

## Treatment of Tuberculosis

a report by

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The treatment of tuberculosis (TB) aims to eradicate the disease from the patient and to prevent its occurrence in other subjects. To achieve this two-fold aim, it is necessary to establish two therapeutic strategies:

- the treatment of TB as an active disease; and
- the treatment of TB as a latent infection.

TB (*Mycobacterium tuberculosis*) has certain specific characteristics it is necessary to be familiar with in order to understand the microbiological basis of treatment. The bacilli population has several metabolic levels and each drug probably acts on one or the other of these subpopulations. It is believed that treatment occurs in two stages. During the first stage, which is rapid and involves a bactericide, the rapid-growth bacilli are eliminated. During the second stage, which is slow and sterilising in its effect, the slow- or intermittent-growth bacilli are eliminated.<sup>1</sup>

However, TB has the capacity to generate enormous resistance. In a TB patient, lesion bacilli that are resistant to drugs appear spontaneously. If only one drug is administered, all the vulnerable bacilli will be eliminated, with the result that the more resistant are selected and the disease remains. To prevent this scenario, it is necessary to administer at least two drugs.<sup>2</sup> In this way, an insufficient number of bacilli survive for resistance to develop.

These particular aspects of the behaviour of TB allow the conclusion that the treatment of the disease must be based on two principles:

- treatment must be administered over a prolonged period; and
- the use of several anti-TB drugs is required.

Failure to comply with these principles can result in two problems. Firstly, if treatment is interrupted prematurely the risk of relapse due to the fact that slow-growth TB have not been eradicated is greater. Secondly, if an insufficient number of anti-TB drugs are administered, there is a greater risk of resistant TB developing, because resistant mutants will have been selected.

### Anti-TB Drugs

There are two categories of drugs – main, or first-choice, drugs and second-line agents.

The main anti-TB drugs are: isoniazid, rifampicin, pyrazinamid and ethambutol. Second-line drugs are the aminoglycosides (streptomycin, amikacin and kanamicine), fluoroquinolones (ciprofloxacin, levofloxacin and moxifloxacin) and others such as closerine, etonamide and para-aminosalicylic acid (PAS). There are also antibiotics such as claritromicin, amoxicillin and clavulanic acid linezoli, which can be used in exceptional cases to combat multi-resistant bacilli.

#### Isoniazid

This is a derivative of nicotinic acid. It probably acts by inhibiting the synthesis of micolic acid. It is a powerful bactericide, acting on TB by means of rapid multiplication<sup>3</sup>, and is usually well tolerated. Its main toxic effects are hepatotoxicity and the possibility of developing neuritis. It affects the metabolism of some anti-convulsive drugs, such as phenytoin and carbamacepin. The usual dosage is 3–5mg/kg at a maximum of 300mg per day.

#### Rifamycins

Rifamycins include rifampicin, rifabutin and rifapentin. They act by interfering with the synthesis of RNA. The most frequently used is rifampicine. This drug acts on the rapid-growth populations of bacilli as well as on slow-multiplying populations. For this reason, its sterilisation capacity is considerable.<sup>4</sup> It is also a generally well-tolerated drug although it produces reddish colouring in the urine and other fluids, and it can cause hepatotoxicity. Another side effect is the appearance of a pseudo-flu syndrome. This can appear if treatment is intermittent or when the habitual dosage is exceeded. It appears to have an autoimmune origin and is a powerful enzyme inductor, which can reduce the effectiveness of hormone contraceptive medication. It also interacts with a large number of other drugs so it is vitally important to give careful

**Table 1: A Summary of the Dosage and Recommended Means of Administration of the Main Anti-TB Medications**

Drug	Route	Mode of action	Daily dose		Maximum	Thrice-weekly dose		Maximum
			Children	Adults		Children	Adults	
Isoniazid	Oral or IM	Bactericidal	5–10mg/kg	5mg/kg	300mg	10mg/kg	10mg/kg	900mg
Rifampicin	Oral or IV	Bactericidal	10–20mg/kg	8–12mg/kg	600mg	10–20mg/kg	8–12mg/kg	600mg
Pyrazinamide*	Oral	Bactericidal	20–30	1.5g <50kg 2.0g (51–74kg) 2.5g >75kg	30–40		2g <50kg 2.5g (51–74kg) 3.0g >75kg	
Ethambutol	Oral	Bacterios Tatic	15–25mg/kg	15–25mg/kg	2.5g	30–50mg/kg	30 mg/kg	

IM = intramuscular; IV = intravenous. \*World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC)/American Thoracic Society (ATS) recommended dosing of pyrazinamide in adults on a weight basis, but dosing based on weight categories as recommended by the British Thoracic Society (BTS) is more useful in practice. Adults weighing less than 45kg can be given a paediatric dose.

consideration to the other drugs that are to be prescribed along with rifampicine. The routine dosage is 6mg/kg at a maximum of 600mg per day.

### Pyrazinamid

The action of pyrazinamid is fundamental in ensuring that duration of treatment is not prolonged. It appears to act on slow-multiplication and intercellular bacilli and has a sterilising effect.<sup>5</sup> It is hepatotoxic and interferes with the metabolism of uric acid by increasing its level. It can produce attacks of gout in individuals who are predisposed to this condition. The usual dosage is 25mg/kg with a maximum of 2g per day.

### Etambutol

The main function of this substance is to prevent the appearance of resistance. It is generally well-tolerated and has few toxic effects. There appears to be a possibility of retrobulbar neuritis. It is therefore not recommended for children who are unable to receive frequent ophthalmological check-ups. The usual dosage is 15–25mg/kg with a maximum of 2g per day.

Table 1 provides a summary of the dosage and recommended means of administration of the main anti-TB medications.

### Treatment

The following must be taken into account when prescribing treatment:

- primary resistance to drugs;
- whether or the patient is being treated for the first time;
- location of the infection (pulmonary or extra-pulmonary);
- immunological situation (HIV positive); and
- the economic resources that each country sets aside for treatment.

### First-time Treatment

The treatment that most organisations recommend for patients who have not been treated previously (with slight variations) is rifampicin, isoniazid, pyrazinamid and ethambutol for two months, followed by rifampicin and isoniazid for a period of four months, administered daily or three times per week.<sup>6–8</sup> Some organisations, including the World Health Organization (WHO), also recommend twice-weekly administration.

In populations with a level of primary resistance of less than 5%, only three drugs can be used. This method can also prove useful in patients with negative bacilloscopy. The recommended programme of treatment in such cases is rifampicin, isoniazid and pyrazinamid on a daily basis for two months, followed by rifampicin and isoniazid for four months.<sup>9,10</sup>

In the event of extra-pulmonary infection, the same recommendations apply, except in the case of tuberculous meningitis, for which a programme of four drugs for two months is required, followed by two drugs over a longer period of time. The presence of HIV is not a reason for altering therapeutic programmes.<sup>11</sup> It is advisable to use four drugs in this group of patients. The main problem arises when rifampicin interacts with one or more of the antiretrovirals drugs. Rifabutin is the drug that interacts least with antiviral treatments and so is an appropriate alternative to rifampicin in patients being treated with antiretrovirals.

### Re-treatment and Cases of Resistance to Drugs

A patient who has previously undergone treatment may well present resistance to the drugs. The action to be taken in such cases is:

- obtaining a clinical history to inform the doctor which drugs have been administered previously;

- commencing a treatment regime containing three drugs that have not been prescribed before;
- maintaining rigorous bacteriological supervision;
- modifying the treatment as responsiveness to the drugs becomes apparent; and
- if first-line drugs cannot be used the treatment will have to be continued for 12 to 18 months after the cultures have become negative.<sup>8</sup>

### Administration of Treatment

The treatment of TB requires time and the use of several different drugs. For this reason one of the main challenges involved is making sure that the treatment is properly administered. Errors in the administration of treatment can lead to failure, relapses and the appearance of resistance. In order to ensure that treatment is administered properly the following two strategies are recommended:

- the direct observation of treatment; and
- the use of prepared pharmaceutical ‘packages’ containing several anti-TB drugs.

Direct observation of the treatment ensures a high probability of treatment completion, reduces the risk of resistance developing, prevents relapse and minimises mortality.<sup>12</sup> The administration of drug compounds containing the necessary combinations of the drugs prescribed also reduces the risk of resistance, as it precludes single-drug therapy.<sup>13</sup>

### Treatment Under Special Circumstances

#### Pregnancy and Breastfeeding

The usual regimes can be applied; however, North American therapists recommend that pirazinamid should not be used when treating patients in this group.<sup>8</sup> Streptomycin should never be administered.

#### Renal Insufficiency

Isoniazid and rifampicine can be used for patients suffering from renal insufficiency. Pirazinamid is metabolised in the liver but metabolites can accumulate in advanced renal insufficiency (creating clearance of less than 30ml/min). Ethambutol is eliminated via the liver and can accumulate leading to a higher risk of optical neuritis. The usual dosage of pyrazinamid and ethambutol is recommended, but only three days per week. When possible, drug levels should be monitored with a view to adjusting the dosage.

### Hepatitis

The WHO recommends against using pyrazinamid for patients with chronic hepatitis.<sup>6</sup> In cases of acute hepatitis, a non-hepatotoxic treatment regime can be applied utilising ethambutol, streptomycin and a fluoroquinolone.

### Treatment of Latent TB Infection

Treatment of the latent infection consists of the daily administration of isoniazid over a six- to twelve-month period. This treatment is effective in 60–90% of cases in reducing the risk of the latent infection progressing to TB disease.<sup>14</sup> Those who benefit most are tuberculin- or HIV-positive individuals, recent contacts with people suffering from the disease (especially children), people who have recently tested positive in tuberculin tests and certain other specific groups of people who risk developing the disease.<sup>15</sup>

### New Drugs for the Treatment of TB

Following a period of three decades during which no new drugs were developed, recent years have seen renewed interest in the area.<sup>16</sup> Essentially, three factors have contributed to this:

- the need to improve the treatment of active TB, to reduce the duration of treatment and to increase the time between doses in the case of intermittent treatment;
- the need to improve the treatment of multi-resistant TB; and
- the need to find effective treatment for latent TB infection.

### Rifapentin

Rifapentin is a derivative of rifamycin that has a longer average activity span. In the first trials, weekly administration was seen to achieve good rates of cure in patients who were HIV negative, with non-cavitary lesions and negative bacilloscopes.<sup>17</sup> However, this is not recommended for patients who are HIV positive, given the high relapse rate with bacilli that are resistant to rifampicine.<sup>18</sup> There are experimental studies underway appearing to indicate that the administration of rifapentin and isoniazid once a week for three months is just as effective as a daily dose of isoniazid during six months in the treatment of the latent TB infection.<sup>19</sup>

### Fluoroquinolones

Over the last 10 years, fluoroquinolones have been used extensively in the treatment of multi-resistant

TB. Studies are now under way that suggest that the addition of a fluoroquinolone might make it possible to reduce the duration of treatment.<sup>20</sup> One of the most promising fluoroquinolones is moxifloxacin – it has the greatest sterilising power. The pharmacological profile of moxifloxacin also suggests that it might be a very useful anti-TB drug. A recent study in animals found that the combination of rifampizin, pyrazinamid and moxifloxacin has greater sterilising power than the standard regime and opens up the possibility that the drug might reduce the duration of treatment.<sup>21</sup> ■

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