Review Article

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Tuberculous meningitis in children: Clinical management & outcome

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Although the occurrence of tuberculous meningitis (TBM) in children is relatively rare, but it is associated with higher rates of mortality and severe morbidity. The peak incidence of TBM occurs in younger children who are less than five years of age, and most children present with late-stage disease. Confirmation of diagnosis is often difficult, and other infectious causes such as bacterial, viral and fungal causes must be ruled out. Bacteriological confirmation of diagnosis is ideal but is often difficult because of its paucibacillary nature as well as decreased sensitivity and specificity of diagnostic tests. Early diagnosis and management of the disease, though difficult, is essential to avoid death or neurologic disability. Hence, a high degree of suspicion and a combined battery of tests including clinical, bacteriological and neuroimaging help in diagnosis of TBM. Children diagnosed with TBM should be managed with antituberculosis therapy (ATT) and steroids. There are studies reporting low concentrations of ATT, especially of rifampicin and ethambutol in cerebrospinal fluid (CSF), and very young children are at higher risk of low ATT drug concentrations. Further studies are needed to identify appropriate regimens with adequate dosing of ATT for the management of paediatric TBM to improve treatment outcomes. This review describes the clinical presentation, investigations, management and outcome of TBM in children and also discusses various studies conducted among children with TBM.

Key words Antituberculosis therapy children - CSF- disease outcome - paediatric - steroids - tuberculous meningitis

Introduction

Globally, almost half a million children become sick with tuberculosis (TB) every year, 20-30 per cent being affected by extrapulmonary TB (EPTB). Almost 10-20 per cent of the children with TB live in high TB burden countries[1]. Mathematical modelling has shown that more than 58 per cent cases of paediatric TB occur in children less than five years and one-fourth of them have EPTB[2]. Infants, young and HIV-infected children are often affected with severe forms such as disseminated TB or tuberculous meningitis (TBM). The most common manifestation of *Mycobacterium tuberculosis* (Mtb) infection in the central nervous system (CNS) is meningitis. Even though TBM constitutes a small proportion of the total reported TB cases (around 1%), it causes a disproportionate amount of suffering with higher rates of mortality and morbidity, especially in young children[3]. TBM has a poor prognosis, and survivors often have severe disabilities[4]. TBM frequently presents with non-specific symptoms in the early stages and is diagnosed in the later stages of the illness when brain damage has already occurred. Early diagnosis and management of TBM is important, as delay in diagnosis leads to poor outcomes such as death, neurological sequelae and neurocognitive

disorders. TBM is diagnosed based on clinical findings, demonstration of Mtb in the cerebrospinal fluid (CSF) by smear microscopy, culture, DNA amplification testing, aided by imaging techniques[5]. Most of the available information regarding paediatric TBM is from retrospective studies, as only a few prospective studies have been conducted. Here we discuss the clinical presentation, investigations, management and outcome of TBM in children.

Epidemiology

Despite advancements in technology for Mtb detection, TB diagnosis, especially EPTB in children is a major challenge. There is a paucity of data about global burden of different types of EPTB in children, including TBM. However, there are isolated reports from different countries regarding local TBM burden. According to surveillance data from Germany, of the total paediatric TB patients, TBM occurred in 3.9 per cent of the children in less than five-year age group, 2.2 per cent in 5 to 9 yr of age and 1.3 per cent in 10 to 14 yr of age[6]. In one hospital in Greece, 43 children were diagnosed with TBM between 1984 and 2008, with a declining trend over the years[7]. A hospital-based study in Beijing showed that among 1212 children admitted for TB treatment between 2002 and 2010, almost half of them had EPTB and around 39 per cent had TBM[8]. It is unclear whether geographic differences exist for the risk of TBM among TB-exposed children related to differences in circulating strains, demographics, genetics or other factors. Most reports describing TBM in children had been hospital based, and very few were from systematic surveillance. Global as well as country-wise disease burden of TBM in children is largely unavailable and understudied.

Pathogenesis

Arnold Rich and Howard McCordock showed the presence of a caseating focus in the brain parenchyma or meninges on autopsy in patients with TBM[9]. CNS is involved following primary infection of the lungs through haematogenous spread to the brain. Initially, small tuberculous lesions known as 'Rich foci' form around the bacteria that are deposited in the brain during bacteraemia of primary TB. These foci located in the subpial or subependymal surface of the brain, meninges and bacilli remain in a dormant state for a prolonged duration. The onset of TBM follows the growth and rupture of these lesions into the ventricular system or subarachnoid space[10]. On an average, TBM occurs 6 to 12 months after the primary infection[11]. Mtb has the ability to invade and traverse the blood-brain barrier which is dependent on the presence of certain virulence factors, exocytosis and longer intracellular survival[12]. One study showed that there was significant elevation of cathelicidin LL-37, interluekin (IL)-13 and vascular endothelial growth factor (VEGF) and reduction of IL-17 in the CSF of children with TBM when compared to children with viral and bacterial meningitis[13]. This biomarker pattern suggests a host immune response which is disease specific and may be of diagnostic and therapeutic importance. TBM is a meningo-encephalitic disease. A thick gelatinous exudate containing erythrocytes, neutrophils, macrophages and lymphocytes[14] is formed around the brain stem, sylvian fissures and basal cisterns, causing obstruction to the flow of CSF from the cerebral aqueduct or fourth ventricle. Absorption of CSF is also interfered leading to raised intracranial pressure (ICP) and hydrocephalus. The basal exudates may lead to periarteritis of the cerebral arteries leading to infarction of the caudate nucleus and internal capsule. There may be oedema of the brain, perivascular infiltration and inflammation of the blood vessel walls leading to narrowing or occlusion by thrombi resulting in infarcts in the distribution of the medial striate and thalamic perforating arteries[15].

Clinical features

The occurrence of TBM is rare in children who are lesser than three months of age[16], but cases have been reported in broader age group ranging from six weeks to 18 yr. The peak incidence of TBM in children occurs between 2 and 4 yr of age[17]. Boys are affected more than girls. The clinical onset of TBM may be acute, subacute or gradual[11] and is characterized by non-specific symptoms in the early stages, such as malaise, low-grade fever, symptoms related to pulmonary TB and/or flu-like illness[17]. Most children present for initial evaluation with symptoms such as headache, fever, vomiting and irritability. Children with more advanced disease may have signs of meningeal irritation, raised ICP (bulging fontanelle, sunsetting sign, papilloedema), cranial nerve palsies, neurological deficits, altered sensorium and movement disorders[15]. The various cranial nerve palsies documented in different studies include second, third, sixth[18] and seventh cranial nerve palsies[7,19,20].

Glasgow coma scale (GCS) is used to measure the consciousness level in these children as well as to determine the prognosis. Eye opening, motor responses and verbal responses contribute to GCS scoring. The

British Medical Research Council (BMRC) staging is used to evaluate the disease severity as well as to establish the prognosis of TBM[21]. The 'modified' MRC scale categorizes patients into three clinical stages[22]. The 'refined' MRC scale and 'modified' MRC scale are similar except that Stage 2 is divided into Stage 2a and Stage 2b in the latter based on GCS score and absence or presence of neurological deficit[22].

Diagnosis

Early diagnosis and treatment of TBM plays a vital role in determining the disease outcome. This is challenging given that, early symptoms are often non-specific, so high degree of suspicion is required. The various methods used in the diagnosis of TBM include CSF cellular and biochemical analysis, microbiologic confirmation in CSF and other supportive testing such as neuroimaging.

CSF analysis

CSF findings in TBM consist of leucocytosis with lymphocyte predominance, protein elevation and decrease in CSF glucose (hypoglycorrhachia) which is reflected as either decreased glucose in CSF or CSF to plasma glucose ratio[23]. When the CSF is left to stand undisturbed, a fine clot resembling cobwebs may form due to the presence of very high level of protein[24]. Thilothammal *et al*[25] showed that 11 and 15 per cent of the children with Stage 2 and 3 disease, respectively, had CSF protein value >100 mg/dl. Yaramiş *et al*[26] reported that around 80 per cent of CSF parameters from children affected with TBM had predominance of lymphocytes, elevated protein and reduced glucose concentrations. Uniform Research Case Definition Criteria[27,28] used the following CSF criteria for scoring in TBM: clear appearance, cells 50-100/µl, lymphocytic predominance of >50 per cent, protein concentration >1 g/l, CSF: plasma glucose ratio of <50 per cent or absolute CSF glucose concentration <2.2 mmol/l[27,28]. Solomons *et al*[29] showed that CSF glucose concentration of <2.2 mmol/l had specificity 0.96 and sensitivity 0.68 and CSF protein more than 1 g/l had specificity 0.94 and sensitivity 0.78 in diagnosing TBM in suspects. CSF to serum glucose ratio of <0.5 had a sensitivity of 0.90. Mean CSF protein and CSF glucose concentration do not differ significantly between microbiologically defined and clinically diagnosed children with TBM[29]. While comparing the confirmed TBM and confirmed bacterial meningitis, CSF lymphocytes >50 per cent were not informative[29]. In a prospective study, Solomons *et al*[30] observed >50 per cent CSF lymphocytes in 89, 84, 60 and 68 per cent in bacteriologically confirmed TBM, TBM but not bacteriologically confirmed, bacterial and viral meningitis patients, respectively.

Bacteriology

Identification of acid-fast bacilli (AFB) in CSF by smear and culture helps in confirmation of CNS TB. Growing Mtb in culture provides opportunity for drug sensitivity testing, which may influence the selection of treatment regimen. However, the sensitivity of both CSF AFB smear microscopy and culture isolation is around 20 per cent in children[23]. A minimum quantity of 5 ml CSF (preferably 10 to 15 ml) is necessary for mycobacterial investigations, and repeat samples with spinning large volumes for 30 min may increase the detection rate; however, collection of these high volumes in infants and young children is highly impractical[24]. Solid culture medium such as Lowenstein-Jensen (LJ) takes 4-6 wk on an average to give a positive result[31]. Farinha *et al*[19] showed that CSF AFB smear and culture was positive in 51 and 39 per cent, respectively, in children with TBM. CSF culture positivity was reported as 35 per cent among Greek children by Mihailidou *et al*[7]. Mtb was isolated from 12 to 30 per cent of the CSF samples in children with TBM in studies from South Africa[32] and Turkey[26] respectively. Miftode *et al*[33] reported that CSF AFB smear was negative in all samples and positive culture was observed in 31 per cent among children in Romania. The conventional solid culture media are Middlebrook 7H10, selective Middlebrook 7H11 (S7H11) and L-J medium. The BACTEC liquid culture system which is valuable for the rapid detection of mycobacteria has been more successful than conventional solid culture methods. Venkataswamy *et al*[34] showed that the isolation rates from CSF of TBM patients were 93 and 39 per cent for BACTEC and L-J, respectively. CSF culture has poor sensitivity and requires days to weeks to yield a final result. Despite prolonged attempts to develop antibody tests for the diagnosis of TBM, currently, no assay is precise enough to take the place of microscopy and culture. Nucleic acid amplification tests (NAAT) are new tools in the diagnostic arsenal for TBM[35]. When definite TBM is used as reference standard, the specificity and sensitivity for the Xpert MTB/RIF test were 100 and 39 per cent, respectively, in children[35]. A meta-analysis of 14 studies which evaluated the accuracy of NAAT in TBM diagnosis reported a sensitivity of 0.56, specificity of 0.98, negative likelihood ratio of 44 and

positive likelihood ratio of 35.1, suggesting their role in confirmation but not ideal for ruling out TBM[36]. Bhatia *et al*[37] reported the sensitivity of GeneXpert and BACTEC Culture as 38.24 and 14.71 per cent, respectively, in children suspected with TBM. Nhu *et al*[38] showed that sensitivities of smear, Xpert and Mycobacteria Growth Indicator Tube (MGIT) culture in TBM patients were 78.6, 59.3 and 66.5 per cent, respectively, in comparison to the clinical diagnosis, and Gene Xpert's specificity was 99.5 per cent. WHO recommends the use of Xpert MTB/RIF as the initial diagnostic test for CSF testing in children suspected with TBM[39]. The limitations of using Xpert for the diagnosis of TBM include false negatives which could lead to missed or delayed diagnosis as well as delayed diagnosis leading to poor outcomes[40]. WHO recommendations for the use of Xpert MTB/RIF had been revised in 2017 and also apply for the use of Xpert Ultra as the initial diagnostic test for CSF testing[41]. Combination of tests including antigen detection, molecular techniques along with smear microscopy and culture is needed for improvement in diagnosis[42]. Multi-targeted loop-mediated isothermal amplification (LAMP), a NAAT assay, has shown good sensitivity and specificity[43] which needs to be studied for further recommendations. Berwal *et al*[44] have shown a specificity of 89.6 per cent and sensitivity of 71.4 per cent for multiplex PCR.

Neuroimaging

The triad of radiological findings in TBM includes hydrocephalus, infarctions and basal meningeal enhancement[45]. The five major computed tomography (CT) features which support the TBM diagnosis include infarcts, hydrocephalus, tuberculomas, basal meningeal enhancement and pre-contrast basal hyperdensities[46]. Hydrocephalus and meningeal enhancement are important signs of TBM in CT scan, observed in 80 and 75 per cent of children with TBM, respectively[27,47,48]. Sensitivity of magnetic resonance imaging (MRI) is more than CT in detecting basal meningeal enhancement, granulomas and infarcts in paediatric TBM[45]. Basal enhancement is seen in almost all patients[49]. More than half of patients have infarcts, especially in the middle cerebral artery territory and basal ganglia[50]; lentiform nucleus infarcts are also seen[45]. Schoeman *et al*[51] reported that there was no correlation between the size of the ventricle and baseline CSF pressure whereas the subarachnoid space size in the initial CT scan correlated with ICP. MRI findings in HIV-infected children when compared to HIV-negative children include high frequency of ventricular dilatation following cerebral atrophy, high frequency of communicating hydrocephalus, less frequency of basal meningeal enhancement and granuloma formation[52,53].

Adenosine deaminase (ADA)

Rana *et al*[54] observed a positive correlation between adenosine deaminase (ADA) levels and protein in CSF; however, it was not observed between ADA levels and pleocytosis in CSF in children with TBM. Gupta *et al*[55] reported that CSF ADA level of 10 U/l or higher had a sensitivity of 94.73 per cent and a specificity 90.47 per cent for differentiating TBM from meningitis caused by other infectious agents.

Evidence of TB outside the CNS

In addition to the tests for diagnosis of CNS TB, thorough clinical examination and investigations to look for evidence of TB in the other sites including ocular examination, lymph node, gastric aspirates, bronchoalveolar lavage and ultrasound abdomen need to be considered.

X-ray chest

Almost half of the children may have an abnormal chest X-ray[56]. Chest X-ray abnormalities observed in these children include parenchymal infiltration, intrathoracic lymphadenopathy, miliary opacities, paratracheal consolidation, airway compression, thickened pleural effusion and atelectasis[26,56-59]. Güneş *et al*[59] reported that children in Stage 3 disease had fewer chest X-ray abnormalities and miliary opacities. While the percentage of children with TBM who have TB in other locations is unknown, a clinically driven thorough evaluation for TB outside the CNS is prudent and can be informative.

Tuberculin skin test (TST)

Tuberculin skin test (TST) in children with TBM contributes to diagnosis as well as prognosis. The mortality rate among children with TBM with negative TST was greater than that with positive TST[58]. TST positivity in children with TBM ranges from 18.9 to 81 per cent[7,19,26,59]. Mahadevan *et al*[60] showed that the size of the tuberculin reaction in children was larger in early stage and smaller in advanced disease of TBM and there was an association between CSF quantitative cellular response and size of TST reaction.

Case definitions of tuberculous meningitis

Before 2010, possible, probable and definite TBM was diagnosed in many different ways[20,32,48,52,61,62]. In

2010, a uniform research case definition was proposed by an international expert panel based on clinical, CSF, cerebral imaging and evidence of TB elsewhere criteria to aid scientific endeavours in this area[27]. TBM is classified as 'definite' when AFB is demonstrated in the CSF by positive culture and/or NAAT; histological changes in the CNS presenting with suggestive symptoms/signs and CSF changes or visible changes in the autopsy. Probable TBM is when diagnostic score is ≥12 and ≥10 when neuroimaging is available and unavailable, respectively, and 'possible' when diagnostic score is 6-11 and 6-9 when neuroimaging is available and unavailable, respectively[27]. The uniform research case definition was applied by Solomons *et al*[28] in a study to differentiate TBM and bacterial meningitis in children. When children with definite TBM and bacterial meningitis were compared, probable TBM score had 86 per cent sensitivity and 100 per cent specificity. The sensitivity was 100 per cent and specificity was 56 per cent for possible TBM score. The ability to detect stage 1 TBM was suboptimal, and almost one-fourth of the TBM children would be missed because of the limitations of the case definition[30].

Treatment

TBM is associated with higher death rates, and even after adequate management, residual neurological sequelae are common. Mortality is higher in early childhood as young children are at higher risk of progression to severe forms of TB[32]. Hence, empirical antituberculosis therapy (ATT) should be started when TBM is suspected. Corticosteroids should be a part of the treatment for all patients irrespective of the disease severity. The recommended steroids are dexamethasone and prednisolone[63].

Antimicrobial treatment

WHO rapid advice for TB treatment in children recommends that the children diagnosed with TBM should receive a standard four-drug treatment regimen comprising isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) for two months [the intensive phase (IP)] followed by 10 months of continuation phase treatment with H and R, and the drug doses are similar to pulmonary TB[64]. The recommended daily doses of ATT include H 10 (7-15) mg/kg, R 15 (10-20) mg/kg, Z 35 (30-40) mg/kg and E 20 (15-25) mg/kg. H has good CSF penetration and can achieve CSF levels over 30 times the minimum inhibitory concentration (MIC) of Mtb rapidly[65]. Usage of higher doses of H (10-20 mg/kg) and R (20 mg/kg) with substitution of ethionamide (Eth) for E has been successful in children in improving the treatment outcomes, but there have been no randomized trials comparing WHO standard of care to this (or other) enhanced regimen in children[66]. Pouplin *et al*[67] showed that individual concentrations of H and Z in CSF were comparable to that in plasma; however, R concentrations were lower than the MIC in most children with TBM. Study in adults with TBM using high-dose R along with a fluoroquinolone showed decline in mortality and disability[68] with supportive data from pharmacokinetic studies[69,70]. The commonly used third drug is Z which attains high concentrations in CSF[71]. The fourth drug is either E or streptomycin (S); both have poor CSF penetration[65]. Fluoroquinolones look promising for TBM treatment, but more studies are needed to prove their efficacy and safety in children[72]. A model-based approach determined the optimal dose of R in children with TBM as 30 mg/kg oral dose or 15 mg/kg intravenous dose daily and oral levofloxacin doses as 19-33 mg/kg to attain target exposures[69]. Other alternative drugs are Eth and prothionamide, used mostly in limited settings for both adults and children with TBM[73].

While WHO recommends a 12-month regimen including standard first-line TB drugs at doses intended for pulmonary TB, at country levels, different regimens are used. This is largely because of the paucity of clinical trials regarding the treatment of paediatric TBM. In one meta-analysis assessing paediatric TBM outcomes in multiple international settings, almost 27 different regimens were used with varied dosage and duration[4]. The Technical and Operational Guidelines 2016, India, recommends two months of IP with HREZ followed by four months of HRE and may be extended for another three to six months[74]. The index TB guidelines for EPTB in India recommends the duration of treatment for a period of at least nine months[75].

Among the adverse effects of ATT in children, the major concern is regarding drug-induced hepatitis (DIH), especially with the use of H, R and Z. A review on the incidence of DIH among 717 children treated for TBM reported abnormal liver function tests in nearly 53 per cent and occurrence of jaundice in 10.8 per cent of the children[76]. van Toorn *et al*[77] studied the safety and efficacy of six and nine months of treatment with RHZEth for HIV-uninfected and HIV-infected children with drug-susceptible TBM respectively in South Africa. DIH was noted in five per cent, and overall mortality was 3.8 per cent. The authors concluded that

these shorter, intensified therapies were effective and safe in children with drug-sensitive TBM irrespective of their HIV status.

All patients diagnosed with TBM should be offered HIV testing. Although the principles of treatment are similar to HIV-uninfected children, the co-existence of HIV complicates the diagnosis of TB due to atypical presentations. Simultaneous administration of antiretroviral therapy (ART) and ATT can result in cumulative toxicities, drug-drug interactions and immune reconstitution inflammatory syndrome (IRIS) thereby complicating the management[66]. While it is recommended that initiation of ART in adult patients with TBM and HIV be delayed[78], the best timing for initiation of ART in children (who are at higher risk for HIV-related sickness and death) is unknown.

There is limited information except for a few case reports regarding paradoxical reaction which is worsening of signs and symptoms of TB after initiation of ATT in children. The frequency, predictors, spectrum of paradoxical reaction and its impact on the outcome had been documented in adult patients; however, this information is limited for children with TBM.

Corticosteroids in tuberculous meningitis (TBM)

A Cochrane review on corticosteroids for managing TBM concluded that corticosteroids reduced mortality in both adults and children by 25 per cent at two months to two years after its initiation. Nine clinical trials were included in this review, of which six used dexamethasone, two used prednisolone and one compared the effects of both with a placebo. Steroids may not have an effect on disabling neurological deficits, and there is a need for further research on the optimum choice and dosing of corticosteroids[79]. It is likely that most patients are helped and some are harmed by steroids, but methods for discriminating these two populations, up to now, do not exist.

Role of host-directed therapies

Host-directed therapies (HDTs) are gaining attention nowadays, and a wide range of drugs are under evaluation to act as adjuncts to standard ATT. Some of the beneficial effects of HDTs studied in human and animal models are reduction of tissue inflammation and necrosis, dissociation of granuloma, enhanced drug penetration into granuloma, accelerated clearance of bacilli and thereby decreasing the chances of relapse[80,81]. Anti-tumour necrosis factor α (TNF-α) inhibitors are being studied in many trials as adjunctive therapy for ATT. Thalidomide showed promising results in animal studies[82], but a clinical trial in children reported deaths and adverse events such as neutropenia, hepatitis and skin rashes[83]. Other newer anti-TNF-α inhibitors such as pentoxifylline, adalimumab and etanercept are currently under testing for shortening the duration of anti-TB treatment[80].

Phosphodiesterase inhibitors-I, matrix metalloproteinase inhibitors, vitamin D and efflux pump inhibitors are group of drugs with potential to improve outcomes and shorten the treatment duration, but their beneficial effects on children with TBM need to be established[80,81]. Varying doses of aspirin does not play a role in improving the motor and neurocognitive outcomes in children with advanced disease[84].

Role of surgery

Hydrocephalus, a frequent complication of TBM, can be managed medically with diuretics, osmotic agents or interventions such as serial lumbar punctures, external ventricular drainage or ventriculoperitoneal shunts (VPS)[14]. The indications for VPS including obstructive hydrocephalus and monitoring of ICP are essential to determine the urgency of the procedure in case of communicating hydrocephalus[85]. Early VPS in children with significant hydrocephalus reduces morbidity and mortality and also is a favourable predictor of good outcome[26].

Drug-resistant TBM

There is a paucity of information regarding TBM due to drug-resistant strains. A study from South Africa reported eight paediatric cases of multidrug-resistant TBM (MDR-TBM)[86]. Mortality was high (87.5%) and HIV co-infection was present among 75 per cent. Risk factors that contributed to high mortality were delay in diagnosis, disseminated disease, HIV co-infection, absence of standardized approach to MDR-TBM treatment and poor penetration of MDR-TB drugs into the CSF[86]. Another South African study investigated the impact of drug resistance on the clinical outcomes of 123 children with TBM[87]. Young age and MDR TB were risk factors for unfavourable outcome whereas there was no significant difference in the outcome between H mono-resistant and drug-susceptible TBM[87]. This suggests that the role of rifampicin is critical in the treatment of TBM. For drug-resistant TB, a drug with similar sterilizing activity that can arrest the progression of TBM to death is urgently needed.

Outcomes

Many of the studies reporting treatment outcomes in paediatric TBM were retrospective chart reviews (Table I). Mortality rates varied between 5 and 23 per cent. Around 14-52 per cent of the children with TBM had post-treatment neurological sequelae. A systematic review of the treatment outcomes of childhood TBM published in 2014 analyzed 19 studies and 1636 children. The risk of mortality despite treatment was 19.3 per cent, and the chances of survival without disability was 36.7 per cent. Children diagnosed in the advanced stages of disease had poor outcomes[4]. van Well *et al*[32] reported that 16 per cent of the children were normal, 52 per cent had mild sequelae, 19 per cent had severe sequelae and 13 per cent died when followed up after six months. In a study from southern India, children treated for TBM were reviewed after 2 to 7 yr, 46 per cent had behavioural problems, 46 per cent had poor schooling performance, 22 per cent had neurological deficit and 15 per cent had seizure disorder[95]. Miftode *et al*[33] reported that children had higher frequency of neurological deficits; however, mortality rates were similar to adults.

Hyponatremia is common in TBM. A study among children with TBM in Mumbai showed that around 39 per cent of the children with TBM had hyponatremia and the cerebral salt-wasting syndrome was more common than syndrome of inappropriate antidiuretic hormone. Higher mortality rate was observed in children with hyponatremia than children with normal levels[96]. Appropriate management of this electrolyte imbalance is important in improving the treatment outcomes.

Prevention

WHO recommends that Bacillus Calmette-Guérin (BCG) needs to be given at birth or shortly after birth[97]. BCG vaccine protects against TBM-associated mortality, especially in the first two years of life[57]. Kumar *et al*[98] reported that BCG failed to give protection for those who were more than five years of age if the weight was 60 per cent less than that of the expected weight for age and in the presence of a household contact with TB. One case of TBM is prevented for every 3500 inoculations of BCG vaccine, and the efficacy against meningitis is around 73 per cent[99]. Even though BCG vaccination does not totally prevent the occurrence of TBM, vaccinated children with TBM have better mentation and outcomes than unvaccinated children[100]. Farinha *et al*[19] reported that none of the BCG-vaccinated children with TBM died or had severe sequelae. Perhaps, the most important way to prevent TBM is to provide TB preventive therapy to young child contacts of TB patients.

Future research

Marais *et al*[101] proposed standardized methods to do research in TBM which could improve the quality of future research and provide basis for a global TBM data repository. Dhawan and Sankhyan[102] suggested additional details which could be included to this set of guidelines. However, these guidelines should be validated to improve future TBM research.

Way forward

Data regarding the global as well as the regional burden of paediatric EPTB, especially TBM are limited. Surveillance system strengthening across the globe, especially in high-burden countries is urgently needed for implementation of appropriate preventative and treatment measures. Clinical features of paediatric TBM often mimic diseases due to viral, bacterial and fungal infections. Children often present in the late stage of the disease which is associated with higher morbidity and mortality. Hence, a high degree of suspicion is needed for the early diagnosis and management. Children have different disease manifestations than adults, with apparently low mortality but high risk for neurocognitive and behavioural disabilities. WHO recommends the use of Xpert MTB/RIF as the initial diagnostic test in children with TBM for testing CSF. The more sensitive Xpert ultra has been introduced but its testing in children is limited. Treatment of TBM is based on the regimen for pulmonary TB. Previous studies show that R concentrations achieved in the plasma and CSF are subtherapeutic; E and S do not penetrate the CSF. Adjunctive and host-directed therapies show promise in small groups of patients (Table II). Most antimicrobial treatment studies have been observational or retrospective reviews; hence, randomized clinical trials need to be planned to identify an ideal regimen with optimal dosages for the paediatric TBM management to improve the treatment outcomes in this population.

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Table I. Treatment outcomes among children with TBM in various studies across different parts of the world

Author(s) and country	Study design and study duration	Study population	Staging/grading of disease severity (%)	ATT and steroids	Treatment outcome (%)			Factors associated with outcome
					Complete recovery	Death	Neurologic sequelae/disability	
Ramachandran *et al*[89], Chennai, India	Three chemotherapy studies	180 children with TBM aged between 1 and 12 yr	1-13 2-77 3-9 (Modified BMRC staging)	2SHR/4S_2EH/6EH or 2SHRZ_2/10EH or 2R_2SHZ/10EH Steroids for 6-12 wk	34	27	39	Presentation at Stage 1 - Better outcome Presentation at Stage 3 - Poor outcome
Mihailidou *et al*[7], Greece	Retrospective record review, 1984-2008	43 children with TBM aged between 7 months to 13 yr	1-37.2 2-37.2 3-25.6 (BMRC staging)	2HRSZ or E/10HR (47%) 2HRS or Z/10HR (26%) HR (27%) Steroids for 3-4 wk		5	14	Presentation at Stage 3 - Poor outcome
Ramzan *et al*[18], Kashmir, India	Prospective study, 2007-2011	65 children diagnosed with TBM, aged 19 months to 13 yr	1-32 2-51 3-17 (Modified criteria of MRC staging)	3HRZE/9HR steroids for initial 4-6 wk		6		Low GCS, seizures and basal exudates, infarcts in CT - Poor outcomes
Farinha *et al*[19], London, UK**	Retrospective cohort study (last 9 patients prospective) 1977-1997	38 children with CNS TB, 23 with TBM, 10 TBM with tuberculomas, 5 with tuberculomas, aged between 8 months and 16 yr	1-6 2-30 3-64 (BMRC staging)	ATT with concurrent steroids		13	47	Past history of BCG vaccination - Better outcome Stage 3 disease - Poor outcome
Karande *et al*[20], Mumbai, India	Prospective observational study, 2000-2003	123 children with TBM, aged between 3 months and 12 yr	1-4 2-10 3-86.2 (BMRC staging)	2 HRZE/4 HR steroids for 4 wk	20	23	57	Hypertonia - Predictor of neurological sequelae Deep coma - Poor outcome
Thilothammal *et al*[25], Chennai, India	Case-control study, 1990-1992	107 children with TBM, aged between 6 months and 12 yr	1-20 2-60 3-20 (Gordon and Parson)[88]	2HRZS/10HR steroids for the first 4-6 wk		22	53	Young age, late stage of the disease and high CSF protein value - Poor outcome
Yaramiş A *et al*[26], Turkey	Retrospective record review, 1988-1996	214 children with CNS TB aged between 3 months and 15 yr	*** 1-10 2-56 3-34	2HRS or Z/10 HR steroid therapy in the first month		23		Early VP shunting for hydrocephalus - Better outcome Children less than five years - Poor outcome

Contd...

Author(s) and country	Study design and study duration	Study population	Staging/grading of disease severity (%)	ATT and steroids	Treatment outcome (%)			Factors associated with outcome
					Complete recovery	Death	Neurologic sequelae/disability	
van Well *et al*[32], Cape Town, South Africa	Retrospective cohort study, 1985-2005	554 children diagnosed with TBM, 2 months to 15 yr	1-2.6 2-57.3 3-40.1 (Modified criteria of MRC staging)	6 HRZEth steroid in the first month	16	13	71	African ethnicity, stage 3 of disease, motor deficits, brainstem dysfunction, and cerebral infarctions - Poor outcome
Miftode *et al*[33], Romania	Retrospective record review, 2004-2013	77 children diagnosed with TBM, 3 months to 15 yr	1-26 2-52 3-22 (Gordon and Parson)[88]	2-3HRZE/7-9 HR_3		8	36	-
Güneş *et al*[59], Turkey	Retrospective record review, 1998-2008	185 children with TBM, 4 months to 18 yr	1-36.8 2-30.8 3-32.4 (BMRC staging)	2HRS, Z or E/10 HR steroids in the first month		13		Diagnosis at early stage - Better outcome
Nabukeera-Barungi *et al*[90], Cape town, South Africa**	Retrospective record review, 2009	40 children with TBM aged between 6 wk to 12 yr	2-50# 3-50 (Modified criteria of MRC staging)	RHZEth with steroids Neurosurgical procedures-25%	43	8	49	Stage 3 on admission, longer mean hospital stay, surgery - Poor outcome
Faella *et al*[91], Italy	Retrospective study, 1986-2001	32 children with TBM aged between 8 and 160 months	1-16 2-30 3-53 (MRC staging)	2 HRS (with E or Z for 10 patients)/10-18 HR, Steroids for 3-6 wk		13	19	Quick normalization of CSF parameters (proteins, glucose, cells) - better outcome Long-lasting pre-admission non-specific symptoms, elevated CSF protein, stage 3 disease and ventricular dilation - Poor outcome
Rohlwink *et al*[92], South Africa	Prospective cohort study, October 2010 and August 2013	44 children with TBM and associated hydrocephalus aged between 3 months to 13 yr	1-9 2a-38.6 2b-31.8 3-20.5 (Refined criteria of MRC staging)	2 HRZEth/4-6 HR Steroids for 3 wk		16	36.6	Elevated polymorphonuclear cells in CSF - Better outcome Multiple or large infarcts, - Poor outcome

Contd...

Author(s) and country	Study design and study duration	Study population	Staging/grading of disease severity (%)	ATT and steroids	Treatment outcome (%)			Factors associated with outcome
					Complete recovery	Death	Neurologic sequelae/disability	
Bang *et al*[93], Vietnam	Prospective descriptive study, October 2009-March 2011	100 children with TBM, aged between 2 and 180 months	*Children >5 yr* (Modified MRC staging) 1-48 2-33 3-18 *Children <5 yr* (Blantyre coma score) 1-64 2-18 3-18	2HRZES/1HRZE/5HRE with adjuvant steroids Outcome Death - 15.7% Severe disability -7.4% Intermediate disability - 26%		15.7		History of coma, seizures, neck stiffness, decreased level of consciousness, FND, Stage 3 disease - Poor outcome
Dhawan *et al*[94], India	Prospective cohort study (October 2010 to June 2012)	130 children	1-20 3-36.9 (Modified MRC staging)	2HREZ/10 HR with adjuvant steroids Outcome at discharge: Death - 29%		29	26.5	Stage 3 at presentation, infarcts in neuroimaging - Poor outcome

**Treatment recommendations as per the National Guidelines changed over the period surveyed and patients received various combinations of anti-TB drugs, ***Staging of disease severity explained but name of the staging method not mentioned, #Staging was done for only 18 patients, for whom GCS was available. VP ratio - ventricular diameter at the midportion of the body of the lateral ventricles and P is the biparietal diameter measured from inner table to inner table. MRC, Medical Research Council; ATT, antituberculosis therapy; BMRC, British MRC; CNS, central nervous system; CSF, cerebrospinal fluid; FND, focal neurological deficit; R, rifampicin; H, isoniazid; E, ethambutol; Eth, ethionamide; Z, pyrazinamide; S, streptomycin; TBM, tuberculous meningitis; GCS, Glasgow Coma Scale; CT, computed tomography; TB, tuberculosis; BCG, Bacillus Calmette-Guérin

Table II. Gaps and needs in the diagnosis and management of paediatric tuberculous meningitis (TBM)

Existing gaps	Research needs
Disease burden of EPTB especially TBM and DR-TBM in children	Strengthening surveillance system across the globe especially in high burden countries[6].
Diagnostic challenges	Role of newer molecular tests such as Xpert Ultra for the early detection of TB in children and in extrapulmonary specimens[41]. Point-of-care rapid tests for diagnosis.
Children prone to poor prognosis	Biomarkers to identify children prone to poor outcomes including death, neurological deficits and neurocognitive, behavioural disabilities. Role of adjunctive therapy in improving the treatment outcomes[80]
Treatment regimens with poor CSF penetration and concentration	PK studies to understand the CSF concentrations of the ATT[67]. Studies to determine the association of CSF concentrations of ATT and treatment outcome.
Use of varied treatment regimen with different dosages and duration in different regions of the globe	Efficacious and effective regimen to improve treatment outcomes[69,77].
H prophylaxis for childhood contacts	Strategies to strengthen the H prophylaxis for contacts of TB patients.
Research methodology	Prospective studies and randomized control trials with uniform strategies and format for better understanding of the disease and improve treatment outcomes[101,102].

TB, tuberculosis; EPTB, extrapulmonary TB; DR, drug-resistant; ATT, antituberculosis therapy; CSF, cerebrospinal fluid; H, isoniazid; PK, pharmacokinetics

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