

## TREATMENT OF TUBERCULOSIS.

### Principles and aims of active TB treatment. First-line anti-TB drugs. Modes of action, dosages and side effects of first-line anti-TB drugs.

The treatment of tuberculosis is based on two bacteriological considerations: the combination of drugs to avoid the selection of drug resistance, and the need for prolonged treatment to ensure that all bacteria in their different phases of metabolic growth are effectively destroyed.

The two aims of tuberculosis treatment are to interrupt tuberculosis transmission by rendering patients noninfectious and to prevent morbidity and death by curing patients with tuberculosis.

Drugs for treating TB are usually classified as first- and second-line drugs (5 groups).

**Table 8-1 – Classification of anti-tuberculosis drugs**

First-line	Second-line			
Isoniazid				
Rifampicin	<b>Injectable</b>			
Pyrazinamide	Kanamycin	<b>Quinolone</b>		
Ethambutol	Capreomycin	Ofloxacin	<b>Other 2<sup>nd</sup> line</b>	
Streptomycin*	Amikacin	Levofloxacin	Etionamide	<b>Other drugs</b>
		Moxifloxacin	Cycloserine	(unclear efficacy)
		Gatifloxacin	PAS	clofazimine
			Terisidone	linezolid
				amoxicillin/clavulanat
				thioacetazone
				clarithromycin
				imipenem

\*Some reports include streptomycin among the second-line drugs, since its use has declined in recent years, due to the high rates of resistance

The appropriate treatment of tuberculosis is chemotherapy consisting of a combination of several anti-tuberculosis drugs. The duration of treatment lasts for 6–8 months and is known as “short-course chemotherapy”.

There are five key (first-line) anti-tuberculosis drugs:

isoniazid

rifampicin

pyrazinamide

streptomycin

ethambutol

The use of any of these drugs as single preparations leads to the selection of naturally resistant strains that normally make up the bacterial populations. This is why several anti-tuberculosis drugs must be given together in order to achieve cure in a patient with tuberculosis.

### Dosages of the essential anti-tuberculosis drugs

Anti-TB drugs	Mode of action	Daily treatment			
		Children in mg/kg (maximum)	Adults		
			Weight class		
			<33 kg, mg/kg	33-50 kg, mg per day	>50 kg mg per day
Isoniazid (H)	Bactericidal	10-15 (300)	4-6	200-300	300
Rifampicin (R)	Bactericidal	10-20 (600)	10-20	450-600	600
Pyrazinamide (Z)	Bactericidal	30-40 (2000)	30-40	1000-1750	1750-2000
Ethambutol (E)	Bacteriostatic	15-25 (1200)	15-25	800-1200	1200-1600
Streptomycin (S)	Bactericidal	20-40	15	0,5	1,0

### Modes of action of anti-TB drugs

A population of TB bacilli in a TB patient consists of the following groups:

- metabolically active, continuously growing bacilli inside cavities;
- bacilli inside cells, e.g. macrophages;
- semidormant bacilli (persisters), which undergo occasional spurts of metabolic activity;
- dormant bacilli, which fade away and die on their own.

Different anti-TB drugs act against different groups of bacilli. Anti-TB drug treatment takes a long time because it is difficult to kill the semidormant TB bacilli.

**Table 8-3 Anti-TB drugs: mechanisms of action and mutations conferring drug resistance**

Drug	Cellular function inhibited	Target	Gene
<i>First-line drugs</i>			
Isoniazid	Mycolic acid synthesis	Enoyl reductase	<i>mabA-inhA</i> , <i>katG</i> , <i>oxyR-ahpC</i>
Rifampicin	RNA synthesis	RNA polymerase	<i>rpoB</i>

Ethambutol	Arabinogalactan synthesis	Arabinosyl transferase	<i>embB</i>
Pyrazinamide	Cell pH homeostasis*		<i>pncA</i>
<i>Second-line drugs</i>			
Fluoroquinolone	DNA supercoiling	DNA gyrase	<i>GyrA</i>
Ethionamide	Mycolic acid synthesis	Enoyl reductase	<i>mabA-inhA</i>
Streptomycin	Protein synthesis	30S ribosomal subunit	<i>rpsL</i> <i>rrs</i>
Kanamycin, Amikacin	Protein synthesis	30S ribosomal subunit	<i>rrs</i>
Capreomycin	Protein synthesis	30S/50S ribosomal subunit	<i>rrs</i>

\*the mechanism of action remains to be not totally clear

### ***Bactericidal drugs***

**Isoniazid** kills 90% of the total population of bacilli during the first few days of treatment. It is most effective against the metabolically active, continuously growing bacilli.

**Rifampicin** can kill the semidormant bacilli that isoniazid cannot.

**Pyrazinamide** kills bacilli in an acid environment inside cells, e.g. macrophages. Pyrazinamide is known to be structural analogue of nicotinamide. Its mechanism of action remains to be not totally clear. Pyrazinamide is a prodrug that diffuses into *M. tuberculosis*, where the enzyme pyrazinamidase converts pyrazinamide to the active form pyrazinoic acid. Under acidic conditions, the pyrazinoic acid that slowly leaks out converts to the protonated conjugate acid, which is thought to diffuse easily back into the bacilli and accumulate. The net effect is that more pyrazinoic acid accumulates inside the bacillus at acid pH than at neutral pH.

**Bacteriostatic drug**, which is much less effective, is **ethambutol**. It is used in conjunction with powerful bactericidal drugs to prevent the emergence of resistant bacilli.

### ***Sterilizing action***

This means killing all the bacilli. The persisters are hardest to kill. The aim of killing all the bacilli is to prevent relapse. Rifampicin is the most effective sterilizing drug. Its effectiveness makes **short-course** chemotherapy possible. Pyrazinamide is also a good sterilizing drug, since it kills the bacilli protected inside cells.

Most TB patients complete their treatment without any significant drug side-effects. However, a few patients do develop side-effects. So clinical monitoring of all TB patients for side-effects is important during TB treatment.

### Side-effects of anti-TB drugs

Drug	Common side-effects	Rare side-effects
Isoniazid (H)	- peripheral neuropathy - hepatitis if age > 40 - sleepiness/lethargy	convulsions, pellagra, joint pains, agranulocytosis, lupoid reactions, skin rash, acute psychosis
Rifampicin (R)	- gastrointestinal: anorexia, nausea, vomiting, abdominal pain, hepatitis - reduced effectiveness of oral contraceptive pill	acute renal failure, shock, thrombocytopenia, skin rash, "flu syndrome" (intermittent doses), pseudomembranous colitis, pseudoadrenal crisis, osteomalacia, haemolytic anaemia
Pyrazinamide (Z)	- joint pains - hepatitis	gastrointestinal symptoms, skin rash, sideroblastic anaemia
Ethambutol (E)	- optic neuritis	skin rash, joint pains, peripheral neuropathy
Streptomycin (S)	- auditory and vestibular nerve damage (also to fetus) - renal damage	skin rash

### Symptom-based approach to management of drug side-effects

Side-effects	Drug(s) probably responsible	Management
<b>Minor</b>		<b>Continue anti-TB drugs</b>
anorexia, nausea, abdominal pain	rifampicin	give tablets last thing at night
joint pains	pyrazinamide	give aspirin or nonsteroidal anti-inflammatory drug
burning sensation	isoniazid	give pyridoxine in feet 50–75 mg daily
orange/red urine	rifampicin	Reassurance
<b>Major</b>		<b>Stop drug(s) responsible</b>
skin itching/rash	streptomycin	stop anti-TB drugs (see below)
deafness (no wax on auroscopy)	streptomycin	stop streptomycin, give ethambutol instead
dizziness (vertigo and nystagmus)	streptomycin	stop streptomycin, give ethambutol instead
jaundice (other causes excluded)	most anti-TB drugs	stop all anti-TB drugs until jaundice resolves (see below)

vomiting and confusion (suspected drug-induced pre-icteric hepatitis)	most anti-TB drugs	stop anti-TB drugs, urgent liver function tests
visual impairment	ethambutol	stop ethambutol
generalized, including shock and purpura	rifampicin	stop rifampicin

### **TB treatment regimens. Initial (intensive) phase and a continuation phase.**

Treatment regimens have an initial (intensive) phase and a continuation phase. The initial phase is designed for the rapid killing of actively growing bacilli and the killing of semidormant bacilli. This means a shorter duration of infectiousness. The continuation phase eliminates bacilli that are still multiplying and reduces failures and relapses. The principles of treatment are the same in all TB patients (adults and children).

There are several possible regimens. The regimen recommended depends on the patients diagnostic category.

### **Category of TB patient for registration on diagnosis**

Diagnostic/registration category	Definition	
New	A patient who has definitely never taken anti-TB drugs or who has taken anti-TB drugs for less than one month.	
Re-treatment cases	Relapse	A TB patient who: a) previously received treatment and was declared cured or treatment completed; and b) has once again developed bacteriologically positive (by smear or culture) TB
	Treatment after failure	A patient who is started on a re-treatment regimen after having failed previous treatment.
	Treatment after default	A TB patient who returns to treatment, bacteriologically positive, following interruption of treatment for 2 months or more.
Transfer in	A TB patient who has been transferred from another TB register to continue treatment.	
Other	All TB patients who do not fit the above definitions. This group includes chronic cases (TB patients who are sputum smear-positive at the end of a re-treatment regimen).	

Based on case definition, all TB patients (adults and children) fall into one of four diagnostic categories for treatment.

**Table 8-7 – Recommended treatment regimens for each diagnostic category**

TB diagnostic category	TB patients	TB treatment regimens	
		Initial phase	Continuation phase
I	New smear-positive patients. New smear-negative pulmonary TB with extensive parenchymal involvement. Severe concomitant HIV disease or severe forms of extrapulmonary TB.	<b>2HRZE</b>	<b>4HR or 6HE</b>
II	Previously treated sputum smear-positive pulmonary TB: - relapse - treatment after default - treatment failure	<b>2HRZES/1HRZE</b>	<b>5HRE</b>
III	New smear-negative pulmonary TB (other than in Category I). Less severe forms of extrapulmonary TB.	<b>2HRZE</b>	<b>4HR or 6HE</b>
IV	Chronic and MDR-TB cases (still sputum-positive after supervised re-treatment)	Specially designed individualized or standardized regimens are suggested for this category	

### **Use of TB drugs in children**

The treatment regimens and drug dosages in mg/kg of body weight are the same for children as for adults. Children usually tolerate TB drugs very well and serious side-effects are unusual. Do not give thioacetazone to HIV-infected children. Ethambutol is safe even in children too young to report early visual side-effects provided that the recommended dose is not exceeded. Since TB drugs are often not available in syrup form, give children portions of tablets according to weight.

### **8.3. Preventing drug resistance. Second-line anti-TB drugs. Principles of DR-TB treatment.**

#### **Preventing drug resistance**

A population of TB bacilli never previously exposed to anti-TB drugs will include a few naturally occurring drug-resistant mutant bacilli. Faced with anti-TB

drugs, these drug-resistant mutant bacilli will grow and replace the drug-sensitive bacilli under the following circumstances:

- a) inadequate anti-TB drug combinations;
- b) inadequate application of anti-TB drug treatment.

Isoniazid and rifampicin are most effective in preventing resistance to other drugs. Streptomycin and ethambutol are slightly less effective.

Any patient with chronic or DR-TB requiring treatment with second-line drugs falls under WHO diagnostic category IV and will require specialized regimens.

**Table 8-8 – Common treatment strategies for DR-TB**

Standardized treatment	Representative DRS data in well-defined patient populations are used to design the regimen. All patients in a patient group or category receive the same regimen.
Standardized treatment followed by individualized treatment	Initially, all patients in a certain group receive the same regimen based on DST survey data from representative populations. The regimen is adjusted when DST results become available (often DST is only done to a limited number of drugs)
Empirical treatment followed by individualized treatment	Each regimen is individually designed on the basis of patient history and then adjusted when DST results become available (often the DST is done of both first- and second-line drugs)

### **Designing a treatment regimen**

- Regimens should be based on the history of drugs taken by the patient.
- Regimens should consist of at least four drugs with either certain, or almost certain, effectiveness.
- The drug dosage should be determined by body weight.
- An injectable agent (an aminoglycoside or capreomycin) is used for a minimum of six months and at least four months past culture conversion.
- The minimum length of treatment is 18 months after culture conversion.
- Each dose is given as directly observed therapy (DOT) throughout the treatment. A treatment card is marked for each observed dose.

Drugs for treating TB are usually classified as first- and second-line drugs (5 groups). This classification use a group system based on efficacy, experience of use and drug class (table 8-1).

### **8.4. Adjunctive therapy, surgical treatment of TB – indications and contraindications.**

### **Deciding on other treatment measures**

Apart from chemotherapy, which is necessary for treating all cases of tuberculosis, adjunctive therapy is indicated for certain sites.

### **Treatment with corticosteroids**

The addition of corticosteroids at a dose of 0.5mg/kg per day for 3 to 6 weeks has been shown to have an impact in the following cases:

1. Tuberculous meningitis of moderate severity, in order to improve neurological outcome and reduce fatality;
2. Tuberculous pericarditis, in order to reduce the need for surgical intervention and reduce fatality.

In pulmonary tuberculosis, tuberculous pleurisy and primary tuberculosis with lymphadenopathy, while treatment with corticosteroids may have short-term effects on symptoms and signs, has no long-term benefits.

### **Surgical treatment**

During the first half of XX century, the finding that *Mycobacterium tuberculosis* was an obligate aerobe led to rapid growth of thoracic surgical operation: thoracoplasty, induced pneumothorax, plombage, and phrenic nerve crushing. Developed in the 1960s, Rifampicin and other anti-TB drugs radically transformed the prognosis of the disease and limited the indications for surgical intervention. During the second part of XX century surgery was not a routine method of treatment but it was considered to be indicated for removing a pocket of bacteria that cannot be killed with long-term medicine treatment (persistent cavity, tuberculoma).

### **Radical surgical procedures are:**

- pneumonectomy
- lobectomy
- segmental resection

Nowadays, the role of surgery in managing TB is enlarging due to the overall increase in global incidence, and the emergence of multidrug-resistant TB or extensive drug-resistant TB. Currently, thoracic surgery offers highly effective treatment of TB and its sequel with less trauma and morbidity than ever before. The advantage of Minimally Invasive Thoracic Surgery allows a wider range of TB patients to be considered for effective surgical management.

### **Currently, the surgical indications in pulmonary TB are:**



- TB complications (e.g., hemoptysis, empyema, cavity formation associated with aspergilloma, adenopathy with fistula, bronchial stenosis);
- cases displaying an inappropriate healing response to medication, in which clinical and radiological pictures remain unchanged or indicate progression (e.g., cavity, tuberculoma);
- acid-fast bacilli sputum smears positivity after 3-month treatment period, with a circumscribed radiological lesion or a destroyed lung;
- previous relapse(s) in patients with histories of TB and proper drug regimen

#### **Indications for surgery in MDR-TB**

- Localized disease
- Persistent cavitory disease
- Persistent sputum positivity MDR-TB with destroyed lobe of lung

### **8.5. Monitoring of TB patients during treatment**

All patients should be monitored to assess their response to therapy. Regular monitoring of patients also facilitates treatment completion and allows the identification and management of adverse drug reactions. All patients, their treatment supporters and health workers should be instructed to report the persistence or reappearance of symptoms of TB (including weight loss), symptoms of adverse drug reactions, or treatment interruptions.

Patient weight should be monitored each month, and dosages should be adjusted if weight changes.

A written record of all medications given, bacteriological response and adverse reactions should be maintained for every patients on the TB Treatment Card

**Table 8-9 – Monitoring of patients with sputum smear-positive PTB**

When to monitor	8-month treatment regimen	6-month treatment regimen
At time of diagnosis	sputum smear	sputum smear
At end of initial phase	sputum smear	sputum smear
In continuation phase	sputum smear(month 5)	sputum smear(month 5)
During last month of treatment	sputum smear(month 8)	sputum smear(month 6)

#### **Sputum smear at end of initial phase**

The vast majority of patients have a negative sputum smear at the end of the initial phase. If the sputum smear is still positive at the end of the initial phase, continue initial phase treatment with the same 4 drugs for 4 more weeks. If you check the sputum smear again at this point, it is unlikely still to be positive. Go on to the continuation phase

(even if the sputum smear after the extra 4 weeks of initial phase treatment is still positive).

### **Sputum smear in continuation phase**

In 8-month regimens, a positive sputum smear at 5 months (or any time after 5 months) means treatment failure. In 6-month regimens, a positive sputum smear at 5 months (or any time after 5 months) means treatment failure. A common cause of treatment failure is the failure of the programme to ensure patient adherence to treatment. The patient's treatment category changes to Category 2 and the re-treatment regimen starts.

### **Sputum smear on completion of treatment**

Negative sputum smears in the last month of treatment and on at least one previous occasion mean bacteriological cure.

**Table 8-10 – Recording treatment outcome**

<b>Cure</b>	patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion
<b>Treatment completed</b>	patient who has completed treatment but does not meet the criteria to be classified as a cure or a failure
<b>Treatment failure</b>	patient who is sputum smear-positive at 5 months or later during treatment
<b>Died</b>	patient who dies for any reason during the course of treatment
<b>Defaulted (treatment interrupted)</b>	patient whose treatment was interrupted for 2 consecutive months or more
<b>Transferred out</b>	patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known

Pulmonary TB patients whose sputum smear microscopy was negative (or not done) before treatment and whose sputum smears are negative at 2 months need no further sputum monitoring. They should be monitored clinically; body weight is a useful progress indicator.