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Review Article

Chemotherapy of tuberculosis: An updates

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Abstract

This review examines the chemotherapy of tuberculosis (TB) in humans which will help in the understanding and treatment of the disease. Tuberculosis is spread primarily by inhalation of aerosolized infectious droplet nuclei of *Mycobacterium tuberculosis* (MTb) from patients with active pulmonary TB.

The most common manifestation of TB in humans is pulmonary disease, but other organs are involved. TB is treated with a combination of anti-tubercular medications given simultaneously such as isoniazide, refampicin, pyrizinamide and ethambutol. The last new drug for treating MTb infections was rifampicin, introduced in 1972. Its use led to development of the short-course regimen, which forms the backbone of the highly effective Directly Observed Treatment Shortcourse (DOTS) strategy. But, the DOTS strategy has its problems. Drug toxicity, the long duration of therapy, and the emergence of multi-drug resistant strains of MTb have highlighted an urgent need for new tools. New drugs that are better tolerated, that permit intermittent chemotherapy, or that affect cure in a shorter time would have a significant impact, making it easier and less expensive to deliver the DOTS strategy.

By spending less time on therapy and reducing the number of treatment failures, savings in the cost of providing healthcare can be made which will help in the control of the disease.

Keywords: *Mycobacterium tuberculosis*, chemotherapy, tuberculosis effect, Drug toxicity

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1. Introduction

Several characteristics of MTb vary in strains from different regions of the world. Those from South India are distinguishable from European and American strains by animal virulence, susceptibility to hydrogen peroxide and certain antibacterial drugs, as well as by phage typing [1, 2].

Those from HongKong also show some differences [3]. *Mycobacterium africanum* is found in West and Central Africa and has characteristics intermediate between MTb and *Mycobacterium bovis*.

The production of a group of monoclonal antibodies directed at tubercle bacilli has been described in research reports [4], The strains used for their production and screening included MTb strains H3RV and H37Ra (the much studied virulent and avirulent variants of a strain from an American patient), strains S1 and 6067 from British patients and strains 7219 from a South Indian patient as well as the virulent strain of *M. bovis valle'e* the attenuated BCG strain (Glaxo).

Positive human immune deficiency virus serology is found in approximately 40% (range 15-57%) of patients with TB from Central and Eastern Africa.

In the United States of America, the incidence of TB has recently increased and there is compelling evidence that this is related to the AIDS epidemic [5].

Until the discovery of streptomycin in 1945, the treatment of TB was limited to rest, good nutrition and artificial collapse of the lung. Unfortunately, the value of streptomycin was restricted by its toxicity to the eight cranial nerve and by the frequent emergency of resistance tubercule bacilli during therapy.

In 1966, rifampicin was introduced for the treatment of TB; this was the last time a novel class of drugs was added to the TB treatment armamentarium. From that notable land mark, TB drug development was devoted primarily to clinical trials for shortening [6,7] and simplifying treatment, for example, by identifying an orally bioavailable regimen to obviate the need for streptomycin, developing and testing various rifampicin analogues and regimens for intermittent delivery, and developing fixed – dose combinations (FDC) formulations of current medications.

The currently recommended treatment regimens are efficacious when administered and taken reliably, but despite the aforementioned efforts, their complexity and duration compromise their ability to ultimately control the global TB epidemic, particularly in the context of high HIV prevalence.
National TB control programmes and their patients therefore need novel therapies to shorten and simplify treatment of active TB (increasing compliance and freeing up valuable human resources), safely treat TB/HIV co-infected patients, improve the therapy of multi drug – resistant tuberculosis (MDR – TB) and shorten the treatment of latent tuberculosis infection (LTBI).

A number of hurdles have hampered efforts to provide such regimens including:

1. A dearth of available drugs with the potential to help shorten therapy;
2. A requirement for safe and effective drug combinations and
3. A lack of TB – specific regulatory guidance to facilitate the drug development process. It is evident [8] that worldwide, far too few resources and too little effort were being focused on TB drug development to overcome these hurdles. The need to ensure affordability, adoptability and accessability of any new regimen further discouraged TB drug development efforts in the private sector. The global pipeline of new candidate TB drugs is virtually empty and adequate efforts and resources to rectify the situation does not appear to exist either in industry among pharmaceutical and biotechnology companies, or in the academic, governmental and non-governmental sectors.

Anti-tuberculosis drugs

Some principles of drug therapy include that long-term treatment was necessary to minimize the rate of relapse, the combinations of two or more drugs delayed the emergence of resistant organisms, that some combinations worked better than the others and that the important drug characteristic included the ability to penetrate macrophages and kill mycobacteria in their acidic environment.

The older drug regimens included streptomycin (SM), Para-aminosalicylic acid (PAS), isoniazide (INH), ethambutol (EMB) replacing PAS or rifampicin (RMP) in various combinations. These regimens were usually continued for 18 to 24 months. More rapid action of the newer regimens has been ascribed to special ability of pyrazinamide (PZA) to kill tubercle bacilli in the acid environments of macrophages; excellent intracellular penetration of INH, RMP and PZA; and the rapid bactericidal activity of RMP and the periodic bursts of metabolic activity of other-wise-dormant bacilli. Dormant bacilli are not susceptible to killing by any available drug.

The most popular regimens now are INH/RMP for 9 months, often supplemented by EMB during the first 2 or 3 months. If it is desired to complete treatment in 6 months, it is best to give INH/RMP/PZA, with or without the addition of SM for the first few months. The suspicion of bacillary drug resistance is the usual indication for adding SM.

Modern chemotherapy should provide a cure for well over 95% of patients on initial treatment; most failures are the result of poor cooperation. Arrangements for supervised and intermittent (twice weekly) drug treatment may be necessary to assure compliance. Ethionamide cycloserine and capreomycin available are reserve drugs in case of drug intolerance or bacillary resistance [8].

These reserve drugs can be called second-line drugs while the aforementioned ones can be called first-line drugs. Second-line drugs considered in these guidelines are those listed in the WHO guidelines for the management of drug resistant tuberculosis. The list comprises of the following drugs aminoglycosides for kanamycin and Amikacin, polypeptides for capreomycin,

viomycine and Enviomycin, fluoroquinolones for ofloxacine and ciprofloxadne, D-cycloserine (Terizidone), Ethionamide, prothionamide and p-amino salicylic acid (PAS)(WHO/CDS/200.288).

One of the most alarming aspects in tuberculosis problems has been the nosocomial outbreaks of multidrug resistant (MDR) *M. tuberculosis* [9]. Although a variety of antimicrobial agents are available for the treatment of mycobacterial diseases, only for tuberculosis and perhaps leprosy is there a consensus on the best treatment regimens. For other mycobacterioses, the clinician is not infrequently faced with a dilemma in choosing a treatment regimen because of a lack of clinical precedence in the treatment of rare mycobacterioses or unclear efficacy.

The situation is further confounded by the need to treat mycobacterial infections with a mixture of agents both to improve efficacy and to 'prevent resistance or overcome inherent resistance. Isoniazid (Isonicotinic acid hydrazide) (INN), a synthetic antimicrobial agent introduced in 1952 for the treatment of tuberculosis, is a remarkably specific and potent bactericidal agent against tubercle bacilli. INH has comparatively low toxicity and is active against virtually all wild-type strains of *M. tuberculosis*. While the exact mechanism of action of INH is not known, the primary effect is on mycolic acid synthesis, as evidenced by increased fragility of the mycobacterial cell, increased intracellular viscosity, decreased cellular hydrophobicity, and loss of acid fastness [10].

Some evidence indicates that INH inhibits a desaturation step in the production of long-chain fatty acids [11] and may also inhibit the elongation of fatty acids and hydroxy lipids [12]. In addition to the effect on mycolic acid synthesis, there is evidence that bactericidal free radicals form as a result of the interaction of INH and catalase or peroxidase [13], observations that are consistent with the established correlation between INH resistance and a loss of catalase activity.

In addition, INH resistance appears to interfere with NAD metabolism, which would lead to interference with NAD metabolism, which would lead to pleiotropic effects on energy metabolism and macromolecular synthesis [14], Rifampin (RMP), or rifampicin, is 3,4 (methyl piperazinyliminomethylidene) rifamycin SV . It was introduced in 1968 as a potent antituberculosis agent.

RMP is active against a wide variety of non-acid-fast bacteria (non-AFB) and several other slowly growing mycobacteria, notably *M. leprae*, *M. kansasii, M. haemophilum* and *M. marinum*, but it is only variously active against the MAC and is inactive against the rapidly growing mycobacteria. RMP inhibits the prokaryotic DNA dependent RNA polymerase by binding to the subunit at the presumed catalytic center of the enzyme. Mammalian RNA polymerase is inhibited by rifampin only at significantly higher concentrations. The RNA polymerase of MAC isolates appears to be susceptible to rifampin, therefore, the primary mechanism of intrinsic resistance is most likely impermeability. PZA is a synthetic derivative (pyrazine analog) of nicotinamide and in combination with INH is rapidly bactericidal for replicating forms of *M. tuberculosis*, with an average MIC of 20 ug/ml. PZA is inactive against non replicating tubercle bacilli and totally inactive against other species of mycobacteria including *M. bovis*, MAC, and the rapidly growing mycobacteria.

PZA is active only at a slightly acidic pH; thus, in vitro susceptibility test media must be adjusted to pH 5.5 to 6 in order to accurately measure the activity of the drug. Most likely, PZA is active only in the acidic milieu of the phagolysosome. Depending on the infection, PZA may be bacteriostatic or bactericidal. PZA is hydrolysed in the liver to the active metabolite pyrazinoic acid, and although the mechanisms of action of PZA are unknown, activity depends on this conversion to pyrazinoic acid. *M. tuberculosis* produces a pyrazinanidase. Most strains of PZA resistant *M. tuberculosis* lack this enzyme. However, some PZA-resistant isolates retain pyrazinamidase activity, suggesting that there are other mechanisms of resistance. PZA is well absorbed from the gastrointestinal tract and widely distributed throughout the body, with maximum levels in serum of approximately 45pg/m1 at 1 to 4 hours after an oral dose of lg (20 to 25 mg/kg of body weight).

Hepatotoxicity occurs in a small number of patients and photosensitivity and rash occur

rarely. Gout is an important contradiction because of the hyperuricemia associated with PZA therapy. PZA is usually discontinued after the first 2 months of short-course for tuberculosis, while INH and RMP are continued for an additional 4 months.

Ethambutol (dextro-2,2- (Ethylene diamino) di-1 butanol dihydrochloride) (EMB) is a potent synthetic antituberculosis compound introduced in 1961. The MICs of EMB tested against wild-type isolates of M. tubercuolosis range from 1 to 5 pg/ml, but activity of the drug against other slowly growing *Mycobacterium spp* is much more variable.

The primary mechanism of action of EMB is a bacteriostatic inhibition of cell wall synthesis, while evidence points to a specific effect on arabinogalactan synthesis [15]. The frequency of mutation to EMB resistance in *M*. *tuberculosis* is in the order of 10^{-5}.

Although most members of the MAC are considered intrinsically resistant to EMB, a variety of studies have shown that combinations of EMB and other agents, notably quinolones and macrolides, are synergestic [16] and that EMB appears to have a permeabilizing effect on the MAC cell wall [17]. Peak serum EMB concentrations of 5ug/ml are achieved by 2 to 4h after a dose of 25mg/kg. The primary adverse effect associated with EMB is a decrease in visual acuity due to optic neuritis that is related to both the dose and the duration of treatment. The effects are generally reversible upon discontinuation of the drug. A variety of other adverse reactions have been reported, but these are infrequent and sometimes difficult to ascribe to EMB, since they may be due to concurrent therapy with other antituberculosis agents.

Rifabutin is a spiropiperidyl rifamycin with potent in vitro activity against *M*. *tuberculosis* [16] and the MAC [17]. The mode of action and mechanism of resistance of rifabutin appear to be identical to those of RMP; however, approximately 30% of RMP-resistant *M*. *tuberculosis* isolates are susceptible to rifabutin, a fact that may be correlated with certain specific mutations in the rpo B gene [18]. Rifabutin decreases the incidence of disseminated MAC disease in human immunodeficiency virus (HIV)-infected patients when it is used as a prophylactic agent, and the drug was recently approved by the U.S Food and Drug Administration for that indication [19]. The role of rifabutin as a therapeutic agent for MAC disease is unclear, but there may be a significant dose effect [18].

In addition to being more active than RMP on a weight basis, rifabutin has a long elimination of half-life in humans, and it concentrates in tissues, notably in lung tissue, where levels are 10-fold higher than those in serum. The propensity may account for the reported effectiveness of rifabutin in the therapy of MAC pulmonary infections [20].

Rifabutin is absorbed from the gastrointestinal tract and reaches peak levels in serum of 0.5ug/ml in about 4h after a 300-mg dose. Adverse drug reactions with rifabutin are similar to those observed with RMP, including an effect on the metabolism of other drugs. Some unique rifabutin toxicities have been described, including leukopenia, thrombocytopenia, arthralgias, and uveitis when it is co-administered with clarithromycin.

The aminoglycosides that are used for the treatment of tuberculosis and other mycobacterial infections include amikacin, kanamycin and streptomycin (SM). In addition, capreomycin and viomycin, basic peptide antibiotics with mechanisms of action similar to that of the amino glycosides, are active against *M*. *tuberculosis* and certain other species of mycobacteria. The other aminoglycosides, gentamycin and tobramycin, are inactive against mycobacteria at the usual concentrations in serum. Kanamycin is a glycoside of 2-deoxystreptamine, and amikacin is a derivative of kanamycin, thus, the structures of these antimycobacterial aminoglycosides are similar.

The primary mechanism of action of the aminoglycosides is inhibition of the post-pretranslocation step of protein synthesis by blocking of the binding of aminoacyl TRNA (e-type binding). Viomycin also blocks aminoacyl-TRNA translocation, and viomycin resistance confers resistance to capreomycin, suggesting that the mechanism of action is the same. Streptomycin MICs for wild-type isolates of *M.tuberculosis* are usually well below the peak concentration in serum of 25 to 50ug/ml achieved

by 1 to 2h following a 1-g intramuscular dose. Amikacin is the most potent of the aminoglycosides, with average MICs of lug/ml for *M. chelonae* and *M. Abscessus*. There is comparatively little clinical experience with amikacin in the treatment of tuberculosis because of the expense of the drug. But amikacin in combination with cefoxitin is a standard empirical therapy for serious infections suspected to be caused by rapidly growing mycobacteria. Amikacin is also active against MAC, with about 75% of isolates susceptible to 30ug/ml, a level that approaches the maximum concentration in serum when the drug is administered by intravenous infusion. In an uncontrolled trial, amikacin was shown to be the active component of a multidrug treatment regimen that was associated with a microbiological and clinical response in HIV-infected patients with disseminated MAC disease [21].

D-cycloserine (4-amino-3-iso-oxazolidinone) is an analog of D-alanine that inhibits the synthesis of D-alanyl-D-alanine, an essential component of the mycobacterial cell wall. Cycloserine is active against all mycobacteria and several other types of bacteria. The average MICs for *M tuberculosis* range from 5 to 20ug/ml, while peak levels in serum of 20 to 40 ug/ml are achieved by 4h after an oral dose of 250mg. The drug is widely distributed through the body, including the CSF. Significant adverse drug reactions are associated with cycloserine treatment, notably peripheral neuropathy and central nervous system dysfunction, including seizures and psychotic disturbances.

Ethionamide (2-ethyl-pyridine-4-carbonic acid thioamide) is a derivative of isonicotinic acid and , like INH, blocks mycolic acid synthesis. However, isolates of *M. tuberculosis* that are resistant to high concentrations of INH are susceptible to ethionamide, suggesting that the sire of action may be different from that of INH. The average MIC for *M. tuberculosis* is 0.6 to 2.5ug/ml, and levels in serum of 2 to 20pg/ml are achieved by 3 to 4h after an oral dose of 0.5 to 1g.

Significant side effects are associated with ethionamide including gastrointestinal irritation with nausea, vomiting, and cramps, and neurologic symptoms may require discontinuation of the drug. Clofazimine, or lamprene (3-) p-chloroanilino)-10 (p-chloropheny1) -2-40-dihydro-2- iso-propyliminophenazine), is a substituted iminophenazine, bright red dye with potent in vitro activity against MAC (MICs range from 0.1 to 5 ug/ml) but unclear therapeutic efficacy either alone or in combination with other agents. The drug also has potent in vitro activity against *M. tuberculosis*, but there is little or no information on in vitro activity.

Ciprofloxacin and ofloxacin are fluorinated carboxylquinolones with moderate in vitro activities against *M. tuberculosis* and variable activities against MAC and rapidly growing mycobacteria. Ciprofloxacin and ofloxacin should be tested on secondary agents or when resistance to other antituberculous agents is suspected or known [22].

Para-Aminosalicylic (PAS) is an antifolate that is active against *M. tuberculosis* but inactive against most other mycobacteria. There is some evidence that PAS may also affect iron transport in *M. tuberculosis*. The average MIC for susceptible isolates of *M. tuberculosis* is 1mg/m1 and peak levels in serum of 7 to 8 ug/ml are achieved by 1 to 2h following a 4-g dose. PAS is incompletely absorbed in the gastrointestinal tract and is associated with significant gastrointestinal side effects that in combination with the need for large dosages (10 to 12 g/day) lead to frequent compliance problems.

Amithiozone (Thiacetazone, Tibione or panthrone) is a thiosemicarbazole that is active against *M. tuberculosis* and has an average MIC of lug/ml. Resistance develops quickly on monotherapy therefore; the drug is administered with a second agent, usually INH. Peak levels in serum of 1 to 4 ug/ml are achieved following an oral dose of 150mg. Adverse drug reactions include gastrointestinal irritation and bone marrow suppression; hepatotoxicity can occur in patients receiving concomitant INH. Amithiozone in combination with INH has been successfully used in Africa for the treatment of tuberculosis. However, recent, evidence associated Stevens-Johnson syndrome and severe epidermal necrolysis in HIV-infected patients with tuberculosis treated with regimens containing amithiozone [23]. As a result, the World Health Organisation recommended that amithiozone

should not be used to treat HIV-infected patients [24].

Amithiozone is not available in the United states and is not used in Europe because of the adverse effects. The criteria for defining drug-resistant *M. tuberculosis* were established on an empirical basis i.e. that there is a certain proportion of drug-resistant mutants above which therapeutic success is less likely to be realized. The procedures used to perform drug susceptibility tests and the criteria for interpreting the results take into account two factors:

i. The critical proportion of drug resistant mutants and
ii. The critical concentration of the drug in the test medium.

On the basis of clinical and bacteriological studies, the significant proportion of bacilli resistant to an antituberculosis drug above which a clinical response is unlikely was generally set at 1% [25].

The critical concentration of a drug is the level of drug that inhibits the growth of most cells within the population of a wild type strain of tubercle bacilli without appreciably affecting the growth of the resistant mutant cells that might be present [26].

In order words, if the proportion of tubercle bacilli that are resistant to the critical concentration of a drug exceeds 1%, it is unlikely that the use of that drug will lead to a therapeutic success. It should be noted that this concentration may not bear a direct relationship to the peak level in serum [27].

The methods generally accepted for determining the antimicrobial susceptibilities of mycobacteria are based on growth of the micro-organisms on or in a solid or liquid medium containing a specified concentration of a single drug. Four methods have been described. These include the proportion method, the radiometric or BACTEC method, the absolute concentration method, and the resistance ratio method. Methods that are commonly used to test rapidly growing aerobic and facultative anaerobic bacteria are for a variety of reasons, unsuitable for testing mycobacteria. For example, the conventional disk diffusion method is not suitable for testing slowly growing mycobacteria because the drug diffuses throughout the medium before the growth of the mycobacteria is significantly affected. BACTEC and agar proportion methods are most commonly used in the United States, and a standard procedure was proposed by the National Committee for Clinical Laboratory standards (NCCLS 1990) [27]. Many scientists have described the technical details of these procedures [28].

The agar proportion method for susceptibility testing of slowly growing mycobacteria was developed in the early 1960s and is the method most commonly used in mycobacteriology laboratories in the United States [29]. The proportion method, as presently used in the United States of America has undergone various modifications [30].

A proposed standard method was published by the NCCLS, and this procedure was updated in 1994 / 1995 [35]. The modified proportion method is also described in detail in other research reports [36].

M. tuberculosis H37RV (ATCC 27294) is susceptible to all primary and secondary antituberculosis drugs and can be used as quality control. Strains of *Mycobacterium tuberculosis* that are resistant to INH, RMP, and other drugs are available from the American type culture collection; however, these strains are resistant to high concentrations of the respective drugs and are not ideal for quality control testing [37]. Aliquots of suspensions of quality control strains of *M. tuberculosis* adjusted to match a Mcfarland 1 standard can be stored at -70°C for up to six months. Quality control testing should be performed with each new batch of medium or antimicrobial agent, and media should be checked for sterility and shown to support adequate growth.

Chemotherapy of tuberculosis

The conquest of tuberculosis with modern chemotherapy was one of the preeminent achievements of 20th century medicine. Between 1944 and 1976, effective drugs for TB went from none to more than 10, and tuberculosis went from a frequently fatal disease to one that could be cured with mostly oral drugs given for a matter of months. Presently, TB can be cured in the vast

majority of patients with regimes received daily or two to three times weekly for 6 months at no cost.

Diagnosis and treatment are free under the DOTS programme in Nigeria.

To clinicians who treat patients with TB, the wonder of cheap and effective antituberculosis drugs is tempered by the counterweight of drug toxicity. Physicians have long dealth with the double-edged sword of medications. For the ancient Greeks, the word Pharmakos meant both remedy and poison- "kill" and "cure" were apparently indistinguishable.

Although drug toxicity has been of intense interest in treating latent tuberculosis, the enormous benefits of antituberculosis agents in active disease have overshadowed the risks.

The following guidelines for TB chemotherapy were obtained from the Nigerian National Tuberculosis and Leprosy Control programme.

Type of patient

New:

Short course chemotherapy: positive	**Pre-treatment weight (kg)**		
Daily for 2 months (E) Ethambutol 400mg (H) Isoniazid 100mg (R) Rifampicin 150mg combined tablets (Z) Pyrazinamide 400mg	>55 3 4 4	40 – 55 2 3 3	25 – 39 1.5 2 2
Daily for 6 months (T) Thiacetazone 150mg (H) Isoniazid 300mg combined tablets	1	1	2 (50/100 mg)
Daily for 6 months (HIV + patients) (E) Ethambutol 400mg (H) Isoniazid 150mg combined tablets	2	2	1

Patient who is sputum smear-positive and has never received anti-tuberculosis treatment in the past, or has previously taken anti-tuberculosis drugs for less than one month in the past.

Relapse:

Patient, who previously received treatment and declared cure from tuberculosis or released from after completion of treatment and has once again developed sputum positive tuberculosis.

Transfer in:

Patient already registered for treatment in one LGA/State who transfers to another LGA/State where he continues treatment.

Return after default:

Patient who completed at least one month of treatment and returned after at least 2months interruption of treatment.

Failure:

This is newly diagonised patient who is sputum smear – positive at 5 months or more after starting treatment.

Others (specify)

TB patient who does not easily fit into any of the above case definitions.

Short course chemotherapy for smear positive TB patients who have never been treated before

Regimen and drug dosages for Adult

Retreatment smear positive relapse/ failures	Pre-treatment weight		
Daily for 3 months (H) Isoniazid 100 mg (r) Rifampicin 150 mg combined tablets (Z) Pyrazinamide 400mg (E) Ethambutol 400mg Add in the first two months only: (S) Streptomycin	>55kg 4 4 3 1gram	40 – 55kg 3 3 2 0.75gram	25-39kg 2 2 1.5 0.5gram
3 times a week for 5 months (Directly Observed) (R) Rifampicin 150mg (H) Isoniazid 100mg combined tablets (E) Ethambutol 400mg	 4 2 4	 3 1 3	 2 1 2

N.B.

(a) Drugs in the initial intensive phase of 2 months must be given on an empty stomach in a single dose under strict supervision by member of staff.
(b) If the sputum smear is positive at the end of 2 months, the intensive treatment should be continued for another month making a maximum of 3 months.
(c) If the intensive phase has been prolonged by 1 month, the continuation phase should last 5 months
(d) Thiacetazone is associated with a high risk of severe and sometimes fatal skin reaction in HIV infection individuals. Use ethambutol instead of thiacetazone in patients with known or suspected HIV infection.

(e) For smear negative and extra Pulmonary Tuberculosis, give SCC with the exception of Ethambutol in the intensive phase.

However, if resources permit, Ethambutol can be included.

Short course chemotherapy for retreatment cases adults

i.e Failure, return after default, relapse cases.

Side effects	***Drug (s) probably responsible***	***Management***
Minor		***Continue Anti TB drugs***
Anorexia Nausea	Rifampicin	Give tablets last thing at night
Abdominal pain		
Burning sensation infeet	Isoniazid	Pyridoxine 100mg daily
Joint pains	pyrazinamide	Aspirin
Orange/red urine	Rifampicin	Reassurance
Major		***Stop drug (s) responsible***
Deafness (no wax on auroscopy)	Streptomycin	Replace streptomycin by ethambutol
Dizziness	Streptomycin	Replace streptomycin by ethambutol
Generalized symptoms (Shock and Purpura)	Rifampicin	Stop rifampicin
Jaundice	Most anti TB drugs	Stop AntiTB drugs until jaundice resolves
Skin itching/rash	Thiacetazone (Streptomycin)	Stop AntiTB drugs- in high HIV endemic areas, Thiacetazone is the drug most likely to cause skin reactions
Visual impairment	Ethambutol	Replace ethambutol by streptomycin (Not in case of pregnant women)
Vomiting Confusion	Most AntiTB drugs	Stop AntiTB drugs Urgent liver function tests

- No Strptomycin should be given to pregnant women
- 0.75g of Streptomycin should be given to patient > 45years
- Every dose taken must be observed
- The tablets should be given in a single dose in an empty stomach before the injection of Streptomycin
- Sputum smear examination should be done at the end of 3 months
- If the sputum smear is positive at the end of 3 months, the initial phase of treatment with four drugs (i.e without the streptomycin) is continued for another month making maximum of 4 months
- If the intensive phase has been prolong by 1 month then the continuation phase should last 4 months.

Drug dosage for children (ages 0 – 14)

Short course chemotherapy positive (children 0 – 14)	Pre-treatment weight (kg)		
Daily for 2 months (S) Streptomycin (H) Isoniazid 100mg (R) Ritampicin 150mg combined tablet (Z) Pyrazinamide 400mg	21–33 500mg 2 2	11–20 500mg 1 1	5–10 250mg 0.5 0.5
Daily for 6 months (T) Thiacetazone 50mg (H) Isoniazid 100mg combined tablet	2	1	0.5

Ethambutol is replaced by Streptomycin in young children because of possible side effects on vision which they cannot report.

Drug dosage for children 0 – 14 smear negative

Short course chemotherapy: negative/EPTB (children 0-4)	Pre-treatment weight (kg)		
Daily for 2 months (H) Isoniazid 100mg (R) Ritampicin 150mg combined tablet (Z) Pyrazinamide 400mg	21-33 2 2	11-20 1 1	5-10 0.5 0.5
Daily for 6 months (T) Thiacetazone 50mg (H) Isoniazid 100mg combined tablet	2	1	0.5

Drug side effects

In management of drug side effects minor symptoms can be on ambulatory basis
However, major symptoms need dose observation.

The patient might have to be admitted in a General Hospital or TBL Referral Hospital

Drug resistant tuberculosis

There are series of definitions used in describing the different types of drug- resistant TB. The term "drug resistant TB" caused by an isolate of *M. tuberculosis* that is resistant to one of the first–line anti-TB drugs: isoniazid, rifampin, pyrazinamide, ethambutol, or streptomycin. The term "multidrug-resistant TB "(MDRTB) refers to an isolate of *M. tuberculosis* that is resistant to at least isoniazid and rifampicin, and possibly additional chemotherapeutic agents.

The term "extensively drug-resistant TB" (XDR-TB) refers to an isolate of *M. tuberculosis* that is resistant to at least isoniazid, rifampin and fluoroquinolones as well as either aminoglycosides (amikacin, kanamycin) or capreomycin, or both. The term "totally drug-resistant TB" (TDR-TB) refers to an isolate of *M. tuberculosis* resistant to all locally tested medications. However, describing TDR-TB did not include susceptibility testing for less frequently used agents with activity against TB, including cycloserine, terizidone, clofazimine, linezolid or carbapenems.

Primary drug resistance is said to occur in a patient who has never received anti-TB therapy while secondary drug resistance refers to the development of resistance during or following chemotherapy in patients who had previously had drug- susceptible TB. MDR-TB is defined as laboratory-confirmed resistance to the most potent first-line medications, isoniazid and rifampin.

Since 2007, XDR-TB has been defined as resistance to both isoniazid and rifampin with additional resistance to at least one fluoroquinone and one injectable agent. (amikacin, kanamycin or capreomycin).

M. tuberculosis strains resistant to all locally tested medications have been defined as "totally drug resistant" or "TDR-TB. However, these TDR isolates were not tested against a complete panel of second-line anti-tuberculosis drugs, including cycloserine, terizidone, clofazimine, linezolid and carbapenems.

Regardless, reports of TDR-TB raise epidemiologic concerns regarding the ability to track complex resistance patterns in resource-limited settings. The emergence of TDR-TB also highlights the limited availability of susceptibility testing for the less commonly anti-tuberculosis drugs, the relative inability to predict synergy or drug activity at the site of infection, and the need for optimized pharmacokinetic strategies.

Multi-drug resistant TB emerged in epidemic proportions in the wake of widespread HIV infection in the world's poorest populations, including sub-Saharan Africa. Extensively drug resistant TB was first reported in 2006 but has now been documented on six continents. These trends are critically important for global health since drug-resistant TB death rates are high and second and third –line agents for treatment of drug-resistant TB are less potent and less tolerable than first-line therapies.

Sorting out adverse reactions to TB therapy

Adverse reactions to tuberculosis (TB) treatment not only lead to significant morbidity and occasional mortality but also may increase the length and cost of therapy. In a retrospective study of patients treated for active TB at a single center in Montreal, researchers assessed the incidence of adverse reaction to first-line TB drugs. A major adverse reaction was defined as any event that resulted in hospitalization, discontinuation of TB therapy, or both.

Among 430 patients with confirmed TB seen between 1990 and 1999, 46 adverse events occurred in 37 patients. Rash and fever were the most common events; hepatitis occurred in 12 patients. No deaths were associated with drug toxicity. When the incidence of major toxicity was calculated per 100 people –months of therapy, pyrazinamide was associated with an adverse event rate of 1.48, significantly higher than that of isoniazid (0.49), rifampin (0.43), and ethambutol (0.07).

These results suggest that pyrazinamide might be associated with an increased risk for adverse events during TB therapy. Because pyrazinamide is used only for the first 2 month of therapy and because most drug toxicity occurs during the first 60 days of treatment, the researcher's use of person-month likely overestimates pyrazinamide toxicity was 6% compared with 4% for isoniazid, a much less striking difference.

Conclusion

The rapid development of resistance to single agent therapy led to the principle of multi-agent chemotherapy of TB that remains the cornerstone of treatment.

Short-course chemotherapy of TB consists of adhering tightly to six months of treatment with drugs with suboptimal toxicity profiles, but in patients co-infected with antirational drugs used to treat advanced HIV disease. Strategic treatment goals include; developing improved treatment for

multi drug resistant tuberculosis (MDR-TB); and identifying and developing drugs that can be safely co-administered with TB/HIV co-infection. Such drugs will substantially improve treatment outcomes, simplify programme implementation; and accelerate TB control efforts.

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