Treatment and outcome in children with tuberculous meningitis – a multi-centre Paediatric Tuberculosis Network European Trials Group study

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Brief summary

This European multi-center study provides data on the management and outcome of TB meningitis in children, highlighting that both morbidity and mortality remain high even in high-resource settings. Several key factors associated with unfavourable outcome were identified.

Abstract

Introduction

Currently, data on treatment, outcome, and prognostic factors in children with tuberculous meningitis (TBM) in Europe are limited. To date, most existing data on TBM originate from adult studies, or studies conducted in low-resource settings.

Methods

Multicentre, retrospective study involving 27 paediatric healthcare institutions in nine European countries via an established paediatric TB research network, before and after the 2014 revision of WHO dosing recommendations.

Results

Of 118 children, 39 (33.1%) had TBM grade 1, 68 (57.6%) grade 2 and 11 (9.3%) grade 3. Fifty-eight (49.1%) children received a standard four-drug treatment regimen; other commonly used drugs included streptomycin, prothionamide, and amikacin. Almost half of the patients (48.3%; 56/116) were admitted to intensive care unit, with a median stay of 10 (IQR 4.5-21.0) days. Of 104 children with complete outcome data, 9.6% (10/104) died, and only 47.1% (49/104) recovered fully. Main long-term sequelae included spasticity of one or more limbs and developmental delay both in 19.2% (20/104), and seizure disorder in 17.3% (18/104). Multivariate regression analyses identified microbiological confirmation of TBM, the need for neurosurgical intervention and mechanical ventilation as risk factors for unfavourable outcome.

Discussion

There was considerable heterogeneity in the use of TB drugs in this cohort. Despite few children presenting with advanced disease and the study being conducted in a high-resource setting, morbidity and mortality were high. Several risk factors for poor outcome were identified, which may aid prognostic predictions in children with TBM in the future.

List of abbreviations

AMK	amikacin
BCG	*Bacillus Calmette-Guérin*
CI	confidence interval
CSF	cerebrospinal fluid
EMB	ethambutol
GCS	Glasgow coma scale
ICU	intensive care unit
IGRA	Interferon-γ release assay
INH	isoniazid
IQR	interquartile range
MDR	multidrug-resistant
MRC	Medical Research Council
MRI	magnetic resonance imaging
NAAT	nucleic acid amplification test
OR	odds ratio
ptbnet	Paediatric Tuberculosis Network European Trials Group
PTH	prothionamide
PZA	pyrazinamide
RMP	rifampicin
SM	streptomycin
TB	tuberculosis
TBM	tuberculous meningitis
TST	tuberculin skin test
WHO	World Health Organization

Key words

Tuberculous meningitis, treatment, dosing, children, outcome

Introduction

In 2018, 52,862 cases of tuberculosis (TB) were reported in the European Union and European Economic Area, of which 4.0% were children <15 years-of-age (1). After TB lymphadenitis, tuberculous meningitis (TBM) is the most common form of extrapulmonary TB in children (2). TBM is associated with higher morbidity and mortality than any other form of focal TB disease (3, 4) (5). TBM diagnosis can be challenging because the onset is often insidious with non-specific symptoms, and classic meningitic symptoms can be absent. Advanced clinical stage at presentation is associated with higher mortality and morbidity: rates of death or severe disability are up to 50% in British Medical Research Council (MRC) grade III TBM despite appropriate treatment (5-9).

The current World Health Organization (WHO) treatment recommendation for children with drug-susceptible TBM comprises isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) and ethambutol (EMB) for the initial 2 months, followed by 10 months of INH and RMP (10). This recommendation is adapted from pulmonary TB treatment and based on limited evidence (11). In view of mounting evidence that the drug doses recommended in the 2006 WHO guidelines achieved only suboptimal serum concentrations in children, higher doses were recommended in a WHO Rapid Advice document in 2010, and subsequently incorporated formally into the 2014 WHO guidelines (10, 12, 13). Steroids are recommended as adjunctive therapy (10, 14).

Published data on management and outcome of paediatric TBM in Europe are limited, and mainly comprise case reports and series from single centres (15-20). This study aimed to describe treatment, outcome, and prognostic factors of TBM in a European cohort of children for whom we have previously reported the performance of immune-based and microbiological diagnostic tests (21).

Methods

Members of the Paediatric Tuberculosis Network European Trials Group (ptbnet) based in Europe, which includes more than 300 clinicians and researchers based in 31 European countries as per November 2020, were invited to retrospectively report all children and

adolescents (0-16 years-of-age) with TBM treated consecutively at their institution between 2006 and 2016. The study opened in February 2016, and reporting closed in August 2016. Anonymised data were collected via a web-based tool that created a standardized dataset for each case. The study approved by the Human Ethics Committee of the Charité University Hospital Berlin and the ptbnet Steering Committee.

Classification of cases and disease severity

Disease severity at diagnosis was classified according to MRC Staging (22). Cases were categorised as definite, probable and possible TBM according to previously published criteria with minor modification, as previously described (21, 23). Briefly, to be eligible for inclusion cases had to meet the clinical entry criteria (presence of symptoms and signs of meningitis), and achieve a Uniform Tuberculous Meningitis Research Case Definition Criteria (UTMRCD) score of ≧6 (supplementary material).

Classification of outcome

The following parameters were collected to assess outcome at the end of treatment: paresis of ≧1 limb(s), spasticity, cranial nerve palsy, seizures, hypothalamic/pituitary gland dysfunction, developmental delay, chronic hydrocephalus, vision, hearing or speech impairment, coma or death. Additional data could be provided as free text. For binary logistic regression modelling, patients were grouped as “fully recovered” or “unfavourable outcome”, the latter if any long-term sequelae or death occurred.

Assessment of drug dosing

Drug dosages were assessed according to the 2010/2014 WHO dosing guidelines for children admitted after 31/12/2010, and according to the 2006 guidelines for children admitted up to that date (10, 12). Currently, the recommended doses for TBM treatment with the WHO 12-month regimen are: INH 10mg/kg (range 7–15mg/kg, maximum 300mg/d), RMP 15mg/kg (10–20mg/kg, maximum 600mg/d), PZA 35mg/kg (30–40mg/kg) and EMB 20mg/kg (15–25mg/kg) (10, 13). The 2010 Rapid Advice differed only in the recommended range for INH (10–15mg/kg). The recommended doses in the 2006 guidelines were: INH 5mg/kg (4–6mg/kg), RMP 10mg/kg (8–12mg/kg), and PZA 25mg/kg (20–30mg/kg), with the same EMB dosing. Patients with higher bodyweight, in whom the maximum daily dose based on mg/kg would be

exceeded, were excluded from this particular analysis. Regarding corticosteroids, currently recommended daily doses of dexamethasone are 0.6mg/kg and prednisone 2–4mg/kg (10, 14). For all corticosteroids used, the prednisolone equivalent dose was calculated (24).

Statistical analysis

Data analyses were conducted with SPSS (V25; IBM, Armonk, NY, U.S.). Patient characteristics are presented as median and interquartile ranges (IQR), and qualitative data as frequencies (number and percentage of patients). When specific data were not available for all patients, the denominator is specified. For analyses of the time between hospital admission and cerebral spinal fluid (CSF) examination, cranial imaging or initiation of anti-TB treatment, only cases in whom data were available and the procedures had been performed between the day of admission and the first 70 days were included.

Binary logistic regression modelling was used for bivariate and multivariate analysis to test the effect of covariates as risk factors for unfavourable outcome. Results are presented as unadjusted and adjusted odds ratios (OR) with 95% confidence intervals (95%CI). For the multivariable analysis, only variables with statistical significance from the bivariate analysis, together with age and gender, were included. A two-tailed p-value <0.05 was considered statistically significant.

Results

Twenty-seven healthcare centres located in Spain (n=12), Germany, Italy, the United Kingdom (n=3, each), Sweden (n=2), Bulgaria, Finland, Greece, and Slovenia (n=1, each) contributed cases. A total of 118 children fulfilled the inclusion criteria and were included in the final analysis; one submitted case was excluded as it did not reach the minimum UTMRCD score. The median age was 2.7 years (IQR:1.1-6.4). Thirty-nine children (33.1%) presented with stage I disease, 68 (57.6%) with stage II, and 11 (9.3%) with stage III. Fifty-four children (45.8%) were categorised as having definite, 38 (32.2%) probable and 26 (22.0%) possible TBM (table 1). Only five had confirmed multidrug-resistant TB (MDR-TB). The demographic data and clinical features of this cohort have previously been detailed (reproduced as table S2, supplementary material) (21).

Time to TBM investigations and treatment initiation

The median time from hospital admission to CSF examination was 1.0 day (IQR:0.0-4.8 days; n=104), between admission and cranial imaging 2.0 days (IQR:0.0-7.0;n=70), between hospital admission and initiation of TB treatment 3.0 days (IQR:1.0-8.8;n=92), and between CSF examination and the initiation of treatment 1.0 day (IQR:0.0-4.0;n=101). Time between admission and treatment initiation varied between disease stages: a median of 5.0 days (IQR:0-17.0;n=33) in stage I disease, 3.0 (IQR:1.0-10.0;n=63) days in stage II, and 4.0 (IQR:0.5-4.5;n=9) days in stage III (p=0.223). The time between admission and treatment initiation was 2.0 days (IQR:0.0-8.0;n=39) in children who fully recovered, and 4.0 days in children with unfavourable outcome (IQR:1.0-11.0;n=47;p=0.431) (Figure 1).

Antituberculosis treatment

The most frequently used initial anti-TB drugs, dosage and duration are shown in table 2. Among 54 children admitted before the end of 2010 in whom both bodyweight and dosing of at least one drug dose were available, 2 (3.7%) were underdosed for one or more anti-TB drugs according to the 2006 WHO dosing recommendations prevalent at the time: one child was underdosed for EMB only and one for both EMB and INH (none underdosed for RMP or PZA). Among 64 patients admitted from 2011 onwards, 18 (28.1%) were underdosed for one or more anti-TB drugs according to the 2010/2014 dosing guidelines used from then onwards: INH in 4 (6.3%) children (using 7mg/kg as lower limit), RMP in 2 (3.1%), PZA in 14 (21.9%), none for EMB. Drug dosing across the entire study population in relation to the 2006 WHO dosing recommendations and the revised 2010/2014 recommendations is shown in Figure S1. Information on dose adjustment with weight gain during the course of therapy is not available.

Twenty-two children were treated for <12 months and three for <6 months (the latter three died before treatment completion). Figure 2 shows the most frequent initial treatment regimens, with 50.4% (58/115) initially receiving standard four-drug combination therapy. In 15 children this regimen was supplemented with streptomycin (SM) (5 children admitted to hospital before 2006) and in eight with amikacin (n=8). Additional anti-TB drugs used included levofloxacin (n=4), ethionamide (n=3), moxifloxacin (n=3), *para*-aminosalycylic acid (n=1), cycloserine (n=2) and ciprofloxacin (n=1).

Anti-inflammatory medication

Overall, 97.4% (113/116) of patients received corticosteroids, mainly dexamethasone (71.6%;n=83/116) or prednisone (19.8%;n=23/116). The median daily dose used initially was 0.57 (IQR:0.12-0.60) mg/kg for dexamethasone and 1.36 (IQR:0.74-3.05) mg/kg for prednisone, with 40.9% (34/83) and 26.1% (6/23) children, respectively, receiving doses below the recommended ranges (10). Median duration of the initial course of steroids was 42 days (IQR: 26.5-60.0;n=77). Sixteen patients (13.8%) had more than one course of corticosteroids. Other anti-inflammatory medication used included thalidomide (8.6%; n=10), acetylsalicylic acid (4.3%;n=5), naproxen (1.3%;n=1), dexketoprofen (1.3%;n=1) and infliximab (1.3%;n=1).

Other adjunctive treatments

Almost one third of patients (32.8%;38/116) received anticonvulsive treatment at some stage either as prophylactic or therapeutical treatment of seizures. Close to one third (29.3%;34/116) received vitamin D, 14.7% (17/116) proton-pump inhibitors and 10.3% (12/116) diuretics.

Neurosurgical intervention

Data on neurosurgery were available in 116 patients. Thirty-eight (32.7%) patients underwent one or more neurosurgical interventions, comprising placement of a ventriculo-peritoneal shunt in 97.4% (37/38), granuloma excision in 5.2% (2/38) and other procedures in 10.5% (4/38) children. Only one patient was reported to have received acetazolamide to reduce intracranial pressure prior to surgery.

Supportive therapy and healthcare facilities

The majority of children were treated in a hospital ward (87.9%;102/116) for a median duration of 28 days (IQR:14.0-78.8 days). Almost half (48.3%;56/116) were admitted to ICU at some stage, with a median ICU stay of 10.0 days (IQR:4.5-21.0 days). Of these, 17.8% (10/56) initially presented at TBM stage I, 66.1% (37/56) at stage II and 16.1% (9/56) at stage III. Mechanical ventilation was required in 20.7% (24/116). Other healthcare facilities included rehabilitation centres (20.7%;n=24) and day-care clinics (13.8%;n=16). The most frequently

used supportive measures were physiotherapy (36.3%;n=42), occupational therapy (17.2%;n=20) and speech therapy (20.7%;n=24).

Initial response to treatment and change of medication

Clinical improvement, as determined by the treating physician, occurred in 82.6% (95/115) of the children, of which 8.4% (8/95) showed initial worsening followed by improvement. No improvement or progressive worsening on treatment was observed in 17.4% (20/115; data missing n=3). Anti-TB treatment was changed in 17.2% (20/116), due to adverse events (n=5), detection of drug-resistant *Mycobacterium tuberculosis* (n=5), clinical or radiological deterioration (n=4), or other reasons (n=6).

Outcome

One-hundred-and-four children with available outcome data were followed up for a median of 20.0 months (IQR:9.0-25.0 months). Ten children died (9.6%) of whom one had MDR-TB. The timepoint of death was available in 5 children: 3 died within the first 4 months of anti-TB therapy; the remaining 2 died at 9 and 12 months. Fewer than half (47.1%;49/104) of the children made a full recovery, while 55 had an unfavourable outcome (52.9%;55/104). Detailed information on outcomes is presented in table 3. Almost half of the children (49.2%;58/118) showed evidence of hydrocephalus on initial imaging, while four (3.4%;4/118) developed hydrocephalus subsequently. In 12.5% (13/104) hydrocephalus was reported to be still present at the end of therapy although not all patient had neuroimaging at the end of therapy; of those, 46.2% (6/13) had a VP shunt. Of 11 children with hearing impairment, 2 had received SM as part of the initial treatment (none amikacin).

Risk analysis for unfavourable outcome at the end of treatment

The multivariate logistic regression analysis included 104 patients. Tables 4 and 5 show predictor variables of unfavourable outcome and the results of the bivariate and multivariate logistic regression models.

In bivariate analysis, more severe TBM stage at presentation, microbiological confirmation of TBM (ie definite TBM), presence of hydrocephalus on initial imaging, the need for neurosurgical intervention, requiring mechanical ventilation and requiring admission to ICU

were significantly associated with unfavourable outcome (table 4). In multivariate analysis, microbiological confirmation of TBM, surgical intervention, and mechanical ventilation remained statistically significantly associated with unfavourable outcome, with TBM stage III approaching statistical significance. No association between INH, RMP and PZA dose and unfavourable outcome was observed (table 5).

Discussion

To our knowledge, this is the largest report focused on treatment and outcome of TBM in children in Europe to date. Our data show that TBM is an extremely severe manifestation of TB disease in European children. More than half of the patients (52.9%) had unfavourable outcomes and close to 10% died.

One notable finding is the considerable heterogeneity in the drug combinations and dosing of TB medications. While underdosing according the 2006 guidelines in children admitted before 2011 was rare, more than a quarter of children admitted from 2011 onwards were underdosed for at least one anti-TB drug, most commonly for INH and PZA. This finding might reflect challenges in implementing the new guidelines, potentially resulting from the lack of appropriate pediatric fixed-dose combinations, as previously highlighted (25).

Notably, recent pharmacokinetic data suggest that INH doses >10-15 mg/kg may be required in children with TBM, particularly with higher doses needed per weight <10kg (26). For PZA and RMP, doses at the higher end of the recommended range have also been advocated for children with TBM (27-31), partly as there are data in adults with TBM suggesting that increased dosing of RMP (35mg/kg or even higher) may be associated with a survival benefit (32-34). Nevertheless, in the statistical analysis, we did not find an association between INH, RMP and PZA dosing and unfavourable outcome.

Some guidelines recommend SM or another aminoglycoside as a fourth or fifth drug in the initial treatment of TBM (35). Aminoglycosides penetrate the CSF poorly once inflammation subsides, and have a substantial risk of nephro- and ototoxicity, although we observed

relatively low rates in our study (22, 36-38). Despite its disadvantageous side effect profile, SM was used in >20% of children in our study (27, 29).

While INH and PZA penetrate the CSF well, RMP diffusion is markedly reduced in uninflamed meninges (26, 39). EMB also crosses the blood-brain-barrier poorly (26). A South African group has been advocating a 6-month intensified 4-drug regimen for drug-susceptible TBM since long before its adoption as an alternative regimen by WHO in 2021, comprising INH (20mg/kg), RMP (20mg/kg), PZA (40mg/kg) and ethionamide (20mg/kg), which has good CSF penetration, instead of EMB (28, 40). Thirteen children in our cohort received a regimen that included ethionamide or prothionamide – the propyl analog of ethionamide. The quinolones levofloxacin and moxifloxacin have been considered a valuable alternative (41-45) and paediatric studies are currently ongoing (TBM-KIDS: https://clinicaltrials.gov/ct2/show/NCT02958709 and SURE: http://www.isrctn.com/ISRCTN40829906). Linezolid, an agent with good CNS penetration, is also currently being investigated as TBM treatment in adults (SIMPLE study:NCT03537495, Laser TBM:NCT03927313, ALTER:NCT04021121, INTENSE-TBM:NCT04145258). In our cohort, anti-TB drugs were tolerated well overall, with treatment changes due to side effects being required in <5% of patients.

Adjunctive anti-inflammatory therapy forms an essential part of TBM treatment. A Cochrane review conducted in 2008 and updated in 2016 found that steroid use in TBM reduces the risk of death significantly (46, 47). The large majority of children in our cohort received either prednisone or dexamethasone, but in a substantial proportion the doses used were lower than recommended. Thalidomide is sometimes used in TBM treatment due to its anti-inflammatory and immunomodulatory properties, and was given to 10 patients in our cohort, 9 of whom also received corticosteroids (48-50).

The patient outcomes in our cohort illustrate the high mortality and morbidity associated with TBM, even in high-income settings. A recent meta-analysis on childhood TBM, which included data from 19 studies, reported a pooled mortality rate of 20%, substantially higher than the mortality rate observed in our cohort (9.6%) (9). However, the meta-analysis only included 6 studies from low TB incidence, high-resource countries, and those studies contributed fewer

than a quarter of the patients included in the analyses (361 of 1636). Also, almost half of the patients included had stage III disease (n=307 (47%) of 657 patients in whom disease stage was reported), compared with only 9.3% in our cohort. Furthermore, none of the children in our cohort had a known immunodeficiency, contrasting with studies in high TB incidence countries with comparatively high rates of HIV-/TB-co-infection. Finally, it appears likely that the greater availability of ICU support in our high-resource setting played a substantial role. Notably, almost half of the patients in our cohort were treated in an ICU, and about a fifth required mechanical ventilation. While admission to ICU may be a precautionary measure in settings with limited TBM expertise, the need for mechanical ventilation reflects severity of disease better and was associated with unfavourable outcome in our study. We observed a high rate of neurosurgical interventions, also likely reflecting the severity of the disease. In our study, a significant proportion of patients had a seizure disorder at the end of treatment requiring long-term anticonvulsant therapy, which aligns with previous data (51-53). Long-term rehabilitation, such as speech therapy and physiotherapy, was also frequently required.

Fewer than half of the children had fully recovered at the end of treatment, despite <10% of the cohort having presented at stage III disease. Studies from high incidence countries report comparable numbers of children with full recovery, despite a higher proportion of children presenting at an advanced disease stage (5, 6, 9). This might be due to differences in the definition of outcome variables, the assessment procedures used and the duration of follow-up between contributing centers. However, our data indicate that full recovery is less likely in children with more advanced disease (ie stage II and stage III disease) than in those presenting earlier (ie at stage I disease). In the aforementioned South African cohort receiving short intensified treatment, 43% of the children showed full recovery, and 37% had only mild impairment, despite 35% presenting with stage III TBM (28).

Delays in treatment initiation can negatively impact on the outcome of TBM (7, 9). Although the time between hospital admission and treatment initiation was shorter in children who fully recovered compared to children with long-term sequelae, this did not reach statistical significance in the bivariate analysis. A recent single-center study on TBM in children from China reported that raised CSF protein concentrations were linked to poor outcome, which we did not observe in our cohort (54). However, we identified definite diagnosis of TBM as a

risk factor for unfavorable outcome in both bi- and multivariate analyses. This could be due to those patients having more advanced disease with higher bacterial burden overall. Support for this hypothesis lies in the observation that microbiological confirmation was achieved in 63.6% (7/11) of patients with stage III disease, compared with only 34.2% (13/38) in those with stage I disease (table 1).

Our study has some limitations. Most importantly, the retrospective study design carries the risk of recall and selection bias. There were also incomplete data available for some variables. The long duration of the study period and inclusion of sites in several countries resulted in the ability to compile a large cohort with this relatively uncommon condition in Europe, but there was considerable variation in clinical practice and local and international guidelines over the study period.

Our data highlight substantial heterogeneity in paediatric TBM treatment in the European setting in recent years. The associated morbidity and mortality were considerable, despite the widespread availability of ICU and neurosurgical support. Early consideration of TBM in the differential diagnosis, application of up-to-date pharmacokinetic data, data on new or repurposed drugs and multidisciplinary management are essential to optimize treatment. The combination of prospective case registries by research collaborations, such as ptbnet, and the results of currently ongoing TBM treatment trials in children, will hopefully provide further insights helping to improve patient outcomes.

Author's contributions: ST and RK conceived of the study. ST, DBG, BSG, MTs, MTe, and RK designed the study and collected the data. ST and RS performed the data analyses. LFN, ON, ANJ, CL, LG, EV, DB, FG, RK, NMA, SV, FB, RB, SBW, MTs and MTe contributed data, reviewed the data and provided input. ST, RB and RK wrote the first draft of the manuscript. All authors and collaborators have reviewed the paper and have provided comments, and have approved the final version of the manuscript for submission.

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Figures and tables

Table 1 *Disease stage at presentation and degree of certainty of TB meningitis diagnosis**

	Stage I	**Stage II**	**Stage III**	**Total**
Definite TBM	13 (24.1%)	34 (63.0%)	7 (13.0%)	54
Probable TBM	14 (36.8%)	20 (52.6%)	4 (10.5%)	38
Possible TBM	11 (42.3%)	15 (57.7%)	0	26
Total	38	69	11	118

* based on Basu Roy et al. (21)

Table 2 *Anti-tuberculosis drugs used, drug dosing during initial treatment and treatment duration in the entire cohort (n=118)*

Anti-TB drug	No. of patients receiving drug	No. of patients with drug dose available	Median dose in mg/kg (IQR)	No. of patients with treatment duration available	Median treatment duration in months (IQR)
Isoniazid	115 (97.5%)	70*	10.0 (5.9-11.1)	73	12.0 (9.0-12.0)
Rifampicin	115 (97.5%)	72**	13.6 (10.0-16.5)	70	12.0 (8.0-12.0)
Pyrazinamide	114 (96.6%)	69	30.0 (27.8-34.7)	69	2.0 (2.0-4.0)
Ethambutol	87 (73.7%)	53	20.8 (18.5-25.0)	55	2.0 (2.0-3.0)
Streptomycin	27 (22.9%)	21	20.0 (20.0-20.0)	27	2.0 (1.0-2.0)
Amikacin	12 (10.2%)	4	16.1 (15.0-21.0)	12	1.0 (1.0-2.0)
Prothionamide	10 (8.5%)	9	15.4 (13.6-18.9)	7	3.0 (2.0-3.0)
Levofloxacin	4 (3.4%)	4	12.1 (3.7-15.8)	4	3.0 (1.2-19.0)
Ethionamide	3 (2.5%)	2	22.50 (n.a.)	3	5.0 (n.a.)
Moxifloxacin	3 (2.5%)	3	9.5 (n.a.)	3	8.0 (n.a.)

*Isoniazid drug dose available for 76 patients, but 6 patients excluded because the maximum daily dose recommendations of INH 300 mg would be exceeded if dosing was based on mg/kg according to the new WHO guidelines (10).
**Rifampicin drug dose available for 75 patients, but 3 patients excluded because the maximum daily dose recommendations of RMP 600 mg would be exceeded if dosing was based on mg/kg according to the new WHO guidelines (10).
IQR = interquartile range; n.a. = not applicable; no. = number.

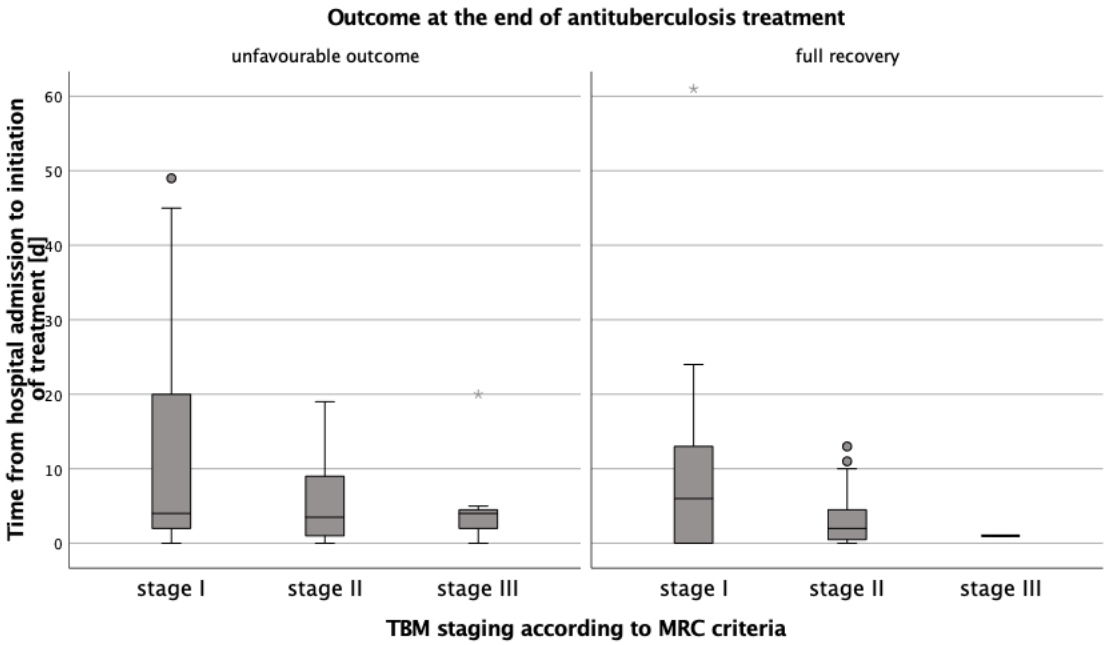

Figure 1 *Comparison of time from hospital admission to initiation of treatment in children with unfavourable outcome and those with full recovery grouped according to MRC TBM staging. MRC = Medical Research Council*

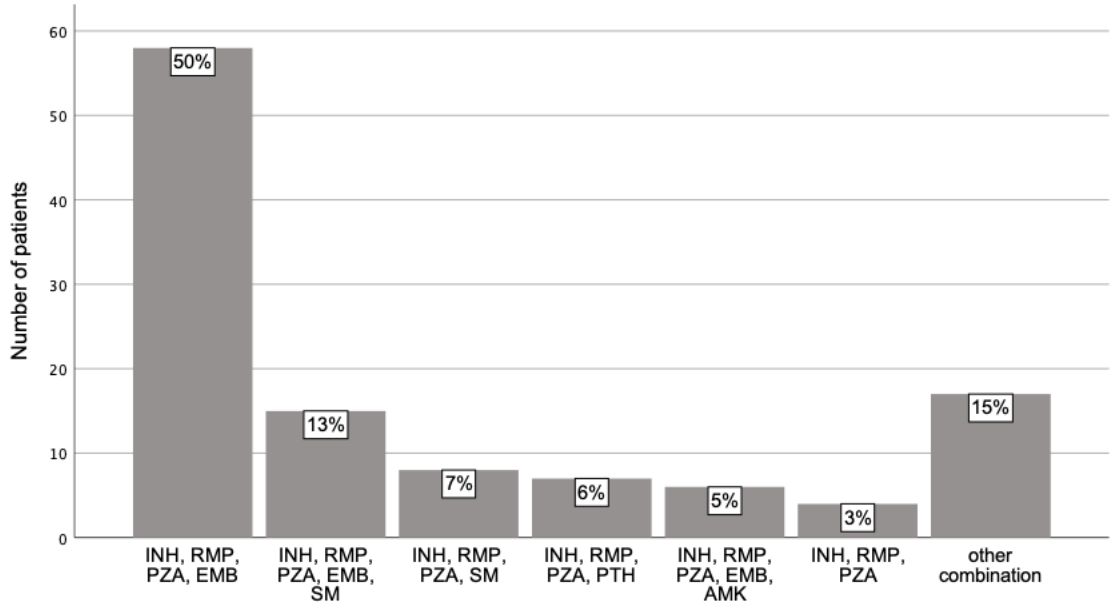

Figure 2 *Most commonly used initial treatment regimens in the study population. INH (isoniazid), RMP (rifampicin), PZA (pyrazinamide), EMB (ethambutol), SM (streptomycin), PTH (prothionamide), AMK (amikacin).*

Table 3 *Outcomes in 104 children with outcome data available at the end of anti-tuberculosis treatment.*

Outcome	All patients (n=104)	Patients with possible TBM*** (n= 21)	Patients with probable TBM*** (n= 35)	Patients with definite TBM*** (n=48)	Patients presenting with stage I disease*** (n=33****)	Patients presenting with stage II disease*** (n=61)	Patients presenting with stage III disease*** (n=10)
Full recovery	49 (47.1%)	14 (66.7%)	19 (54.3%)	16 (33.3%)	22 (66.7%)	25 (41.0%)	2 (18.2%)
Spasticity of one or more limbs	20 (19.2%)	1 (4.8%)	5 (14.3%)	14 (29.2%)	4 (12.1%)	12 (19.7%)	4 (40.0%)
Developmental delay	20 (19.2%)	0	7 (20.0%)	13 (27.1%)	2 (6.1%)	12 (19.7%)	6 (60.0%)
Seizure disorder	18 (17.3%)	1 (4.8%)	3 (8.6%)	14 (29.2%)	2 (6.1%)	12 (19.7%)	4 (40.0%)
Paresis of one or more limbs	15 (14.4%)	0	4 (11.4%)	11 (22.9%)	1 (3.0%)	10 (16.4%)	4 (40.0%)
Speech impairment	13 (12.5%)	0	3 (8.6%)	10 (20.8%)	1 (3.0%)	9 (14.8%)	3 (30.0%)
Visual impairment	14 (13.5%)	1 (4.8%)	3 (8.6%)	10 (20.8%)	0	10 (16.4%)	4 (40.0%)
Chronic hydrocephalus	13 (12.5%)	1 (4.8%)	2 (5.7%)	10 (20.8%)	4 (12.1%)	5 (8.2%)	4 (40.0%)
Hearing impairment	11 (10.6%)	0	3 (8.6%)	8 (16.7%)	0	8 (13.1%)	3 (30.0%)
Cranial nerve palsy	8 (7.7%)	1 (4.8%)	2 (5.7%)	5 (10.4%)	0	5 (8.2%)	3 (30.0%)
Neuroendocrine dysfunction	7 (6.7%)	0	2 (5.7%)	5 (10.4%)	0	4 (6.6%)	3 (30.0%)
Persistent coma*	3 (2.9%)	0	1 (2.9%)	2 (4.2%)	0	2 (3.3%)	1 (10.0%)

Outcome other**	11 (10.6%)	3 (14.3%)	5 (14.3%)	5 (10.4%)	4 (12.1%)	5 (8.2%)	4 (40.0%)
Patient died	10 (9.6%)	3 (14.3%)	3 (8.6%)	4 (8.3%)	1 (3.0%)	7 (11.5%)	2 (20.0%)

* One child was comatose at the end of treatment and died following 12 months of treatment.

** Includes mood disorders, behavioral, memory and school difficulties, urinary incontinence, and narcolepsy.

*** based on Basu Roy et al. (21)

Table 4 *Bivariate regression analysis of risk factors for unfavourable outcome in 104 patients with available data on outcome. Statistically significant values are highlighted in bold.*

	Bivariate regression analysis		
Predictor variable	Unadjusted odds ratio	95%CI	p-value
Gender (male)	1.369	0.632-2.965	0.426
Age at hospital admission	0.953	0.875 – 1.038	0.268
BCG vaccination	1.046	0.364 – 3.008	0.934
TBM stage I	Ref.	-	-
TBM stage II	**2.880**	**1.188 – 6.982**	**0.019**
TBM stage III	**8.000**	**1.447 – 44.240**	**0.017**
Possible TBM	Ref.		
Probable TBM	1.684	0.547-5.187	0.364
Definite TBM	**4.000**	**1.348-11.871**	**0.012**
Time from admission to start of treatment [d]	1.006	0.965 – 1.049	0.769
Leukocytes count in initial CSF sample [/µl]	1.000	0.999 – 1.001	0.731
Neutrophil percentage in initial CSF sample	0.993	0.974 - 1.012	0.491
Protein concentration in initial CSF sample [g/l]	0.951	0.863 – 1.049	0.318
Glucose concentration in initial CSF sample <2.2mmol/l	2.182	0.879-5.414	0.092
RMP dose [mg/kg] during initial treatment	0.973	0.859 – 1.102	0.666
INH dose [mg/kg] during initial treatment	0.923	0.804 – 1.060	0.254
PZA dose [mg/kg] during initial treatment	0.961	0.874-1.056	0.410
Steroid dose (prednisolone equivalent) [mg/kg]	1.241	0.924 - 1.666	0.152
Hydrocephalus on initial imaging	**2.556**	**1.159 - 5.640**	**0.020**
Neurosurgical intervention	**5.182**	**2.191 - 12.258**	**0.000**
Mechanical ventilation required	**5.033**	**1.559 – 16.243**	**0.007**
Admission to intensive care unit	**2.197**	**1.001-4.820**	**0.050**

BCG = *Bacillus Calmette-Guérin*; CI = confidence interval; CSF = cerebrospinal fluid; d = days; INH = isoniazid; RMP = rifampicin; TBM = tuberculous meningitis.

Table 5 *Multivariate regression analysis of risk factors for unfavourable outcome in 104 patients with available data on outcome. Statistically significant values are highlighted in bold.*

	Multivariate regression analysis		
Predictor variable	Adjusted odds ratio	95%CI	p-value
Gender (male)	2.248	0.838-6.029	0.107
Age at hospital admission	0.995	0.895-1.106	0.924
TBM stage I	Ref.	-	-
TBM stage II	2.683	0.866 - 8.313	0.087
TBM stage III	7.810	0.815 - 74.837	0.075
Possible TBM	Ref.		
Probable TBM	2.609	0.622-10.938	0.190
Definite TBM	**5.862**	**1.349 – 25.470**	**0.018**
Hydrocephalus on initial imaging	1.001	0.359-2.795	0.998
Neurosurgical intervention	**4.408**	**1.364 – 14.241**	**0.013**
Mechanical ventilation required	**5.601**	**1.143 – 27.452**	**0.034**
Admission to intensive care unit	0.273	0.072 – 1.044	0.058

CI = confidence interval; TBM = tuberculous meningitis.

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