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Mini-symposium: Childhood TB in 2010

Treatment of paediatric TB: revised WHO guidelines

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EDUCATIONAL AIMS

- To describe the current recommendations for dosages of first-line TB treatment in children following recent revision
- To outline the rationale for these revisions
- To highlight clinical and pharmacokinetic data that helped inform the revised recommendations

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SUMMARY

The World Health Organization has recently revised the recommended dosages of the main first-line anti-tuberculosis drugs for use in children. The recommended dosages and range of isoniazid, rifampicin, pyrazinamide and ethambutol have been increased from the previous recommended dosages. Ethambutol is now recommended for use in children of all ages including those of less than 5 years of age. This review explains the rationale for these recent revisions. Children require higher dosages than adults to achieve the same serum concentrations. Available data in HIV-uninfected children suggest that the revised dosages are within limits that have a very low risk of toxicity. An important challenge will be to examine the impact of higher dosages on clinical response, drug-drug interactions and risk of toxicity in HIV-infected children.

INTRODUCTION

The World Health Organization (WHO) has estimated that around 10% of global tuberculosis (TB) caseload occurs in children (0-14 years).[1] Disease burden data in children is rarely reported from TB endemic countries. However, there are reports that children account for up to 40% of all cases being treated for TB.[2–4] Marked variability is expected because the reported burden of disease will depend on epidemiological and demographic differences between communities[5] as well as differences in diagnostic and notification practices. While there may be uncertainty of actual disease burden, clinical and autopsy data from the sub-Saharan African region show that TB is a major cause of morbidity and mortality in children.[6–9] Children are also susceptible to the dual epidemic of TB/HIV. HIV-infected children are at 20-times greater risk of TB disease than HIV-uninfected children and at much higher risk of TB-related death.[8–12]

Paediatric TB has until recently not been a main priority of global TB control efforts for various reasons. The control strategy has in the past primarily focused on the identification and effective management of the most infectious cases of TB in order to reduce the transmission of infection with *Mycobacterium tuberculosis*. These cases are usually adults or adolescents with sputum smear-positive pulmonary TB (PTB). Further, although there is evidence that paediatric TB makes an important contribution to the global burden of TB, it has been difficult to accurately determine (and provide advocacy for) the burden of disease in children because most cases are not confirmed. The burden of paediatric disease in TB endemic settings is usually skewed towards the infants and young children (< 5 years of age)[2–5] from whom it is difficult to obtain sputum, and the nature of disease in this age group is usually paucibacillary meaning that culture is required to improve yield of diagnostic confirmation. Therefore, most children with a diagnosis of TB are categorised by National TB Programmes (NTPs) as either "sputum smear-negative" PTB or extra-pulmonary TB (EPTB) cases.[3,4] These cases were not traditionally and are often still not being routinely recorded and reported by NTPs.

RECENT ATTENTION BY WHO TO THE CHALLENGES OF PAEDIATRIC TB

The direct observed treatment strategy [DOTS] has recently been incorporated into WHO's broader Stop TB Strategy[13] which

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Table 1
Treatment regimens for children recommended by WHO

TB cases and diagnostic category	Anti-TB drug regimens	
	Intensive phase	Continuation phase
New Patient Regimen		
New smear-positive PTB	2HRZE	4HR
Smear-negative PTB with extensive parenchymal involvement		
Severe forms of EPTB other than TB meningitis		
New Patient Regimen		
Smear-negative PTB without extensive parenchymal involvement	2HRZ	4HR
Less severe forms of EPTB (e.g TB cervical adenitis)		
New Patient Regimen		
TB meningitis	2HRZS[a]	4HR
Retreatment regimen		
Previously treated smear-positive PTB (relapse, treatment after interruption or treatment failure)	2HRZES/1HRZE	5HRE
If low risk for MDR TB or risk unknown: continue with retreatment regimen		
If high risk for MDR TB: use MDR TB regimen below		
MDR Regimen		
MDR-TB	Individualized regimens	

The Table represents WHO recommendations up until August 2010 which have since been changed (and approved by Guidelines Review Committee) and this process is mentioned in text below. The main changes are that all TB types (except TBM and OA TB) in HIV endemic setting should receive a fourth drug in intensive phase 2RHZE/4RH, that TBM and osteoarticular TB should receive 2 RHZE/10RH and that streptomycin is no longer recommended as first-line in children.
H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; S: streptomycin
[a] : Other regimens are recommended for treatment of TB meningitis that include replacing streptomycin with ethionamide and treating for 9-12 months

gives due emphasis to all types of TB disease and vulnerable at-risk groups, thereby including TB in children. As part of this new strategy in response to the challenges of improving child TB management, the child TB subgroup of the DOTS Expansion Working Group of the Stop TB partnership was formed in 2003. This has facilitated a number of important initiatives aimed at greater engagement by NTPs to address child TB issues:

1. Published guidelines for NTPs on TB management in children[14]
2. Revision of recommended drug dosages of the four first-line anti-TB drugs for children[15,16]
3. The development of guidelines for national TB and HIV programmes on TB management in HIV-infected children[17]
4. Recommendations to include routine reporting by NTPs of children receiving TB treatment in two age categories (0-4 years and 5-14 years)[18]
5. A research agenda for child TB[19]

A major challenge that remains is to implement recent guidelines and recommendations in resource-limited settings through guidance and training of paediatric and NTP health workers to increase effectiveness. This review aims to highlight the rationale and evidence base behind these initiatives, focusing particularly on revised WHO guidelines for the treatment of paediatric TB which relate to the first three points above.

PRINCIPLES OF TB TREATMENT

The principles of TB treatment are the same for adults and children. The combination regimens used to treat active disease aim to eliminate actively replicating and dormant or near-dormant mycobacteria using a combination of drugs with different actions whilst preventing the emergence of drug-resistant organisms, and all being achieved with a minimum of toxicity.[20] Bactericidal drugs that kill actively metabolizing and replicating organisms are important to achieve a rapid reduction in microbial load which leads to clinical improvement, contains disease progression and terminates transmission.[21] Isoniazid (H) and rifampicin (R) are important first-line bactericidal drugs with isoniazid having the most potent early bactericidal activity. Sterilizing drugs aim to eradicate those organisms that are less active metabolically and those that are in an acidic environment in order to prevent relapse. Rifampicin and pyrazinamide (Z) are important first-line sterilizing drugs. Protection against emergence of drug-resistant organisms is achieved by the combination of effective early bactericidal activity to reduce microbial load combined with effective sterilising activity of more slowly replicating organisms, and strengthened by the addition of a fourth drug such as ethambutol (E) or streptomycin (S).

The recommended treatment regimens for each TB diagnostic category are also generally the same for children as for adults. Table 1 lists the regimens by disease category as currently recommended by WHO in 2010.[15] The most common TB diagnostic category in children is smear-negative PTB and so the commonest regimen used in children is 2HRZ 4HR: denotes a two-month intensive phase of daily isoniazid, rifampicin and pyrazinamide followed by a four-month continuation phase of daily isoniazid and rifampicin. A fourth drug is important for cure of disease with a large microbial load such as sputum smear-positive PTB or PTB with extensive parenchymal involvement, and to reduce the risk of development of drug-resistance.[21] These regimens are currently being reviewed by an expert panel and are likely to change before end of 2010. The use of a fourth drug in the intensive phase for the common forms in children, PTB and TB adenitis, may in the future be determined by epidemiological context i.e. population prevalence of HIV and isoniazid resistance, rather than by extensiveness of pulmonary disease. The recommended treatment of TB meningitis and osteoarticular TB are also under review and treatment for 12 months may be the preferred option.

The WHO guidelines of 2003 included 6HE as an alternative to 4HR for the continuation phase of new patient regimens. Rifampicin is important in the continuation phase to kill slowly metabolizing organisms whilst isoniazid is less potent for bactericidal activity in that context and when combined with rifampicin, is added to provide protection against drug resistance.[21] In the alternative combination of 6HE, isoniazid is used for bactericidal activity but is less potent than rifampicin especially against slowly metabolizing organisms, while ethambutol has less potent bactericidal activity and is used for protection against development of drug resistance. A multi-centre randomised trial that compared HR to HE in continuation phase in adults with TB found that relapse was more common in those in the 6HE arm than for those in the 4HR.[22] As a result, 4HR is now the only recommended option for the continuation phase.