



The treatment of tuberculosis in childhood

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The treatment of tuberculosis (TB) in children and adults has remained unchanged for more than 30 years, and although new drugs are at last entering clinical trials it will be 5 - 10 years before their precise place in therapy is established. It is therefore necessary to continue to use our current drugs with care and prudence and be particularly careful about preventing the further development of drug resistance. The principles of treatment in adults and children are the same, but there is an increasing appreciation that the spectrum of disease seen in childhood is different and that children also differ from adults with regard to the pharmacokinetics of drugs.

Drugs differ in their action on different populations of mycobacteria

Several populations of mycobacteria can be identified within TB lesions.¹ Within the walls of cavities there is a large population of actively multiplying organisms. A typical cavity might contain 10^8 bacilli, and this large population increases the probability that mutations will occur that select for drug resistance. Smaller populations of progressively less active or dormant organisms will be found in caseation tissue and within macrophages. Killing the metabolically active organisms is a relatively easy task, and isoniazid (INH) is responsible for the death of 90% of these bacilli within 48 hours. The elimination of the intermittently active or dormant organisms is more difficult and it is failure to sterilise lesions by killing these persistent bacilli that leads to relapse. Drugs that rapidly eliminate the great bulk of metabolically active bacilli are termed bactericidal drugs, and the most active bactericidal agent is INH, with rifampicin (RMP) being about half as active in this respect.² Drugs that eliminate persisting intermittently active or dormant bacilli are termed sterilising agents, the most important being RMP and pyrazinamide (PZA); without them 6-month short-course treatment is not possible. INH will also ultimately sterilise lesions but this requires at least a year of treatment.

Essential anti-TB agents

Five drugs, INH, RMP, PZA, ethambutol (EMB) and streptomycin (SM), are regarded as essential agents by the World Health Organization (WHO).³ RMP, INH and PZA are

the most important elements in our current 'first-line' regimen. For most forms of uncomplicated childhood TB these three drugs are adequate. PZA completes most of its activity within the first 2 months of treatment; it is therefore customary to talk of an 'intensive' phase of treatment with INH, RMP and PZA, the main focus being to eliminate the bulk of the bacilli, and a 4-month 'sterilising' or 'continuation' phase with INH and RMP, when the main focus is the elimination of all remaining viable bacilli. When cavitation is present or in the case of more serious forms of disease a fourth drug is advisable, usually EMB or SM. The purpose of the fourth drug is to prevent the development of drug resistance in the face of a much larger bacterial load and prevent the further broadening of the resistance spectrum should initial INH resistance be present. Neither EMB nor SM has much sterilising activity and although EMB is moderately bactericidal at higher doses, SM has very low bactericidal activity, as do the other aminoglycosides, kanamycin (KM) and amikacin (AMK). The ability to prevent resistance in companion drugs is also important, and agents that are highly bactericidal will usually be best able to prevent resistance in other drugs.

Reserve anti-TB agents

In addition to the five 'first-line' drugs mentioned above there are a number of other less effective and often more toxic drugs classified by the WHO as reserve agents for use in drug resistance or in the event of toxicity or intolerance to the first-line agents. These agents include ethionamide (ETH) or prothionamide, KM or AMK, terizidone/cycloserine (CS), capreomycin (CP), viomycin (VM) and para-aminosalicylic acid (PAS). Although they have never been formally evaluated as anti-TB agents, the fluoroquinolones now have a well-established role in the management of drug-resistant TB. There is also considerable interest in the possibility that some of the more recently developed agents such as gatifloxacin or moxifloxacin may contribute to reducing duration of treatment; several studies are under way to evaluate this possibility.⁴ Of the two fluoroquinolones available in South Africa at present, ofloxacin is to be preferred to ciprofloxacin.

Multidrug resistance (MDR) in children

MDR in children is fully dealt with in an accompanying paper by Schaaf.⁵

Response to TB treatment in children

One of the main differences between adult and childhood TB is the treatment response. In adult TB this can be measured



microbiologically in nearly all cases and relatively little value is accorded to clinical or radiological changes. In much childhood TB we lack such a 'gold standard', but rely on clinical response, weight gain and improvement in radiological features.

However radiology can be misleading and some changes, especially mediastinal lymph node enlargement, persist for more than a year after successful treatment completion.^{6,7} Persistence of changes does not mean that treatment must be prolonged if there has been improvement in symptoms and weight gain.

Influence of HIV/AIDS on TB treatment in children

As with other aspects of TB, HIV has complicated childhood TB treatment considerably. There is some anecdotal evidence that HIV-infected TB patients may benefit from an extension of TB treatment from 6 to 9 months.^{8,9} Very few data are available with regard to this aspect of TB treatment in children, but in more serious forms of disease it would be prudent to continue INH and RMP until 9 months in HIV-infected children. It must also be kept in mind in planning antiretroviral treatment that RMP has important interactions with some antiretroviral agents. This is particularly true of the non-nucleoside reverse transcriptase inhibitors. If in doubt in this regard, seek advice from those who regularly manage TB in HIV-infected children.

Pharmacokinetics of anti-TB agents in children

In calculating the dosage of drugs for children it is recognised that body surface area provides a more accurate measure of appropriate dose than mg/kg body weight; nonetheless dosages currently recommended by the WHO for TB treatment are the same in adults and children. Several recent studies show that children receiving the same mg/kg body weight doses of anti-TB agents as adults have lower serum

concentrations than adults.^{10,11} Until this position is resolved it would be wise to calculate dosages for children making use of the upper limits of the suggested ranges.

The dosages recommended by the WHO for the treatment of TB in children and their commonest side-effects are summarised in Table I and the recommended regimens for the different categories of TB in Table II.^{3,12} Whenever possible children should be included in one of these categories to ensure the full integration of childhood TB into national programmes. Most children will be sputum or gastric aspirate smear-negative and thus be included in category III. Children presenting in category III with limited lung opacification and non-cavitating disease, without any other complicating factor such as HIV infection, can be treated without EMB. In the case of TB meningitis it is recommended that SM replace EMB, but neither drug has very good entry into the cerebrospinal fluid. In South Africa a regimen of INH, RMP, PZA and ETH, all given for 6 months, has been used with success and a low relapse rate in the management of TB meningitis in children.¹³

INH may cause symptomatic pyridoxine deficiency, so it is recommended that children who are malnourished, HIV-infected children, breastfeeding infants or pregnant adolescents should receive supplemental pyridoxine 5 - 10 mg/kg/d.¹²

Directly observed therapy, short course (DOTS)

It is the bitter experience of TB services worldwide that a significant proportion of patients fail to comply with treatment recommendations. In the case of children a further element is introduced as young children are dependent on their parents or caregivers for their treatment. As support for patients to encourage completion of treatment as prescribed, the WHO now advocates DOTS. This approach emphasises standardised short-course chemotherapy under proper case management conditions, including direct observation of treatment. This

Table I. World Health Organization recommended dosages and side-effects of essential antituberculosis agents^{3,12}

Drug	Dose in mg/kg (range)		Commonest side-effects
	Daily	Thrice weekly	
Isoniazid	5 (4 - 6) Maximum 300 mg	10 (8 - 12)	Hepatotoxicity, peripheral neuropathy, less commonly optic neuritis or psychosis, concentrations of carbamazepine and phenytoin may increase
Rifampicin	10 (8 - 12) Maximum 600 mg	10 (8 - 12)	Hepatotoxicity, exfoliative dermatitis in HIV-infected patients. With intermittent use flu syndrome and thrombocytopenia may occur. Induction of enzymes increases dosage requirements for corticosteroids, oral hypoglycaemic agents, digitalis and other agents
Pyrazinamide	25 (20 - 30)	35 (30 - 40)	Hepatotoxicity, hyperuricaemia with arthralgia and arthritis, particularly of shoulders, hypersensitivity reactions, especially flushing of the skin
Ethambutol	20 (15 - 25)	30 (25 - 35)	Dose-dependent optic neuritis with impairment of visual acuity and colour vision. Rare in children at recommended doses
Streptomycin	15 (12 - 18)	15 (12 - 18)	Irreversible auditory nerve damage, hypersensitivity reactions

Table II. Regimens recommended by the World Health Organization for management of tuberculosis^{3,12}

Diagnostic category	TB patient	TB treatment regimens	
		Intensive initial phase (daily or thrice weekly)	Continuation phase (daily or thrice weekly)
I	New smear-positive patients; new smear-negative PTB with extensive lung involvement; severe concomitant HIV disease or severe extrapulmonary TB	2HRZE	4HR or 6HE daily
II	Previously treated smear-positive PTB following relapse, treatment after interruption or treatment failure	2HRZES/1HRZE	5HRE
III	New smear-negative PTB (other than category I); less severe forms of extrapulmonary TB	2HRZE	4HR or 6HE daily
IV	Chronic and MDR TB	Specialised treatment needed under the guidance of a specialist	

H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; S = streptomycin. The numerical prefix refers to the length of time in months. TB = tuberculosis; PTB = pulmonary tuberculosis; MDR = multidrug-resistant.

implies technically sound and socially supportive treatment services. While the principles underlying DOTS are clear, their application to children is uncertain, and it has not been established how far a family-orientated approach to TB treatment of children can be adopted, and whether parents or other family members can be reliable treatment supervisors. The application of DOTS to childhood TB requires further study.

Future developments

The HIV/AIDS pandemic has focused attention on the serious nature of the ongoing TB epidemic in developing countries, and the devastating interaction of HIV and TB has dispelled any illusions that TB is under control. Explosive epidemics of drug resistance have exposed the limits of the anti-TB drug armamentarium. There is now an awareness of the urgent need for new anti-TB agents. In 2000 the Global Alliance for TB Drug Development was established to accelerate the development of new anti-TB agents.¹⁴ For the first time in decades there is a promising pipeline of more than 20 compounds in development under the guidance of the Global Alliance or pharmaceutical companies. Several drugs with very promising characteristics during *in vitro* and *in vivo* animal studies^{15,16} have already completed preliminary studies. However, before they can be used in routine regimens, a considerable amount of work must still be done; at any stage problems may be encountered precluding further development. Therefore, despite a more optimistic outlook than has been justified for several decades, it behoves all concerned about TB control and

treatment to use existing regimens and drugs with due care and to do everything possible to prevent the development of drug resistance.

References

- Mitchison DA. Basic mechanisms of chemotherapy. *Chest* 1979; 76: suppl 6, 771-781.
- Donald PR, Sireg FA, Venter A, et al. Early bactericidal activity of antituberculosis agents. *Expert Rev Anti-infect Ther* 2003; 1: 141-155.
- World Health Organization. *Treatment of Tuberculosis. Guidelines for National Programmes*. Geneva: WHO, 2003. WHO/CDS/2003.313.
- Johnson JL, Hadad DJ, Boom WH, et al. Early and extended bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2006; 10: 605-612.
- Schaaf HS. Drug-resistant tuberculosis in children. *S Afr Med J* 2007; 97: 995-997 (this issue).
- Reis FJC, Bedran MBM, Moura JAR, Assis I, Rodrigues MESM. Six-month isoniazid-rifampin treatment for pulmonary tuberculosis in children. *Am Rev Respir Dis* 1990; 142: 996-999.
- Al-Dossary FS, Ong LT, Pa-C, Correa AG, Starke JR. Treatment of childhood tuberculosis with a six month directly observed regimen of only two weeks of daily therapy. *Pediatr Infect Dis J* 2002; 21: 91-97.
- El-Sadr WM, Perlman DC, Denning E, Matts JP, Cohn DL. A review of efficacy studies of 6-month short-course therapy for tuberculosis among patients infected with human immunodeficiency virus: differences in study outcomes. *Clin Infect Dis* 2001; 32: 623-632.
- Driver CR, Munsiff SS, Li J, Kundamal N, Osahan SS. Relapse in persons treated for drug-susceptible tuberculosis in a population with high coinfection with human immunodeficiency virus in New York City. *Clin Infect Dis* 2001; 33: 1762-1769.
- Schaaf HS, Parkin DP, Seifart HI, et al. Isoniazid pharmacokinetics in children treated for respiratory tuberculosis. *Arch Dis Child* 2005; 90: 614-618.
- Donald PR, Maher D, Maritz JS, Qazi S. Ethambutol dosage for the treatment of children: literature review and recommendations. *Int J Tuberc Lung Dis* 2006; 10: 1318-1330.
- World Health Organization. *Guidance for National Programmes on the Management of Tuberculosis in Children*. Geneva: WHO, 2006 (WHO/HTM/TB/2006.371).
- Donald PR, Schoeman JF, Van Zyl LE, De Villiers JN, Pretorius M, Springer P. Intensive short course chemotherapy in the management of tuberculous meningitis. *Int J Tuberc Lung Dis* 1998; 2: 704-711.
- O'Brien RJ. Scientific blueprint for tuberculosis drug development. *Tuberculosis* 2001; 81: suppl 1, 1-51.
- Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science* 2005; 307: 23-227.
- Matsumoto M, Hashizume T, Tomishige T, et al. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis *in vitro* and in mice. *PLoS Med* 2006; 3: 2131-2144.