Chemotherapy of osteoarticular tuberculosis

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ABSTRACT

Tuberculosis (TB) of the bones and joints is rampant in India with the dorsolumbar spine as the most common site of osseous involvement. For diagnosis, clinical suspicion needs to be confirmed through appropriate laboratory and imaging investigations, and increasingly nowadays, nucleic acid amplification techniques. Chemotherapy remains the cornerstone of management complemented by rest, nutritional support and splinting, as necessary. Operative intervention is required if response to chemotherapy is unsatisfactory and for spinal stabilization. The drugs and regimens are fundamentally similar to those for pulmonary TB. However, there is lack of consensus on the appropriate duration of treatment. The prevailing practice of extending treatment till radiological evidence of healing is complete, may be unnecessary in view of recent reports that 6-9 months of therapy is sufficient for the majority of cases. Relapse rates are not drastically improved by extending treatment to 12 months or even longer, except perhaps in pediatric cases. However, prolonged treatment may be required if surgical debridement is indicated but cannot be done. Multidrug-resistant TB should be suspected if disease activity shows no signs of abating after 4-6 months of uninterrupted therapy. These cases are therapeutically challenging and will require second line or experimental antiTB drugs, supported by resistance testing where feasible. Coexistent HIV/AIDS may also necessitate prolonged treatment. Interactions between first line antiTB drugs and antiretroviral medication can complicate matters. Close monitoring is essential in all cases, with dechallenge and cautious reinstitution of drugs in the event of toxicity. While awaiting the arrival of long overdue new antiTB medication, existing drugs and regimens must be used in an informed manner with emphasis on patient compliance.

KEY WORDS: Bone tuberculosis, caries spine, antitubercular drugs, MDR-TB

Tuberculosis (TB) remains one of the major killer infections worldwide. About 2.2 million new cases of TB occur every year. As per the World Health organization (WHO) 1999 report on global tuberculosis control, South East Asia accounts for approximately 40% - two out of five cases of TB in the world. Within South-East Asia, more than 95% of cases are found in India, Indonesia, Bangladesh, Thailand, and Myanmar. It is estimated that there are about 60 lakh active pulmonary TB cases in India and annual death rate due to TB is about 500,000. Of the various secondary forms of the disease, TB of the bones and joints is a common orthopedic problem in India and in many other developing countries. Indeed, after decades of consistent decline in incidence, a resurgence of TB is occurring in developed countries, partly linked to the prevalence of human immunodeficiency virus (HIV) infection, and this includes osteoarticular TB.[1,2]

Sites of infection and etiopathology

In India, the incidence of osteoarticular TB appears to be higher in children, adolescents and young adults, than in the elderly.

The spine is probably the most common site of osseous involvement,[2] followed by the hip and knee.[3] Spinal disease is found in about 1% of all TB cases.[4] In the spine, the usual involvement is vertebral bodies and intervertebral disks in the dorsolumbar regions. Less commonly the cervical vertebrae,[5] craniovertebral junction,[6,7] sacrum[8] and sacroiliac joints may be involved. Atypical presentations of spinal TB, such as intradural spinal TB, may occur and may be misdiagnosed as neoplasm without a high index of clinical suspicion.[9] Other sites of involvement reported in the literature are ribs, pelvic bones, small bones of the foot,[10] long bones,[11] sternoclavicu-

lar joint,[12] sternum,[13] calvarial bones[14] and bursae.[15,16]

Multifocal skeletal TB is an uncommon entity but has been reported from India[17] and other countries.[18-20]

The human subtype of *Mycobacterium tuberculosis* is almost invariably the causative organism in India. The skeletal focus is always secondary to another focus, usually in the lungs or in the mediastinal lymph nodes. The spread is via the blood stream and the infection settles in bone usually near the epiphyseal cartilage in proximity to the synovial membrane.

The 'tubercle' is the microscopic pathological lesion with central necrosis surrounded by epithelioid cells, giant cells and mononuclear cells. Two types of microscopic lesions have been described – (a) the caseating exudative type where caseating necrosis and cold abscess formation predominate, and (b) the proliferating type where cellular proliferation predominates with minimal caseation. The tuberculous granuloma is the extreme form of this type.

In children the lesion is commonly of the caseating type with rapid and extensive destruction of bone and cartilage, whereas in adults the proliferating type with less bone destruction is usual.

Clinical features and investigations

Clinically the onset of TB in any bone or joint is insidious. Constitutional symptoms like low-grade fever, anorexia and weight loss usually precede localizing symptoms and signs such as pain, tenderness and swelling of the affected part. Other local features may be muscle spasms and discharging sinuses. There may be additional features referable to the primary site of involvement, such as the lungs, but these may be minor or even absent.

In addition to the usual array of diagnostic tests for TB, advanced imaging modalities such as computerized tomography (CT),[6,21] magnetic resonance imaging (MRI)[6,21,22] and bone scans[19] can be very helpful. Indeed, MRI, with gadolinium enhancement if necessary, is considered an ideal modality for making the diagnosis, demonstrating the extent of disease, identifying complications and assessing response to treatment.[2] It provides better delineation of vertebral lesions with adjoining soft tissue involvement and nerve compressions, than CT. The imaging modalities can guide aspiration cytology and the tissue aspirates can be subjected to smear examination and culture.[21,23] Biopsy of the bony lesion, synovium or soft tissue masses may be needed to clear up diagnostic confusion.[24,25]

Molecular diagnostic techniques like the polymerase chain reaction (PCR)[26] and other forms of nucleic acid amplification tests are being applied nowadays to tissue samples. Although DNA-based PCR can be quite sensitive, it may not distinguish between viable and non-viable bacilli. Messenger-RNA based reversed transcription PCR may be more specific in this regard.

Testing for HIV may also be needed if the clinical circumstances so dictate.

General principles of management

If osteoarticular TB is diagnosed and treated at an early stage, the large majority of patients are expected to achieve healing with near normal function. The mainstay of treatment is multidrug antitubercular chemotherapy and active or assisted non-weightbearing exercises of the involved joint throughout the period of healing.[27] An initial period of rest is to be followed by supervised gradual mobilization. In caries spine, various types of spinal support in the form of collars, braces and corsets, may need to be used. Adequate nutritional support is also essential, as in all forms of TB. The goals of treatment are to:[28]

- Contain and eradicate the infection
- Relieve pain
- Preserve and restore bone and joint function
- Preserve and restore neurological function

An initial period of hospitalization enables supervised treatment. Continuation treatment can be on a domiciliary basis. However, it is always advisable to follow the principle of directly observed treatment wherever feasible. Intermittent (thrice weekly) regimens have not received adequate trials in skeletal TB. Intermittent regimens, if resorted to for logistical reasons, should be directly supervised.

Operative intervention is required when the patient is not responding to an adequate trial of chemotherapy (e.g. synovectomy and debridement); if the therapeutic outcome is not satisfactory (e.g. excisional arthroplasty of the hip or the elbow); or the healed status has resulted in a painful ankylosis (e.g. arthrodesis for the ankle, the wrist, or the knee). It is also required for an unstable spine. Joint replacement can be considered only if the disease process has remained quiescent for at least a year or more. Multidrug resistance should be suspected if the disease activity does not subside after 4 to 6 months of uninterrupted combination chemotherapy.[27] Such patients (an estimated 5-10%) or those unable to tolerate first-line antitubercular drugs require specialist intervention.

Principles of antiTB chemotherapy

As in other forms of TB, multidrug therapy is the norm in bone and joint TB. *Mycobacterium tuberculosis* is a complex pathogen. It produces at least 250 distinct enzymes compared to only 50 for *Escherichia coli*. Mutations capable of conferring drug resistance occur frequently. Multiple drugs used in combination will reduce the possibility of selecting drug-resistant strains and hence chances of relapse. Among the first-line drugs, pyrazinamide, being active in an acidic environment, takes care of the persistent intracellular bacilli.

In general, regimens that are adequate for treating pulmonary TB are also effective for treating extrapulmonary TB. The problem lies in deciding on the appropriate duration of treatment for various osteoarticular sites and in selecting appropriate drugs when resistance to the first-line drugs is encountered. The general dosage recommendations for first-line antiTB drugs are presented in Table 1.

For the purpose of rationalizing and initiating treatment, WHO categorizes TB patients into four categories depending upon clinical severity and priority.[29] Treatment in a category is divided into initial, intensive, and subsequent continuation phases. The intensive phase comprises maximum number of drugs given daily (preferably under supervision) and is intended

Table 1

Dosage recommendations for the treatment of TB in children (less than 12 years) and adults

Drug	Dose in mg/kg (maximum dosage)					
	Daily regimens		Twice weekly regimens		Thrice weekly regimens	
	Child	Adult	Child	Adult	Child	Adult
Isoniazid (INH)	10-20 (300 mg)	5 (300 mg)	20-40 (900 mg)	15 (900 mg)	20-40 (900 mg)	15 (900 mg)
Rifampin (RIF)	10-20 (600 mg)	10 (600 mg)	10-20 (600 mg)	10 (600 mg)	10-20 (600 mg)	10 (600 mg)
Pyrazinamide (PZA)	15-30 (2 g)	15-30 (2 g)	50-70 (4 g)	50-70 (4 g)	50-70 (3 g)	50-70 (3 g)
Ethambutol (EMB)	15-25	15-25	50	50	25-30	25-30
Streptomycin (SM)	20-40 (1 g)	12-18(1 g)	25-30 (1.5 g)	25-30 (1.5 g)	25-30 (1.5 g)	25-30 (1.5 g)

• Doses based on weight must be adjusted as the patient's weight changes. • All patients prescribed an intermittent regimen should be given directly observed therapy. • Pyrazinamide and streptomycin should not be used to treat pregnant women. There is not enough information about how PZA affects the fetus. SM has been shown to have harmful effects on the fetus. • Ethambutol is not recommended for children who are too young to be monitored for changes in their vision. However, it should be considered for all children who have TB that is resistant to other drugs but susceptible to EMB. • Daily dose of streptomycin should not exceed 0.75 g for patients over 50 years of age. • When isoniazid and rifampicin are given daily in the continuation phase, the doses are the same as in the initial phase. • The World Health Organization does not recommend twice weekly regimens because of the greater risk of treatment failure from missed doses.

to bring about rapid clinical amelioration and achieve non-infectivity. Treatment is then continued with 2 or 3 drugs given daily or intermittently to eliminate residual bacilli and prevent relapse. These regimens are presented in Table 2. It may be noted that apart from newly diagnosed TB spine patients being placed in Category I, there is no specific categorization of other sites of osteoarticular involvement.

Tables 3 and 4 summarize the characteristics of standard first-line and current second-line antiTB drugs.

Duration of chemotherapy

Although the first-line regimens are now standardized, the problem lies in deciding upon the appropriate duration of chemotherapy in osteoarticular TB. This is an area where there is no consensus. WHO categorizes caries spine as a severe form of extrapulmonary TB with new cases assigned to Category I. Therefore, by WHO criteria, all caries spine cases should be treated for a minimum of 6 months. Many surgeons in India prefer to continue treatment till there is adequate radiological evidence of healing, which can take much longer than 6 months. It is a moot point whether treatment really needs to be so long.

In various studies, the duration of therapy has varied widely – 6 months in sacral TB,[30] 12-18 months in afflictions of various spinal sites,[5,31,32] 12-18 months in TB of craniovertebral junction,[6,7] 14 -18 months in sternoclavicular joint involvement,[12] 12-20 months in TB affecting the talus,[33,34] etc. However, certain suggestions can be made from a perusal of the literature:

- The initial intensive phase drugs may need to be maintained into the continuation phases, in the same doses, particularly in the absence of surgical debridement.[35] Triple therapy regimens, with either pyrazinamide or ethambutol, with appropriate precautions to avoid drug-related toxicity, appear to achieve satisfactory results in caries spine.[31,36]
- The minimum duration of therapy should be 6 months. In a systematic review[36] of chemotherapeutic treatment for spinal TB, it was concluded that 6 months of therapy is probably sufficient for the majority of patients. Both 6 and 9-month treatment regimens appear to give acceptable relapse rates of within 2%.
- The United States Centers for Disease Control[37] recommend that for infants and children with miliary TB or bone and joint TB treatment should last at least 12 months. For adults with these forms of extrapulmonary TB, the patient's response to therapy should be monitored closely. If response is slow or inadequate, treatment may be prolonged on a case-by-case basis.
- Treatment would probably be needed to be prolonged in immunocompromised subjects[38] and in the absence of surgical debridement.

Treatment in HIV-positive individuals

The treatment regimens as outlined above are also effective in the presence of HIV infection. However, HIV-positive patients should be closely monitored and should be re-evaluated if response appears inadequate. Unfortunately, complex interactions between rifampicin and antiretroviral drugs may force withdrawal of conventional regimens. Rifabutin has been used as an alternative to rifampicin in such situations.

Treatment of MDR-TB

Multi-drug-resistant TB (MDR-TB) is defined as resistance to both isoniazid and rifampicin, with or without resistance to any other antituberculosis drugs. As already stated, resistance to multiple first-line antiTB drugs should be suspected if disease activity does not show signs of subsiding after 4-6 months of uninterrupted multidrug therapy.[27] Many crucial management issues in MDR-TB treatment remain unanswered and the existing primary literature consists almost entirely of retrospective cohort studies.[39,40] There are no standardized regimens or guidelines. Second-line and potential antitubercular drugs will have to be tried. If reliable laboratory facilities are available, drug susceptibility should be determined and treatment commenced with relevant second-line or experimental drugs. It has been suggested that four or five (at least three) antitubercular drugs, including the fluoroquinolones, must be included in the regimen and that, if needed, these drugs should be changed at the same time, not one by one.[41] Further, treatment with these drugs takes 2 years or longer, as opposed to 6 to 9 months with isoniazid-ri-

Table 2

WHO-recommended regimens for short-course multidrug chemotherapy of tuberculosis

Treatment category	*Disease status*	*Regimen*	
		Initial phase [Daily or 3 times per week]	*Continuation phase*
I	Freshly diagnosed smear-positive pulmonary TB or smear-negative pulmonary TB with extensive parenchymal involvement; new cases with severe forms of TB e.g. miliary TB, TB meningitis, tuberculous pericarditis, tuberculous peritonitis, intestinal TB, genitourinary TB, bilateral or extensive tuberculous pleurisy, spinal disease with neurological complications	2HRZE (HRZS) 2HRZE (HRZS) 2HRZE (HRZS)	4HR $4H_3R_3$ 6HE
II	Relapsed and treatment failure (smear-positive) cases or treatment after substantial interruption. These patients are at risk of developing MDR-TB and therefore should receive fully supervised intensive treatment for at least the first 3 months. If reliable laboratory facilities are available, a pretreatment sputum sample should be collected for culture and drug susceptibility testing. Patients who remain sputum-positive at the end of 3 months should continue to receive supervised therapy till sputum conversion is documented or till they are categorized as chronic cases. Smear-negative relapsed or treatment failure patients are to be managed by similar regimes.	2HRZES / 1 HRZE 2HRZES / 1 HRZE	5HRE $5H_3R_3E_3$
III	Freshly diagnosed smear-negative pulmonary TB with limited parenchymal involvement (pulmonary disease is almost always smear-negative in children; adolescents with primary TB may present with a smear-negative small parenchymal lung lesion or a small pleural effusion); non-category I extrapulmonary TB.	2HRZ 2HRZ 2HRZ	4HR $4H_3R_3$ 6HE
IV	Chronic cases – still smear-positive after supervised retreatment. They are likely to be suffering from MDR-TB and management is highly problematic - even with optimal retreatment no more than 50% will be cured.	NO DEFINITE REGIMEN RECOMMENDED.If reliable laboratory facilities are available drug susceptibility should be determined and treatment commenced with second-line or experimental drugs. Second line drugs are more expensive and toxic and treatment should therefore be supervised in a hospital. If resources are limited, such patients may be put on indefinite isoniazid treatment to keep the disease as much suppressed as possible and to reduce infectivity.	

• E = Ethambutol; H = Isoniazid; R = Rifampicin; S = Streptomycin; Z = Pyrazinamide. • The numerical prefix to a regime indicates the duration in months. • The subscript 3 denotes thrice weekly administration. • For Category I patients with serious forms of TB, like miliary TB, TB meningitis, spinal TB with neurological signs, some authorities recommend a 7-month continuation phase with daily isoniazid plus rifampicin (7HR).

fampicin-containing regimens.[42,43] However, studies have also reported reasonably satisfactory responses in shorter periods through regimens incorporating fluoroquinolones like ofloxacin and sparfloxacin.[44-46]

In general, second-line drugs are more expensive and toxic and treatment, at least in the initial part, should therefore be supervised in a hospital. Therapeutic drug monitoring has been employed.[47] Immunomodulatory therapy with levamisole and *Mycobacterium vaccae* has been disappointing. Other immunomodulators, such as recombinant human interleukin-2 and recombinant interferon-alpha2b, are being tried.[48,49] Unfortunately, no separate guidelines exist for managing multidrug-resistant osteoarticular TB.

In the event of toxicity[50]

As evident from Tables 3 and 4, a number of adverse drug reactions are possible from the use of antiTB drugs. If a reaction occurs but its nature does not single out a particular drug, cautious rechallenge is the only way to identify the offending drug or drugs; starting with the one least likely to be responsible for the symptoms. Rechallenge is started with one drug in a small challenge dose, which is increased stepwise to full therapeutic dose over a few days. This procedure is repeated, with one drug added at a time. The step-up should be even more gradual if the initial reaction is severe. Needless to say that if the reaction recurs, the offending drug has been identified, it must be withdrawn. Combination tablets are not suitable for this purpose and rechallenge should not be attempted if the patient is uncooperative or if a close watch is not possible. Any reaction to thioacetazone, even if it is simple itching, should prompt immediate withdrawal of the drug and rechallenge should not be attempted with this drug. Treatment may be continued by replacing the offending drug with a suitable alternative, or with a reduced number of drugs if none is suitable. Specialist advice may be sought. It is also noteworthy that the resumed regimen is considered to be a new start to the treatment. This prolongs the duration of therapy but, on the other hand, reduces the chance of recurrence.

Most antiTB drugs, particularly pyrazinamide, rifampicin, and isoniazid, can cause hepatotoxicity, while ethambutol is

Table 3

First-line drugs for tuberculosis

Drug (Route)	*Activity*	*CSF penetr-ation*	*Relative activity*	*Molecular target and mechanism*	*Resistance genes and mutation rate*	*Adverse drug reactions*	*Comments*
Isoniazid (oral)	Bacteriostatic for resting bacilli but kills actively dividing ones. Active against ICB, ECB, BCL	Good	++++	Inhibits cell wall mycolic acid synthesis. Metabolized to isonicotinic acid, which is incorporated into NAD+ to form a false form of this cofactor.	inhA, katg 10^{-8}	GI disturbances; hepatotoxicity - asymptomatic elevation of liver enzymes to fulminant hepatic failure (specially over age 35); hypersensitivity reactions - fever, rashes including purpura; ANA-positive vasculitis; drug -induced lupus, agranulocytosis; pellagra; neurotoxicity - peripheral neuropathy (common), optic neuritis, convulsions, psychoses; gynecomastia	Use with pyridoxine 10 mg daily. Monitor liver function. Remarkably selective for *Mycobacterium* spp. Also used against *Mycobacterium kansasii*. Resistance develops due to failure of penetration into bacillus; no cross-resistance with other anti-TB drugs except structurally related ethionamide.
Rifampicin (oral)	Bactericidal Active against ICB, ECB, BCL	Good	++++	Inhibits DNA-dependent RNA polymerase	rpoB 10^{-10}	GI disturbances including pseudomembranous colitis; hepatotoxicity (transient elevation of liver enzymes common); flu-like syndrome; shortness of breath; collapse and shock; thrombocytopenic purpura; hemolytic anemia and acute renal failure; hypersensitivity reactions; orange discoloration of body fluids and contact lenses; risk of hormonal contraceptive failure	Use on empty stomach. Monitor liver function and blood counts. Active against various *Mycobacterium* spp. *including M. leprae*; also used in resistant staphylococcal infections (combination), brucellosis (with doxycycline), Legionnaire's disease, prophylaxis of meningococcal meningitis *and Haemophilus influenzae* Type b infections. Resistance develops if used alone
Pyrazinamide (oral)	Bactericidal Active against ICB	Very good	+++	?Activity appears to be dependent on metabolism by a deamidase to pyrazinoic acid. Mechanism of action unknown	pncA 10^{-3}	GI disturbances; hepatotoxicity - asymptomatic elevation of liver enzymes to hepatic necrosis; urticaria, fever, arthralgia; sideroblastic anemia; hyperuricemia	Baseline serum uric acid estimation and liver function monitoring recommended. Excellent activity at acidic pH and against intracellular dividing bacilli; not active against *Mycobacterium bovis*. resistance develops rapidly if used alone - mechanism again unknown.
Ethambutol (oral)	Bacteriostatic Active against ICB, ECB, BCL	Poor	++	? Inhibits cell wall synthesis (structurally resembles trehalose monomycolate, a const-ituent of the bacterial cell wall) by Inhibiting incorp-oration of mycolic acid into mycobacterial cell wall	emb A, B & C 10^{-7}	Optic neuritis - reduced visual acuity, loss of red-green discrimination (risk greater at doses > 15 mg/kg daily; drug not recommended in children below 6 y - cannot report visual symptom); peripheral neuropathy; hyperuricemia	More active against dividing bacilli. resistance develops slowly; no cross-resistance. Has activity against *Mycobacterium kansasii*, *M. avium* complex and *M. marinum*.
Streptomycin (IM injection)	Bactericidal Active mostly against ECB	Poor	+++	Inhibit protein (binds to 30S Ribosomal subunit) synthesis	rpoL, rts, strA, S12 10^{-8}	Ototoxicity (vestibular more than cochlear); nephrotoxicity; rash and fever; neuromuscular blockade at high doses	Although bactericidal, may achieve only suppression of infection in vivo because of poor cell penetration.

Abbreviations: ICB = intracellular bacilli; ECB = extracellular bacilli; BCL = bacilli in caseous lesions; IM = intramuscular; GI = gastrointestinal; ANA = antinuclear antibodies

Table 4

Other (second) line drugs for tuberculosis

Drug (Route)	*Activity*	*CSF penetration*	*Relative activity*	*Molecular target and mechanism*	*Resistance genes and mutation rate*	*Daily dose (adult and child)*	*Adverse drug reactions*	*Comments*
Thiacetazone (Oral)	Bacterio-static	Poor	+	Not clearly known	? 10^{-3}	150 mg PO	GI disturbances; skin reactions including exfoliative dermatitis; hepatotoxicity; myelosuppression	Not used in AIDS patients.
p-amino salicylic acid (Oral)	Bacterio-static	Poor	+	Inhibits folate biosynthesis – interferes with incorporation of *p*-amino-benzoic acid.	? 10^{-8}	150 mg/kg PO in divided doses with meals. Maximum 12 g.	GI disturbances; hypersensitivity reactions like rash, fever, malaise, arthralgia, leucopenia, agranulocytosis, eosinophilia, lymphocytosis, atypical mononucleosis, thrombocytopenia, hemolytic anemia	Active only against *Mycobacterium tuberculosis*.
Ethionamide (Oral)	Bacterio-static	Good	+++	Nicotinamide analog -– possibly inhibits incorporation of cysteine and methionine into proteins.	? 10^{-3}	15 - 20 mg/kg PO in divided doses with meals. Maximum 1 g.	GI disturbances; neurotoxicity - visual disturbances, olfactory disturbances, peripheral neuropathy, convulsions; hepatotoxicity; hypersensitivity reactions; alopecia; gynecomastia	Use pyridoxine supplements. Monitor liver function. Resistance develops readily when used alone, cross-resistance with thioacetazone
Cycloserine (Oral)	Bacterio-static	Very good	++	Inhibits cell wall synthesis (enol form is D-alanine analog).	? 10^{-10}	10 - 20 mg/kg PO in 2 divided doses. Maximum 500 mg twice daily.	Mostly neurological - headache, dizziness, vertigo, drowsiness, tremor, convulsions, depression, psychosis; abnormal liver function; megaloblastic anemia; rashes	Monitor hematological, renal and hepatic function.
Capreomycin (IM injection)	Bacterio-cidal	Poor	++	Ribosomal proteins (binds to 30S subunit).	? 10^{-3}	15 - 30 mg/kg IM. Maximum 1 g. After 2 - 4 months reduce dosing to 2 - 3 times weekly.	Pain-induration at injection site; ototoxicity; nephrotoxicity; fever; rashes; eosinophilia; neuromuscular blockade at high doses	Resistance develops, cross-resistance with aminoglycosides.
Amikacin, Kanamycin (IM injection)	Bacterio-cidal	Poor	+++	Ribosomal proteins.	? 10^{-6}	15 mg/kg IM. Maximum 1g.	Ototoxicity; nephrotoxicity; pseudomembranous colitis; neuromuscular blockade at high doses	Resistance develops, cross-resistance among aminoglycosides and with capreomycin.

Note: Newer drugs being evaluated include fluoroquinolones (e.g. Gatifloxacin; Levofloxacin; Moxifloxacin; Ofloxacin; Sparfloxacin - none recommended in children), macrolides (e.g. Azithromycin; Clarithromycin), rifamycins (e.g. Rifabutin and the long-acting Rifapentine) and nitroimidazoles (e.g. PA-824 – a drug under development by the Global Alliance for TB Drug Development); ?=resistance genes yet to be identified.

seldom responsible. If a patient on antiTB drugs develops hepatitis, and no other cause is likely, drug-induced hepatitis must be presumed and the drugs stopped. Once the hepatitis has resolved, the same regimen may be cautiously reintroduced. If the hepatitis has been severe, then it is probably safer to avoid pyrazinamide, and possibly also rifampicin, altogether. An alternative regimen in such patients can be a 2-month initial phase of daily isoniazid, ethambutol and streptomycin followed by a 10-month continuation phase of isoniazid plus ethambutol. A severely ill TB patient with drug-induced hepatitis may die without antiTB treatment. In this case the patient may be treated with the two least hepatotoxic drugs, namely streptomycin and ethambutol instead of interrupting TB treatment. Isoniazid may be cautiously reintroduced after the hepatitis has resolved.

Follow-up and prognosis

Chemotherapy in osteoarticular TB not only helps to control the infection per se but timely surgery can also be done safely, if efficient conservative treatment is carried out in the first instance with rest and chemotherapy. Whatever the goal the importance of regular follow-up to assess disease activity and to ensure patient compliance cannot be overemphasized.[51] Supervised drug treatment programs will facilitate the latter. The diagnosis of quiescence is as important as the diagnosis of the lesion itself and has to be judged through clinical (local and systemic), radiological and laboratory criteria.

The prognosis in general is good with adequate treatment regimens sustained for an appropriate length of time. In some series children appear to fare better than adults.[52] In spinal TB, established deformity and neurological deficits are more difficult to reverse,[21,52] which points to the importance of stabilization surgery.

Conclusion

TB continues to kill approximately two million people each year around the globe. Yet, according to WHO estimates based on 2001 data, worldwide, only 30% of active TB cases are being diagnosed and treated under directly observed therapy, short-course (DOTS) programs. The global targets of 70% case detection and 85% cure rates for those detected must be reached by 2005 in order to halve TB prevalence and deaths by 2010. The opportunity provided by the World TB Day (March 24) should be taken for increasing awareness of various stakeholders on the importance of effective TB control and for social mobilization.

On the chemotherapy front, we continue to fight with the available drugs against the formidable challenges posed by MDR-TB and the HIV-TB vicious cycle. It is sad but true that there have been no new antitubercular drugs for at least the past three decades. However, the Global Alliance for TB Drug Development has been set up and is committed to delivering its first new drug by 2010. The total funding is expected to exceed US$ 150 million. The Alliance also seeks to make antiTB drugs available, particularly in the countries worst hit by the disease, at prices that are affordable to their populations. Cost-effective new antiTB drugs are badly needed to shorten the duration of TB treatment, simplify the regimens, improve the treatment of latent TB infection and overcome the resilience of MDR-TB. Till then we must continue to apply existing drugs and regimens in an informed manner with the maximum emphasis on patient adherence to treatment.

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