Supplement-Indian J Pediatr 2000; 67: S14-S20

Treatment of Tuberculosis

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Abstract : Early diagnosis and prompt treatment of tuberculosis is important in order to minimise complications and sequale. It is important to select the proper regimen and ensure that hte patient is getting adeuqate number of drugs for adequate duration. The principles of short course chemotherapy and the rationale behidn the currently recommended regimens are outlined in this article. Standard (daily or intermittent) 6-month short course regimens are sufficient to cure most forms of tuberculosis in children and only severe form slike miliary, meningitis and neuro-tuberculosis require a longer duration of treatment. Worldwide, the DOTS strategy is now recommended in order to ensure cure and cut down the transmission of disease in the community and wherever possible, should be employed in the treatment of tuberculosis in children also.

Key Words : *Chemotherapy; Direct observed therapy short course; Tuberculosis.*

The therapy of tuberculosis has undergone major changes in the past 15-20 years. Upto the early 1980s, the recommended treatment duration for adults and children was as long as 18 months. These "standard" regimens were associated with poor compliance and therefore high failure and relapse rates. Though it was known from the 1960s that supervised intermittent treatment was as effective as daily treatment this mode of therapy was not widely followed. With the introduction of rifampicin and the re-discovery of pyrazinamide in the 1970s, "short course" regimens evolved which led to the modern era of chemotherapy of tuberculosis. Initially, most trials were conducted in adults and the results extrapolated to children; however, most of these recommendations have now been validated by controlled trials in children.

MICROBIOLOGIC BASIC FOR TREATMENT

Types of Bacterioal Population

M. tuberculosis exists as distinct bacterial populations in the host, each with different rates of metabolic activity and replication. The tubercle bacillus can be killed only during replication and being an obligate aerobe, its activity varies with oxygen supply. Bacilli are present in extracellular locations within cavitary walls (rapidly multiplying) and also wihin the caseous material. In additionl, they are present within macro-phages as they are able to resist lysosomal killing. Cavitary lesions with high oxygen tension lead to a very large bacterial population (10^7-10^9), closed cas-eous lesions with neutral pH have moderate numbers of bacilli (10^5-10^7) replicating intermittently while the bacterial population in macrophages with acidic pH (10^4-10^6) is small and multiples very slowly.[1,2]

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Presence of Natural Drug Resistant Mutants

Another important consideration is the occurrence of natural drug-resistants in bacterial populations of *M. Tuberculosis*.[3] The mean frequency of these mutants is 1 in 10^5 bacilli for streptomycin, 1 in 10^6 for isoniazid and 1 in 10^7 for refampicin. A cavity with 10^9 bacilli would therefore have several hundred drug - resistant mutuants wheras lesions of primary tuberculosis or extra-pulmonary TB have few, if any, mutants. The chance that a mutant is naturally resistant to two drugs is very small (10^{11} to 10^{13}). If patients are treated with a single drug, the drug resistant mutants will selectively multiply.

Size of the Bacillary Population

Adults with cavitary lesions housing large bacterial populations, must be trated with at least 3 to 4 drugs to prevent the multiplication of drug resistant mutants. However, children with primary pulmonary tuberculosis and patients with extra pulmonary tuberculosis have smaller bacterial loads and can be treated with fewer drugs (minimum 2) without much risk of drug - resistant mutants multiplying. Patients with infection (positive skin test) but no disease have a very small bacterial population (10^3 to 10^4 organisms) and can be managed with a single drug.

Actions of Anti-Tuberculosis Drugs

Antituberculosis drugs work in 3 ways: bactericidal, sterilization and prevention of resistance. Each drug acts in a slightly different manner (Table 1). The large population of actively replicating extracellular tubercle bacilli (Group A) are rapidly killed by isoniazid, rifampicin and streptomycin. Rifampicin and isoniazid kill organisms in closed caseous lesions while intracellular organisms (Group C) are affected mainly by pyrazina-

TABLE 1 : Bacillary Population and Drug Actions

Bacillary Population	Drug
Group - A Metabolically active, continuosly growing bacilli in neutral pH	Streptomycin Isoniazid Rifampicin
Group -B Dormant most of the time, occasionally growing for short periods	Rifampicin
Group -C Intracellular bacilli in acidic pH	Pyrazinamide
Group -D Dormant bacilli	No drug

mide. Thus a combination of isoniazid, rifampicin and pyrazinamide would take care of bacilli in different stages of matabolic activity, producing sterilization of the lesion.

Lag Phase

M. tuberculosis exhibits a lag period in growth in response to anti-TB drugs. After exposure to the drug, the growth of the bacillus is inhibited for a variable period of time ranging from 2 to 40 days (Table 2). This property enables intermittent administration of drugs with good therapeutic effect. However, it is important that the peak drug concentration achieved should be above the MIC. A controlled clinical trial undertaken at the Tubeculosis Research Centre (TRC) had shown that a twice - weekly intermittent regimen of streptomycin and isoniazid was as effective as a daily oral regimen of PAS and isoniazid, both regimens being given for 12 months4. Various attempts to reduce the frequency to once a week have not been successful, hence intermittent chemotherapy should be given at least twice a week.

PRINCIPLES OF SHORT - COURSE CHEMOTHERAPY

The bilogic characteristics of tubercle bacilli listed above determine the principles of short course treatment for tuberculosis.

1. A combination of at least 3 to 4 drugs should be used inthe initial intensive phase (2 months). The drugs are isoniazid, rifampicin, pyrazinamide and either streptomycin or ethambutol. This combination ensures rapid killing of all populations of bacilli.
2. Drugs can be given either daily or intermittently (twice or thrice weekly)
3. The minimum duration of treatment is 6 months when

TABLE 2 : Lag in Growth of *M. tuberculosis* After Temporary Exposure to Drugs.

Drug	Concentration mg/1	Lag (days) after exposure for 6h	24h
Isoniazid	1	0	6 - 10
Streptomycin	5	8 - 10	8 - 10
Rifamicin	0.2	2 - 3	2 - 3
Pyrazinamide	50	5 - 40*	40
Ethambutol	10	0	4 - 5
Ethionamide	5	0	10
Thoacetazone	10	0	0

* Depending on the pH of the medium (6.2 - 5.6)

rifampicin is used throughout and pyrazinamide is used in the intial intensive phase. If only 2 drugs are used, the duration of treatment has to be at least 9 months.

4. The drugs should preferably be given together and administered as a single dose.

The advantages of SSC are:

i) It has a faster and more powerful bactericidal and sterilizing action so that even if the patient defaults after the first few months of therapy, he is likely to be cured.

ii) The patient is exposed to potentially toxic drugs for shorter periods of time.

iii) The regimens are less expensive and more cost-effective than traditional therapy.

iv) More time and resources can be allotted to ensuring compliance.

Various studies in adults have shown that with a combination of rifampicin, isoniazid and pyrazinamide with either streptomycin or ethambutol, about 90% of patients become culture-negative by the end of 2 months (bactericidal effect of the regimen)[5]. Continuing the treatment with rifampicin and isoniazid for further 4 months results in almost 100% of patients with drug sensitive organisms becoming culture-negative and bacteriological relapse occuring in only about 5% of patients (sterilizing effect of the regimen)[2,6]. If the second phase is without rifampicin, the total duration has to be at least eight months. Chemotherapy of less than 6 months duration is associated with higher relapse rates.

The principles of short course chemotherapy may be combined with intermittment chemotherapy to devise highly effective regimens, which can be given under supervision to avoid non-compliance. The WHO is now implementing the DOTS strategy (directly observed treatment, short-course) in places with a high incidence of tuberculosis. By ensuring cure, this strategy aims at reducing the number of infectious cases in the community and also preventing the emergence of drug resistance.

CHEMOTHERAPY

The principles of chemotherapy in children and adults are the same. However, the exact regimens used vary depending onthe nature and severity of illness e.g. tuberculous meningitis, bone and joint TB and certain other severe forms need longer regimens. Most other forms of extra pulmonary TB like abdominal TB, pleural effusion and TB lymphadenitis can be effectively treated using the standard 6 month regimens.

The drug abbreviations are as follows: E-Ethambutol, H-Isoniazid, R-Rifampicin, S-Streptomycin and Z-Pyrazinamide. The number in front of the regimen denotes the number of months and the subscript after the drugs denote the frequency of administration (number of doses per week).

TRC Trial of short Course Chemotherapy for Pulmonary Tuberculosis.

This trial was undertaken to study the efficacy of a 6-month intermittent regimen and compare it with a standard (daily) 9-month regimen7. A total of 137 children with pulmonary tuberculosis were treated with one of the following 2 regimens:

i) Isoniazid and rifampicin administered daily for 9 months (9HR) - the drugs were collected once a week and administered at home.

ii) Isoniazid, rifampicin and pyrazinamide thrice a week for the first two months followed by isoniazid and rifampicin twice a week for the next 4 months ($2HRZ_3$/ $4HR_2$) - all doses were fully supervised.

The diagnosis was based on radiological abnormality which was classified as most probable (category A) and probable (B). Sixty eight (50%) patients had parenchymal lesions alone, 34 (25%) had adenitis alone (mediastinal, hilar or both), 10 (7%) had cavitary lesions while the remaining 25 (18%) had combined lesions. On admission, 56% of the patients were less than five years old, tuberculin test with ITU was positive in 72% and a history of contact with a known case of TB was pesent in 78%. Culture was positive for M. tuberculosis in a total of 44 (32%) patients. Of the 137 patients, 68 received regimen I and 69 regimen II.

The response to treatment was similar with both the regimens. Of the 137 patiens, 3 (2%) died, in 74 (54%) the radiological lesions disappeared completely while 60 (44%) had residual lesions. Of the patients with residual lesions, 9 (5 in regimen I and 4 in regimenII) continued treatment for a further period of 3 months because their lesions showed minimal or no clearance. The residual lesions in the other patients continued to improve even after stopping treatment.

The main conclusions from this trial were:

a) Short course chemotherapy (SCC) with an intermittent 6 month regimen was found to be as effective as a daily 9 month regimen in pediatric pulmonary TB.

b) The mortality and drop out rates were very low.

c) The adverse reactions were negligible.

d) Radiological clearance at the end of therapy was similar in both nodal and parenchymal lesions and the improvement continued even after stopping the treatment.

There have been a few other studies of SCC in children (Table 3)[12]. The results of most have been similar with high sucess rates, low adverse reactions and low relapse rates. Therefore, the present recommendation would be to treat pulmonary tuberculosis in children with a 6 month regimen consisting of at least isoniazid, rifampicin and pyrazinamide in the initial (2 months) intensive phase followed by 2 drugs for the remaining 4 months (2 HRZ / 4 HR or 2 HRZ_3/4HR_3). The drugs may be given daily or intermittently. However, in the presence of extensive parenchymal lesions or a child who is seriously ill, it would be advisable to add a 4th drug (ethambutol or streptomycin) to the intensive phase. The ATS and CDC both recommend the addition of a 4th drug (usaually ethambutol) to the intensive phase. The ATS and CDC both recommend the addition of a 4th drug (usually ethambutol) to the initial regimen if the risk of drug resistance is high (greater than 4% incidence in the community or the patient already has been treated for tuberculosis)13. In most parts of India, the prevalence of INH-resistance is about 20%, hence the use of 4 drugs initially is probably justified[14]. Children with minimal/ mild lesions or lymph node disease alone, however, can still be managed satisfactorily with the 3 drug regimen.

The Indian Academy of Pediatrics Working Group arrived at a consensus on the treatment of childhood tuberculosis at a meeting in January 1997[15]. In their recommendations, tuberculosis is classified into five groups based on clinical types and severity. Of these, preventive therapy forms the first gropu and clinical disease is classified into the other 4 groups. The main recommendations are outlined below:

1. Primary Complex, pleural effusion and isolated lymphadenitis may be treated with 2HRZ/ 4HR.
2. Progressive pulmonary disease and multiple lymphadenitis should be treated with 2 HRZE / 4 HR.
3. Severe forms of tuberculosis like miliary / disseminated disease, osteoarticular abdominal, pericardial or genitourinary disease with 2 HRZE / 7 HRE.
4. Neuro tuberculosis with 2 HRZE/ 10 HRE.

TABLE 3 : Results of Six - Month Treatment Regimens for Tuberculosis

Author, Country and Year	Diagnostic Criteria	No. of Children	Regimen	Results
Ibanez and Ross[8] Chile, 1980	Smear and culture Positive pulm. TB Culture positive pulm. TB	15	2 SHRZ /4SHZ_2	1 failure, 0 relapses
		39	2 HRZ / 4HZ_2	0 failures 0 relapses
Varudkar[9] India, 1985	Clinical and bacteriological	100	2 HRE /4 HE	0 failures
		40	2 HZE/ 4 HE	0 relapses
		45	6 HRE_3	
Biddulph[10] New Guinea, 1990	Clinical and bacteriological	639	2 SHRZ /4 HR_2	12 (2%) died 7 (1%) relapses 5/ 7 relapses in poorly complaint patients.
Kumar et al[11] India, 1990	Clinical and bacteriological	37	2 HRZ2 /4 HR_2	2 deaths not related to TB
		39	2 HRZ/ 4 HR_2	0 relapses
		45		
Ramachandran et al India, 1998	Clinical, radiological and bacteriological	68	9 HR	3(2%) died 0 failures
		69	2 HRZ_3/ 4 HR_2	3 relapses

Table 4 lists the commonly used drugs along with their dosages,mechanisms of action and adverse reactions.

Extra Pulmonary Tuberculosis

Controlled trials for various forms of extra pulmonary tuberculosis in children are rare. Several of the 6-month 3-drug trials in children included extra pulmonary cases. Most non-life threatening forms of extra pulmonary TB in children respond well to a 9 month course of isoniazid and rifampicin or to a 6 month regimen including isoniazid, rifampicin and pyrazinamide. A trial conducted by TRC on lymph node TB in children showed that a short course fully supervised intermittent regimen ($2SHRZ_3/4SH_2$) was successful[16]. Clinical response was favourable in most patients at the end of treatment and only 3% required re0treatment for TB, after 36 months of follow up. However, 30% of patiens had residual nodes> 10mm diameter at the end of treatment which regressed subsequently without further treatment. Appearance of new nodes, sinuses and abscesses and enlargement of existing nodes was observed both during treatment and follow up.

Tuberculous meningitis (TBM) usually is not included in trials of extra pulmonary tuberculosis because

TABLE 4 : Commonly used Drugs for the Treatment of Tuberculosis

Drug	Dosage forms	Dose (mg/kg) Daily	Dose (mg/kg) Thrice Weekly	Mechanism of action	Adverse reactions
Isoniazid	Tablets 100 mg 300 mg Syrup 100 mg / 5ml	5	10-15	Bactericidal, exact mechanism not known. Damages cell membrane.	GI, psychosis, allergic reaction, peripheral neuropathy, hepatitis, lupus
Rifampicin	Capsules 150 mg 300 mg 450 mg 600 mg Syrup 100 mg / 5ml	10	10	Inhibits DNA dependant RNA polymerase Bactericidal	Hepatotoxicity, GI allergic reaction, renal impairment Intermittment-flu syndrome, purpura.
Pyrazinamide	Tablets 250 mg 500 mg 750 mg 1 g 300 mg disp tap Syrup 250 mg / 5ml	20 - 30	35 - 50	Bactericidal, exact mechanism not known. Sterilising effect. Little effect when used beyond 2 months	Arthralgia, hyperuricemia, gastrointestinal, allergic reaction, hepatotoxicity.
Ethambutol	Tablets 200 mg 400 mg 600 mg 800 mg 1 g	15 - 20	25 - 35	Bacteriostatic. Acts mainly against rapidly multiplying organisms	Optic neuritis, colour blindness, gastro intestinal, allergic reaction
Streptomycin (i.m. admin.)	Vials 0.75 g 1.0 g	20	20	Bactericidal in higher concentrations. In meningitis, therapeutic concentrations are achieved in CSF.	Hypersensitivity reactions, vestibular dyfunction, optic neuritis, deafness, renal damage.

of its serious nature and low incidence. A trial conducted by TRC on 180 patients with TBM tried 3 different regimens, each for 12 months[17].

i) 2SHR/4S_2EH/6EH
ii) 2SHRZ / 10EH
iii) 2R_2SHZ / 10EH

The response to treatment was similar with the 3 regimens. There was a clear association between the stage on admission and tuberculosis deaths, the mortality being 9% for stage I patients, 25% for stage II and 73% for stage III.

A study from Thailand showed that a 6-month regimen including pyrazinamide (6SHRZ) for serious TBM led to fewer deaths and better outcomes than did longer regimens that did not contain pyrazinamide[18]. Donald et al treated 95 children with tuberculous meningitis with an intensive 6-month short course regimen consisting of isoniazid rifampicin, ethionamide (20mg/kg) and pyrazinamide (40 mg/kg). The mortality was 26% in stage III and 6% in stage II disease. Eighteen children (20%) developed a mildly elevated serum bilirubin concentration during the first month of treatment and in 5 the drugs had to be temporarily subtituted with streptomycin and ethambutol[19]. Currently, most centres treat children with TBM, initially with 4 drugs (isoniazid, rifampicin, pyrazinamide and ethambutol or streptomycin). The pyrazinamide and 4th drug are stopped after 2 months and isoniazid and rifampicin are continued for a total of 9 to 12 months. Intensive initial therapy may be important to minimize neurologic sequealae. However, the most important factor that determines outcome in TBM is the stage of disease at which the patient is brought to hospital.

Drug - Resistant Tuberculosis in Children

The incidence of drug - resistant tuberculosis is increasing in India mainly due to poor treatment adherence by the patient and poor management by physicians.Initial drug resistance to isoniazid is reported to be in the range of 20 to 25% and for rifampicin, range is 2 - 3%[14]. These rates are much higherin patients who have taken prior, irregular treatment. Patterns of drug resistance in children tend to mirror those found in adult patients in the population. As it is difficult to culture *M. tuberculosis* from children with TB the clue to drug resistance usually comes from the adult contact. Drug resistant tuberculosis should be suspected inthe following circumstances :

i) The child is in contact with a known case of drug-resistant tuberculosis.
ii) Child's adult contact has been on chronic irregular treatment and continues to be sputum positive.
iii) Adult contact died after taking irregular treatment.
iv) Child showed some intial improvement to anti-tuberculosis treatment but then deteriorated (clinically and radiologically)

The only definitive way of diagnosing drug resistance is by isolating the strain and assessing its susceptibility pattern which takes months. New rapid culture and susceptibility tests namely BACTEC, mycobacterial growth indicator tuber (MGIT) and luciferase reporter assay have been developed which offer the possibility of early sensitivity results. In addition, advanced molecular biologic techniques like polymerase chain reaction, DNA fingerprinting and SSCP (single) strand conformation polymorphism) are rapid and help by identifying the mutations that cause drug resistance. However, these are not available for routine use.

Therapy for drug-resistant tuberculosis is successful when at least two bactericidal drugs to which the infecting strain of *M. tuberculosis* is susceptible are given. Exact treatment regimens can be tailored to the specific pattern of drug resistance, if known. If not, at least 3 drugs to which the patient has not been exposed earlier should be given[20]. Resistance to isoniazid or streptomycin alone can usually be managed with any of the standard 4-drug regimens with good results. However, when resistance to both isoniazid and rifampicin is present (MDRTB), management is more complicated and requires the use of second line drugs. Duration of therapy is usually extended to 9-12 months if either isoniazid or rifampicin can be used and to at least 18-24 months if resistance to both drugs is present. Occassionally, surgical resection of a diseased lung or lobe is required.

Corticosteroids

Corticosteroids are most beneficial in situations where the host inflammatory reaction contributes to tissue damage or impairs function. They should never be used except under cover of effective anti-tuberculosis drugs. Steroids are a useful addition to anti-tuberculosis drugs in the following situations[21].

1. In patients with tuberculous meningitis and raised intracranial pressure. They help to reduce vasculitis, inflammation and intracranial pressure and reduce long-term neurologic sequelae[22].
2. In patients with pericardial effusion in whom tamponade is imminent.
3. In patients with pleural effusion in whom there is mediastinal shift with acute respiratory embrassment.
4. In patients with miliary tuberculosis if the

inflammatory reaction is severe enough to produce cyanosis.

5. In patients with enlarged mediastinal nodes causing respiratory difficulty or a severe collapse-consolidation.

The dosage of steroids should be in the anti-inflammatory range, i.e. prednisolone 1-2 mg / kg/ day for 4 to 6 weeks with gradual withdrawal.

Conclusion

Short course chemotherapy of tuberculosis is reliable, efficacious as well as cost-effective 23,24. Wherever feasible, chemotherapy should be given under direct supervision (DOTS) as this will ensure cure in the majority of cases[25].

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