int J Tuberc Lung Dis* 2000; 4: 758–764.
 - 29 Tahaoglu K, Törün T, Sevim T, et al. The treatment of multidrug-resistant tuberculosis in Turkey. *N Engl J Med* 2001; 345: 170–174.
 - 30 Narita M, Alonso P, Lauzardo M, Hollender E S, Pitchenik A E, Ashkin D. Treatment experience of multidrug-resistant tuberculosis in Florida, 1994–1997. *Chest* 2001; 120: 343–348.
 - 31 Van Deun A, Hamid Salim M A, Kumar Das A P, Bastian I, Portaels F. Results of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh. *Int J Tuberc Lung Dis* 2004; 8: 560–567.
 - 32 Iseman M D, Madsen L, Goble M, Pomerantz M. Surgical intervention in the treatment of pulmonary disease caused by drug-resistant *Mycobacterium tuberculosis*. *Am Rev Respir Dis* 1990; 141: 623–625.
 - 33 Chan E D, Laurel V, Strand M J, et al. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2004; 169: 1103–1109.
 - 34 Park S K, Lee C M, Heu J P, Song S D. A retrospective study for the outcome of pulmonary resection in 49 patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2002; 6: 143–149.
 - 35 Mitchison D A. The segregation of streptomycin-resistant variants of *Mycobacterium tuberculosis* into groups with characteristic levels of resistance. *J Gen Microbiol* 1951; 5: 596–604.
 - 36 Caminero J A. Management of multidrug-resistant tuberculosis and patients in retreatment. *Eur Respir J* 2005; 25: 928–936.
 - 37 Caminero J A. A tuberculosis guide for specialist physicians. Paris, France: International Union Against Tuberculosis and Lung Disease, 2005.
 - 38 Kim S J. Drug-susceptibility testing in tuberculosis: methods and reliability of results. *Eur Respir J* 2005; 25: 564–569.
 - 39 Canetti G. The J. Burns Amberson lecture. Present aspects of bacterial resistance in tuberculosis. *Am Rev Respir Dis* 1965; 92: 687–703.
 - 40 Iseman M D. Treatment of multidrug-resistant tuberculosis. *N Engl J Med* 1993; 329: 784–791.
 - 41 Tuberculosis Division, International Union Against Tuberculosis and Lung Disease. Tuberculosis bacteriology—priorities and indications in high prevalence countries: position of the technical staff of the Tuberculosis Division of the International Union Against Tuberculosis and Lung Disease. *Int J Tuberc Lung Dis* 2005; 9: 355–361.
 - 42 Kim S J, Espinal M A, Abe C, et al. Is second-line anti-tuberculosis drug susceptibility testing reliable? *Int J Tuberc Lung Dis* 2004; 8: 1157–1158.
 - 43 Caminero J A. Number of drugs to treat multidrug-resistant tuberculosis. From the authors. *Am J Respir Crit Care Med* 2004; 169: 1337.
 - 44 Iseman M D. Statements of ATS, CDC, and IDSA on treatment of tuberculosis. From the authors. *Am J Respir Crit Care Med* 2004; 169: 317.
 - 45 Mukherjee J, Socci A, Acha J, et al. The PIH guide to management of multidrug-resistant tuberculosis. International edition. Boston, MA, USA: Partners in Health, 2003.
 - 46 Mukherjee J S, Rich M L, Socci A R, et al. Programmes and principles in treatment for multidrug-resistant tuberculosis. *Lancet* 2004; 363: 474–481.
 - 47 Alberghina M, Nicoletti G, Torrisi A. Genetic determinants of aminoglycoside resistance in strains of *Mycobacterium tuberculosis*. *Chemotherapy* 1973; 19: 148–160.
 - 48 Lefford M J. The ethionamide sensitivity of East African strains of *Mycobacterium tuberculosis* resistant to thiacezone. *Tubercle* 2000; 50: 7–13.
 - 49 Tsukamura M, Mizuno S. Cross-resistance relationships among the aminoglycoside antibiotics in *Mycobacterium tuberculosis*. *J Gen Microbiol* 1975; 88: 269–274.
 - 50 Alangaden G J, Manavathu E K, Vakulenko S B, Zvonok N M, Lerner S A. Characterization of fluoroquinolone-resistant mutant strains of *Mycobacterium tuberculosis* selected in the laboratory and isolated from patients. *Antimicrob Agents Chemother* 1995; 39: 1700–1703.
 - 51 McClatchy J K, Kanes W, Davidson P T, Moulding T S. Cross-resistance in *M. tuberculosis* to kanamycin, capreomycin and viomycin. *Tubercle* 1977; 58: 29–34.
 - 52 Chambers H F, Kocagöz T, Sipit T, Turner J, Hopewell P C. Activity of amoxicillin/clavulanate in patients with tuberculosis. *Clin Infect Dis* 1998; 26: 874–877.
 - 53 Nadler J P, Berger J, Nord J A, Cofsky R, Saxena M. Amoxicillin-clavulanic acid for treating drug-resistant *Mycobacterium tuberculosis*. *Chest* 1991; 99: 1025–1026.
 - 54 Jagannath C, Reddy M V, Kailasam S, O'Sullivan J F, Gangadharam P R J. Chemotherapeutic activity of clofazimine and its analogues against *Mycobacterium tuberculosis*. In vitro, intracellular, and in vivo studies. *Am J Respir Crit Care Med* 1995; 151: 1083–1086.
 - 55 Buriánková K, Doucet-Populaire F, Dorson O, et al. Molecular basis of intrinsic macrolide resistance in the *Mycobacterium tuberculosis* complex. *Antimicrob Agents Chemother* 2004; 48: 143–150.

- 56 Rastogi N, Labrousse V, Seng Goh K. In vitro activities of fourteen antimicrobial agents against drug susceptible and resistant clinical isolates of *Mycobacterium tuberculosis* and comparative intracellular activities against the virulent H37Rv strain in human macrophages. *Curr Microbiol* 1996; 33: 167-175.
- 57 Luna-Herrera J, Reddy V M, Daneluzzi D, Gangadharam P R J. Antituberculosis activity of clarithromycin. *Antimicrob Agents Chemother* 1995; 39: 2692-2695.
- 58 Ipuge Y A I, Rieder H L, Enarson D A. Adverse cutaneous reactions to thiacetazone for tuberculosis treatment in Tanzania. *Lancet* 1995; 346: 657-660.
- 59 Crowle A J, Sbarbaro J A, Judson F N, Douvas G S, May M H. Inhibition by streptomycin of tubercle bacilli within cultures human macrophages. *Am Rev Respir Dis* 1984; 130: 839-844.
- 60 Pomerantz M, Mault J R. History of resectional surgery for tuberculosis and other mycobacterial infections. *Hist Thoracic Surg* 2000; 10: 131-133.
- 61 Hrdlicka A. Disease, medicine and surgery among the American aborigines. *Ind Med* 1932; 99: 1661-1666.
- 62 Grzybowski S, Enarson D A. The fate of cases of pulmonary tuberculosis under various treatment programmes. *Bull Int Union Tuberc* 1978; 53(2): 70-75.
- 63 Freixinet J, Rivas J J, Rodríguez de Castro F, et al. Role of surgery in pulmonary tuberculosis. *Med Sci Monit* 2002; 8: CR782-CR786.
- 64 World Health Organization. The WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Anti-tuberculosis drug resistance in the world. Report No. 3. WHO/CDS/TB/2004.343. Geneva, Switzerland: WHO, 2004.
- 65 Espinal M A, Kim S J, Suarez P G, et al. Standard short-course chemotherapy for drug-resistant tuberculosis. Treatment outcomes in 6 countries. *JAMA* 2000; 283: 2537-2545.
- 66 Bayona J, Chavez-Pachas A M, Palacios E, Llaro K, Sapag R, Becerra M C. Contact investigations as a means of detection and timely treatment of persons with infectious multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2003; 7 (Suppl 3): 501-509.

RÉSUMÉ

Au cours de la dernière décennie, la tuberculose résistante à plusieurs drogues (TB-MR) est devenue un problème épidémiologique de première priorité au niveau mondial. Il est nécessaire de simplifier et de standardiser la prise en charge des cas puisque un nombre élevé de cas de TB-MR dans de nombreux pays ne peuvent pas bénéficier d'une approche individualisée par des médecins spécialistes. Toutefois, toute décision concernant la standardisation doit être précédée par une analyse soignée des faits prouvés et des controverses concernant les diverses recommandations publiées. Malheureusement, les controverses l'emportent sur les faits prouvés. La difficulté ne réside pas seulement dans l'absence d'essais contrôlés validant les recommandations spécifiques mais aussi dans les résultats extrêmement différents et même contradictoires observés dans la littérature. Il paraît essentiel dès lors d'analyser ces discordances avant d'élaborer des recommandations raisonnées et uniformes.

L'analyse devrait comporter les problèmes les plus importants et les plus controversés concernant la prise en charge des patients atteints de TB-MR, tels que : 1) la confirmation du diagnostic chez un patient suspect de TB-MR et la détermination de la valeur des tests de sensibilité aux médicaments ; 2) le nombre de médicaments antituberculeux nécessaires pour traiter la TB-MR ; 3) l'utilisation la plus rationnelle des médicaments efficaces contre la tuberculose ; 4) la durée conseillée de l'administration parentérale des médicaments ou de la phase initiale du traitement ; 5) la contribution de la chirurgie à la prise en charge des patients atteints de TB-MR ; et 6) la recherche du régime optimal de traitement de la TB-MR (régime standardisé versus individualisé). Les faits prouvés et les controverses concernant chacune des questions ci-dessus sont analysés dans la perspective de faciliter la prise de décision sur le traitement de ces cas complexes.

RESUMEN

En la última década, la tuberculosis multidrogorresistente (TB-MDR) se ha convertido en una prioridad epidemiológica a nivel mundial. Al ser tantos los casos y al ser muchos los países que no pueden ofrecer a todos sus casos una atención individualizada por médicos especialistas, se hace necesario simplificar y estandarizar el manejo de estos difíciles enfermos. Sin embargo, previo a este intento de estandarización se debe realizar un detenido análisis de las evidencias y controversias que existen detrás de las diferentes recomendaciones publicadas. Desafortunadamente, las controversias superan claramente las evidencias. La dificultad no sólo procede de la completa ausencia de ensayos clínicos validando recomendaciones específicas, sino también de los diferentes y contradictorios resultados encontrados en la literatura. Por lo tanto, es esencial analizar estas discrepancias antes de desarrollar recomendaciones uniformes.

Este análisis debe enfocar los aspectos más esenciales y controvertidos respecto al manejo de los pacientes con TB-MDR, como son : 1) confirmación del diagnóstico en un enfermo con sospecha de TB-MDR y determinación del valor de las pruebas de susceptibilidad a drogas ; 2) número de fármacos antituberculosos necesario para tratar una TB-MDR ; 3) el uso más racional de las drogas antituberculosas ; 4) duración recomendable del fármaco utilizado por vía parenteral, o de la fase inicial del tratamiento ; 5) aporte de la cirugía al manejo de los pacientes con TB-MDR ; y 6) aproximación al régimen ideal para tratar la TB-MDR : regímenes estandarizados versus individualizados. En este artículo se analizarán las evidencias y controversias que existen respecto a los temas expuestos previamente, con el objetivo de poder facilitar el manejo de estos complejos enfermos.