Review Article: Update Management of Tuberculosis

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Tuberculosis is a disease of great antiquity and evidence of bone disease has been found in the Egyptian and pre Columbian mummies. Until specific antituberculosis drugs became available treatment of tuberculosis was empirical. The diagnosis was a lifetime sentence. Bed rest, plenty of food, fresh air and sunshine in sanatoria built on hillsides used to be the only ways of treating tuberculosis[1,2].

Later collapse therapy was introduced in which artificial pneumothorax and artificial pneumoperitoneum were widely used procedures. This was supplemented by phrenic crush. Probably the disease was arrested by the closure of cavity, and hence reducing bacterial multiplication. With the improvement in anaesthesia, thoracoplasty (in which resection of most of the upper 5-8 ribs to form a flap and collapse the lung was carried out) and plombage (creation of an extrapleural space and filling it with supposedly inert material) were introduced for the treatment of pulmonary tuberculosis. This surgical era ended by 1960.

Chemotherapy for tuberculosis started after streptomycin(S) was discovered in the 1940s. Clinical and radiological improvement within 2-3 months was soon followed by deterioration due to drug resistance[3]. Later on it was found that by combining INH (H) and para amino salicylic acid (PAS) with streptomycin prevents drug resistance[4]. Standard chemotherapy of the 1960s and early 1970s was effective but unpleasant. In the initial phase INH, PAS and streptomycin were given for three months followed by a continuation phase of 15 months of INH and PAS.

Bacteriology - Mycobacterium Tuberculosis

Mycobacterium Tuberculosis is a strict aerobe. It grows best at pH 7.4. It is readily killed by heat and ultraviolet radiation. It divides every 16-20 hours. There may be 1:100,000 or more of single drug resistant mutants in a newly diagnosed patient. Many more secondary mutants may be present in an inadequately treated patient. An accepted hypothesis states that tubercle bacilli may exist in tuberculous patients in 4 pools.

Population one (P1): Extracellular pool in cavities. These are metabolically active. These are in large number.

Population Two (P2): These exist in extracellular close caseous lesions. These are small in number and divide more slowly or intermittently.

Population Three (P3): These are within the macrophages intracellular organisms. These are relatively metabolically inactive and small in number. Their turn over is slow and can persist for long periods of time.

Population Four (P4): Dormant bacilli. They may live for years and multiply after years when immune system is weakened.

Drugs Used In The Treatment

Primary Drugs:-

Mostly used Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E), and Streptomycin (S).

Second Line Drugs:-

Thiacetazone, Para amino salicylic acid, Ethionamide, Prothionamide, Cycloserine, Kanamycin, Capreomycin, Viomycin.

Newer Drugs:-

Flourinated quinolones, Ofloxacin, Ciprofloxacin, Ansamycin, Cyclo-rifamycin Rifabutane, Clarithromycin, Erythromycin.

Mechanism And Site Of Action Of Commonly Used Drugs

Rifampicin, Isoniazid, Pyrazinamide and Streptomycin are bactericidal drugs. Ethambutol is mainly bacteriostatic drug but when given in the dose of 50mg/kg in intermittent therapy it becomes bactericidal.

Rifampicin(R)

It kills all the three bacterial populations except dormant bacilli (P1, P2, P3).

Isoniazide (H).

It is active against intracellular and extra cellular organisms (P1 and P3).

Pyrazinamide (Z)

It is effective against intracellular organisms and is a sterilizing drug. It is most effective within the first 2 months of therapy. It is effective in acidic pH.

Streptomycin (S)

This drug is effective against extra cellular organisms (P1 and P2).

Ethambutol (E)
It is effective against all the populations. It prevents emergence of drug resistance.
Drugs are used in combination to prevent drug resistance.

Current Standard Chemotherapy[1,5,6]

Initial Phase: (2 Months) Isoniazid, Rifampicin and Pyrazinamide.
There is difference of opinion between UK and USA whether the fourth drug in the form of Ethambutol or Streptomycin be used in the initial phase [1]. Some how current consenses is that if there is no drug resistance, three drugs HRZ should be given only. Suggested doses for adults in the initial treatment are the following.

Isoniazid:- 5mg/kg body weight, 200mg (patients weighing < 40kg) or 300mg (patients weighing > 40 kg) once daily.
Rifampicin:- 450mg (patients weighing < 50kg) or 600mg (patients weighing > 50kg) once daily.
Pyrazinamide:- 1.5gm (patients weighing < 50kg) or 2.0gm (patients weighing 50 to 70 kg) or 2.5gm (patients weighing > 70kg) once daily.
Continuation phase (4 months):
PZA is withdrawn while Rifampicin and INH are continued in the same dosage for another four months (Table 1 and 2)

Table - 1 Dose regimens of the main Antituberculosis drugs

Drug	Daily dose regimen			Intermittent dose regimen		
	Adults and children (mg/kg)	Adults(Weight)	Dose	Adults and children(mg/kg)	Adults(Weight)	Dose
Isoniazid	5	-	300mg	15 3times/week	-	-
Rifampicin	10	50 Kgs	450mgs	15	-	600-900mg
		50 Kgs	600mgs	3 Times/Week		
Streptomycin	15-20	50 Kgs	750mgs	15-20	50Kgs	750mgs
		50 Kgs	1.0gm	3 Times/Week	50 Kgs	1.0gm
Pyrazinamide	25-30	50Kgs	1.5gms	50	50Kgs	2.0gms
				3 Times/Week	50 Kgs	2.5gms
		50 Kgs	2.0gms	75	50Kgs	3.0gms
				3 Times/Week	50 Kgs	3.5gms
Ethambutol	25 for 2 months then 15	-	-	30 3 Times/Week	-	-
				45 3 Times/Week		
Thiacetazone	4 (for Children)	-	-		-	-

Table - 2 Second-line Anticuberculosis drugs

Drug	Daily Dose	Adverse effects
Ethionamide	500-1000mgs p.o (In divided doses if necessary for tolerance)	Gastrointestinal intolerance, hapatitis, endocrine disturbances, hypersensitively
Cycloserine	250-750 mg p.o (in divided doses) (adjust for renal impairment	Neurological and psychiatric disturbances
Capreomycin	15 mg/kg i.m.	Hearing loss, vestibular
Amikacin/Kanamycin	5 days a week (adjust for renal impairment)	damage, renal toxicity electrolyte disturbances
Para-aminosalicylic Acid (PAS)	10-20 g p.o. (in divided doses	Gastrointestinal intolerance, hepatitis, hypersensitivity
Ciprofloxacin/Ofloxacin	500-1000 mg o.d. p.o. 400-800 mg o.d. p.o.	Gastrointestinal intolerance, headache, restlessness, hypersensitivity, drug interactions
Clofazimine	100-300 mg o.d. p.o	Abdominal pain, skin discoloration (both dose related), photosensitivity

Multiple Drug resistance (MDR) (7)
It is defined as resistance to both isoniazid and rifampicin with or without the presence of resistance to another drug.
Risk factors for MDR are:

- Close contact with another MDR patient.
- Previous treatment if prolonged, or if there is selection of inadequate regimen or under dosing of the individual drugs.
- HIV infection.
- Country of origin. Asia, Africa, Latin America.
- Age. Younger children exposed to MDR patients.
- Intravenous drug abusers, homelessness.

Drug Resistance Status In Pakistan [8,9,10,11]
Drug resistance has always remained problem in Pakistan In 1967, 87% of the previously treated patients were resistant to one or more antitubercular drugs which decreased to 31.6% in 1989 [8]. Resistance to INH through out has been high. Primary drug resistance has varied from 24.5% (1976-80), to 29% in 1995. While secondary drug resistance to INH has remained high at different

centers, 57% (1976-80), 53% (1981-82), 36% (1983-87), 52% (1993), 53% (1995). [9,10,11]

Table - 3 Adverse reactions to the main Antituberculosis drugs

Drug	Common reactions	Less common reactions
Isoniazid	None usual	Hepatitis Cutaneous hypersensitivity Peripheral neuropathy
Rifampacin	None usual	Hepatitis Cutaneous reactions Gastrointestinal reactions Thrombocytopenic purpura Febrile reactions 'Flu syndrome'
Pyrazinamide	Anorexia Nausea Flushing	Hepatitis Vomiting Arthralgia Cutaneous hypersensitivity
Ethambutal	None usual	Retrobulbar neuritis Arthralgia
Streptomycin	Cutaneous hypersensitivity Giddiness Numbness Tinnitus	Vertrigo Ataxia Deafness
Thiacetazone	Gastroinstestinal Cutaneous hypersensitivity Vertigo Conjuctivitis	Hepatitis reactions Erythema multiforme Exfoliative dermatitis Haemolytic aneamia

Resistance to other primary drugs is fortunately still low, rifampicin 5.4%, pyrazinamid 4%, ethambutol 4% [10]. Keeping in view these findings, virtually every second or 3rd patient has resistance to INH. While prescribing medicines, where culture/sensitivity facilities for mycobacterium tuberculosis are not available, this has to be kept in mind. For this reason in Pakistan in the initial phase four drugs HREZ(S) has to be given as recommended by WHO and TB Control Board of Pakistan[5,6]. In the initial phase due to this drug resistance the drugs have to be given for three months. In the continuation phase ethambutol has to be added in the dose of 15mg/kg body weight, otherwise patients may develop drug resistance and may become incurable. Some how in those individuals where culture and sensitivity of mycobacterium is available and the organisms are sensitive to both INH and rifampicin, in the continuation phase both of these drugs will be given.

Duration Of Therapy

Treatment duration has to be based on radiological stabilization. It takes minimum of 3-4 months for radiological clearance[1,12]. After radiological stabilization has been attained, anti tuberculosis drugs should be given for another six months even if the duration is prolonged[12].

Usually when the patients present initially in the under developed countries the disease is advanced radiologically[13,14]. In such individuals radiological stabilization may not be attained until 12 months after the start of the treatment [1]. For this reason it is recommended that in the continuation phase 3 drugs (HRE) be given and the duration of therapy should be from 9-12 months. This is also based on the observation that short course chemotherapy study in Pakistan was followed by a relapse rate of 10% to 19% within 18 months[15]

Duration of therapy for extrapulmorany tuberculosis, including tuberculous pleural effusion should not be less than one year.

Drug Therapy In Small Children

Ethambutol is not recommended because children cannot tell the vision problem. INH should be given 5mg/kg body weight and Rifampicin 10mg/kg body weight. PZA is also given.

Compliance:-

Compliance on the part of patient is one of the major factors which decides cure of the disease. About one third of the patients can be expected to be non compliant. Default rates of 40-60% are common [12,16,17]

Compliance can be improved either by dedicated services and proper advice to the patients or by directly observed therapy **DOTS** (Short Course)[18]

Non Compliance on the part of the doctors and health workers has to be checked. Doctors in the community write inadequate regimens, under dose the patients which leads to treatment failure[19,20]

Corticosteroids And Tuberculosis

They can be tried in any patient in whom systemic symptoms or local pressure effects are a problem, provided that the patient is taking anti tuberculous drugs to which the organisms are sensitive[21]. They may be useful in miliary and meningeal tuberculosis, pleural effusion, pericaidral effusion and ascities. If rifampicin is a companion drug the dose is 1mg/kg body weight. When refampicin is not included, the dose is 0.5 mg/kg body weight.

Interactions And Special Problems

Isoniazid.

It Interacts with Carbamazepine (Tegretol) and Phenytoin. The dosage of these drugs should be reduced when used concomitantly.

Rifampicin:

It induces hepatic microsomal enzymes and hence reduces the serum half lives and clinical efficacy of many drugs. The drugs affected include oral hypoglycemic agents, digoxin, anticonvulsants, sex harmones including

contraceptive pills, steroids and vitamin D.

Pyrazinamide:

It blocks renal excretion of uric acid and may precipitate acute gout. It also interferes with urine testing for ketones.

Streptomycin:

Avoid streptomycin in infants, young children and during pregnancy.

Treatment During Pregnancy

HRZE:

All are safe during pregnancy and treatment should not be delayed - Streptomycin should not be used. It may lead to fetal ototoxicity .

Treatment In Renal Failure:

Patients with chronic renal failure are ten times more prone to develop tuberculosis. INH is metabolized by the liver and excreted through kidneys. Both INH and its metabolite are dialyzable. Dose is 5mg/kg body weight and be given 2-3 times in a week. If the patient is on dialysis then it should be given after the dialysis.

Another school of thought recommends administration of INH in the normal dose on daily basis along with rifampicin and pyrazinamide[1].

The dose of ethambutol be given in the normal dose after the dialysis 2-3 times per week. While patient should have regular check up for color vision and visual acuity. If patient is not on dialysis then 8-10mg/kg body weight can be given.

Streptomycin and ethambutol can also be given 4-6 hours, before dialysis, giving time for the therapeutic effect before removal.

Treatment in Liver Disease

In tuberculosis, of the Liver, the hepatic dysfunction improves with treatment. INH or rifampicin are given in the normal way. In cirrhosis the dosage is decreased.

Drug Resistant Tuberculosis

If the patient has not previously used INH or rifampicin, then two new drugs be added, one of them being INH or rifampicin. If there is resistance to both of these drugs, then at least 4 drugs or as many as possible be added. For our country we can use PAS, ofloxacin, thiacetazone, Streptomycin if previously has not been used. Even if there is resistance to INH, it should be continued as it has always some beneficial effect.

Relapse Of Tuberculosis

Relapse after successful therapy should be less than one percent. Because these patients present with symptoms and are almost never found by routine X-rays, patients may be discharged from follow up at the completion of therapy[12]. Faced with relapse in a previously treated patient a major concern should be the possibility of drug resistance. The resistance studies of organism should be obtained from a reference laboratory. In one third of patients who relapse after adequate therapy, the relapse is caused by drug resistant organisms. Some how if the patient was non complaint or the previous regimen was inadequate, then the likelihood of drug resistance is two chances in three. Therapy for the presumed drug resistance should be instituted while waiting for the sensitivity report of organism accordingly.

HIV Infection

In Pakistan HIV infection is uncommon. Faced with the problem, the regimen is same as recommended earlier. Higher rates of relapse are found among those with HIV infection so that, more prolonged treatment may be required.

Lymph Node Disease

Tuberculosis of the lymph nodes is a common problem. Treatment regimen is the same as for pulmonary tuberculosis [2HRZ/4HR][5,6] or [3HRZE/9HRE] as discussed before. Lymph nodes may enlarge or discharge during or after therapy. This is normally transient. Where enlarged lymph nodes exist and the diagnosis of tuberculosis is not in doubt, steroids may be of benefit. Rarely total excision of all enlarged or suppurating glands may be necessary.

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