GUIDELINES *for the* MANAGEMENT

of

DRUG–RESISTANT

TUBERCULOSIS

WORLD HEALTH ORGANIZATION

GUIDELINES FOR THE MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS

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1. About one third of the world's population is infected by *M. tuberculosis*. Worldwide in 1995 there were about nine million new cases of tuberculosis with three million deaths. *M. tuberculosis* kills more people than any other single infectious agent. Deaths from tuberculosis comprise 25% of all avoidable deaths in developing countries. 95% of tuberculosis cases and 98% of tuberculosis deaths are in developing countries; 75% of these cases are in the economically productive age group (15 - 50 years).

2. As a consequence, the world is facing a much more serious situation as we approach the twenty-first century than in the mid-1950s. Due to demographic factors, socio-economic trends, neglected tuberculosis control in many countries, and in addition, the HIV epidemic, there are many more smear-positive pulmonary tuberculosis cases, often undiagnosed and/or untreated. When tuberculosis cases are treated, poor drug prescription and poor case management are creating more tuberculosis patients excreting resistant tubercle bacilli.

3. In 1991, the World Health Assembly adopted Resolution WHO 44.8, recognizing *"effective case management as the central intervention for tuberculosis control"*, and recommending the strengthening of national tuberculosis programmes by introducing short course chemotherapy and improving the treatment management system. Since 1992, the WHO Global Tuberculosis Programme has developed a new strategy, to meet the needs of global tuberculosis control. "DOTS" is the brand name of the WHO recommended tuberculosis control strategy.

   Tuberculosis control requires effective, inexpensive, simple and largely standardized technology, and the managerial skills to implement them as a large scale intervention in each country.

4. The success of the DOTS strategy depends on the implementation of a five-point package:

   ● government commitment to a National Tuberculosis Programme;
   ● case detection through case-finding by sputum smear microscopy examination of TB suspects in general health services;
   ● standardised short-course chemotherapy to, at least, all smear-positive TB cases under proper case management conditions;
   ● regular uninterrupted supply of all essential anti-TB drugs;
   ● monitoring system for programme supervision and evaluation.

5 In all countries that have adopted the DOTS strategy, under programme conditions the cure rates (and the success rates) for the treatment of smear-positive tuberculosis cases are already over 80%. When this strategy is implemented over a long period for the standardized treatment of smear-positive tuberculosis cases, there will be a huge reduction in sources of infection and in transmission.

For the future, the top priority remains to administer standardized short course chemotherapy regimens to all smear-positive cases (new and retreatment cases). This priority requires the maximum of effort, time, drugs and money in a national tuberculosis programme, without diverting funds and resources to smear negative and/or chronic cases.

6 The issue of the treatment of those pulmonary tuberculosis patients who remain sputum smear-positive following fully supervised WHO retreatment regimen should be considered. Although these cases represent a small minority of tuberculosis patients, they constitute an on-going problem for programme managers.

Due to the lack of financial resources, many countries cannot provide the range of the expensive second-line drugs which might give some hope of cure to these patients. However, more economically prosperous countries might wish to do so, especially if they have inherited a significant number of patients with multi drug resistant (MDR) tuberculosis from a period when treatment was unorganized and chaotic. Many countries also lack information about the correct use of second-line drugs.

The WHO Tuberculosis Control Workshop held in Geneva, October 1995, discussed this issue and recommended that a country prepared to go to this expense should only provide these second-line drugs for a **specialized unit** (or units in large countries), in close connection with a **laboratory** able to carry out cultures and reliable susceptibility tests of *M. tuberculosis* to the drugs.

The WHO Global Tuberculosis Programme has prepared these *"Guidelines for the Management of Drug-Resistant Tuberculosis"*, to meet the need for clear advice on this issue.

1.1 DEFINITIONS

a *Drug-resistant tuberculosis*. This is a case of tuberculosis (usually pulmonary) excreting bacilli resistant to one or more antituberculosis drugs.

In patients who have not had prior treatment with antituberculosis drugs, the bacterial resistance is called *primary resistance* (if it is certain that the patient has not had previous treatment). After clinical assessment, if it is doubtful that the patient really has not received prior treatment, this is called *initial resistance*. *Initial resistance* is a mixture of *primary resistance* and undisclosed *acquired resistance*.

In patients with some record of previous treatment, the bacterial resistance is called *acquired resistance*.[1]

In new patients, the WHO standard first-line regimens (6 months or 8 months) overcome the risk of failure due to primary resistance.

In the majority of previously treated patients (more than one month), the WHO standard retreatment regimen (8 months) reduces the risk of failure due to acquired resistance.

b *Failure of retreatment*. The definition of *failure* of the WHO *retreatment* regimen is a tuberculosis patient excreting bacilli either after 5 months, or after completion, of the 8-month retreatment regimen, given under direct observation by a health worker. *(1)*

This retreatment regimen consists of three drugs throughout (isoniazid, rifampicin, ethambutol) supplemented by pyrazinamide during the first 3 months and streptomycin during the first 2 months. The conventional abbreviation for this regimen is 2SHRZE/1HRZE/5HRE. If it is properly administered to the patient, any bacilli remaining after 5 months (or more) of chemotherapy are usually resistant to at least one or two of the main bactericidal drugs given (isoniazid and/or rifampicin).

c *Chronic case*. A *chronic case* is now defined by the failure of the WHO retreatment regimen given under direct observation by a health worker. *(1)* A chronic case has received at least 2 courses of chemotherapy, and sometimes more than two courses (complete or incomplete). Chronic cases are usually, but not always, excretors of resistant bacilli (the rate of acquired resistance is very high in this category of patients) and often excretors of MDR bacilli.

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[1] Occasionally, with single-drug treatment or inappropriate drug combinations, resistance can occur after only two or three weeks. It may be necessary to consider this when prescribing drug combinations for an individual patient.

d *MDR bacilli and MDR tuberculosis*. *MDR bacilli* are resistant to at least isoniazid and rifampicin, the main antituberculosis drugs. MDR is the most severe form of bacterial resistance today. It is why *MDR tuberculosis* is an important concern for tuberculosis control in many countries. *(2, 3)*

Since the early 1990s, several outbreaks of MDR tuberculosis have been reported in different regions of the world, as a consequence of inappropriate use of essential antituberculosis drugs. Usually MDR tuberculosis occurs in chronic cases, after failure of WHO or other retreatment regimens and represents a significant proportion of tuberculosis patients with acquired resistance. Exceptionally, MDR tuberculosis is observed in new cases, i.e. in patients who have never taken antituberculosis drugs, and who have been infected by MDR bacilli. In most settings, these new cases with MDR bacilli represent a very small proportion of new tuberculosis patients with primary resistance.

1.2   HOW IS MDR TUBERCULOSIS PRODUCED? *(4, 5)*

As with other forms of drug resistance, the phenomenon of MDR tuberculosis is entirely man-made.

Drug resistant bacilli are the consequence of human error in any of the following:

- prescription of chemotherapy
- management of drug supply
- case management
- process of drug delivery to the patient.

The most common medical errors leading to the selection of resistant bacilli are the following:

a the prescription of inadequate chemotherapy to the multibacillary pulmonary tuberculosis cases (e.g. only 2 or 3 drugs during the initial phase of treatment in a new smear-positive patient with bacilli initially resistant to isoniazid);

b the addition of one extra drug in the case of failure, and repeating the addition of a further drug when the patient relapses after what amounts to monotherapy.

The most common errors observed in the management of drug supply are the following:

a the difficulty experienced by poor patients in obtaining all the drugs that they need (due to lack of financial resources or social insurance);

   b frequent or prolonged shortages of antituberculosis drugs (due to poor management and/or financial constraints in developing countries);

   c use of drugs (or drug combinations) of unproven bioavailability.

The following also have the effect of multiplying the risk of successive monotherapies and selection of resistant bacilli:

   a the patient's lack of knowledge (due to a lack of information or due to inadequate explanation before starting treatment);

   b poor case-management (when the treatment is not directly observed, especially during the initial phase).

1.3   MAGNITUDE OF THE PROBLEM *(6, 7, 8, 9, 10, 11)*

In programme conditions, there are two groups of bacteriologically positive (smear and/or culture) tuberculosis patients:

- *New cases*, i.e. patients who have never taken antituberculosis drugs (or for less than 1 month).
- *Old cases*, i.e. patients previously treated with antituberculosis drugs during one or more courses of chemotherapy, whether or not completed.

During the early stages of implementation of a national tuberculosis control programme, *old cases* (previously treated by usually inappropriate and non-standardized chemotherapy regimens) may represent up to half of notified cases. In this situation, acquired resistance emerges as a priority problem, as the rate of acquired resistance is 50% to 80% in previously treated cases. The priority solution is to standardize at country level and to adopt the WHO recommended standard regimens of chemotherapy for new cases and for retreatment cases, in order to stop the creation of more cases with bacterial resistance. Even if the proportion of MDR tuberculosis among drug resistant tuberculosis is high, **the top priority is not the management, but the prevention, of MDR tuberculosis**.

Experience from a number of successful national control programmes assisted by WHO or IUATLD suggests that, when a national tuberculosis control programme has been well implemented for several years, the proportion of "old cases" decreases and represents 10%-20% of all pulmonary tuberculosis cases. The rate of acquired resistance is around 20% among "old cases" (previously treated patients), in whom the rate of MDR tuberculosis is 4%-10%. *(8)*

Whatever the stage of implementation of a national tuberculosis control programme, the occurrence of bacterial resistance in new patients (never previously treated), or *primary resistance*, is a consequence of the level of acquired resistance in the community.

The greater the number of patients who are excretors of resistant bacilli during or after treatment, the higher the risk of transmission of resistant bacilli to healthy individuals and of emergence of new cases with primary resistance. Primary and acquired resistance differ in terms of their prevalence and severity *(7)*:

a The rate of primary resistance in new patients is lower than the rate of acquired resistance. The rate of primary resistance is usually 5% or less in good national programmes, and 15% or more in new programmes implemented after a period of unorganized and chaotic tuberculosis chemotherapy.

b Primary resistance is less severe than acquired resistance:

● Primary resistance is more often to one drug (streptomycin or isoniazid) than to two drugs (usually streptomycin <u>plus</u> isoniazid). Primary resistance to three drugs and primary multidrug resistance are exceptional. By contrast, acquired resistance usually concerns two drugs or more, and multidrug resistance is relatively frequent.

● The level of resistance (i.e. minimum inhibitory concentration of antibiotics) is lower in primary than in acquired resistance.

This is why primary resistance hardly affects the outcome of treatment with a WHO standard regimen combining four drugs in the initial phase of treatment in new smear-positive patients.

In patients previously treated with one course of chemotherapy, the WHO standard retreatment regimen combining five drugs, then four during the initial phase of treatment, is necessary to overcome the risk of failure due to resistance to isoniazid or to isoniazid and streptomycin.

Primary MDR arises in settings where antituberculosis chemotherapy has been applied inappropriately for several years. In these settings, the rate of primary MDR cases may be as high as 7.5% in new cases *(8)*. In contrast, in settings where programmes have delivered chemotherapy effectively for several years, the primary MDR rate is very low, typically 1% or less, in new patients. *(8)*

Whatever the situation, the priority decision is to standardize the treatment regimen applied to all new cases of tuberculosis, and to give four drugs during the first two months of treatment in all new cases of smear-positive pulmonary tuberculosis. Susceptibility testing is not recommended for all new cases since it is not practicable, it is expensive and it is useless in those high tuberculosis prevalence, low or middle income countries. Susceptibility testing should be used in representative samples of new cases as a tool for monitoring bacterial resistance and as a measure of epidemiological surveillance of a national programme.

1.4   HOW TO PREVENT MDR TUBERCULOSIS?   *(12, 13)*

1.4.1   In new cases

The best prevention is to give each new case of sputum-positive pulmonary tuberculosis an effective regimen of short course chemotherapy (6 months or 8 months) with four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol or streptomycin) during at least the first 2 months, given under direct observation.

WHO recommended regimens are as effective in patients with bacilli initially resistant to isoniazid and/or streptomycin as in patients with susceptible bacilli. The cumulative rate of failure and relapses after 3 years is from 0%-4% in *new cases*, 0-3% in patients with initially susceptible bacilli and 0-13% in patients with primary resistance.

Theoretically, infection with MDR bacilli will be the cause of failure of very few individuals to respond to the initial regimen. Failure to respond because of infection with MDR bacilli represents an exceptional situation. Even when transmission of MDR bacilli from an "old" patient to a new patient is clearly demonstrated, it has still not been documented that primary MDR contributes significantly to the treatment failure rate of WHO standard regimens for new cases in programme conditions.

1.4.2   In old cases

In the group of tuberculosis patients previously treated with one or several courses of chemotherapy and who remain sputum positive (by smear and/or culture), three subpopulations can be observed:

- patients excreting bacilli still susceptible to all antituberculosis drugs;

- patients excreting bacilli resistant to at least isoniazid, but still susceptible to rifampicin;

- patients excreting bacilli resistant to at least, isoniazid <u>and</u> rifampicin.

The respective proportion of the three subpopulations varies according to the chemotherapy applied in the community during the past years. It varies also with the number of courses of chemotherapy received by the patients. *(14)*

    a In patients who have failed after the **first course of chemotherapy** (WHO recommended regimens or any other), the proportion of patients excreting bacilli still susceptible to all drugs is usually higher than the proportion of the two other subpopulations. The standard WHO retreatment regimen of 8 months (using 5 drugs for the first 2 months, then 4 drugs for the third month, and then 3 drugs for the remaining 5 months of treatment i.e. 2SHRZE/1HRZE/5HRE) given under direct

observation, can cure the majority of patients: those having still susceptible bacilli, and those having bacilli resistant to isoniazid and/or streptomycin, but still susceptible to rifampicin.

b In patients who have failed after **two courses of chemotherapy** (the second being the fully supervised standard WHO retreatment regimen), the proportion of patients excreting resistant bacilli is the majority (up to 80%). The proportion of patients with MDR tuberculosis can be as much as 50% of this group of patients with bacterial resistance. For this reason, a second application of the standard WHO retreatment regimen is likely to fail.

BASIC PRINCIPLES FOR MANAGEMENT OF MDR TUBERCULOSIS

2.1   SPECIALIZED UNIT

Treatment of patients with MDR tuberculosis (especially those with resistance to rifampicin and isoniazid) may have to involve **"second line" reserve drugs**. These are drugs other than the "standard" essential antituberculosis drugs, i.e. rifampicin (R), isoniazid (H), streptomycin (S), ethambutol (E), pyrazinamide (Z), thioacetazone (T). These reserve drugs are much more expensive, less effective and have many more side effects than standard drugs. They should only be made available to a **specialized unit** and not in the free market. **It is the responsibility of national health authorities to establish strong pharmaceutical regulations to limit the use of second-line reserve drugs in order to prevent the emergence of incurable tuberculosis**.

2.2   DESIGNING AN APPROPRIATE REGIMEN

Designing an appropriate regimen for the individual patient needs experience and skill. It includes allocating the time and patience to define precisely the following:

a which regimen(s) the patient had previously received;

b whether the patient took all the drugs in each regimen prescribed and for how long;

c to find out what happened bacteriologically, in terms of sputum positivity (at least by direct smear, if possible also by culture and susceptibility tests) during and after the administration of each regimen. Clinical and radiological progress or deterioration is much less reliable but may be used as a check on the bacteriological results.

2.3   RELIABLE SUSCEPTIBILITY TESTING

The specialized unit must have the services of a laboratory able to carry out culture and reliable tests for drug resistance (to the essential drugs and also to second-line drugs). The quality of the susceptibility tests carried out in this laboratory should be regularly checked by another reference laboratory at national or supranational level.

2.4   RELIABLE DRUG SUPPLIES

The unit must also be guaranteed reliable supplies of the expensive "second line" reserve drugs, so as to ensure that any treatment undertaken for an individual patient can be successfully completed.

2.5   PRIORITY IS PREVENTION

A country with limited resources may reasonably decide that its resources should be concentrated on ensuring that all new patients complete the standard national treatment and are thereby cured. With good standard treatment meticulously prescribed and meticulously administered, multidrug resistance should not occur.

The proper assumption is that the emergence of **MDR tuberculosis is always due to medical error**: prescribing an unreliable regimen, using unreliable drugs, or failing to ensure (by directly observed treatment and education of the patient and his family) that the patient takes the drugs as prescribed and for the full period prescribed. **MDR tuberculosis should always be regarded as a result of a failure of effective implementation of the national programme**. Top priority should be given to preventing such failure.

2.6   USING WHO STANDARD REGIMENS FOR NEW CASES
AND RETREATMENT

The following patients should be given the WHO retreatment regimen *(1)*: patients with treatment failure after the standard national regimen; relapses; patients returning after premature interruption of treatment. The vast majority will be cured with this retreatment regimen. Most failures are due to the use of an incorrect regimen and/or failure to ensure that the regimen is fully administered and directly observed.

Very rarely failure may be due to initial resistance to three or more of the five drugs used in the retreatment regimen (owing to gross errors in previous therapy for that patient).

2.7   MDR TUBERCULOSIS AS A CONSEQUENCE OF POOR
TREATMENT

In some countries MDR tuberculosis has arisen from poor treatment before the introduction of the National Programme or because some patients received poor treatment outside the National Programme (from private qualified, or even unqualified, practitioners). As a wide variety of different poor regimens may have been used for such patients, the MDR tuberculosis cases which arise will require detailed assessment by the specialized unit.

2.8   LONG-TERM INVOLVEMENT OF STAFF AND FINANCIAL
RESOURCES

With these considerations in mind, **a specialized unit for dealing with MDR tuberculosis may reasonably be regarded as an expensive luxury which is only affordable where national resources are moderate or good**, and after full implementation at country level

of WHO recommended standardized treatment regimens (for new and retreatment cases). If such a unit is set up (or perhaps more than one in a very large country) a gross waste of resources will occur unless it is run by skilled and experienced specialists who are given ongoing long-term responsibility for it, and who work closely with a reference laboratory able to carry out reliable tests for drug resistance. It must be provided with the resources outlined above. An inadequately resourced unit can do more harm than good. It may perpetuate and spread MDR tuberculosis, with the result that tuberculosis patients and health workers lose confidence in the treatment.

ASSESSING THE INDIVIDUAL CASE
OF APPARENT MDR TUBERCULOSIS

The suspicion of MDR tuberculosis occurs in two situations:

a when you receive a report from a laboratory indicating at least "strains resistant to isoniazid and rifampicin";

b when you observe in a smear-positive patient no response to the standard WHO retreatment regimen.

3.1   SOME PROVISOS

a Apparent MDR strains reported by a local laboratory should not be taken uncritically at face value. **Errors** occur in laboratories as elsewhere. Some laboratories are less reliable than others. The specimen may have been mislabelled or have come from another patient. If the result is a single one, and if it does not accord with clinical data (see below), repeat at least one, and preferably two tests.

b If there is no response to the standard WHO retreatment regimen, remember that many apparent treatment failures are due to the **patient having failed to take his treatment** and not due to MDR bacilli. Such patients should respond to the fully supervised standard WHO retreatment regimen.

c **Explain to the patient** how essential it is to know exact details of his previous treatment. If you are going to be able to cure this patient, you must know exactly what and how much of the prescribed treatment the patient actually took. The patient may not be able to admit that failure is the patient's own fault, so also question the family in the same way, and in the patient's absence. Also check with the patient's previous records and previous medical advisors.

d Just because there is a standard national regimen, do not assume that the patient has necessarily received it. Check with the records, the patient, the patient's family, the patient's previous doctors. There may well have been errors. In some cases the patient may have received other and unreliable treatment from a private practitioner, an unqualified person or even, in some countries, from a shopkeeper. From your knowledge of local conditions you can judge how likely this is. But even if you think it unlikely you should enquire. Enquire also whether the patient has been given the doctor's advice or prescription in writing. If so make careful notes from these documents of the dose of each drug, its frequency of administration, the accompanying drugs, and the dates when each drug was started and stopped.

3.2 COLLECTING CAREFULLY THE DATA CONCERNING THE PATIENT

Use a table based on Table 1 to tabulate information in a series of vertical columns.

Column 1
Date column. Date of diagnosis followed by dates of starting and completing regimens with exact doses and frequency of all the drugs taken. Enter subsequent data opposite the relevant date in this column.

Column 2
Tabulate opposite the relevant dates sputum direct smear results.

Column 3
Ditto for culture results (if available).

Column 4
Ditto for each resistance test (if available). Do this for each drug which the patient has received (plus, if available, results for drugs which the patient has not received). If your laboratory is a reliable one, regard any degree of drug resistance reported as likely to be of clinical significance provided it is consistent with the patient's treatment history. *(15)*

Column 5
Record, by date, radiological results. Compare each X-ray both with pretreatment X-ray and with the previous X-ray.

Column 6
Record clinical improvement or deterioration if details are available.

Table **1**   *Collecting data for a patient with suspected MDR*

Patient's name ....
Age ....Sex.......................
Address ....

1 Dates and chemotherapy	2 Smear results	3 Culture results	4 Susceptibility test results	5 Radiological results	6 Clinical status
a Date of diagnosis: .... b Date of starting **first** course of chemotherapy: .... Drugs taken (dose, frequency, duration) i.e.: H300, 7/7, 6 Months R450, 7/7, 6 Months S1g, 7/7, 2 Months ....., ..., ... c Date of completing or stopping **first** course of chemotherapy:					
d Date of starting **second** course of chemotherapy: .... Drugs taken (dose, frequency, duration) ...., ..., ..., ..., ..., ..., ..., ..., ... e Date of completing **second** course of chemotherapy:					
f Date of starting **third** course of chemotherapy: .... (to be continued ...)					

Note: this table is a model which you can use enlarged to accommodate the necessary information.

3.3   CONSIDERING THE CRITERIA OF FAILURE OF THE RETREATMENT REGIMEN.

The criteria of failure are mainly bacteriological. But not all positive bacteriological results necessarily mean "failure". *(4, 13)*

3.3.1   Persistently positive sputum

a If the patient is still direct smear-positive after 2-3 months of the retreatment regimen, check carefully that he/she has taken the drugs as prescribed. This is the commonest cause of "failure". However, some patients with severe disease may take longer to convert from sputum positive to negative. Do not rush into changing treatment. If the number of bacilli in direct smear is less and he/she is improving clinically and radiologically, this is particularly reassuring.

b Persistent positivity at 5-6 months makes genuine treatment failure much more likely. Again the commonest cause is failure to take the drugs. If you are certain that the patient is taking the drugs, it is highly probably that the bacilli are resistant to <u>all</u> the drugs he/she is receiving. Check the apparent persistent positivity by further sputum smears and culture. For example, occasionally a patient with a large cavity or cavities may have intermittently positive smears, due to dead bacilli, for a month or two after negative culture.

If drug susceptibility testing is available, request susceptibility tests on positive cultures from the sputum specimen collected at 4-5 months in order that results be available as early as possible.

c Positive culture at the above times is even more important. If direct smear has become negative, but culture is still positive, e.g. at 2-3 months, this may only be a stage towards complete sputum conversion.

3.3.2   Fall and rise phenomenon

Sputum smear initially becomes negative (or even less positive), and then later becomes persistently positive. This indicates failure usually due to *either* the patient having ceased to take the drugs *or* sometimes to the development of resistance to <u>all</u> the drugs he/she is receiving. Check by further cultures and susceptibility tests on positive culture.

3.3.3 Report of drug resistance

Do not accept such a report uncritically. As mentioned above, laboratories vary in reliability and errors may occur. Look at the clinical evidence, especially trends in sputum positivity, but also trends in the other criteria outlined above. If the susceptibility test results do not fit in, discuss them with the bacteriologist (if possible) and repeat the test. Don't rush into changing treatment. You should decide the appropriate treatment in the light of all the evidence available for this particular patient.

3.3.4 Radiological deterioration?

Deterioration in a chest X-ray may be a sign of failure but deterioration may be due to one of the following:

a intercurrent pneumonia

b pulmonary embolism

c supervening carcinoma.

A repeat X-ray after 2-3 weeks will probably show improvement in the case of (a) or (b). Apparent radiological deterioration, if it is not accompanied by bacteriological deterioration, is less likely to be due to tuberculosis.

3.3.5 Clinical deterioration?

This is the least reliable evidence of failure. It may be due to many conditions other than tuberculosis. If there is no accompanying bacteriological or radiological deterioration, clinical deterioration is unlikely to be due to tuberculosis.

3.4 INTERPRETING THE DATA FOR AN INDIVIDUAL PATIENT.

Assess the details of the tabulations you have made (para. 3.2 above). Use the criteria of failure (para. 3.3) to decide whether resistance was likely to have developed during each regimen which the patient received. Remember that, if definite failure occurred, (principally bacteriological failure) it must have been due *either* to the patient not taking the drugs *or* to the development of resistance to all drugs being used (usually for more than 3 months). If you have all the relevant details, it is usually possible to assess to what drugs the patient's bacilli will be resistant. This can in due course be confirmed by susceptibility tests.

Although it is vital to collect the relevant information if you can, in some cases it may remain uncertain which drugs the patient has received. Doctors may have neglected serial sputum tests, or indeed any sputum tests at all. You will therefore have to make the best estimate you can in the light of whatever evidence is available. This will include what you know of the most likely (poor) treatment which non-specialist practitioners might have used in the area where the patient was treated. It may also include what you may know about the frequency of resistance to individual drugs in that community.

In general, in cases of failure or relapse following the WHO retreatment regimen, acquired resistance to isoniazid and rifampicin is highly likely. While waiting for the results of susceptibility tests, the physician must prescribe a regimen which initially does not contain isoniazid and rifampicin.

The chosen regimens will consists of a mix of **essential drugs**, and **second-line drugs**.

The choice of drugs depends on the interpretation of data collected from each individual patient.

4.1   ESSENTIAL ANTITUBERCULOSIS DRUGS

a Streptomycin

Resistance to streptomycin has become less common since the wider use of ethambutol as a fourth drug in the WHO standard regimen for new cases, and the use of streptomycin only during the first 2 months in the WHO standard retreatment regimen.

b Pyrazinamide

Resistance to pyrazinamide is neither easy to acquire nor to prove by susceptibility testing. As pyrazinamide has a bactericidal effect in an acid medium (bacilli inside macrophages), it would be wise to use pyrazinamide in combination with streptomycin or another aminoglycoside (active against actively multiplying bacilli, outside macrophages) to obtain a maximal bactericidal effect against all populations of bacilli (inside and outside macrophages).

c Ethambutol and thioacetazone

Ethambutol and thioacetazone, when they are used during the continuation phase of WHO standard regimens (for new cases and retreatment cases), are probably useless for the treatment of apparent MDR tuberculosis. If a reliable susceptibility test shows that ethambutol is still active, this bacteriostatic agent might be valuable as a companion drug for preventing the emergence of resistance to other active drugs.

Thiacetazone, a very poor bacteriostatic agent, has no place (except as a last resort) in the treatment of MDR tuberculosis. There is a risk of cross-resistance with thioamides and additional toxicity when thioacetazone is associated with a thioamide. [16] The risk of severe adverse reactions prohibits the use of this drug in HIV- positive patients.

4.2 SECOND-LINE ANTITUBERCULOSIS DRUGS *(17, 18, 19, 20)*

Second line antituberculosis drugs are applicable in the treatment of apparent or proved MDR tuberculosis.

Classes of second-line antituberculosis drugs

a **Aminoglycosides**

When resistance to streptomycin is proved or highly suspected, one of the other aminoglycosides can be used as a bactericidal agent against actively multiplying organisms:

- **kanamycin**, the least expensive, but largely used for indications other than tuberculosis in some countries.

- **amikacin**, as active as kanamycin and better tolerated, but much more expensive.

- **capreomycin**,[2] very expensive but very useful in cases with tubercle bacilli resistant to streptomycin, kanamycin and amikacin.

b **Thioamides**

Ethionamide or **prothionamide** are 2 different presentations of the same active substance, with bactericidal activity. Prothionamide may be better tolerated than ethionamide in some populations.

c **Fluoroquinolones**

Ofloxacin and ciprofloxacin are two different drugs, but with complete cross-resistance within the group. These drugs have a low bactericidal activity, and are useful in association with other drugs. The pharmacokinetics of ofloxacin are better than the pharmokinetics of ciprofloxacin. Sparfloxacin should be avoided because of severe cutaneous side effects (photo-sensitisation). Norfloxacin should not be used, because it does not give adequate serum levels.

d **Cycloserine (or terizidone)**

This is the same bacteriostatic agent, with 2 different formulations. It has no cross-resistance with other antituberculosis agents. It might be valuable to prevent resistance to other active drugs, but its use is limited by its high toxicity.

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[2] Strictly speaking, capreomycin is not an aminoglycoside, but is related in terms of activity and side effects.

e **Para-aminosalicylic acid (PAS)**

This is a bacteriostatic agent, valuable for preventing resistance to isoniazid and streptomycin in the past and to other bactericidal drugs today.

f **Others**

Other drugs, sometimes mentioned as second line antituberculosis drugs, have no place in the treatment of MDR tuberculosis:

- rifampicin derivatives, like rifabutin *(21)*, cannot be used since there is almost complete cross-resistance between rifabutin and rifampicin (especially when there is acquired resistance to rifampicin);

- clofazimine has some activity against *Mycobacterium leprae* and *Mycobacterium ulcerans*, but no activity against *Mycobacterium tuberculosis*.

4.3 CROSS-RESISTANCE

Consideration of cross-resistance is important for selecting the drugs acceptable for treatment of apparent or proven MDR tuberculosis. As usual in the treatment of infectious diseases when the combination of several drugs is required, it is ineffective to combine two drugs of the same group or to combine in the prescribed chemotherapy regimen a drug potentially ineffective because of cross-resistance.

4.3.1 Thioamides and thioacetazone *(16)*

Ethionamide, in the group of thioamides, induces complete cross-resistance with prothionamide. They should be considered as the same drug. Frequently there is also cross-resistance between thioamides and thioacetazone: strains naturally resistant to thioacetazone are usually still susceptible to ethionamide-prothionamide; strains resistant to ethionamide-prothionamide are usually resistant also to thioacetazone, in more than 70% of cases.

4.3.2 Aminoglycosides

- Strains resistant to streptomycin are susceptible to kanamycin-amikacin.

- Resistance to kanamycin induces a complete cross-resistance with amikacin: they should be considered as the same drug. Resistance to kanamycin-amikacin induces also resistance to streptomycin.

- Strains resistant to streptomycin, kanamycin, amikacin are still susceptible to capreomycin.

4.3.3 Fluoroquinolones *(22)*

Ofloxacin, ciprofloxacin and sparfloxacin induce complete cross-resistance for all fluoroquinolones. It is why the use of ofloxacin must be carefully considered, since some new more active quinolones (e.g. levofloxacin) could replace ofloxacin in the future.

There is no cross-resistance with other classes of drugs.

4.3.4 Cycloserine and terizidone

There is complete cross-resistance between these two drugs: they should be considered as the same drug. There is no cross-resistance with other classes of drugs.

4.4 CLASSIFICATION OF ANTITUBERCULOSIS DRUGS FOR TREATMENT OF MDR TUBERCULOSIS

Several criteria are used for classifying antituberculosis drugs available for treatment of MDR tuberculosis.

4.4.1 According to their activity

The main criteria are based on underlined biological data, which determine 3 groups of antituberculosis drugs available according to their activity and cross-resistance: *(17, 19, 23, 24, 25)*

- drugs with bactericidal activity: aminoglycosides, thioamides and, in special conditions of pH acid, pyrazinamide

- drugs with low bactericidal activity: fluoroquinolones

- drugs with bacteriostatic effect (when given at usual dosages in man) e.g.: ethambutol, cycloserine and PAS (Table 2)

Table **2** *Ranking of antituberculosis drugs for treatment of MDR Tuberculosis*

Rank	Drugs	Average daily dosage	Type of antimycobacterial activity	Ratio of peak serum level to MIC
1	Aminoglycosides a. Streptomycin b. Kanamycin or Amikacin c. Capreomycin	15 mg/kg	bactericidal against actively multiplying organisms	 20-30 5-7.5 10-15 5-7.5
2	Thioamides (Ethionamide Prothionamide)	10-20 mg/kg	bactericidal	4-8
3	Pyrazinamide	20-30 mg/kg	bactericidal at acid pH	7.5-10
4	Ofloxacin	7.5-15 mg/kg	weakly bactericidal	2.5-5
5	Ethambutol	15-20 mg/kg	bacteriostatic	2-3
6	Cycloserine	10-20 mg/kg	bacteriostatic	2-4
7	PAS acid	10-12 g	bacteriostatic	100

4.4.2 According to some other clinical criteria

Apart from the acceptable daily dosages, other criteria should also be considered for clinical use:

- acceptability to the patient (linked to the bulk or total volume of drug to be injected or swallowed, painful injection, taste);
- tolerance;
- potential toxicity.

Additional criteria result from meta-analysis of several controlled trials conducted before and after the rifampicin era [26-35].
All these characteristics are summarized in Table 3 (see Annex for further details).

Table **3** *Formulation, acceptable daily dosages and main characteristics of antituberculosis drugs available for treatment of MDR tuberculosis*

Drugs	*Formulation*	*Daily dosage (mg)*		*Acceptability*	*Tolerance*	*Toxicity*
		Minimum	*Maximum*			
1 Aminoglycosides						
a. Streptomycin	vial, 1 g	750	1 000	injection	moderate	medium
b. Kanamycin	vial, 1 g	750	1 000	injection (painful)	poor	medium
Amikacin	vial, 1 g	750	1 000	injection		
c. Capreomycin	vial, 1 g	750	1 000	injection (painful)	moderate	medium
2 Thioamides						
a. Ethionamide	tablet, 250 mg	500	750	good	moderate	medium
b. Prothionamide	tablet, 250 mg	500	750	good	moderate	medium
3 Pyrazinamide	tablet, 400 mg or 500 mg	1 200	1 600	good	moderate	low
4 Fluoroquinolones						
a. Ofloxacin	tablet, 200 mg	600	800	good	good	low
b. Ciprofloxacin	tablet, 250 mg	1 000	1 500	good	good	low
5 Ethambutol	tablet, 400 mg	1 000	1 200	good	good	low
6 Cycloserine	tablet, 250 mg	500	750	good	moderate	high
Terizidone	tablet, 300 mg	600	600			
7 PAS	tablet, 500 mg	10 g	12 g	bad (bulk, taste)	poor	low
	granules packet 4 g	10 g	12 g	good	moderate	low

4.4.3 According to their cost

Finally, the crucial criterion for the choice of second-line antituberculosis drugs is the cost of these drugs. The costs vary considerably from one country to another, according to the suppliers, the market conditions, and the size of the market (Table 4). Information regarding suppliers of these drugs and their costs is available on request from WHO and IUATLD.

Table 4   *Cost of antituberculosis drugs for the treatment of MDR tuberculosis*

Rank of choice	Defined daily dose (DDD)	Cost of 30 DDD (one month) in US dollars		
		Lowest price obtainable (a)	Paris (b)	New York (c)
1 Aminoglycosides				
a. Streptomycin	1g	2.2	38.4	-
b. Kanamycin	1g	10.9	44.0	29.4
or Amikacin	1g	-	641.0	-
c. Capreomycin	1g	148	253.0	428.7
2 Ethionamide	750 mg	14.8	9.3	76.05
Prothionamide	750 mg	92.6	-	-
3 Pyrazinamide	1 500 mg	2.9	7.8	59.77
4 Ofloxacin	800 mg	-	198.2	87.00
Ciprofloxacin	1 500 mg	-	-	153.00
5 Ethambutol	1 200 mg	2.3	7.8	70.35
6 Cycloserine	750 mg	63.00	57.3	179.10
or Terizidone	600 mg	101.00	-	-
7 PAS acid				
tablet	12 g	17.00	199.00	-
granules	12 g	-	-	239.45

(a) FOB price, special tariff proposed in 1995 to international aid organizations for national tuberculosis programmes.
(b) 1996 price in Assistance Publique, Hopitaux de Paris.
(c) 1996 price in New York City, Department of Health.

CHOOSING A CHEMOTHERAPY REGIMEN FOR A PATIENT WITH APPARENT MDR TUBERCULOSIS

We assume that all patients **with apparent drug-resistant tuberculosis will have bacilli resistant to isoniazid**.

Patients with **additional resistance**, or suspected resistance, to streptomycin and/or thioacetazone (but not to rifampicin) should respond well to the WHO standard retreatment regimen (2HRZES/1HRZE) in the initial phase. [1]

The following therefore applies to MDR patients with **resistance at least to isoniazid and rifampicin**, patients considered to have **failed on the WHO standard retreatment regimen**, and other patients who have received a variety of bad regimens outside national programmes.

Such patients will often require the use of at least some **second-line drugs**. These drugs are less effective and have more side effects than the present standard essential drugs. It must be made clear to the patient and staff that meticulously taking the prescribed reserve regimen is all that stands between the patient and death. The patient must try to tolerate any unpleasant side effects in order to achieve survival. He/she must agree to remain under direct observation, with each dose supervised, at least until the sputum is negative. The patient must receive clear and complete explanations before treatment, and permanent psychological support and attention.

In designing a regimen **do not aim to keep drugs in reserve**. That is the way to lose one battle after another. The patients has already lost several battles. This last battle must be won. As outlined above, decide to what drugs the patient's bacilli are, or likely to be, still sensitive. Then prescribe what is likely to be the most effective regimen available to him/her.

In the first place **prescribe drugs which the patient has not had previously**. The bacilli are fairly certain to be sensitive to these. The practice of adding isoniazid to these drugs confers no advantage.

If, on the evidence, it is possible that the bacilli remain sensitive to a "standard" drug (para. 4.1), in spite of the patient having received it in an unreliable combination, you may <u>add</u> it to the regimen in case it is still useful but <u>do not rely on it</u> to prevent further resistance; if tests later show resistance to that drug, you may have failed to protect the newly introduced drugs. On the other hand, if the bacilli turn out to be still sensitive to it, it will give an additional effect. This may later, after you have the results of resistance tests, permit you safely to withdraw a weaker second-line drug which is causing the patient side effects, but still leave an effective regimen which will prevent further resistance.

The initial regimen should consist of at least three drugs, preferably four or five, to which the bacilli are likely to be fully sensitive, i.e. drugs not previously used for that patient.

Among these drugs, it is desirable to use in combination an injectable aminoglycoside (according to the rank of choice) and pyrazinamide (even if previously used, because resistance is usually unlikely). This combination has a good bactericidal activity.

When the patient's sputum has converted to negative, you can withdraw one or more drugs, preferably a weaker drug which is causing side effects.

The treatment with these weaker regimens should be continued for at least 18 months after sputum conversion to prevent relapse.

In any regimen chosen, especially when weaker drugs are used, the treatment should be given daily and should be directly observed. It is also mandatory to monitor bacteriological results (smear and culture) monthly from the second month until the sixth month, and then quarterly until the end of treatment.

5.2 EXAMPLES OF ACCEPTABLE REGIMENS IN PROGRAMME CONDITIONS *(34, 35, 36, 37, 38)*

In programme conditions, even in specialized units in connection with a reliable laboratory, susceptibility test results are not obtainable immediately: a delay of 2-4 months is usual. Sometimes, the results cannot be obtained for various reasons: initial cultures negative or contaminated; failures in logistics (transport of specimens, temporary shortage of reagents, etc.). In practice, two situations should be considered depending on the availability of susceptibility test results.

5.2.1 Situation A: Susceptibility test results are not available before starting the new treatment

A new chemotherapy regimen should be initiated before receiving susceptibility test results.

- In this situation, after a failure of the WHO standard retreatment regimen, a "third line" regimen should be prescribed containing:

  - at least **3 drugs never used**: kanamycin, ethionamide, ofloxacin
  - and **pyrazinamide**.

- After bacteriological conversion (usually after three to four months), if the initial susceptibility test results cannot be obtained, the continuation phase during 18 months should employ the **two** drugs best tolerated and more usually more active: ethionamide and ofloxacin. (Table 5)

Table **5** *Acceptable "third-line" regimen before (or without) susceptibility test results*

Initial phase		Continuation phase	
Drugs	*Minimum duration in months*	*Drugs*	*Duration in months*
1 Aminoglycoside[a]	3	**1** Ethionamide	18
2 Ethionamide	3	**2** Ofloxacin[b]	18
3 Pyrazinamide	3		
4 Ofloxacin[b]	3		

[a] *Kanamycin, or amikacin, or capreomycin*
[b] *The daily dose of 800 mg can be reduced to 400 mg if poorly tolerated. If ofloxacin is not available, use cycloserine.*

5.2.2 Situation B: susceptibility test results are available,

either before prescribing a new treatment, or during the initial phase of the regimen prescribed in situation A. Several regimens are acceptable, depending on the results of susceptibility tests.

5.2.2.1 *Resistance to isoniazid, but rifampicin still active*

● Resistance to **isoniazid alone** or in **combination with resistance to streptomycin** (and/or with **thioacetazone**).

It may be simplest to use the WHO standard retreatment regimen during the first three months (2SERHZ/1ERHZ), though isoniazid and streptomycin are redundant and could be omitted. After smear conversion, use rifampicin and ethambutol until the end of the ninth month.

● **Resistance to isoniazid and ethambutol** (with or without resistance to **streptomycin**)

Use rifampicin and ethionamide for nine months at least, with pyrazinamide and one aminoglycoside (kanamycin or amikacin if resistance to streptomycin; capreomycin if resistance to streptomycin and kanamycin) during the initial phase until smear conversion. If ethionamide is not available, ofloxacin can be used. (Table 6)

Table **6** *Acceptable "third line" regimens if there is resistance to
isoniazid but susceptibility to rifampicin*

Resistance to	Initial phase		Continuation phase	
	Drugs	Minimum duration in months	Drugs	Duration in months
● Isoniazid (streptomycin, thioacetazone)	**1** rifampicin **2** aminoglycoside[c] **3** pyrazinamide **4** ethambutol	2-3 2-3 2-3 2-3	**1** rifampicin **2** ethambutol	6 6
● Isoniazid and ethambutol (streptomycin)	**1** rifampicin **2** aminoglycoside[c] **3** pyrazinamide **4** ethionamide[d]	3 3 3 3	**1** rifampicin **2** ethionamide[d]	6 6

[c] streptomycin, if still active; if resistance to streptomycin, use kanamycin or capreomycin
[d] if ethionamide is not available or poorly tolerated (even at a dose of 500 mg/day), use ofloxacin.

5.2.2.2 Resistance to at least isoniazid and rifampicin

● Resistance to **isoniazid and rifampicin** (with or without resistance to **streptomycin**)

When the two most important antituberculosis drugs are not active, a five-drug regimen is mandatory.

During the initial phase, use ethionamide plus ofloxacin plus another bacteriostatic drug (ethambutol if possible) with pyrazinamide and an aminoglycoside available for a minimum of 3 months, or until smear conversion.

During the continuation phase, use ethionamide plus ofloxacin plus another bacteriostatic drug for at least 18 months after smear conversion (Table 7).

● Resistance to **isoniazid**, **rifampicin**, **ethambutol** (with or without resistance to **streptomycin**)

During the initial phase, use ethionamide plus ofloxacin plus another bacteriostatic drug (cycloserine or PAS) with pyrazinamide and an aminoglycoside available for a minimum of 3 months or until smear conversion. During the continuation phase, use ethionamide plus ofloxacin plus cycloserine (or PAS) for at least 18 months after smear conversion (Table 7).

Table **7**   Acceptable "third line" regimen for the treatment
of MDR Tuberculosis

Resistance to	Initial phase		Continuation phase	
	Drugs	Minimum duration in months	Drugs	Duration in months
● Isoniazid, rifampicin and streptomycin	**1** aminoglycoside[e] **2** ethionamide **3** pyrazinamide **4** ofloxacin[f] **5** ethambutol	3 3 3 3 3	**1** ethionamide **2** ofloxacin[f] **3** ethambutol	18 18 18
● Isoniazid, rifampicin, streptomycin, and ethambutol	**1** aminoglycoside[e] **2** ethionamide **3** pyrazinamide **4** ofloxacin[f] **5** cycloserine[g]	3 3 3 3 3	**1** ethionamide **2** ofloxacin[f] **3** cycloserine[g]	18 18 18

[e] Kanamycin or amikacin, or capreomycin
[f] The daily dose of 800 mg can be reduced to 400 mg if poorly tolerated
[g] PAS if cycloserine is not available or too toxic.

Usually, reliable information on susceptibility of *M. tuberculosis* to pyrazinamide is not available. But if the resistance to pyrazinamide is duly proven and compatible with clinical data, pyrazinamide should be stopped and cycloserine or PAS may be included in the regimen.

6.1   INDICATION FOR SURGERY

Surgery should be considered for a patient with bacilli resistant, or probably resistant, to all except two or three relatively weak drugs. Unfortunately many such patients will have too extensive disease and/or too poor lung function for surgery to be possible. If the patient has a large localised cavity with little other disease, reasonable lung function and only two or three (weak) drugs available, surgery should be seriously considered.

6.2   TIMING OF SURGERY

To avoid serious, and potentially fatal tuberculosis complications of surgery, operate when the bacillary population is likely to be at it lowest. If only a very weak regimen is available, experience has shown that the most favourable time is after two months' treatment.

6.3   ANTI-TUBERCULOSIS CHEMOTHERAPY AFTER SURGERY

After surgery, the same regimen should be continued for at least 18 months.

- AMINOGLYCOSIDES
  - Kanamycin and amikacin
  - Capreomycin

- THIOAMIDES
  - Ethionamide
  - Prothionamide

- FLUOROQUINOLONES
  - Ofloxacin
  - Ciprofloxacin

- CYCLOSERINE (AND TERIZIDONE)

- PARA-AMINOSALICYCLIC ACID (PAS)

Kanamycin and Amikacin

These are bactericidal agents of the aminoglycoside class, obtained from a streptomyces. Their bactericidal effect *in vitro* and *in vivo* against *Mycobacterium tuberculosis* is very similar and their adverse reactions are those of other aminoglycosides.

Their bactericidal effect might be valuable in patients with bacilli resistant to streptomycin. Cross-resistance between kanamycin and amikacin is usual.

● *Preparation and dose*

The drugs are presented as sterile white powder for intramuscular injection in sealed vials containing the equivalent of 250 mg, 500 mg or 1 g of drug. The drug should be dissolved in 2 ml of 0.9% sodium chloride injection or water for injection.

The optimal dose is 15 mg/kg bodyweight, usually 750 mg to 1 g given daily or five days per week, by deep intramuscular injection. Rotation of injection sites avoids local discomfort. The duration of daily therapy is usually 3 to 4 months. When necessary, it is possible to give the drug at the same dose 2 or 3 times weekly during the continuation phase, under close monitoring for adverse reactions.

● *Adverse reactions*

These are similar to the side-effects associated with streptomycin and capreomycin.

Ototoxicity, deafness or vertigo may occur. Reversible nephrotoxicity may occur.

● *Precautions*

In patients with impaired renal function, the daily dose should be reduced and/or the intervals between doses increased, to avoid accumulation of the drug. In these patients, renal function should be monitored regularly during use. This drug should not be used in pregnant women except as a last resort.

Capreomycin

This is a bactericidal agent from the aminoglycosides class, obtained from *Streptomyces capreolus*.

Its bactericidal effect might be valuable in patients with bacilli resistant to streptomycin, kanamycin and amikacin: there is no cross-resistance with the other aminoglycosides.

● *Preparation and dose*

Capreomycin sulphate is supplied as a sterile white powder for intramuscular injection in sealed vials each containing 1000 units approximately equivalent to 1g capreomycin base. This should be dissolved in 2 ml of 0.9 per cent sodium chloride injection in water. Two or three minutes should be allowed for complete solution. The usual dose is 1g in a single dose daily, not exceeding 20 mg/kg for 40-120 days after which the dose must be reduced to 2/3 times weekly, as the risk of important side-effects rises sharply at that time.

● *Adverse reactions*

These are similar to the side-effects with streptomycin, mainly tinnitus and vertigo with a lesser risk of deafness. Kidney damage may occur with elevation of serum and urine creatinine. Hypokalaemia, hypocalcaemia and hypomagnesaemia have also been reported. General cutaneous reactions and hepatitis may occur rarely. There may be pain and swelling at injection sites if it is not given by deep intramuscular injection.

● *Precautions*

Capreomycin should be avoided if possible in patients with impaired hearing or renal function. Serum urea and electrolytes should be monitored during treatment. It is contra-indicated in pregnancy and best avoided in children.

Ethionamide (or Prothionamide)

These are bactericidal agents from the class of thioamides. Their chemical structure resembles thioacetazone with which there is frequent and partial cross-resistance. (Bacilli resistant to thioacetazone are often sensitive to thioamides, but the reverse is seldom the case).

Before the rifampicin era, ethionamide (or prothionamide, the drug is similar in its antibacterial effects and adverse reactions) was a basic component of retreatment regimen for tuberculosis patients with bacilli resistant to isoniazid and streptomycin.

● *Presentation and dose*

Ethionamide and prothionamide are normally administered in the form of tablets containing 125 mg or 250 mg of drug. The maximum optimum daily dose is 15-20 mg/kg or 1 g. The usual dose is 500 mg to 1 g daily, depending upon body weight and tolerance. Few persons can take more than 750 mg daily. (750 mg for patients weighing 50 kg or more, 500 mg for patient weighing less than 50 kg)

Patients may find the drug was more acceptable if it is administered with orange juice or milk or after milk, or at bed-time to avoid nausea. Among patients on directly observed treatment, a daily dose of 750 mg can be given as 250 mg under strict observation and 500 mg self-administered 10-12 hours later.

● *Adverse reactions*

Prothionamide is generally considered to be less unpleasant and better tolerated than ethionamide. But adverse reactions are essentially similar. The main troubles are epigastric discomfort, anorexia, nausea, metallic taste and sulphurous belching. Vomiting and excessive salivation can occur. Tolerance varies in different populations: the drug is usually well tolerated in Asia and in Africa.

Psychotic reactions including hallucinations and depression may occur. Hypoglycaemia is a rare but dangerous occurrence, obviously particularly important in diabetic patients.

Hepatitis may occur in about 10% of cases, but is rarely serious. When major liver damage occurs, jaundice and highly symptomatic disease is created, with prolonged elevation of transaminases (6-8 weeks) and drug administration should be interrupted. Other rare side-effects have included gynaecomastia, menstrual disturbance, impotence, acne, headache and peripheral neuropathy.

● *Precautions*

This drug should not be administered in pregnancy as it has been shown to be teratogenic to animals. It should be very carefully monitored if given to patients with diabetes, liver disease, alcoholism or mental instability.

Ofloxacin and Ciprofloxacin

These are weakly bactericidal agents of the fluoroquinolones class. Both ofloxacin and ciprofloxacin have a bactericidal effect *in vitro* against *Mycobacterium tuberculosis*. Although neither drug has been studied extensively in controlled clinical trials, evidence suggests that they are equivalent in therapeutic efficacy when one of these is used, along with other effective drugs.

There is no cross-resistance with other antituberculosis agents, but complete cross-resistance between ofloxacin and ciprofloxacin (and between the other fluoroquinolones like levofloxacin).

● *Presentation and dose*

Fluoroquinolones are supplied in the form of tablets containing:

- 200 mg of ofloxacin
- 250 mg of ciprofloxacin

The usual daily dose is 600-800 mg (3-4 tablets) of ofloxacin or 1000-1500 mg (4-6 tablets) of ciprofloxacin during initial phase. If the dose of 800 mg is poorly tolerated, the daily dose can be reduced (400 mg ofloxacin) during the continuation phase. Either can be given in single daily dose (especially applicable in directly observed treatment) or the daily dose can be divided into 12-hour intervals.

● *Adverse reactions*

Adverse reactions are uncommon but consist of gastrointestinal disturbance (anorexia, nausea, vomiting) or central nervous system symptoms (such as dizziness, headache, mood changes and rarely convulsions).

● *Precautions*

These drugs should not be used in pregnant women or growing children because they may impair growth and produce injury to growing cartilage.

Because of drug interaction, the following drugs should be avoided: antacids, iron, zinc, sucralfate.

Cycloserine (or Terizidone)

Cycloserine is bacteriostatic at the usual dosage. Terizidone is a combination of two molecules of cycloserine. This antibiotic does not share cross-resistance with other drugs. It was valuable in preventing resistance to ethionamide in the retreatment regimens (ethionamide, cycloserine, pyrazinamide or kanamycin) used before rifampicin era. Nowadays, its value remains to prevent resistance to other reserve drugs.

● *Preparation and dose*

The drug is given orally in tablets or capsules containing:

- 250 mg of cycloserine
- 300 mg of terizidone.

The maximum daily dose is 15-20 mg/kg; the usual dose is 500-750 mg of cycloserine, 600 mg of terizidone. Few patients tolerate more than 750 mg daily, and in

the continuation phase more than 500 mg daily. The daily dose can be given in two intakes:

- cycloserine: 250 mg, in the morning, and 500 mg 12 hours later.

- terizidone: 300 mg twice a day at 12-hour intervals.

● ***Adverse reactions***

These include dizziness, slurred speech, convulsions, headache, tremor, insomnia, confusion, depression and altered behaviour. The most dangerous risk is that of suicide so mood should be carefully watched. Very rarely there may be a generalised hypersensitivity reaction or hepatitis.

● ***Precautions***

In view of the above adverse reactions, monitoring for central nervous system reactions is essential when cycloserine is prescribed. To prevent minor adverse reactions like insomnia, administration of small doses of a tranquilliser is sometimes recommended. Pyridoxine may decrease central nervous system effects. The nurses in charge of treatment of inpatients and the families of outpatients should be warned to report any undue depression or personality change immediately.

Cycloserine (and terizidone) should be avoided in patients with a history of epilepsy, mental illness or alcoholism. It should be used very cautiously in patients with renal failure.

Para-Aminosalicylic Acid (PAS)

This is a bacteriostatic agent: its principal value was as an effective companion drug to isoniazid, preventing the emergence of isoniazid-resistant organisms. PAS was commonly used 30 years ago, but rarely nowadays.

● ***Preparation and dose***

PAS is bulky and unpleasant to take because of gastrointestinal discomfort.
Two presentations are available on the market:

- <u>Tablets</u>, sugar-coated, containing sodium salt: sodium para-aminosalicylate, each tablet containing 0.5 g of PAS

- <u>Granules</u> of PAS with an acid-resistant outer coating rapidly dissolved in neutral media. Granules are supplied in packets containing 4 g per packet.

The daily dosage of the usual tablet preparation is 150 mg/kg or 10-12 g daily in two divided doses. The recommended schedule is 5 to 6 g (10 to 12 tablets) every 12 hours. The daily dosage of the granular preparation is the same. There is some evidence that a lower dose of 4 g every 12 hours (8 g/day) of the granular preparation is associated with good blood levels and improved tolerance.

● *Adverse reactions*

The main adverse reactions are gastrointestinal disturbance and general skin or other hypersensitivity including hepatic dysfunction. Hypokalaemia may also occur.

Anorexia, nausea, vomiting and abdominal discomfort are more common than diarrhoea. They may be lessened by administering the drug after food or with milk. Our experience is that one should not enquire of the patient how well he/she is tolerating the drug. The patient who expects to experience nausea and vomiting is much more likely to do so. Wait until the patient complains. You may if necessary lower the dose slightly and then increase over a few days.

Prolonged administration in large doses may produce hypothyroidism and goitre as PAS has an antithyroid effect. These will reverse when the drug is withdrawn.

● *Precautions*

PAS is best avoided in renal failure as it may make acidosis worse. The sodium salt should not be given when a restricted sodium intake is indicated. The old preparation (tablets) impaired the absorption of rifampicin, on account of an excipient (bentonite). The new preparation (granules) will not interfere with rifampicin absorption. A urine test for the drug is available (ferric chloride test).[3]

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