Update on the Treatment of Pediatric Tuberculous Meningitis

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Introduction

At the 2018 high level United Nations meeting on tuberculosis (TB), treatment targets were set for the 5-year period 2018-2022. These targets included the treatment of 3.5 million children. However, by 2020 only 41% of this target had been achieved with further stasis highly likely due to the havoc wreaked by the COVID-19 pandemic on access to healthcare.(1) Tuberculous meningitis (TBM), is considered the most devastating manifestation of TB, with peak incidence in the vulnerable early childhood age group, coinciding with critical brain development. Early diagnosis in childhood is difficult due to non-specific clinical features and the paucibacillary nature of the disease complicating cerebrospinal fluid (CSF) mycobacterial confirmation, resulting in delayed diagnosis and treatment. Untreated, TBM is uniformly fatal, and even when treated, the neurological sequelae can be severe. Unfortunately, the evidence to guide treatment is limited. We present a summary of existing pediatric TBM treatment, recent updates, clinical trials which may potentially inform anti-tuberculous dosing regimens, and practical clinical recommendations.

Drugs, dosing regimens and evidence

Good CSF penetration is a logical prerequisite for an anti-tuberculous agent to be effective at the site of disease. However, only a handful of anti-tuberculous agents have good CSF penetration. Of the first-line anti-tuberculous drugs, isoniazid and pyrazinamide have the best CSF penetration, while ethambutol and rifampin have poor CSF penetration, although rifampin CSF concentration increases as dosage increases.(2) Second-line anti-tuberculous drugs with good CSF penetration include ethionamide, the fluoroquinolones (levofloxacin, moxifloxacin and ofloxacin), terizidone,(2) and linezolid. Newer drugs, such as bedaquiline and delamanid,

requires further evaluation. Until recently, the World Health Organization (WHO) recommended a 12-month treatment regimen for drug-susceptible TBM, for both adults and children, comprising 2 months of rifampin, isoniazid, pyrazinamide and ethambutol followed by 10 months of rifampin and isoniazid, based on low quality evidence.(3) Dosing is similar to that used for pulmonary TB (Table 1).

Shorter pediatric dosing regimens

For the 2022 Child and Adolescent TB Guideline, WHO reviewed the evidence relating to the treatment of pediatric TBM. A systematic review was conducted to compare the current WHO-recommended 12-month regimen with a shorter intensive regimen (isoniazid, rifampin and pyrazinamide, given at higher dosages, combined with ethionamide; given for 6 months if HIV-negative and for 9 months if HIV-positive). Dosing is shown in Table 1.(3) Mortality was lower in the children treated with the intensive 6-month regimen compared to those treated with the standard WHO-recommended 12-month regimen. WHO subsequently decided that the intensive 6-month regimen could be used as an alternative to the 12-month regimen. The rationale for using ethionamide, in preference to ethambutol, in the 6-month intensive regimen is the good CSF penetration compared to ethambutol. A further advantage of ethionamide is that isoniazid mono-resistant *katG* TBM is overcome when ethionamide and pyrazinamide are used continuously for 6 months. However, hepatotoxicity, gastrointestinal irritability and hypothyroidism are recognized complications of ethionamide. For this reason, the fluoroquinolones are being evaluated as the alternative fourth drug.

While the recommendation of the alternative 6-month intensive pediatric TBM regimen is welcomed, the evidence base for childhood TBM treatment regimens remains poor. To address

this, two clinical trials are exploring pediatric TBM treatment. TBM-KIDS (NCT02958709) is a recently completed phase I/II trial in which children with TBM were randomized to one of three regimens for the first 8 weeks of their treatment. The control arm comprised standard dose isoniazid, rifampin, pyrazinamide, and ethambutol, with the first intervention arm using an increased dosage of rifampin (30mg/kg) and the second intervention arm using this higher rifampin dose as well as substituting ethambutol with levofloxacin. All arms then completed the same 10 months of a standard continuation phase (isoniazid at 10mg/kg and rifampin at 15mg/kg). Pharmacokinetic and safety data will be available imminently. Short Intensive Treatment for Children with Tuberculous Meningitis (SURE) (ISRCTN40829906) is a randomized trial with a factorial design of enhanced anti-tuberculosis and anti-inflammatory treatment for children with TBM. Children are first randomized to either the standard WHO-recommended 12-month TBM regimen or to an optimized regimen consisting of rifampin (30mg/kg), isoniazid (20mg/kg), pyrazinamide (40mg/kg) and levofloxacin (20mg/kg) daily for 6 months. Each child is then randomized to receive either aspirin or placebo for the first 8 weeks of treatment. The study will recruit 400 children over the next 1-2 years.

New insights into drug dosing strategies

While both TBM-KIDS and SURE evaluate rifampin at a dose of 30mg/kg, modelling studies suggest that even higher dosages are required.(4) Given children generally require higher milligram per kilogram oral dosages to achieve the same serum concentration as adults, it is likely that dosages much greater than 40mg/kg would be needed in children to achieve the same exposures as seen in adults given 40mg/kg. A recent pharmacokinetic and safety study using higher dosages of rifampin in children, the Opti-Rif trial, explored short term dosages of up to 75mg/kg.(5) Higher dosages were generally well tolerated, and few adverse events were

seen. Much higher dosages of rifampin may soon be used in an attempt to improve outcomes in children with TBM.

Host-directed therapy

Many of the sequelae seen in TBM can be attributed to a dysregulated host immune response. Effective host directed therapies (HDT) are therefore likely to be critical in improving survival and clinical outcomes. Currently the only HDTs that have been shown to reduce TBM mortality in adults are the corticosteroids. However, there is no evidence that corticosteroids reduce morbidity and the mechanism of action for mortality reduction is unclear.(6) Leukotriene A4 (LTA4H) genotype may predict adjunctive corticosteroid responsiveness and once validated, the exciting prospect of genotype-directed adjunctive therapy may be possible. Aspirin reduces the risk of new infarctions in adult TBM patients but does not affect mortality, though larger studies powered for survival are needed.(7) Dose uncertainty (low for anti-platelet or high for anti-inflammatory effects) and duration of therapy necessitates further exploration before aspirin can be advocated as standard therapy. One promising HDT approach is to restrict the immunopathology arising from tumour necrosis factor (TNF)-α excess via TNF-α inhibitors such as thalidomide, anti-TNF-α monoclonal antibodies (infliximab, adalimumab) and the soluble TNF-α receptor fusion protein (etanercept).(8) Low dosage adjunctive thalidomide has been found to be safe and effective in treating tuberculous mass lesions and blindness related to optochiasmatic arachnoiditis.

Adult trials relevant to children

In addition to SURE and TBM-KIDS there are multiple phase II and III adult TBM trials that have either recently completed or are ongoing that may inform future childhood TBM treatment. Investigation of fluroquinolones has largely halted after the seminal Vietnamese trial found that adjunctive levofloxacin only reduced mortality in adults with isoniazid-resistant TBM. Studies into high-dose rifampicin with or without linezolid are gaining momentum. The phase III INTENSE-TBM trial (NCT04145258) has a factorial design, randomizing participants to either a standard WHO regimen or an optimised regimen containing high dose rifampin and linezolid with a second randomization comparing low dose (100 mg) aspirin to placebo. HARVEST is a phase III trial evaluating rifampicin 35 mg/kg/day compared to the standard WHO regimen in Uganda, South Africa and Indonesia. Definitive answers about the impact of intensified treatment on survival and functional outcomes are awaited in 2024 from these phase III studies.

There is a body emerging compelling evidence about the safety and optimal pharmacokinetics of higher-dose rifampicin in TBM. Interest in rifampicin was triggered by an Indonesian phase II trial that found intravenous rifampicin reduced mortality in HIV-negative Indonesians with TBM. Since then the RifT trial (ISRCTN42218549) reported on the safety of high-dose rifampicin in people with advanced HIV infection and the resulting plasma and CSF exposures of intravenous administration of 20mg/kg rifampicin and oral dosing at 35mg/kg, as compared to a standard dosing of 10mg/kg. Both the higher oral dose and intravenous administration led to higher exposures in the CSF with no excess toxicity. ReDEFINe (NCT02169882) evaluated 450mg, 900mg or 1350mg oral dosing of rifampicin and found that higher dosages led to substantially higher plasma and CSF exposures, without increases in adverse events in HIV-negative Indonesians. Results of the recently completed phase II LASER-TBM trial

(NCT03927313) which recruited HIV-positive South Africans and evaluated elevated dosages of rifampin and linezolid, with or without high dose (1000 mg) aspirin are awaited.

The ALTER trial (NCT04021121) in Uganda and the SIMPLE trial (NCT03537495) in Indonesia are exploring higher dosages of rifampicin and the inclusion of linezolid with the focus on pharmacokinetics and safety.

Finally, in Vietnam, LAST ACT (NCT03100786) explores stratifying dexamethasone by LTA4H genotype in HIV-negative adults, with all individuals found to have a TT-genotype being given dexamethasone, while those with CC- or CT-genotypes being randomized to dexamethasone or placebo. ACT HIV (NCT03092817), also in Vietnam, has recently completed recruitment with the trial randomizing HIV-positive individuals to dexamethasone or placebo.

Research Gaps

In a recent review by Huynh and colleagues,(9) research gaps in pediatric TBM treatment were identified. These included 1) unclear optimal anti-tuberculous drug dosing, regimen and duration (short versus 12 month) to effectively treat pediatric TBM, 2) lack of pediatric pharmacokinetic studies, 3) whether the dosage of isoniazid should be adjusted in fast compared to slow acetylators, and 4) which of ethambutol (first-line anti-tuberculous drug), ethionamide or the fluoroquinolones (second-line anti-tuberculous drugs) is the best option as the fourth drug in a drug-susceptible TBM regimen in addition to rifampin, isoniazid, and pyrazinamide. Research gaps were also identified relating to whether host-directed therapy

including high-dose aspirin, thalidomide, and monoclonal-antibodies such as TNF-alpha inhibitors can reduce neurological morbidity and mortality in pediatric TBM.

Practical clinical recommendations

Early diagnosis and treatment initiation are crucial to improve TBM outcome. The authors' preference is for the short intensive regimen comprising rifampin, isoniazid, pyrazinamide and ethionamide given for 6 months if HIV-negative or 9 months if HIV-positive. Ethionamide-related gastrointestinal irritability can be overcome by giving the ethionamide separately as a night-time dose. Concurrently, prednisolone should be given, at a dose of 2mg/kg for 4 weeks followed by a tapering period of 2 weeks.(6)

Cerebral salt wasting and syndrome of inappropriate secretion of anti-diuretic hormone are important causes of hyponatremia in TBM. Irrespective of the cause, fluid restriction should be avoided, and the management of choice is hypertonic saline (slow infusion with the aim to increase serum sodium by 1mmol/L/hour). Currently, there is insufficient evidence for routine aspirin use, however if neuroimaging demonstrates cerebral venous sinus thrombosis, arterial ischemic infarction and/or vasculitis, aspirin can be considered. Treatment of tuberculous hydrocephalus depends on the level of CSF obstruction which can be determined using either air-encephalogram or MRI CSF flow studies. Medical therapy, consisting of furosemide 1mg/kg/day and acetazolamide 50-100mg/kg/day, has been shown to normalize raised intracranial pressure within seven days of treatment.(10) Both are usually given for one month. Non-communicating hydrocephalus should be treated by neurosurgical CSF diversion. In the rare cases of a tuberculoma in a critical area, a tuberculous abscess or optochiasmatic

arachnoiditis, usually seen in paradoxical immune reconstitution inflammatory syndrome, there is evidence for improvement on low dose adjunctive thalidomide (or infliximab).

Conclusions

After years of neglect, substantial research into childhood TBM has recently completed or is underway. Several studies in adults with TBM will provide crucial information for the treatment of children and WHO has updated guidance to make optimised treatment an option in all contexts. Despite these advances, TBM remains a devastating condition and much remains unknown in the field of childhood TBM therapy.

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Table 1. Drug dosing for the 12-month WHO drug-susceptible TBM regimen and the 6-month intensive regimen with characteristics of potential second-line anti-tuberculous drugs for pediatric TBM

		12-month regimen			6-month intensive regimen		
	CSF penetration	**Dosage and range (mg/kg)**	**Maximum dose (mg)**	**Duration (months)**	**Dosage (mg/kg)**	**Maximum dose (mg)**	**Duration (months)**
Isoniazid (H)	Good	10 (7-15)	300	12	20	300	6
Rifampin (R)	Poor (the higher dosage the higher the CSF concentration)	15 (10-20)	600	12	20	600	6
Pyrazinamide (Z)	Good	35 (30-40)	2000	2	40	2000	6
Ethambutol (E)	Poor	20 (15-25)	1000	2			
Ethionamide (Eto)	Good (>80%)	Not recommended			20	1000	6
Other 2nd line agents							
	CSF penetration	**Dosage (mg/kg)**					
Levofloxacin (Lfx)	Good	20					
Terizidone (Trd)	Good	15-20					
Linezolid (Lzd)	Good	10					
Delamanid (Dlm)/Pretomanid (Pa)	Poor						
Bedaquiline (Bdq)	Poor						