Drug therapy in spinal tuberculosis

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Abstract Although the discovery of effective anti-tuberculosis drugs has made uncomplicated spinal tuberculosis a medical disease, the advent of multi-drug-resistant *Mycobacterium tuberculosis* and the co-infection of HIV with tuberculosis have led to a resurgence of the disease recently. The principles of drug treatment of spinal tuberculosis are derived from our experience in treating pulmonary tuberculosis. Spinal tuberculosis is classified to be a severe form of extrapulmonary tuberculosis and hence is included in Category I of the WHO classification. The tuberculosis bacilli isolated from patients are of four different types with different growth kinetics and metabolic characteristics. Hence multiple drugs, which act on the different groups of the mycobacteria, are included in each anti-tuberculosis drug regimen. Prolonged and uninterrupted chemotherapy (which may be ‘short course’ and ‘intermittent’ but preferably ‘directly observed’) is effective in controlling the infection. Spinal Multi-drug-resistant TB and spinal TB in HIV-positive patients present unique problems in management and have much poorer prognosis. Failure of chemotherapy and emergence of drug resistance are frequent due to the failure of compliance hence all efforts must be made to improve patient compliance to the prescribed drug regimen.

Keywords Spinal tuberculosis · Drug therapy

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Tuberculosis (TB) is probably as old as man himself and its causative organism *Mycobacterium tuberculosis* has possibly caused more mortality and morbidity than any other microbial pathogen till date [1]. The history of the management of this deadly disease can be broadly divided into ‘Pre’ and ‘Post’ chemotherapy era as the rate of cure, prognosis for recovery and duration of treatment have all considerably changed since the discovery of effective anti-TB drugs (Table 1) [2]. Although more than five decades have passed since the availability of anti-tubercular chemotherapy, yet someone in the world dies from tuberculosis every 15 s, and a person is newly infected with *M. tuberculosis* every second [3]. With the advent of HIV and multi-drug-resistant TB, the “King’s evil” has re-emerged as a major global public health problem and is currently one of the top 10 causes of death worldwide.

Musculo-skeletal affection is seen in 4 % of all cases of TB, 50 % of which involves the spine [2].

Before the availability of anti-tubercular chemotherapy, the natural history of the disease was protracted through three stages: the stage of onset, the stage of destruction and the stage of repair and ankylosis, overall spanning 3–5 years and resulted in high morbidity and mortality [4]. Anti-tubercular chemotherapy brought about dramatic resolution of tubercular lesions. This helped to establish chemotherapy as the mainstay of treatment of uncomplicated Spinal TB and also helped to improve the results of surgery by improving healing and reducing recurrence. The necessity for complete surgical extirpation of the disease focus ceased to exist and the surgical interventions became less frequent, less invasive, safer and more successful. The availability of streptomycin in 1944, INH in 1948 and PAS in 1949 brought an end to the unchallenged supremacy of

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Table 1 The impact of chemotherapy on the management of tuberculosis [2]

	Before availability of chemotherapy	After availability of chemotherapy
Mortality	30–50 %	<1 % (except MDR-TB)
Complete recovery	30–44 %	83–96.8 %
Duration of treatment	2–5 years	9–18 months
Healing after surgery	30 %	80–96 %

Table 2 The discovery of chemotherapeutic agents active against tuberculosis [2]

	Drug	Available for use against TB
1.	INH	1952
2.	Rifampicin	1967
3.	Pyrazinamide	1952
4.	Ethambutol	1961
5.	Streptomycin	1944
6.	PAS	1949

the Mycobacteria and revolutionized treatment of Spinal TB. This was followed by the availability of more drugs in the 50s which improved the survival considerably (Table 2) [2]. The fundamental principle of chemotherapy in TB is that any regime chosen must include multiple drugs and must be given for a prolonged period of time.

Principles of drug treatment of spinal tuberculosis

The principles of drug treatment of spinal TB are derived mostly from our understanding of the treatment of pulmonary tuberculosis. *Mycobacterium tuberculosis* and related species that cause the disease are strict aerobes and thrive best in regions with high tissue oxygen tension such as the lungs. Hence the lesions in the lungs are multi-bacillary. In osseous tissue with rich blood supply like the vascular cancellous vertebral bone, the organism can multiply only moderately and the lesions contain much fewer organisms and hence are ‘pauci-bacillary’ (less than 10^4 colony forming units per ml) [5]. Treatment regimens which work for the multi-bacillary lesions in the lungs will surely work for the lesions in the bones which have a lesser bacterial load. The general principles guiding drug therapy in TB are as follows:

1. *Mycobacterium tuberculosis* is a slow growing bacillus: Most mycobacteria causing human infection take 18–20 h for replication. This is advantageous because the TB lesions grow slowly but this is also a major

disadvantage as the drugs that act on the rapidly multiplying group of bacteria are less effective against *M. tuberculosis*.

2. Most antibiotics are ineffective against mycobacteria: The mycobacterial cell wall lipids are linked to underlying arabinogalactans and peptidoglycans resulting in very low permeability of the cell wall to the usual antibiotics. Hence most antibiotics are unable to penetrate the cell wall and act on the mycobacterium. Also Lipoarabinomannan, a molecule in the cell wall of mycobacterium, facilitates the survival of the organism within the macrophages which are impermeable to most antibiotics [6]. The macrophages in an attempt to engulf and destroy the mycobacteria, tend to shelter them from the usual antibiotics.
3. Multi-drug chemotherapy is essential in TB: Multiple antibiotics are needed against TB as there are different types of *M. tuberculosis* in each colony with different growth kinetics and metabolic characteristics.

Mycobacterium tuberculosis can be divided into four types [7]:

- (a) Extracellular rapidly dividing bacilli.
  - (b) Extracellular slowly or intermittently dividing bacilli.
  - (c) Intracellular intermittently dividing bacilli.
  - (d) Dormant bacilli.
4. Drugs act differently depending on the nature of Mycobacteria: rifampicin is bactericidal for the extracellular bacilli which are slowly multiplying or showing spurts of metabolism. Isoniazid, streptomycin and ethambutol act on extracellular rapidly dividing bacilli. Pyrazinamide penetrates the macrophages and kills intracellular bacilli. No drug acts against the dormant group of bacilli, which can lie dormant for extended periods and can get activated later in life causing relapses [8].
  5. Primary and acquired resistance to chemotherapy drugs are common in TB: The average frequency of resistant mutants in a lesion of tuberculosis is 1 in 10^6 to isoniazid and 1 in 10^8 to rifampicin. The probability of having a bacterium resistant to both is 1 in 10^{14} . Hence to reduce de novo drug resistance, combination of at least two drugs is used [9].
  6. The ‘lag effect’ and the rationale of ‘intermittent therapy’: Most anti-tubercular drugs have demonstrated an extended period of effect on the mycobacterium, known as the lag effect, which lasts for several days even after termination of therapy (notable exception being thioacetazone), which makes daily dosage unnecessary. Intermittent therapy significantly improves patient compliance which is a major problem of all prolonged antibiotic therapies [10, 11]. The efficacy of intermittent therapy has been proven in various clinical trials [12–15].

Drugs effective against tuberculosis:

Drugs used in TB have different pharmacokinetics and are potentially toxic as they have to be used for a prolonged period of time. It is important that a good understanding of the use and disadvantages of each drug is well understood so that the iatrogenic complications, some of which are potentially fatal, are avoided (Tables 3, 4) [16–18]. Standard drug treatment regimens have been established and any deviation from them must be done only in special circumstances and with the supervision of an expert physician.

The first line drugs (Table 3) [16, 17] are the most effective group of agents active against tuberculosis. A number of other drugs are also found to be active against tuberculosis. However, they are less effective, more toxic and more expensive than the first line drugs and are called as the second line drugs (Table 4) [16, 18].

Categories of tuberculosis and their treatment regimens have been recommended by WHO (Table 5) [16]. Spinal tuberculosis is classified to be a severe form of extrapulmonary tuberculosis and hence should be given Category I treatment (2HRZE + 4HR i.e. 2 months of H,R,Z and E followed by 4 months of H and R). The regimen recommended by WHO has two phases: an initial ‘Intensive phase’, consisting of four to five drugs to rapidly destroy the majority of the organisms and a ‘continuation phase’ which consists of two to three drugs.

Intermittent short-course chemotherapy

Historically, the recommended duration of anti-tubercular chemotherapy was from 18 to 24 months and this was followed without much scientific basis or evidence. Even today there is lack of consensus regarding the ideal duration of treatment for spinal TB. Uncertainty about the penetration of osteoarticular lesions by the available drugs and the fear of early or late recurrence forced the surgeons to continue chemotherapy for prolonged periods. Modern anti-tuberculous drugs have been shown to penetrate osseous tissue in amounts much higher than the minimal inhibitory concentrations (MIC) [19]. Wallace Fox for the first time proved that addition of R or Z to regimens containing H made it possible to shorten the duration of treatment [20]. The British MRC trials also clearly elucidated that the duration of treatment could be successfully reduced to only 6 months by giving both R and Z [12, 21].

The drive towards short-course chemotherapy over the conventional longer duration regimens was due to its many inherent advantages:

1. Improved patient compliance: Many patients were unable to comply with the conventional chemotherapy regimen as it lasted up to 2 years. A shorter course of therapy significantly improved patient compliance.
2. Lower failure rates: Better patient compliance decreased the treatment failure rates.
3. Lower cost: The cost of treatment was lowered by the use of lesser drugs and by decreasing the cost of

Table 3 Chemotherapeutic agents against tuberculosis: The first line drugs [16]

First line drugs	Effects	Complications
Isoniazid (H) 5 (4–6) mg/kg/day	Penetrates the cell, inhibits synthesis of cell wall mycolic acid. It is bacteriostatic against resting bacilli and bactericidal against both intracellular and extracellular bacilli which are rapidly dividing. Also crosses the blood brain barrier. Because of its potency, infrequent toxicity, small bulk, and low cost, it is widely used in the treatment of tuberculosis	Peripheral neuropathy which can be prevented by pyridoxine (vitamin B6). Light headedness, lethargy, fatigue and reversible hepatotoxicity. Rarely psychosis and seizures
Rifampicin (R) 10 (8–12) mg/kg/day	Binds to and blocks DNA-dependent RNA polymerase. It is highly bactericidal against both intracellular and extracellular bacilli which are multiplying slowly	Hepatotoxicity, orange-red discoloration of body secretions, cutaneous syndrome, abdominal syndrome, “flu” syndrome, respiratory syndrome, purpura and rarely haemolytic anaemia
Pyrazinamide (Z) 25 (20–30) mg/kg/day	Disrupts membrane energetics (potentials) and inhibits membrane transport function in mycobacterium, is bactericidal in the acidic medium (pH <6.0) [17] and can penetrate the macrophages harboring the mycobacteria	Hyperuricemia, hepatotoxicity, and arthralgia
Ethambutol (E) 15 (13–17) mg/kg/day	Mechanism of action is unknown. It is bacteriostatic against rapidly multiplying bacteria	Retrobulbar optic neuritis is the most serious side effect. Can cause reduced visual acuity, central scotoma and loss of ability to see green color. Contraindicated in children who might not report the visual changes at an early period
Streptomycin (S) 15 (12–18) mg/kg/day	Disrupts the ribosomal function by affecting protein synthesis. It is bactericidal against the rapidly dividing extracellular bacteria. Diffusion into cerebrospinal fluid (CSF) is poor	Affects both vestibular and hearing functions and can cause nephrotoxicity. Can also cause perioral paresthesia, eosinophilia, drug rash and fever

Table 4 Chemotherapeutic agents against tuberculosis: The second line drugs [16]

Second line drugs	Effects	Complications
Thioacetazone (Tzn) 2.5 (2–3) mg/kg/day	Bacteriostatic drug that is absorbed orally	Nausea, vomiting, drug rash
Para-aminosalicylic acid (PAS) 10–12 g/day	Bacteriostatic drug	Main side effect is GI disturbance. It may also cause hypersensitivity, hepatic dysfunction, hypokalemia and hypothyroidism. May interfere with rifampicin absorption and therefore is not recommended along with it
Ethionamide (Et) 15–20 mg/kg/day	Bacteriostatic agent. Absorbed orally and evenly distributed across all tissues including CSF	GI intolerance, drug-induced hepatitis, hypothyroidism (reversible antithyroid effect), peripheral neuropathy, psychotic reactions like hallucinations and depression. These drugs may also cause hypoglycemia, especially in diabetics
Cycloserine (Cs) 0.5–1 gm/day	Distributed widely in CSF also	Psychosis, seizures, headache, sleepiness and peripheral neuropathy
Kanamycin (Km) 12–18 mg/kg/day	Aminoglycoside obtained from Streptomyces. Bactericidal	Same as streptomycin
Amikacin (Am) 12–18 mg/kg/day	Aminoglycoside obtained from Streptomyces. Bactericidal	Same as streptomycin
Capreomycin (Cpr) 12–18 mg/kg/day	Bactericidal agent. Administered by deep intramuscular injection. Capreomycin has no cross-resistance with other aminoglycosides	Same as streptomycin. Also may cause electrolyte imbalances like hypokalemia, hypocalcemia and hypomagnesemia
Ciprofloxacin (Cipro) (Fluoroquinolone, 'Q') 1–1.5 g/day	Bactericidal agent. Prevents synthesis of DNA through the inhibition of DNA gyrase. The side effects include: Mycobacterial resistance to quinolones develops rapidly. The cross-resistance is across all quinolones [18]	Gastrointestinal (GI) intolerance, rash, dizziness, headache, confusion, seizures and acute renal failure

Table 5 Categories of tuberculosis and their treatment regimens as recommended by WHO [16]

Categories	Patients	Treatment
Category I	New smear-positive pulmonary TB, smear-negative pulmonary TB with parenchymal involvement, seriously ill pulmonary TB, extrapulmonary TB, severe concomitant HIV disease	2HRZE + 4HR
Category II	Previously treated sputum/smear-positive pulmonary TB relapse, treatment after interruption, treatment failure	2HRZES/1HRZE + 5HRE
Category III	New smear-negative pulmonary TB, less severe form of extrapulmonary TB	2HRZE + 4HR
Category IV	Chronic and MDR-TB	Specially designed/individualized regimens

The number before the letters refers to the number of months of treatment

H isoniazid, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin

managing patients with failure of (or resistance to) treatment due to non-compliance.

- Lower incidence of drug resistance: Better compliance led to better cure rates and significantly decreased the chance for the mycobacterium to become drug resistant.

Also *M. tuberculosis* demonstrates the 'lag effect' (as explained before) due to which the effect of most anti-tubercular drugs lasts for some duration even on discontinuation of the drugs. This allows for intermittent treatment regimens where the drugs are administered twice or thrice a week. Intermittent short-course chemotherapy

has been found to be clinically effective in a large number of trials (Table 6) [13–15, 22].

The role of directly observed therapy short course (DOTS)

Similar to other chronic diseases, patients with TB have a very high default rate for medicine intake [23]. Erratic drug consumption is one of the most common causes for treatment failure and the emergence of acquired drug resistance. Even in inpatients the compliance for prolonged

Table 6 Summary of some of the major trials that proved the efficacy of intermittent short-course chemotherapy [13–15, 22]

Country	Year of study	Regimen	Duration of treatment (months)	No. of patients assessed	Relapse rate after 2 years (%)
Hong Kong	1974	4H3R3Z3S3/2H2Z2S2	6	71	6
		2H3R3Z3S3/4H3R3S3	6	220	3
Madras (Now Chennai, India)	1980	2H3R3Z3S3/4H2R2S2	6	111	2
		2H3R3Z3S3/4R2H2	6	101	3
		2H2R2Z2S2/4H2R2S2	6	108	3
		2H2R2Z2S2/4R2H2	6	102	6
		2H3R3Z3E3/4H2R2	6	519	7

The number before the letters refers to the number of months of treatment and the subscript after the letters refers to the number of doses per week

H isoniazid, *R* rifampicin, *Z* pyrazinamide, *E* ethambutol, *S* streptomycin

drug therapy regime is low. It is expected that the compliance of patients treated in a home-setting would be even worse. Directly observing the patient while he/she swallows the drug is probably the best method to ensure that the patients follow the drug regimen without interruption. Direct observation has become even simpler due to the proven efficacy of intermittent drug regimens which permit drug intake just for two or three times a week.

Advantages of DOTS [24]

1. Not only does the observer ensure regular drug intake but also keeps a check on the correct timing and dosage of the medicines.
2. Adverse effects of the drugs can be identified early and treated accordingly.
3. Repeated contacts with the observer makes the time between treatment interruption and action to retrieve the patient, shorter.
4. Increased compliance leads to better treatment outcomes and reduction in the incidence of drug resistance.

The only disadvantage is the higher cost of personnel and program implementation. However, this cost is clearly offset by the savings in the costs of re-treatment, the costs of treating drug resistance and the costs of treating new cases of tuberculosis (many with drug resistance) which would arise if the treatment is not observed directly [25].

Multi-drug-resistant (MDR)-TB

Resistance to both INH and rifampicin is termed as MDR and extensively drug-resistant tuberculosis (XDR-TB) is defined as resistance to INH and rifampicin along with resistance to any fluoroquinolone and at least one injectable second-line anti-tuberculosis drug. Increasing incidence of

drug-resistant TB, especially when associated with HIV co-infection, is one of the major global health threats today as MDR-TB and XDR-TB lead to relentlessly progressive disease with very high morbidity and mortality.

Multi-drug resistance is rarely innate and is usually the result of inappropriate drug therapy. WHO reported the median prevalence of primary and acquired MDR-pulmonary TB to be 3.4 and 25 %, respectively, [26] although an extremely high percentage of *M. tuberculosis* (51 %) were reported to be multi-drug-resistant in an urban centre in Mumbai (India) [27]. There is paucity of data on prevalence and treatment of MDR-TB of the spine.

Principles of management of MDR-TB [28, 29]

1. In every patient, all efforts must be made to culture the bacilli and obtain drug sensitivity results, which then should guide therapy.
2. Never add a single drug to a failing regimen.
3. Regimens should consist of minimum four drugs not used previously (Table 7). Second line drugs are potentially more toxic than primary drugs and a physician experienced in the treatment of MDR-TB must be included in the management of the patient.
4. An injectable aminoglycoside preferably should be added for a minimum period of 2 months.
5. Minimum recommended duration of treatment is 24 months.

TB and HIV co-infection

3–5 % of patients with pulmonary TB develops musculoskeletal lesions but the incidence of musculoskeletal lesions increases to 60 % in patients who are HIV positive [30]. HIV-positive patients who complete treatment show

Table 7 Suggested drug regimens for multidrug-resistant cases [18]

Susceptibility testing to essential drugs	Initial phase		Continuation phase	
	Drugs	Duration	Drugs	Duration
Not available	Km + Et + Q + Z ± E	At least 6 months	Et + Q + Z ± E	12–18 months
Resistance to H + R	S + Et + Q + Z ± E	At least 6 months	Et + Q + Z ± E	12–18 months
Resistance to all essential drugs	1 injectable + 1 fluoroquinolone + 2 of these 3 oral drugs: PAS, Et, Cs	At least 6 months	The same drugs except injectable	18 months
Susceptibility to reserve drugs available	Tailor regimen according to susceptibility pattern			

H isoniazid, *R* rifampicin, *E* ethambutol, *Z* pyrazinamide, *S* streptomycin, *Et* ethionamide, *Km* kanamycin, *Q* ofloxacin/ciprofloxacin

the same clinical, radiographic, and microbiological response to chemotherapy as HIV-negative patients although the mortality rate of ‘HIV plus *M. tuberculosis*’ infected patients is higher than those patients suffering from TB who are HIV negative [31]. Direct observational therapy is even more important for HIV-positive tuberculosis patients and is known to significantly decrease mortality in these patients [32].

It is essential to note that there is evidence to suggest that the addition of rifampicin to the drug regimens in these patients significantly reduces mortality [33], however, most protease inhibitors and non-nucleoside reverse transcriptase inhibitors which constitute standard anti-retroviral therapy interact with rifampicin and therefore should not be prescribed along with rifampicin [34, 35]. Also initiation of anti-retroviral therapy in a patient being treated for tuberculosis is known to cause paradoxical worsening of symptoms, probably due to improvement in the inflammatory response. Similarly anti-retroviral is known to activate latent tuberculosis in HIV-positive patients which is supposed to be due to the immune reconstitution syndrome [36]. Data and evidence relating to spinal tuberculosis in HIV-positive patients are lacking which prohibit making sound recommendations regarding optimum drug therapy for these patients.

Conclusion

Fortunately, we have many drugs that are effective against *M. tuberculosis* making uncomplicated spinal TB a medical disease. Multidrug, prolonged and un-interrupted chemotherapy is important for success and unless there is a contraindication, well established regimens proposed by WHO must be followed. Adequate, appropriate, preferably directly observed chemotherapy can lead to favorable outcome and prevent the hazards of drug resistance. Failure of chemotherapy is frequently due to the failure of compliance and sufficient care must be taken to educate the patient on the need for compliance. Spinal MDR-TB and

spinal TB in HIV-positive patients present unique problems in management and have much poorer prognosis. Also the second-line chemotherapeutic agents are less efficacious but more toxic than the first-line drugs. Hence all efforts must be made to prevent drug resistance in the patients receiving treatment for the first time.

Conflict of interest None.

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