



South African National Department of Health

Brief Report of NEMLC Limited Review¹

Corticosteroids for the treatment of tuberculous meningitis (TBM)

February 2026

Medicine details:

Medicine Class	Corticosteroids	<i>If applicable Please consider therapeutic interchange policy</i>
Medicine/s name -INN: - South African name (if differs from INN)	Prednisone Prednisolone Dexamethasone	http://www.whocc.no/atc_ddd_index/
Medicine/s (ATC5):	H02AB07 H02AB06 H02AB02	http://www.whocc.no/atc_ddd_index/
Indication (ICD-10 code):	A17.0	https://www.health.gov.za/icd-10-master-industry-table/
SAHPRA Approved	Yes	SAHPRA registered health products database https://medapps.sahpra.org.za:6006/
Dosage form/s	tablet, suspension, solution for injection	
Route of administration/s	oral, intravenous	
Patient population	Adults and children with and without HIV	
Prevalence and/or incidence of condition	Overall, in 2012, 6.8 cases per 100 000 persons. In people living with HIV 34.9 cases per 100 000 persons. (Britz et al. PloS One. 2016)	<i>May refer to estimates or routine data (DHIS, StatsSA), not necessarily published data.</i>
Level of Care	Hospital level (initiation) Primary Healthcare (continuation)	
Prescriber level	Doctor initiated	

¹ This template was informed by examples of previous NEMLC limited reviews, input from the Essential Drug Programme Oversight Group and the NEMLC Medicine Review Template which was updated with support through the Evidence-to-Decision (E2D) project which is a collaboration between National Department of Health, the South African Medical Research Council and the University of Stellenbosch.

Current Standard of Care

In adults: Combination anti-tuberculosis treatment for 9 months duration. In people without HIV, with grade II to III TBM, adjunctive corticosteroids are recommended. No recommendation is currently made for corticosteroid use in people living with HIV (PWH) and TBM.

In children: Combination anti-tuberculosis treatment for 6 to 9 months duration. In all children, irrespective of HIV status or TBM grade, adjunctive corticosteroids are recommended.

Executive Summary

- TB meningitis (TBM) is associated with significant mortality, with a pooled case fatality rate of 53% in people with HIV (PWH) and 22% in HIV-negative people.[1]
- The current standard treatment guidelines recommend the use of corticosteroids in HIV-negative adults with Grade II² or III TBM, and in children with TBM, only. These recommendations are based on a 2008 Cochrane systematic review [2]
- We conducted an updated rapid systematic review of the evidence for the use of corticosteroids in the management of TBM in HIV-negative children and adults, as well as in children and adults with HIV. Only guidelines, systematic reviews with meta-analyses, and randomised controlled trials published subsequent to 2008 (and not included in the previous reference) were included.
- We identified three clinical practice guidelines:
 - Clinical practice guidelines from WHO (2025) and ATS/CDC/ERS/IDSA³ (2025) recommend using corticosteroids in people with TBM, irrespective of TBM grade, and without any differential recommendation based on HIV status. These recommendations had not been updated since 2016-2017.[3,4]
 - The Tuberculous Meningitis International Research Consortium clinical practice guideline (2026) was identified as the most up-to-date clinical practice guideline for the management of TBM. [5] This guideline recommends using adjunctive corticosteroid therapy for TBM in people without HIV (strong recommendation, high certainty of evidence). In the absence of an effective alternative adjunctive therapy for HIV-associated tuberculous meningitis, and based on the safety and potential effectiveness of corticosteroids, they recommend using corticosteroids on a case-by-case basis in PWH (weak recommendation, high certainty of evidence).
- We identified one updated Cochrane systematic review and meta-analysis of adjunctive corticosteroids in predominantly HIV-negative adults and children with TBM.[6] Key findings include:
 - Corticosteroids reduce mortality moderately (RR 0.75, 95% CI 0.65 to 0.87, high certainty of evidence).
 - This reduction in mortality is consistent across all grades of the disease.
 - Corticosteroids may reduce severe disability (RR 0.92, 95% CI 0.71 to 1.20, low certainty of evidence).
 - Corticosteroids result in little to no difference in serious adverse events (RR 0.88, 95% CI 0.67 to 1.17).
 - Therefore, we recommend using corticosteroids in HIV-negative adults, and children, with any grade of TBM.

² British Medical Research Council Staging. Grade I TBM: No focal neurological signs, Glasgow Coma Scale (GCS) 15; Grade II TBM: GCS 11 to 14 or GCS 15 with focal neurological deficits; Grade III TBM: GCS ≤ 10.

³ American Thoracic Society/United States Centers for Disease Control and Prevention/Infectious Diseases Society of America, the European Respiratory Society.

- We identified one systematic review and meta-analysis from the Tuberculous Meningitis International Research Consortium clinical practice guideline (2026) and one randomised controlled trial (RCT) of adjunctive corticosteroids in adult PWH with TBM.[5,7] The methods and GRADE assessment underpinning the systematic review and meta-analysis from the clinical practice guideline were poorly reported. Key findings include:
 - Corticosteroids may result in lower mortality (RR 0.90, 95% CI 0.77 to 1.05).
 - Corticosteroids may increase severe disability, but the confidence interval is very wide (RR 1.34, 95% 0.65 to 2.87).
 - Corticosteroids did not increase serious adverse events.
 - These findings are based largely on data from the one RCT identified, in which the majority of PWH and TBM had a CD4 cell count ≤ 200 cell/mm³.
 - It is biologically plausible that in PWH with TBM and relatively preserved CD4 counts, the mortality benefit of adjunctive corticosteroids would approximate that observed in HIV-negative patients.
 - The exact CD4 count at which this mortality benefit would approximate that observed in HIV-negative individuals has not been established, and there is insufficient data to define this threshold.
 - Given the high mortality of TBM, the absence of demonstrated harm associated with corticosteroids, and the potential for a small mortality benefit specifically in PWH with higher CD4 counts, withholding corticosteroids from all PWH may not be appropriate.
 - We pragmatically suggest, based on expert opinion and aligned with the National Department of Health programmatic definitions of advanced HIV disease (AHD), that corticosteroids be used in PWH with TBM and CD4 cell counts > 200 cells/mm³.
 - In PWH with TBM and CD4 cell counts ≤ 200 cells/mm³ we suggest not using corticosteroids.
- In children with HIV and TBM
 - No randomized controlled trials evaluating corticosteroids in children with HIV and TBM were identified.
 - There is currently no direct evidence to indicate that children with HIV and TBM fail to derive a mortality benefit comparable to that observed in HIV-negative children with TBM.
 - In children, with or without HIV, with TB meningitis, we recommend using corticosteroids.

Key Recommendations *(if more appropriate, describe in narrative form)*

Type of ERC recommendation	We recommend against the option and for the alternative (strong)		We suggest not to use the option or to use the alternative (conditional)		We suggest using the option (conditional)		We recommend the option (strong)	
	☐		✓ See recommendation 2		✓ See recommendation 3		✓ See recommendation 1 and 4	
High level summary of conclusions	1. In HIV-negative adults with TB meningitis of any grade, we recommend using corticosteroids. 2. In adults with HIV and TB meningitis of any grade, with CD4 count ≤ 200 cells/mm³, we suggest not using corticosteroids. 3. In adults with HIV and TB meningitis of any grade, with CD4 count >200 cells/mm³, we suggest using corticosteroids. 4. In children, with or without HIV, with TB meningitis of any grade, we recommend using corticosteroids.							
NEMLC Ratification	Date		Comments/Recommendation					
	26 Mar 2026		NEMLC ratified the ERCs recommendation as detailed above, pending agreement with the national TB and HIV programs. (Program confirmation received by email communication April 2026).					
Therapeutic Interchange Considerations (if applicable)*	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval		If NO, tick box	
							✓	
Trigger for review								

Background and rationale

The current Adult Hospital standard treatment guidelines recommend the use of adjunctive corticosteroids alongside standard anti-tuberculosis therapy in adults with grade II to III tuberculous meningitis (TBM) (**Figure 1**). This recommendation (level of evidence IIa) is based on evidence from Prasad et al.'s 2008 Cochrane review which demonstrate that corticosteroids can reduce the risk of neurological deficits and death in adults with TBM.[2] However, in adults living with HIV co-infected with TBM, the standard treatment guidelines highlight ongoing uncertainty regarding the benefits of corticosteroids therapy (level of evidence IIa, Prasad et al. Cochrane. 2008).[2] The 2008 Cochrane systematic review on which these recommendations are based was subsequently updated in 2016 and more recent studies in people living with HIV (PWH) have emerged as of 2023. [6,7]

The current Paediatric Hospital standard treatment guidelines recommend the use of adjunctive corticosteroids alongside standard anti-tuberculosis therapy in all children irrespective of HIV status or grade of TBM. No reference or level of evidence for this recommendation is provided (Figure 2).

This rapid review aims to evaluate the most up to date evidence for adjunctive corticosteroid therapy in people with TBM, and to inform a more refined and specific recommendation in PWH.

MEDICINE TREATMENT	
Treat with standard combination tuberculosis therapy according to National protocol and extend duration of therapy to 9 months (2 months intensive phase, 7 months continuation phase). See Section 16.9: Tuberculosis, Pulmonary for details.	
In HIV-negative individuals:	
Corticosteroid use may be of benefit in reducing neurological deficit in patients with grade II to III disease (focal neurological disease, depressed levels of consciousness, or a Glasgow Coma Scale of 14 or less).	
Dexamethasone, IV, dosing as follows:	
Weeks	Dosing regimen
Initial dose	0.3-0.4 mg/kg/day for 2 weeks.
Week 3	0.2 mg/kg daily.
Week 4	0.1 mg/kg daily.
Week 5 to 8	4 mg/day, tapering daily dose by 1 mg each week.
OR	
- Corticosteroids (intermediate-acting) e.g.: LoE:IIa^{vi} - Prednisone, oral, 60 mg daily for 2 weeks. - Then taper gradually over the next 6 weeks (see Appendix II for an example of a dose reduction regimen). LoE:IVb^{vi}	
In people with HIV:	
Note: There is uncertainty whether the use of corticosteroids is beneficial in PLWH with TBM. LoE:IIa^{ix}	
LoE:IIa^{ix}	

Figure 1. Adult Hospital. Chapter 14 Neurological Disorders. 14.8.1.1 TB meningitis

CHAPTER 10	TUBERCULOSIS
Steroid therapy:	
- Prednisone, oral, 2 mg/kg as a single daily dose for 4 weeks. - Maximum daily dose: 60 mg. - Taper to stop over further 2 weeks.	

Figure 2. Paediatric Hospital. Chapter 10 Tuberculosis. Section 10.4: Meningitis, tuberculosis (TBM) in children

Purpose/Objective i.e., PICO question (if relevant):

PICO 1

Population Subgroups	HIV-negative adults and children with TBM
Intervention(s)	Corticosteroids (prednisone, prednisolone or dexamethasone) plus standard anti-TB treatment
Comparator(s)	Anti-tuberculous treatment (ATT) alone or with placebo
Outcome(s)	Mortality, severe disability, adverse events
Study types	Guidelines, systematic reviews with meta-analysis, randomised controlled trials

PICO 2

Population Subgroups	Adults and children living with HIV co-infected with TBM
Intervention(s)	Corticosteroids (prednisone, prednisolone or dexamethasone) plus anti-TB treatment
Comparator(s)	Anti-tuberculous treatment (ATT) alone or with placebo
Outcome(s)	Mortality, severe disability, adverse events
Study types	Guidelines, systematic reviews with meta-analysis, randomised controlled trials

Methods

1. Data Sources

Clinical practice guidelines: We searched for relevant clinical practice guidelines from the American Thoracic Society and World Health Organization.

Systematic reviews and randomised controlled trials: We searched PubMed for guidelines, systematic reviews, and randomised controlled trials.

2. Search Strategy

The following search terms were used:

((TB meningitis) OR (tuberculous meningitis)) OR (tuberculosis meningitis) AND (corticosteroids)

We restricted our search to studies published from 2004, since the most recent study included in the 2008 Prasad et al. Cochrane review referenced in the current standard treatment guidelines was from 2004. PubMed searches were filtered by year (from 2004), guideline, systematic review, meta-analysis and randomised controlled trials.

3. Study selection and eligibility criteria, data extraction and analysis, and evidence synthesis

The study screening, selection and data extraction, analysis and evidence was conducted by 1 reviewer. Evidence was synthesised narratively.

Results

1. Result of the search

Three clinical practice guidelines were identified: the ATS/CDC/ERS/IDSA⁴ Clinical Practice Guideline (2025), the World Health Organisation (WHO) consolidated guidelines on tuberculosis. Module 4: Treatment and care (2025), and the Tuberculous Meningitis International Research Consortium guideline (2026).[3-5] In both the ATS/CDC/ERS/IDSA and WHO guidelines, specific recommendations relating to corticosteroids use in TBM have not been updated since 2016 – 2017.

The PubMed search identified 23 studies and 1 clinical practice guideline from the European Respiratory Society 2009. Of the 23 studies identified, there were 9 systematic reviews, 13 randomised controlled trials (RCTs) and 1 retrospective cohort study. Of the 9 systematic reviews, only 1 (Prasad (2016)) was eligible for inclusion.[6] Of the 13 RCTs, 3 were eligible for inclusion: Thwaites (2004); Malhotra (2009); Donovan, (2023).[7-9]

The WHO and ATS/CDC/ERS/IDSA clinical practice guidelines were based on systematic reviews of the same 5 primary studies.[8-12] The Tuberculous Meningitis International Research Consortium guideline included all 5 of these studies, 8 of 9 primary studies included in the Prasad (2016) systematic review, and the most recent RCT identified by Donovan (2023).[7] This clinical practice guideline was therefore the most up-to-date guideline and selected for inclusion.

The search results are illustrated in **Figure 3. Search Flow Chart**. Specific reasons for inclusion or exclusion of studies identified in the search are listed in **Appendix 1**. **Appendix 2** includes a comparison of the specific recommendations and primary studies included in the WHO, ATS/CDX/ERS/IDSA and Tuberculous Meningitis International Research Consortium guidelines.

⁴ American Thoracic Society/United States Centers for Disease Control and Prevention/Infectious Diseases Society of America, the European Respiratory Society.

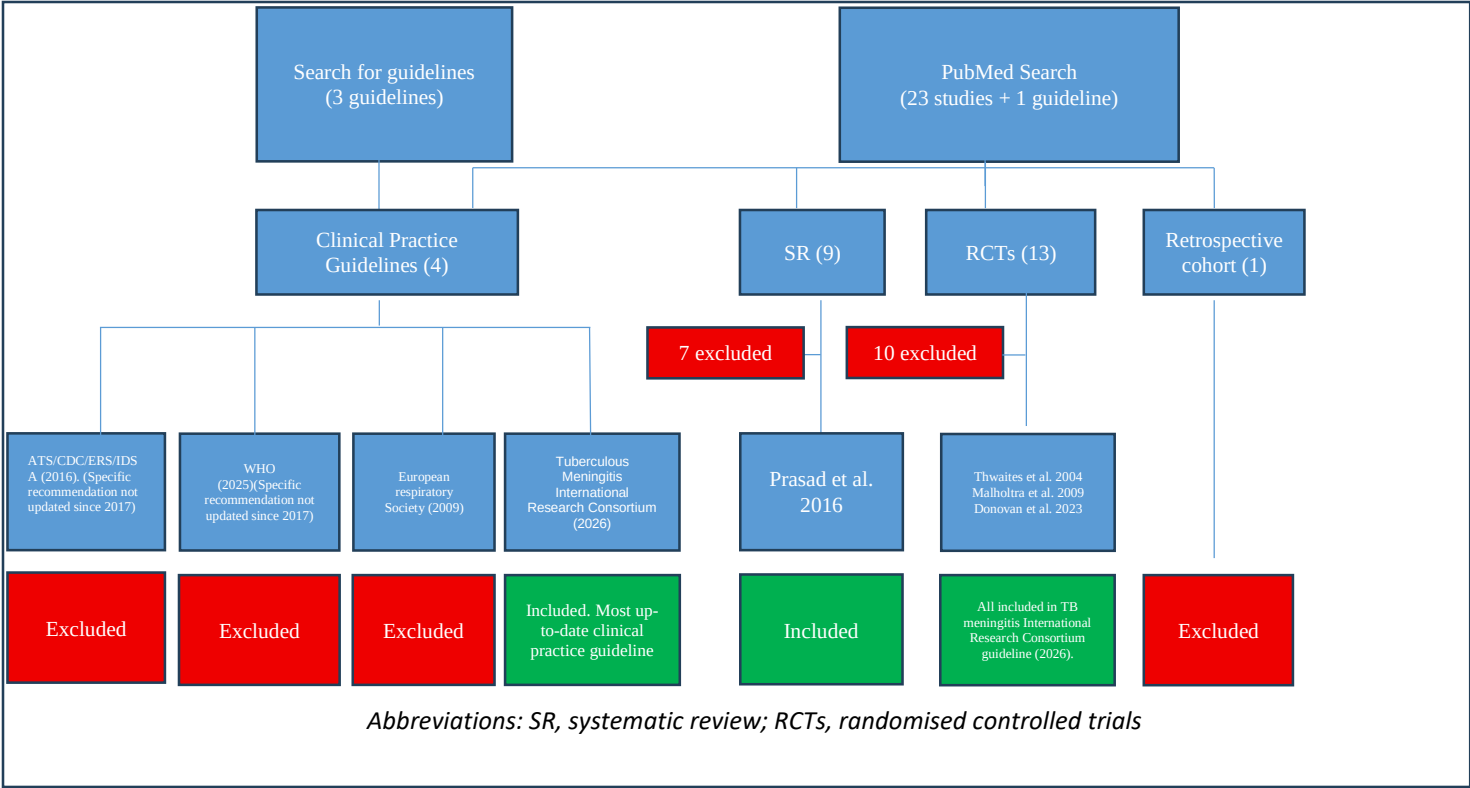


Figure 3. Search Flow Chart

2. Description of included studies

2.1. Clinical Practice Guidelines

The Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026) was considered the most up-to-date clinical practice guideline which included subgroup considerations by HIV status. The recommendations from this guideline are summarised in **Table 1**. Insufficient detail was provided in the clinical practice guideline concerning the underlying systematic review methodology and GRADE assessment, therefore, the quality of the underlying systematic review was not assessed. The results of the systematic review and meta-analyses are reported in **Results Section 3**.

Table 1. Summary of the recommendation from the Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026)

Recommendation	Justification	Subgroup considerations	Studies included in the systematic review (9)	Outcomes considered	AGREE II
In people without HIV, we recommend the use of adjunctive corticosteroid therapy. (strong recommendation, high certainty of evidence) In the absence of an effective alternative adjunctive therapy for HIV-associated tuberculous meningitis, and the safety and potential effectiveness of corticosteroids, we recommend their use on a case-by-case basis in people living with HIV (weak recommendation, high certainty evidence).	Corticosteroids reduced case fatality, especially in children and adults without HIV. There is no signal for a change in disability among survivors in these groups. In people living with HIV and tuberculous meningitis, the benefits of corticosteroids are uncertain.	Separate recommendations for those with and without HIV.	O'Toole (1969)[7] Girgis (1991)[13] Kumaravelu (1994)[10] Chotmongkol (1996)[11] Schoeman (1997)[12] Lardizabal (1998)[14] Malhotra (2009)[9] Thwaites (2004)[8] Donovan (2023)[7]	Mortality Morbidity	Overall: 60 % Domain 1- Scope and Purpose: 90% Domain 2 – Stakeholder involvement: 57% Domain 3 - Rigour of development: 61% Domain 4 – Clarity of presentation: 67% Domain 5 - Applicability: 32% Domain 6 – Editorial independence: 64%

2.2. Systematic reviews

One systematic review was eligible for inclusion, Prasad (2016).[6] This systematic review is the update of the Prasad (2008) Cochrane systematic review.[2]

This systematic review evaluated the effects of adjunctive corticosteroids on death and severe disability in people with tuberculous meningitis. It included only RCTs that compared corticosteroids plus ATT with ATT treatment alone, and which included death or disability as an outcome.

Nine RCTs with 1337 participants were included. The 9 RCTs were: O'Toole (1969); Girgis (1991); Kumaravelu (1994); Chotmongkol (1996); Schoeman (1997); Lardizabal (1998); Thwaites (2004); Prasad (2006 (unpublished data only); Malhotra (2009).[8-15] The characteristics of these RCTs are summarised in **Table 2**. All but one of the RCTs included in the Prasad (2016) systematic review are included in the Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026). The Prasad (2006) trial (unpublished data) is not included in the Tuberculous Meningitis International Research Consortium Clinical Practice Guideline,

One RCT included only young children.[12] Two RCTs included adults and children.[13,15] Six RCTs included only adults or adults and adolescents ≥ 14 years of age. Only one RCT reported on HIV-co-infection.[8] One RCT included prolonged follow-up to 5 years. At least 5 RCTs were considered to be at high risk of bias (including the unpublished data from the Prasad (2006) RCT).[9,10,13,14] Three RCTs had unclear risk of bias.[11,12,15] One RCT was considered to be at low risk of bias (**Figure 4**).[8]

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (death)	Blinding of outcome assessment (disabling neurological deficit at the end of follow-up)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Chotmongkol 1996	?	+	+	+	?	?	?
Girgis 1991	+	?	?	?	-	?	?
Kumarvelu 1994	+	-	?	+	-	-	?
Lardizabal 1998	?	?	?	+	-	+	+
Malhotra 2009	+	?	?	+	-	+	+
O'Toole 1969	?	+	+	+	+	+	?
Prasad 2006	+	+	+	+	?	?	-
Schoeman 1997	?	?	?	+	+	?	+
Thwaites 2004	+	+	+	+	+	+	+

Figure 4. Risk of bias summary from Prasad (2016) systematic review

Table 2. Summary of studies included in Prasad (2016) systematic review

Study	Methods	Participants	Interventions	Outcomes
O'Toole 1969	Randomized parallel group 2-arm study with allocation ratio 1:1. Length of follow-up: unclear.	Setting: Infectious Diseases Hospital, Calcutta, India - tertiary referral centre. Number of participants: 23 participants in total, 11 females, 12 males; 11 received dexamethasone, 12 received no steroid. Inclusion criteria: not explicitly specified, but the trial authors state that due to the trial institution's admissions policy only participants with a short history or acute signs and symptoms of meningitis were selected; due to limited bed availability only moderate to severely unwell participants were included (MRC Stage II and III). All age groups were included. Treatment allocation was stratified for age and disease severity. HIV status: not reported.	1. ATT plus dexamethasone given for up to 4 weeks in an adult dose of 9 mg/day during the first week, 6 mg/day during the second week, 3 mg/day during the third week, and 1.5 mg/day during the 4th week; dose for children was calculated according to their body surface area (no more details available). 2. ATT alone. ATT: isoniazid intramuscular or oral (10 mg/kg/day, except in children < 2 years of age who received 20 mg/kg/day) and streptomycin (20 mg/kg/day, maximum 1 g), duration not specified	1. Death at the end of follow-up (duration unclear). 2. Number with elevated CSF opening pressure on days 1, 4, 7, and 14. 3. CSF sugar, protein, and cell count on days 1, 4, 7, 14, 21, and 28 in decreasing number of participants, depending apparently on the surviving number. Number with residual deficits not given. Surviving participants all been described as "significantly improved". 4. Adverse events recorded: upper gastrointestinal bleed, invasive bacterial infection, hypoglycaemia, and hypothermia. 5. Resolution of CSF findings
Girgis 1991	Randomized parallel group, 2-arm study with allocation ratio: 1:1. Length of follow-up: 24 months.	Setting: Abbassia Fever Hospital, Cairo, Egypt - tertiary referral centre. Number of participants: 280 participants; 158 males, 122 females; 145 received dexamethasone, 135 received no steroid. Age: all ages included, 37% aged 0 to 5 years, 22% aged 5 to 16 years. Inclusion criteria: clinically diagnosed tuberculous meningitis based on history and examination (duration of illness > 30 days, consisting of fever, headache, vomiting, altered sensorium, generalized weakness or cranial nerve deficits); comparison of first and second CSF findings; and a poor response to antibacterial therapy for 48 hrs. Exclusion criteria: not reported. HIV status: not reported.	1. ATT plus dexamethasone given intramuscularly (12 mg/day to adults and 8 mg/day to children weighing < 25 kg) for 3 weeks and then tapered during the next 3 weeks). 2. ATT alone. ATT: isoniazid (10 mg/kg/day, maximum 600 mg) intramuscularly for 2 weeks then orally for 2 years, streptomycin intramuscular (25 mg/kg/day, maximum 1000 mg) for 6 weeks, and ethambutol oral (25 mg/kg/day, maximum 1200 mg) for 6 weeks, then 15 mg/kg/day for 2 years.	1. Death during 2-year follow-up. 2. Residual neurological sequelae. 3. Neurological complications developing during therapy. 4. CSF leucocytes, glucose, and protein on day 15 and day 30 after initiation of treatment. Trial authors reported case-fatality rate, which by definition includes all deaths caused by tuberculous meningitis, but not deaths attributed to other causes. They did not report whether any death during the follow-up period was considered to be due to any cause other than tuberculous meningitis.
Kumarvelu 1994	Randomized parallel group 2-arm study with allocation ratio 1:1. Length of follow-up: 3 months.	Setting: all India Institute of Medical Sciences (AIIMS), New Delhi, India - tertiary referral centre. Number of participants: 47 participants; 22 females, 25 males; 24 received dexamethasone, 23 received no steroid. Inclusion criteria: aged over 10 years; clinically diagnosed tuberculous meningitis (meeting any 3 of the following criteria). 1. Fever, headache, neck stiffness for 2 weeks. 2. CSF profile of > 20 cells/mm3 predominantly lymphocytes, protein > 1 g/L, and sugar < 2/3 of corresponding blood sugar with no malignant cells on cytological examination and bacteria/fungi on culture. 3. Head contrast-enhanced CT showing basal exudates or hydrocephalus. 4. Clinical, radiological, or histological evidence of extracranial TB). All stages of severity and any duration of disease included. Exclusion criteria: aged < 10 years, received ATT for more than 4 weeks prior to admission, received corticosteroids before admission. HIV status: not reported.	1. ATT plus dexamethasone (intravenous 16 mg/day in 4 divided doses for 7 days, then oral tablet 8 mg/ day for 21 doses, and in children 0.6 mg/kg/day for 7 days, reducing to 0.3 mg/kg/day for 21 days). 2. ATT alone. ATT: rifampicin (450 mg), isoniazid (300 mg), and pyrazinamide (1500 mg) all oral daily; for those weighing < 30 kg 15 mg/kg, 10 mg/kg, and 30 mg/kg respectively. Duration of treatment: 1 year.	1. Death at 3 months. 2. Major sequelae (totally dependent for activities of daily living) at 3 months. 3. Minor sequelae (activities of daily living with no or minimal assistance) at 3 months. 4. Adverse effects. 5. Time to recover from altered sensorium, from fever, and from headache.
Chotmongkol 1996	Randomized parallel group study. Length of follow-up: 6 months but post-study follow-up continued for 16 to 45 months (mean = 30 months).	Setting: Sringarind Hospital, Khon Kaen, Thailand - tertiary referral centre. Number of participants: 59 participants; 27 females, 32 males; 29 received prednisolone, 30 received no steroid. Inclusion criteria: age > 15 years; clinically diagnosed tuberculous meningitis (characteristic clinical features with typical CSF profile consisting of lymphocytic meningitis with low glucose level and elevated protein), all stages of disease included. Exclusion criteria: children <15 years old, HIV-positive, VDRL positive for syphilis, cryptococcal antigen positive, CSF positive for bacterial or fungal infection on latex agglutination or culture, malignant cells in CSF. HIV status: HIV-positive participants excluded.	1. ATT plus prednisolone orally on tapering dosage for 5 weeks (week 1 =60 mg, week 2 = 45 mg, week 3 = 30 mg; week 4 = 20 mg, week 5 = 10 mg). 2. ATT alone. ATT: isoniazid oral (300 mg), rifampicin oral (600 mg, 450 mg for those weighing < 50 kg), pyrazinamide oral (1500 mg), and streptomycin intramuscular (750 mg) for the first 2 months; followed by isoniazid and rifampicin in above dosage for 4 months.	1. Death at the end of 6 months. 2. Residual neurological deficits at the end of 6 months. 3. Time until resolution of fever. 4. Time until disappearance of headache. Adverse events recorded were gastrointestinal bleeding and hyperglycaemia.
Schoeman 1997	Randomized parallel group 2-arm study with allocation ratio 1:1. Length of follow-up: 6 months.	Setting: Tygerberg Hospital, Tygerberg, South Africa. Number of participants: 141 randomized (gender balance not specified); 70 received prednisolone and 71 received no steroid. Inclusion criteria: children (age limit not specified); diagnosis of tuberculous meningitis based on history and "typical CSF changes" with at least 2 of the following: strongly positive (> 15 mm) Mantoux test, chest x-ray suggesting TB or CT head showing basal enhancement and acute hydrocephalus. Only MRC Stage II and III included. HIV status: not reported.	1. ATT plus prednisolone (given to first 16 participants in a dose of 2 mg/kg/day and to the remaining 54 participants in a dose of 4 mg/kg/day (once in the morning); decision to double the dose after the first 16 participants). 2. ATT alone. ATT: isoniazid (20 mg/kg/day), rifampicin (20 mg/kg/day), ethionamide (20 mg/kg/day), and pyrazinamide (40 mg/kg/day) for 6 months.	1. Deaths at 6 months. 2. Disability (mild and severe) at 6 months. 3. Serious side effects.++ 4. Baseline and pulse pressure of lumbar CSF. 5. Changes in ventricular size in CT. 6. Proportion of participants with successful treatment of raised intracranial pressure. 7. Proportion of participants with basal ganglia infarcts, tuberculomas, meningeal enhancement, and enlarged subarachnoid spaces.

Study	Methods	Participants	Interventions	Outcomes
Lardizabal 1998	Randomized parallel group, 2-arm study with allocation ratio 1:1 Length of follow-up: 2 months	Setting: University of the Philippines College of Medicine, tertiary care facility, single centre Number of participants: 58 participants; 31 males and 27 females; 29 received dexamethasone, 29 received no steroid. Inclusion criteria: aged 18 years and above; probable tuberculous meningitis diagnosed using ASEAN Neurological Association criteria based on the following. 1. Insidious onset fever for at least 1 week, headache and vomiting, with or without nuchal rigidity followed by altered consciousness, cranial nerve palsies, or long tract signs. 2. CSF profile of lymphocyte predominance, elevated protein and reduced glucose. 3. CSF negative for cryptococcal antigen plus 1 or more of the following: basilar/meningeal enhancement on contrast CT scanning, active pulmonary disease, positive purified protein derivative (PPD), history of contact with TB; confirmed tuberculous meningitis based on positive CSF culture or microscopy, or both. 4. British MRC stages II and III disease. Exclusion criteria 1. Aged under 18. 2. British MRC stage I TB meningitis, or bacterial or fungal meningitis diagnosed on CSF culture. 3. Pregnancy or lactation. 4. History of diabetes mellitus or hypertension. 5. Upper gastrointestinal bleeding, or history of peptic ulcer disease in the previous month. 6. Raised bilirubin, SGPT or serum creatinine.	1. ATT plus dexamethasone (16 mg/day for 3 weeks (first 5 days intravenous thereafter orally or via nasogastric tube); after 3 weeks corticosteroid was tapered by 4 mg decrements every 5 days). 2. ATT alone. ATT: rifampicin (10 to 15 mg/kg/day), isoniazid (5 to 10 mg/kg/day), pyrazinamide (15 to 30 mg/kg/day), and ethambutol (15 to 20 mg/kg/day) for the first 2 months; thereafter, rifampicin and isoniazid only for 10 months; total treatment duration 12 months; route of administration was not stated. An H2-antagonist (famotidine or ranitidine) was given during the period of corticosteroid administration.	1. Death on days 15, 30, and 60 post-randomization. 2. Functional independence assessed by attending doctor on admission and 60 days after randomization: Functional Independence Measure (FIM) used assesses self-care, sphincter control, mobility, locomotion, and social cognition on a 7-point scale. 3. Potential adverse reactions to corticosteroids including weakness, oedema, hypertension, euphoria, psychosis, epigastric discomfort, Cushingoid facies, hirsutism, acne, insomnia, and increased appetite.
Thwaites 2004	Randomized parallel group 2-arm study with allocation ratio 1:1. Length of follow-up: 9 months (initial report), followed by a 5-year follow-up trial.	Setting: Pham Ngoc Thach Hospital for Tuberculosis and Lung Disease and the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam - two tertiary referral centres. Number of participants: 545 randomized, 331 males, 214 females; 274 received dexamethasone, 271 received placebo. Inclusion criteria: aged over 14 years, clinical meningitis (defined as combination of nuchal rigidity and CSF abnormalities). Tuberculous meningitis defined as "definite" if acid-fast bacilli were seen in CSF, "probable" if at least 1 of the following present: suspected active pulmonary TB on chest radiography, acid-fast bacilli in any specimen other than CSF, clinical evidence of extrapulmonary TB, and "possible" if at least 4 of the following were present: history of TB, predominance of lymphocytes in CSF, duration of illness more than 5 days, ratio of CSF to plasma glucose less than 0.5, altered consciousness, yellow CSF, focal neurological signs. Exclusion criteria: contraindication to corticosteroids; received more than 1 dose of any corticosteroid, or more than 30 days of ATT immediately before the trial. HIV status: 98/545 HIV-positive, 44/274 (16.1%) in dexamethasone group, 54/271 (19.9%) in placebo group. Three participants in the dexamethasone group, and eight participants in the placebo group were not tested for HIV.	1. ATT plus dexamethasone, dose stratified by disease severity*. 2. ATT plus placebo. ATT: For previously untreated participants: oral isoniazid (5 mg/kg), rifampicin (10 mg/kg), pyrazinamide (25 mg/kg, maximum, 2 g/day), and intramuscular streptomycin (20 mg/kg, maximum 1 g/day) for 3 months followed by 6 months of isoniazid, rifampicin, and pyrazinamide at the same daily doses; ethambutol (20 mg/kg; maximum 1.2/day) substituted for streptomycin in HIV-positive participants and was added to the regimen for 3 months for participants previously treated for TB. *Grade II and III disease: intravenous dexamethasone sodium phosphate given 0.4 mg/kg/day for week 1, 0.3 mg/kg/d for week 2, 0.2 mg/kg/d for week 3, and 0.1 mg/kg/day for week 4, and then oral dexamethasone for 4 weeks decreasing by 1 mg each week. Grade I disease: intravenous dexamethasone sodium phosphate 0.3 mg/kg/day for week 1 and 0.2 mg/kg/day for week 2 followed by 4 weeks of oral dexamethasone (0.1 mg/kg/day for week 3 then a total of 3 mg/day, decreasing by 1 mg each week).	Assessed at 9 months post-randomization. 1. Death or severe disability. 2. Adverse events: hepatitis; gastrointestinal bleeding, bacterial sepsis, septic shock, brain herniation syndrome, decreased visual acuity, hyponatraemia, hyperglycaemia, hypertension, vertigo, deafness, Cushingoid features, pruritis, polyarthralgia, streptomycin reaction, rifampicin flu, rash, and others. 3. Coma clearance time. 4. Fever clearance time. 5. Time to discharge. 6. Time to relapse. 7. Presence of focal neurological deficit (9 months post-randomization). Assessed during 5-year follow-up study (9 months to 5 years post-randomization). 1. Death. 2. Disability status. 3. TB relapse.
Prasad 2006	Double-blind, randomized, concurrent placebo-controlled parallel group trial. Length of follow-up: 18 months. A 10-year follow-up was planned but not completed.	Setting: All India Institute of Medical Sciences, New Delhi, India - tertiary referral centre. Number of participants: 87 participants; 39 females, 48 males; 41 received dexamethasone, 46 received placebo. Inclusion criteria: clinically diagnosed tuberculous meningitis based on meeting these 3 criteria. 1. Gradual onset of any 2 of fever, progressive headache, or impaired consciousness with at least 1 symptom of 3 weeks duration. 2. At least 1 sign of meningeal irritation for example, neck stiffness, Kernig's sign, Brudzinski's sign (except in deeply comatose cases). 3. CSF profile characteristic of tuberculous meningitis (containing more than 0.02 Å~ 109 cells per litre with predominant lymphocytes , protein more than 1 g/Pl, sugar less than two-thirds of simultaneous blood sugar). Exclusion criteria: 1. Alternative diagnosis (including non-tubercular infection, malignancy) made on CSF testing or imaging. 2. Treatment with steroids regularly for more than 10 days used during the current illness. 3. Liver disease or gout. 4. History of gastric or duodenal ulcer, gastrointestinal haemorrhage, malignant hypertension. 5. Pregnant women. HIV status: not specified.	1. ATT plus dexamethasone 0.15 mg per kg body weight (up to a maximum of 4 mg) every 6 hours for 3 weeks then tapered gradually. 2. ATT plus placebo (0.9% saline). ATT: oral (through nasogastric tube in unconscious participants) administration of isoniazid 10 mg/kg up to 300 mg, rifampicin 15 mg/kg up to 450 mg, and pyrazinamide 30 mg/kg for participants less than 30 kg and 1500 mg for participants over 30 kg daily, plus pyridoxine 50 mg daily. Total duration was 9 months	Outcomes identified in trial protocol 1. Treatment success, defined as resolution of meningitic symptoms and achievement of good neurologic function and stability of this state for 3 consecutive months. 2. All-cause death in the first 3 months. 3. Secondary treatment failure. 4. Adverse events related to ATT or dexamethasone, for example deranged liver function tests, hypertension, hyperglycaemia, secondary infection, rash, gastrointestinal bleeding. Outcomes reported in results 1. Death. 2. Non-disabling neurological deficit. 3. Disabling neurological deficit. 4. Bad outcome (death plus disabling neurological deficit). 5. Any deficit (non-disabling neurological deficit plus disabling neurological deficit).

Study	Methods	Participants	Interventions	Outcomes
Malhotra 2009	Randomized parallel group 3-arm study with allocation ratio 1:1:1. Length of follow-up: 10 months.	Setting: Chhatrapati Shahuji Maharaj Medical University (CSMMU), Lucknow, India - tertiary referral centre. Number of participants: 91 participants; 48 males, 43 females (6 participants randomized but lost to follow-up); 32 randomized to dexamethasone (1 lost to follow-up), 33 randomized to methylprednisolone (3 lost to follow-up), 32 randomized to no steroid (2 lost to follow-up). Inclusion criteria: age > 14 years; meningitis syndrome; tuberculous meningitis defined as "definite" if acid-fast bacilli were seen in CSF, "probable" if one or more than one of the following present: suspected active pulmonary TB on chest radiography, acid-fast bacilli in any specimen other than CSF, clinical evidence of extrapulmonary TB, and "possible" if at least 4 of the following were present: history of TB, predominance of lymphocytes in CSF, duration of illness > 5 days, ratio of CSF to plasma glucose < 0.5, altered consciousness, yellow CSF, or focal neurological signs. Exclusion criteria: age < 14 years; HIV-positive; contraindication to corticosteroids; received corticosteroid or ATT before presentation at the CSMMU, evidence of space occupying lesion on CT brain, refused consent.	1. ATT + dexamethasone (intravenous for 4 weeks as (at 0.4, 0.3, 0.2 and 0.1 mg/kg/day during weeks 1, 2, 3, 4 respectively); daily oral dose for following 4 weeks as 4, 3, 2, 1 mg/day on weeks 5, 6, 7, 8 respectively). 2. ATT + methylprednisolone (intravenous for 5 days (1 g/day for participants weighing > 50kg and 20 mg/kg/day for participant weighing < 50 kg). 3. ATT alone. ATT: rifampicin (15 mg/kg/day), isoniazid (10 mg/kg/day), pyrazinamide (30 mg/kg/day) and either ethambutol (20 mg/kg/day) or streptomycin (15 mg/kg/day) for 2 months and isoniazid (10 mg/kg/day) for 7 months.	Assessed at 6 months post-randomization. 1. Death or severe disability. 2. Adverse events: hepatitis; anti-epileptic toxicity, gastro-intestinal bleeding, paradoxical tuberculoma. 3. Deterioration in vision, development of new focal neurological deficit and new-onset seizures.

2.3 Randomised controlled trials (RCTs)

Only one additional RCT published subsequent to the Prasad (2016) systematic review was identified.[7] This RCT is included in the Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026).

This RCT was a double-blind, placebo-controlled trial that included only adults living with HIV and TBM. Participants were recruited from the Hospital for Tropical Diseases and Pham Ngo Thach Hospital for Tuberculosis and Lung Disease in Ho Chi Minh City, Vietnam and from Dr Cipto Mangunkusumo National Reference Hospital and Persahabatan National Respiratory Referral Hospital in Jakarta, Indonesia. Eligible participants were 18 years or older, living with HIV, had been clinically diagnosed with TBM based on ≥ 5 days of meningitis symptoms and cerebrospinal fluid abnormalities, and had started ATT. Participants were further classified as having definite, probable, and possible TBM.

Enrolled participants were randomly assigned in a 1:1 ratio to receive a 6- to 8-week tapering course of dexamethasone or placebo in addition to 12 months of standard ATT and antiretroviral therapy (ART). Randomisation was computer-generated using randomly permuted block sizes of 4 and 6. Randomisation was stratified by participating site and modified Medical Research Council tuberculous meningitis severity grade⁵.

First-line ATT followed Vietnamese and Indonesian national guidelines. Rifampin (10mg/kg/24 hrs; maximum 600mg), isoniazid (5mg/kg/24hrs; maximum 300mg), pyrazinamide (25mg/kg/24hrs; maximum 2g) and ethambutol (20mg/kg/24 hrs; maximum 1.2g) were given the first 2 months of treatment, provided drug resistance was not suspected or proven. Pyrazinamide was then stopped and rifampin, isoniazid and ethambutol were continued until at least 12 months of ATT in total had been completed. In ART naïve participants, ART was started 6 to 8 weeks after initiation of ATT according to national guidelines.

Participants with grade II or III TBM randomised to the intervention arm received intravenous dexamethasone for 4 weeks (0.4 mg per kilogram of body weight per day for the first week, 0.3 mg per kilogram per day for the second week, 0.2 mg per kilogram per day for the third week, and 0.1 mg per kilogram per day for the fourth week) and then oral dexamethasone for 4 weeks, starting at 4 mg per day and decreasing by 1 mg each week. Participants with grade I TBM randomised to the intervention arm received intravenous dexamethasone for 3 weeks (0.3 mg per kilogram per day for the first week, 0.2 mg per kilogram per day for the second week, and 0.1 mg per kilogram per day for the third week) and then oral dexamethasone for 3 weeks, starting at 3 mg per day and decreasing by 1 mg each week.

The primary endpoint was death from any cause during the 12 months after randomisation. Secondary endpoints included neurological disability (defined as a modified Rankin scale score of 3-5) at 12 months after randomisation and neurological immune reconstitution inflammatory syndrome (IRIS) during the first 6 months. Additional secondary endpoints assessed at 12 months after randomisation included first new neurologic event or death, HIV-associated cancer, use of open-label glucocorticoid treatment for any reason, shunt surgery, and serious adverse events.

The study sample size calculation assumed a 9-month mortality of 40% in the dexamethasone arm and a hazard ratio of death for the dexamethasone arm compared to the placebo arm of 0.69. An estimated 520 PWH with TBM were required for 80% power, allowing 5% loss to follow-up.

Between 25 May 2017 and 29 April 2021, 520 participants were enrolled, with 263 participants randomly assigned to the dexamethasone arm and 257 participants randomly assigned to placebo arm. Almost half (49%) of participants were ART naïve. In participants with a baseline CD4 count ($n = 484$), 51.9% ($n = 251$) had a baseline

⁵ Modified Medical Research Council tuberculous meningitis severity grade: Grade I, Glasgow coma scale (GCS) of 15 with no focal neurological deficit; Grade II, GCS 11 to 14 OR GCS 15 with focal neurological deficit; Grade III, GCS ≤ 10 with or without focal neurological deficit.

CD4 count ≤ 50 cells per cubic millimetre. The median age of participants was 36 years. Overall, 40.8% of participants had definite TBM, 48.7% had probable TBM and 10% had possible TBM. The majority of participants (86%) had grade I or II disease. In total, 16 participants (10 in the dexamethasone arm and 6 in the placebo arm) had multidrug-resistant TBM.

Overall this RCT was assessed to be at low risk of bias (**Appendix 3**)

3. Results: Effectiveness and/or safety

3.1 PICO 1: Corticosteroids plus standard anti-tuberculous treatment compared to anti-tuberculous treatment alone or with placebo in HIV-negative adults and children with TBM

3.1.1 Outcome 1: Mortality and Outcome 2: Severe disability

3.1.1.1 Guideline: Tuberculous Meningitis International Research Consortium Clinical Practice Guideline, 2026.

Clinical Practice Guideline (2026). Corticosteroids be used as an adjunctive agent for TBM irrespective of HIV status.

Certainty assessment							No of patients		Effect	
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroids	no corticosteroids	Relative (95% CI)	Absolute (95% CI)
Mortality (follow-up: range 9 months to 12 months)										
9	Randomised trials, ¹⁰⁵⁻¹¹³	Not serious	Not serious	Not serious	Not serious	None	316/910 (34.7%)	367/860 (42.7%)	RR 0.81 (0.72-0.92)	79 fewer per 1,000 (from 34 fewer to 125 fewer)
Morbidity as defined by modified Rankin Scale 3-5 (compared to 0-2) amongst survivors with follow-up from 9 to 12 months)										
8	Randomised trials, ¹⁰⁵⁻¹¹²	Not serious	Serious	Not serious	Not serious	None	102/589 (17.3%)	100/490 (20.4%)	RR 0.85 (0.66-1.09)	31 fewer per 1,000 survivors (from 78 fewer to 16 more)

CI=confidence interval. OR=odds ratio. RR=risk ratio. TBM=tuberculous meningitis.

Note: these estimates are based on ALL RCTs including 2 RCTs that enrolled 614 PWH.

Insufficient methodological detail was provided in the clinical practice guideline to allow appraisal of the underpinning systematic review. The transparency of the guideline's GRADE assessment was limited, as explicit justifications for decisions to downgrade (or not downgrade) the certainty of evidence were not reported. Consequently, the certainty of evidence ratings are not presented here.

3.1.1.2 Systematic review: Prasad (2016)

Table 4. Summary of findings table from Prasad (2016) systematic review

Summary of findings for the main comparison. Any corticosteroid compared to control for tuberculous meningitis					
Any corticosteroid compared to control for tuberculous meningitis					
Participant or population: adults or children with tuberculous meningitis on tuberculosis (TB) chemotherapy					
Settings: hospital care					
Intervention: any corticosteroid					
Comparison: placebo or no corticosteroid					
Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk*	Corresponding risk			
	Control	Corticosteroid			
Follow-up to 2 to 24 months					
Death	41 per 100	31 per 100 (27 to 36)	RR 0.75 (0.65 to 0.87)	1337 (9 trials)	⊕⊕⊕⊕ high 1,2,3,4,5
Disabling neurological deficit	8 per 100	7 per 100 (6 to 10)	RR 0.92 (0.71 to 1.20)	1314 (8 trials)	⊕⊕⊕⊕ low 6,7,8
Follow-up to 5 years					
Death	47 per 100	44 per 100 (37 to 53)	RR 0.93 (0.78 to 1.12)	545 participants (1 trial)	⊕⊕⊕⊕ moderate 9,10
Disabling neurological deficit	15 per 100	14 per 100 (7 to 25)	RR 0.91 (0.49 to 1.69)	244 (1 trial)	⊕⊕⊕⊕ very low 10,11,12
*The assumed risk is from the median control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio; TB: tuberculosis.					
1	Not downgraded for risk of bias. There are few uncertainties regarding allocation concealment or sequence generation in one of the two largest studies, but the largest trial was high quality and effects between these two trials were consistent.				
2	Not downgraded for inconsistency: low statistical heterogeneity, and the forest plot shows a consistent benefit.				
3	Not downgraded for indirectness in relation to age: all the participants in Schoeman 1997 and 59% of the participants in Girgis 1991 were children, and the effect is consistent with the other large trial, Thwaites 2004, which included participants aged 14 and over.				
4	Not downgraded for indirectness for HIV status: one trial included 98 HIV-positive participants, with no obvious qualitative heterogeneity when compared to HIV-negative participants (Thwaites 2004). If making recommendations for HIV-positive participants only, a guidelines panel may wish to downgrade on indirectness.				
5	Not downgraded for serious imprecision: the overall meta-analysis is adequately powered to detect this effect but is only adequately powered when the trials at unclear or high risk of bias are included. The effect is clinically important.				
6	Downgraded by one for risk of bias: four of the eight trials were at high risk of bias due to lack of blinding of outcome assessors, which could impact on the interpretation of assessments of disability.				
7	Not downgraded for indirectness: trials included children, adults, some HIV-positive people, and people from different continents.				
8	Downgraded by one for imprecision: effects range from clinically important benefits of 29% reduction to 20% increase in disability.				
9	Not downgraded on risk of bias or imprecision: number of participants followed up was high: 91% at five years.				
10	Downgraded by one for indirectness. This was a single trial conducted in a high-quality health care unit in a population with high levels of infectious diseases endemicity and poverty. The attenuation of the effect may be less marked in populations with lower exposure to infectious diseases and other causes of reduced life expectancy associated with poverty. The authors were not able to establish the cause of death in most of the people who died after 9 months follow-up, and so it is not possible to assess whether these deaths were related to tuberculous meningitis or to other causes.				
11	Not downgraded on risk of bias. Although the assessors were not blind to the allocation, and some assessments were conducted by telephone, the numbers of disabled participants in the two groups were the same, and it is unlikely that systematic bias in the observers is present.				
12	Downgraded by two for imprecision. There were few events, and the confidence interval ranges from substantive harms to substantive benefits.				

The effect of corticosteroids appeared to be consistent across all grades of the disease although this analysis is underpowered (Grade I TBM RR 0.50, 95% CI 0.29 to 0.85; six trials, 305 participants); Grade II (RR 0.72, 95% CI 0.56 to 0.93; seven trials, 581 participants); and Grade III (RR 0.69, 95% CI 0.54 to 0.88; eight trials, 651 participants).

3.1.2 Outcome 3: Adverse events

3.1.2.1 Guideline: Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026).

No summary of findings table for adverse events was included in the publication.

3.1.2.2 Systematic review: Prasad (2016)

No summary of findings table for adverse events was included in the publication. There was no difference in incidence of hyperglycaemia/glycosuria, hepatitis, gastrointestinal bleeding, or invasive bacterial infection (Figure 5).

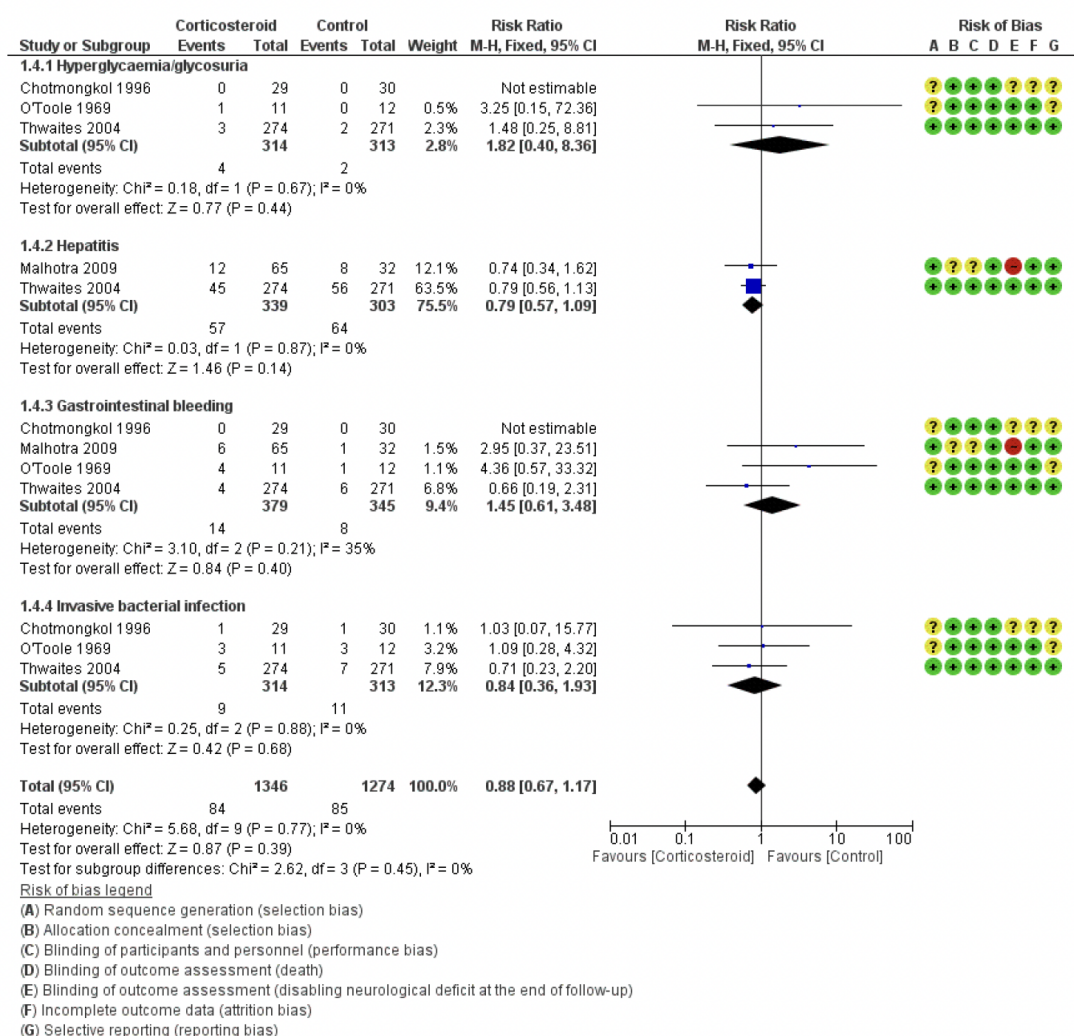


Figure 5. Forest plot of comparison any corticosteroid versus control, outcome adverse events from Prasad (2016)

3.2 PICO 2: Corticosteroids plus standard anti-tuberculous treatment compared to anti-tuberculous treatment alone or with placebo in adults and children living with HIV and co-infected with TBM

3.2.1 Outcome 1 and 2: Mortality and severe disability

3.2.1.1 Guideline: Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026)

Table 5. Summary of findings table from Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026). Corticosteroids used as an adjunctive agent for TBM with HIV co-infection.

Certainty assessment							№ of patients		Effect	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	no corticosteroids	Relative (95% CI)	Absolute (95% CI)
Mortality (follow-up: range 9 months to 12 months)										
2	Randomised trials ^{111,112}	Not serious	Not serious	Not serious	Not serious	None	143/307 (46·6%)	163/311 (52·4%)	RR 0·90 (0·77 to 1·05)	52 fewer per 1,000 (from 121 fewer to 26 more)
Morbidity as defined by modified Rankin Scale 3-5 (compared to 0-2) amongst survivors with follow-up from 9 to 12 months)										
2	Randomised trials ^{111,112}	Not serious	Not serious	Not serious	Not serious	None	15/147 (10·2%)	10/131 (7·6%)	RR 1·34 (0·62 to 2·87)	25 more per 1,000 (from 41 fewer to 93 more)

CI=confidence interval. OR=odds ratio. RR=risk ratio. TBM=tuberculous meningitis.

Note: The two RCTs included in the systematic review and meta-analysis are Thwaites (2004) which included 98 PWH and Donovan (2023) which included 520 PWH. [7,8] Neither of these RCTs enrolled children < 14 years of age.

Insufficient methodological detail was provided in the clinical practice guideline to allow appraisal of the underpinning systematic review. The transparency of the guideline's GRADE assessment was limited as explicit justifications for decisions to downgrade (or not downgrade) the certainty of evidence were not reported. For example, despite a low event rate and wide confidence interval for the morbidity outcome, the certainty of evidence was not downgraded for imprecision. Consequently, the reported certainty of evidence ratings are not presented here.

3.2.1.2 Systematic review: Prasad (2016)

No summary of findings table for PWH specifically was included in the publication. In a subgroup analysis by HIV status, only one RCT specifically mentioned that 98 participants were PWH. Analyses stratifying the outcomes of death and disabling neurological deficit in PWH did not detect any large differences and showed no apparent effect of HIV status on the effect estimates, but the analysis is underpowered.

Table 6. Any corticosteroid versus control stratified by HIV status from Prasad (2016)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	534	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.66, 1.02]
1.1 HIV-positive	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.67, 1.20]
1.2 HIV-negative	1	436	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.06]
2 Disabling neurological deficit	1	534	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.73, 1.79]
2.1 HIV-positive	1	98	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.08, 19.07]
2.2 HIV-negative	1	436	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.73, 1.80]
3 Death or disabling residual neurological deficit	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.09]
3.1 HIV-positive	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.68, 1.20]
3.2 HIV-negative	1	447	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.74, 1.14]

3.2.1.3 Randomised controlled trial: Donovan (2023)

Death occurred in 116 of 263 participants (44.1%) in the dexamethasone group and in 126 of 257 participants (49.0%) in the placebo group (HR 0.85; 95% CI 0.66 to 1.10; $p = 0.22$) (RR 0.90; 95% CI 0.75 to 1.08; $p = 0.26$; 49 fewer per 1000 (122 fewer to 39 more per 1000)). No benefit associated with dexamethasone was observed in any prespecified subgroup in the intention-to-treat population, including modified MRC disease-severity grade, or CD4 cell count at enrolment. However, in subgroup analyses by diagnostic category, the apparent benefit of corticosteroids appeared to be driven by participants classified as having possible tuberculous meningitis, although the small size of this subgroup and the issue of multiple testing limit the interpretability of this finding (Table 7).

Table 7. Death from any cause in pre-specified subgroups of PWH in the intention-to-treat population adapted from Donovan (2023)

Subgroup	Dexamethasone (n = 263)	Placebo (n = 257)	Hazard Ratio (95% CI)
Overall	116/263	126/257	0.85 (0.66–1.10)
Modified MRC disease-severity grade			
I	22/99	28/97	0.72 (0.41–1.25)
II	60/125	68/126	0.82 (0.58–1.16)
III	34/39	30/34	1.03 (0.63–1.69)
Diagnostic category			
Definite tuberculous meningitis	48/108	49/104	0.90 (0.61–1.35)
Probable tuberculous meningitis	61/129	61/124	0.91 (0.64–1.30)
Possible tuberculous meningitis	5/24	15/28	0.34 (0.12–0.94)
ART status at enrolment			
No previous ART	64/133	64/122	0.85 (0.60–1.21)
>3 months of ART	20/46	26/58	0.96 (0.54–1.72)
ART of undetermined duration	19/58	19/48	0.80 (0.42–1.51)
CD4 cell count at enrolment (1)			
≤ 50 per cubic millimetre	67/126	67/125	0.96 (0.69–1.35)
51–100 per cubic millimetre	12/45	19/44	0.52 (0.25–1.06)
101–200 per cubic millimetre	14/36	13/35	1.04 (0.49–2.22)
>200 per cubic millimetre	11/37	15/36	0.70 (0.32–1.52)
CD4 cell count at enrolment (2)*			
≤ 50 per cubic millimetre	67/126	67/125	0.96 (0.69–1.35)
>50 per cubic millimetre	37/118	47/118	0.79 (0.56–1.11)

*Note: the effect estimates for CD4 cell count at enrolment (2) were conducted post-hoc by the reviewer.

3.2.2 Outcome 2: Adverse events

3.2.2.1 Guideline: Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026)

No summary of findings table for adverse events was included in the publication.

3.2.2.2 Systematic review: Prasad (2016)

No summary of findings table for adverse events in PWH was included in the publication.

3.2.2.3 Randomised controlled trial: Donovan (2023)

The numbers of participants with at least one serious adverse event were similar between the dexamethasone group compared to the placebo group (73% vs. 75.5%, $p = 0.52$). Fewer participants had serious neurologic adverse events in the dexamethasone group than in the placebo group (36.1% vs. 44.7%). These serious neurologic adverse events included depressed consciousness and new focal neurologic signs.

Gastrointestinal bleeding events and other adverse events possibly, probably, or definitely related to glucocorticoids occurred with a similar incidence in the two trial groups. The incidence of clinical grade 3 or 4 adverse events (including hyperglycaemia and psychiatric disorders), adverse events leading to interruptions in ATT or ART (including sepsis), and grade 3 or 4 laboratory abnormalities was similar in the two groups, except for elevated ALT levels, which occurred more often in the dexamethasone arm than in the placebo arm (13.7% versus 7.8%).

Table 8. Serious adverse events from Donovan (2023)

Event	Dexamethasone (N=263)		Placebo (N=257)	
	no. of participants (%)	no. of events	no. of participants (%)	no. of events
Any selected serious adverse event	192 (73.0)	486	194 (75.5)	442
Nervous system disorder	95 (36.1)	128	115 (44.7)	147
Infection or infestation	60 (22.8)	79	50 (19.5)	63
Metabolism or nutrition disorder	51 (19.4)	66	59 (23.0)	68
Respiratory, thoracic, or mediastinal disorder	39 (14.8)	40	37 (14.4)	39
Hepatobiliary disorder	38 (14.4)	44	29 (11.3)	29
Gastrointestinal disorder	32 (12.2)	33	21 (8.2)	25
Blood or lymphatic system disorder	20 (7.6)	23	17 (6.6)	17
Investigation†	14 (5.3)	14	9 (3.5)	9
General disorder or administration-site condition	14 (5.3)	15	7 (2.7)	7
Vascular disorder	10 (3.8)	10	11 (4.3)	11
Skin or subcutaneous-tissue disorder	12 (4.6)	13	5 (1.9)	6
Cardiac disorder	7 (2.7)	7	4 (1.6)	4
Renal or urinary disorder	4 (1.5)	4	6 (2.3)	6
Musculoskeletal or connective-tissue disorder	4 (1.5)	4	2 (0.8)	2
Psychiatric disorder	3 (1.1)	3	1 (0.4)	1
Eye disorder	0	0	3 (1.2)	3
Endocrine disorder	1 (0.4)	1	2 (0.8)	2
Ear or labyrinth disorder	1 (0.4)	1	1 (0.4)	1
Injury, poisoning, or procedural complication	1 (0.4)	1	1 (0.4)	1
Immune system disorder	0	0	1 (0.4)	1

* Events were summarized according to the system organ class of the *Medical Dictionary for Regulatory Activities* hierarchy. The number of participants with any adverse events and specific events were summarized and compared between the two trial groups on the basis of chi-square tests or (if the expected number in one of the table cells was <1) Fisher's exact test.

† Abnormal results of investigations were reported.

Costs

As the use of adjunctive corticosteroids is already included in the paediatric STG as standard of care, there is no change in recommendation and no resultant incremental budget impact. The historic absence of a definitive recommendation for the use of corticosteroids for the treatment of TBM in PLWH is likely to have resulted in discretionary clinical judgement being applied in clinical practice. An accurate assessment of any budget impact is not possible, however, we do not anticipate any significant incremental budget impact with the CD4 stratified treatment approach included in our recommendation above.

TBM - cost of corticosteroids as adjunctive therapy (PAEDIATRICS)								
Prednisolone oral								
Formulation	Price per pack (Rands)	STG dosing guidance		Assumed weight per patient (kg)	Dose per day (mg)	Dose per course (mg)	Equivalent number of bottles per patient	Cost per course (Rands)
15mg/5mL solution (50mL pack) = 150mg per bottle	95,21	Weeks 1 -4	2mg/kg/day	10	20	560	5	R444,31
		Weeks 5-6	1mg/kg/day		10	140		
		Weeks 1 -4	2mg/kg/day	20	40	1120	10	R952,10
		Weeks 5-6	1mg/kg/day		20	280		
		Weeks 1 -4	2mg/kg/day	>30	60	1680	14	R1 332,94
		Weeks 5-6	1mg/kg/day		30	420		
Notes: 1. Based on 3 weight bands (10kg, 20kg and >/=30kg) 2. Total dose per course rounded to nearest full pack 3. Prices based on MHPL (Feb 2026) 4. Weeks 5-6 dose taper calculated at 50% of treatment dose for pragmatic reasons								
TBM - cost of corticosteroids as adjunctive therapy (ADULTS)								
Dexamethasone IV								
STG dosing guidance		Formulation	Price per ampoule (Rands)	Daily dose for 70kg (mg)	Equivalent number of amps per day	Cost per week (Rands)		
Week 1	0.3-0.4mg/kg/day	4mg/mL as 1mL inj	6,83	28	7	334,67		
Week 2	0.3-0.4mg/kg/day			28	7	334,67		
Week 3	0.2mg/kg/day			14	4	191,24		
Week 4	0.1mg/kg/day			7	2	95,62		
Week 5	4mg/day			4	1	47,81		
Week 6	3mg/day			3	1	47,81		
Week 7	2mg/day			2	1	47,81		
Week 8	1mg/day			1	1	47,81		
Cost per course						R1 147,44		

Prednisone oral (ADULTS)					
STG dosing guidance		Formulation	Price per tablet (Rands)	Equivalent number of tablets per day	Cost per week (Rands)
Week 1	60mg/day	5mg tablet	0,19	12	15,96
Week 2	60mg/day			12	15,96
Week 3	40mg/day			8	10,64
Week 4	25mg/day			5	6,65
Week 5	20mg/day			4	5,32
Week 6	15mg/day			3	3,99
Week 7	10mg/day			2	2,66
Week 8	5mg/day			1	1,33
Cost per course					R62,51
Notes: 1. Based on 70kg adult for weight-based dosing 2. Doses rounded to nearest ampoule/tablet 3. Prices based on MHPL (Feb 2026) 4. Where dose ranges recommended - max dose applied for costing 5. For prednisone, ave price per tablet applied as multiple products on tender					

Key findings and discussion

- In adults and children with TBM who are HIV-negative[6]:
 - Corticosteroids reduce mortality moderately (RR 0.75, 95% CI 0.65 to 0.87, high certainty of evidence). This reduction in mortality is consistent across all grades of the disease.
 - Corticosteroids may reduce severe disability (RR 0.92, 95% CI 0.71 to 1.20, low certainty of evidence).
 - Corticosteroids result in little to no difference in serious adverse events (RR 0.88, 95% CI 0.67 to 1.17).
- In adult PWH and TBM:
 - Corticosteroids may result in lower mortality (RR 0.90, 95% CI 0.77 to 1.05).[5]
 - Corticosteroids may increase severe disability, but the confidence interval is very wide (RR 1.34, 95% 0.65 to 2.87).[5]
 - Corticosteroids did not increase serious adverse events (73% vs. 75.5%, $p = 0.52$).[7]
 - These findings are predominantly based on data from one RCT in which the majority of PWH and TBM had CD4 cell count ≤ 200 cell/mm³.
 - It is biologically plausible that in PWH with TBM and relatively preserved CD4 counts, the mortality benefit of adjunctive corticosteroids would approximate that observed in HIV-negative patients.
 - The exact CD4 count at which this mortality benefit would approximate that observed in HIV-negative individuals has not been established, and there is insufficient data to define this threshold.
 - Given the high mortality of TBM, the absence of demonstrated harm associated with corticosteroids, and the potential for a small mortality benefit, specifically in those PWH with higher CD4 counts, withholding corticosteroids from all PWH may not be appropriate.

- We pragmatically suggest, based on expert opinion and aligned with the National Department of Health programmatic definitions of advanced HIV disease (AHD), that corticosteroids be used in PWH with TBM and CD4 cell counts > 200 cells/mm³. In PWH with TBM and CD4 cell counts ≤ 200 cells/mm³ we suggest not using corticosteroids.
- In children with HIV and TBM
 - No randomized controlled trials evaluating corticosteroids in children with HIV and TBM were identified. Consequently, there is currently no direct evidence to indicate that children with HIV and TBM fail to derive a mortality benefit comparable to that observed in HIV-negative children with TBM.

Recommendations

- In HIV-negative adults with TB meningitis of any grade, we recommend using corticosteroids.
- In adults with HIV and TB meningitis, with CD4 count ≤ 200 cells/mm³, we suggest not using corticosteroids.
- In adults with HIV and TB meningitis, with CD4 count >200 cells/mm³, we suggest using corticosteroids.
- In children, with or without HIV, with TB meningitis of any grade, we recommend using corticosteroids.

Review Team

The following people were involved in this review:

Name	Affiliation	Role and Contribution	Interest declaration
Jessica Taylor	University of Cape Town	PICO; Title, abstract and full text screening; Write-up, referencing and appendices; Quality appraisal, Clinical expertise; Formulation of recommendations; Quality assurance	None
Zahiera Adam	CHAI, Affordable Medicines Directorate, NDoH	Costing; Quality assurance; Formulation of recommendations	None
Gayle Tatz	University of Cape Town	Clinical expertise; Formulation of Recommendations	None
Halima Dawood	Infectious diseases specialist, Greys Hospital, KZN	Clinical expertise; Formulation of recommendations	None
Jeremy Nel	Infectious diseases specialist, Helen Joseph Hospital and the University of the Witwatersrand.	Clinical expertise; Formulation of recommendations	None
Karen Cohen	University of Cape Town	Clinical expertise; Formulation of recommendations	None

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References

- [1] Seid G, Alemu A, Dagne B, et al. Microbiological diagnosis and mortality of tuberculosis meningitis: Systematic review and meta-analysis. *PLOS ONE*. 2023;18(2):e0279203.
- [2] Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev*. 2008(1):Cd002244.
- [3] WHO Guidelines Approved by the Guidelines Review Committee. WHO consolidated guidelines on tuberculosis: Module 4: Treatment and care. Geneva: World Health Organization © World Health Organization 2025.; 2025.
- [4] Saukkonen JJ, Duarte R, Munsiff SS, et al. Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis: An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2025;211(1):15-33.
- [5] Donovan J, Cresswell FV, Tucker EW, et al. A clinical practice guideline for tuberculous meningitis. *Lancet Infect Dis*. 2026;26(2):e96-e111.
- [6] Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev*. 2016;4(4):Cd002244.
- [7] Donovan J, Bang ND, Imran D, et al. Adjunctive Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults. *N Engl J Med*. 2023;389(15):1357-1367.
- [8] Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med*. 2004;351(17):1741-51.
- [9] Malhotra HS, Garg RK, Singh MK, et al. Corticosteroids (dexamethasone versus intravenous methylprednisolone) in patients with tuberculous meningitis. *Ann Trop Med Parasitol*. 2009;103(7):625-34.
- [10] Kumarvelu S, Prasad K, Khosla A, et al. Randomized controlled trial of dexamethasone in tuberculous meningitis. *Tuber Lung Dis*. 1994;75(3):203-7.
- [11] Chotmongkol V, Jitpimolmard S, Thavornpitak Y. Corticosteroid in tuberculous meningitis. *J Med Assoc Thai*. 1996;79(2):83-90.
- [12] Schoeman JF, Van Zyl LE, Laubscher JA, et al. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. *Pediatrics*. 1997;99(2):226-31.
- [13] Girgis NI, Farid Z, Kilpatrick ME, et al. Dexamethasone adjunctive treatment for tuberculous meningitis. *Pediatr Infect Dis J*. 1991;10(3):179-83.
- [14] Lardizabal DV, Roxas AA, Jr. Dexamethasone as adjunctive therapy in adult patients with probable tuberculous meningitis stage II and III: An open randomized controlled trial. *Philippine Journal of Neurology*. 1998.
- [15] O'Toole RD, Thornton GF, Mukherjee MK, et al. Dexamethasone in tuberculous meningitis. Relationship of cerebrospinal fluid effects to therapeutic efficacy. *Ann Intern Med*. 1969;70(1):39-48.

Appendix 1: Search results and reasons for exclusion

	Reference	Study Type	Included/Excluded	Reason
1.	Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2016 Apr 28;4(4):CD002244. doi: 10.1002/14651858.CD002244.pub4. PMID: 27121755; PMCID: PMC4916936.	Systematic review	Included	
2.	Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC, Nguyen QH, Nguyen TT, Nguyen NH, Nguyen TN, Nguyen NL, Nguyen HD, Vu NT, Cao HH, Tran TH, Pham PM, Nguyen TD, Stepniowska K, White NJ, Tran TH, Farrar JJ. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 2004 Oct 21;351(17):1741-51. doi: 10.1056/NEJMoa040573. PMID: 15496623.	Randomised controlled trial	Included	
3.	Donovan J, Bang ND, Imran D, Nghia HDT, Burhan E, Huang DTT, Hiep NTT, Ngoc LHB, Thanh DV, Thanh NT, Wardhani ALS, Maharani K, Gasmara CP, Hanh NHH, Oanh PKN, Estiasari R, Thu DDA, Kusumaningrum A, Dung LT, Giang DC, Ha DTM, Lan NH, Chau NVV, Nguyet NTM, Gekus RB, Thuong NTT, Kestelyn E, Hamers RL, Phu NH, Thwaites GE; ACT HIV Investigators. Adjunctive Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults. N Engl J Med. 2023 Oct 12;389(15):1357-1367. doi: 10.1056/NEJMoa2216218. PMID: 37819954; PMCID: PMC7615197.	Randomised controlled trial	Included	
4.	Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J; British Infection Society. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect. 2009 Sep;59(3):167-87. doi: 10.1016/j.jinf.2009.06.011. Epub 2009 Jul 4. PMID: 19643501.	Guideline	Excluded	Never updated. More up-to-date clinical practice guidelines available.
5.	Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD002244. doi: 10.1002/14651858.CD002244.pub3. Update in: Cochrane Database Syst Rev. 2016 Apr 28;4:CD002244. doi: 10.1002/14651858.CD002244.pub4. PMID: 18254003.	Systematic review	Excluded	2016 update included.
6.	Critchley JA, Young F, Orton L, Garner P. Corticosteroids for prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2013 Mar;13(3):223-37. doi: 10.1016/S1473-3099(12)70321-3. Epub 2013 Jan 29. PMID: 23369413.	Systematic review	Excluded	Incorrect population – includes any TB diagnosis, not specifically TBM.
7.	Thuong NTT, Heemskerk D, Tram TTB, Thao LTP, Ramakrishnan L, Ha VTN, Bang ND, Chau TTH, Lan NH, Caws M, Dunstan SJ, Chau NVV, Wolbers M, Mai NTH, Thwaites GE. Leukotriene A4 Hydrolase Genotype and HIV Infection Influence Intracerebral Inflammation and Survival From Tuberculous Meningitis. J Infect Dis. 2017 Apr 1;215(7):1020-1028. doi: 10.1093/infdis/jix050. PMID: 28419368; PMCID: PMC5426373.	Randomised controlled trial	Excluded	Non-interventional, mechanistic study nested within randomised controlled trial.
8.	Saluja A, Vibha D, Pandit AK, Shukla G, Srivastava AK, Tripathi M, Srivastava MVP, Prasad K, Dwivedi SN. Comparison of dexamethasone regimens in tubercular meningitis (TBM): a randomized open label clinical trial. J Infect Dev Ctries. 2023 Dec 31;17(12):1769-1774. doi: 10.3855/jidc.17563. PMID: 38252729.	Randomized controlled trial	Excluded	Incorrect intervention and comparator – oral and intravenous dexamethasone.
9.	Diallo A, Diallo BD, Diallo OH, Carlos-Bolumbu M, Camara M, Sidikba S. Corticosteroids for reducing tuberculosis mortality in persons living with HIV: a systematic review and meta-analysis using reconstructed individual patient data. BMJ Glob Health. 2025 Aug 14;10(8):e017923. doi: 10.1136/bmjgh-2024-017923. PMID: 40813100; PMCID: PMC12352167.	Systematic review	Excluded	Incorrect population – includes any TB diagnosis, not specifically TBM.
10.	Malhotra HS, Garg RK, Singh MK, Agarwal A, Verma R. Corticosteroids (dexamethasone versus intravenous methylprednisolone) in patients with tuberculous meningitis. Ann Trop Med Parasitol. 2009 Oct;103(7):625-34. doi: 10.1179/000349809X12502035776315. PMID: 19825284.	Randomised controlled trial	Included	
11.	Prasad K, Volmink J, Menon GR. WITHDRAWN: Steroids for treating tuberculous meningitis. Cochrane Database Syst Rev. 2007 Jul 18;(1):CD002244. doi: 10.1002/14651858.CD002244.pub2. Update in: Cochrane Database Syst Rev. 2008 Jan 23;(1):CD002244. doi: 10.1002/14651858.CD002244.pub3. PMID: 17836701.	Systematic review	Excluded	Study withdrawn
12.	Madani N, Dendane T, Zekraoui A, Abidi K, Zegwagh AA, Aboual R. Effects of corticosteroids on adults with tuberculous meningitis admitted to intensive care unit: a propensity score analysis. Rev Med Interne. 2009 Jan;30(1):12-9. French. doi:10.1016/j.revmed.2008.06.023. Epub 2008 Aug 15. PMID: 18706739.	Retrospective cohort study	Excluded	Incorrect study type
13.	Rustami R, Ganien AR, Dian S, Apriani L, Achmad TH, van der Ven AJ, Born G, Aarnoutse RE, van Crevel R. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. Lancet Infect Dis. 2013 Jan;13(1):27-35. doi: 10.1016/S1473-3099(12)70264-5. Epub 2012 Oct 25. PMID: 23103177.	Randomised controlled trial	Excluded	Incorrect intervention – moxifloxacin and rifampicin.
14.	Kalita J, Misra UK, Prasad S, Bhoi SK. Safety and efficacy of levofloxacin versus rifampicin in tuberculous meningitis: an open-label randomized controlled trial. J Antimicrob Chemother. 2014 Aug;69(8):2246-51. doi:10.1093/jac/dku103. Epub 2014 Apr 20. PMID: 24752957.	Randomised controlled trial	Excluded	Incorrect intervention – levofloxacin.
15.	Moloughgi K, Sheybani F, Naderi H, Mirfeizi Z, Morovatdar N, Baradaran A. Central nervous system infections in patients with systemic lupus erythematosus: a systematic review and meta-analysis. Lupus Sci Med. 2022 Jan;9(1):e000560. doi: 10.1136/lupus-2021-000560. PMID: 34980679; PMCID: PMC8724813.	Systematic review	Excluded	Incorrect population – systemic lupus erythematosus.
16.	Verma R, Chakraborty R. A Clinico-Immunological Perspective of Paradoxical Reaction in HIV-ve Tuberculous Meningitis with Therapeutic Possibilities. Neurol India. 2025 Jul 1;73(4):678-691. doi: 10.4103/neuro-india.Neurol-India-D-24-00443. Epub 2025 Jul 24. PMID: 40705281.	Systematic review	Excluded	Incorrect population - people with TBM with paradoxical reactions
17.	Green JA, Tran CT, Farrar JJ, Nguyen MT, Nguyen PH, Dinh SX, Ho ND, Ly CV, Tran HT, Friedland JS, Thwaites GE. Dexamethasone, cerebrospinal fluid matrix metalloproteinase concentrations and clinical outcomes in tuberculous meningitis. PLoS One. 2009 Sep 30;4(9):e7277. doi: 10.1371/journal.pone.0007277. PMID: 19789647; PMCID: PMC2748711.	Randomised controlled trial	Excluded	Non-interventional, mechanistic study nested within Thwaites, 2008 randomised controlled trial.
18.	Simmons CP, Thwaites GE, Quyen NT, Chau TT, Mai PP, Dung NT, Stepniowska K, White NJ, Hien TT, Farrar J. The clinical benefit of adjunctive dexamethasone in tuberculous meningitis is not associated with measurable attenuation of peripheral or local immune responses. J Immunol. 2005 Jul 1;175(1):579-90. doi:10.4049/jimmunol.175.1.579. PMID: 15972695.	Randomised controlled trial	Excluded	Mechanistic study nested within Thwaites, 2008 randomised controlled trial
19.	Contopoulos-Ioannidis DG, Ioannidis JP. Claims for improved survival from systemic corticosteroids in diverse conditions: an umbrella review. Eur J Clin Invest. 2012 Mar;42(3):233-44. doi: 10.1111/j.1365-2362.2011.02584.x. Epub 2011. Aug 31. PMID: 21880039.	Systematic review	Excluded	Incorrect population – any indication for corticosteroids
20.	Misra UK, Kalita J, Nair PP. Role of aspirin in tuberculous meningitis: a randomized open label placebo controlled trial. J Neurol Sci. 2010 Jun 15;293(1-2):12-7. doi: 10.1016/j.jns.2010.03.025. Epub 2010 Apr 24. PMID: 20421121.	Randomised controlled trial	Excluded	Incorrect intervention – aspirin.
21.	Schoeman JF, Springer P, van Rensburg AJ, Swanevelder S, Hanekom WA, Haslett PA, Kaplan G. Adjunctive thalidomide therapy for childhood tuberculous meningitis: results of a randomized study. J Child Neurol. 2004 Apr;19(4):250-7. doi: 10.1177/088307380401900402. PMID: 15163089.	Randomised controlled trial	Excluded	Incorrect intervention – thalidomide.
22.	Nguyen TH, Tran TH, Thwaites G, Ly VC, Dinh XS, Ho Dang TN, Dang QT, Nguyen DP, Nguyen HP, To SD, Nguyen vV, Nguyen MD, Campbell J, Schultz C, Parry C, Torok ME, White N, Nguyen TC, Tran TH, Stepniowska K, Farrar JJ. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. N Engl J Med. 2007 Dec 13;357(24):2431-40. doi: 10.1056/NEJMoa070852. PMID: 18077808.	Randomised controlled trial	Excluded	Incorrect population – bacterial meningitis.
23.	Garg RK, Pandey S, Mahdi RA, Singhal S. Movement Disorders in Central Nervous System Tuberculosis: A Systematic Review. Can J Neurol Sci. 2025 Sep 29;1-10. doi: 10.1017/cjn.2025.10436. Epub ahead of print. PMID: 41017616.	Systematic review	Excluded	Incorrect population – people with TBM and with movement disorders
24.	Beardsley J, Hoang NLT, Kibengo FM, Tung NLN, Binh TQ, Hung LQ, Chieraki W, Thwaites GE, Chau NVV, Nguyen TTT, Gekus RB, Day JN. Do Intracerebral Cytokine Responses Explain the Harmful Effects of Dexamethasone in Human Immunodeficiency Virus-associated Cryptococcal Meningitis? Clin Infect Dis. 2019 Apr 24;68(9):1494-1501. doi: 10.1093/cid/ciy725. PMID: 30169607; PMCID: PMC6481995.	Randomised controlled trial	Excluded	Incorrect population – cryptococcal meningitis

Appendix 2. Summary of clinical practice guidelines and recommendations

Clinical Practice Guideline	Recommendation	Justification	Subgroup considerations	Studies included in the systematic review	Outcomes considered
Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026)	In people without HIV, we recommend the use of adjunctive corticosteroid therapy, (Strong recommendation, high certainty of evidence) In the absence of an effective alternative adjunctive therapy for HIV-associated tuberculous meningitis, and the safety and potential effectiveness of corticosteroids, we recommend their use on a case-by-case basis in people living with HIV (weak recommendation, high certainty evidence)	Corticosteroids reduced case fatality, especially in children and adults without HIV. There is no signal for a change in disability among survivors in these groups. In people living with HIV and tuberculous meningitis, the benefits of corticosteroids are uncertain.	Separate recommendations for those with and without HIV.	O'Toole RD et al. Ann Intern Med 1969 Girgis N et al. Pediatr Infect Dis J 1991 Kumarvelu S et al. Tuber Lung Dis 1994 Chotmongkol V et al. J Med Assoc Thai 1996 Schoeman JF et al. Pediatrics 1997 Lardizabal DV et al. Philippine Journal of Neurology 1998 Malhotra HS et al. Ann Trop Med Parasitol 2009 Thwaites GE et al. N Engl J Med 2004 Donovan J et al. N Engl J Med 2023	Mortality Morbidity
WHO consolidated guidelines on tuberculosis. Module 4: Treatment and care. (2025). (Note: specific recommendation not updated since 2017)	4.1 In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6 – 8 weeks should be used. (Strong recommendation, moderate certainty of evidence) This recommendation was first put forward in the 2017 guideline update and are copied without modification into the 2025 guideline update.	In patients with tuberculous meningitis, evidence from randomized controlled trials in the systematic review showed lower rates of mortality, death or severe disability, and disease relapse when patients were treated with steroids in addition to anti-TB treatment. The benefits in terms of mortality increased with the increasing TB meningitis stage (i.e. increasing severity of disease).	Steroids should be given regardless of the severity of meningitis. No subgroup consideration by HIV status.	Kumarvelu S et al. Tuber Lung Dis 1994 Chotmongkol V et al. J Med Assoc Thai 1996 Schoeman JF et al. Pediatrics 1997 Malhotra HS et al. Ann Trop Med Parasitol 2009 Thwaites GE et al. N Engl J Med 2004	Mortality Death or severe disability Relapse Adverse events

		Additionally, rates of adverse events and severe adverse events, including severe hepatitis, were lower in the patients receiving steroids.			
ATS/CDC/ERS/IDSA ⁶ Clinical Practice Guideline (2025) (Note: specific recommendation not updated since 2016)	Recommendation 8. We recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6 – 8 weeks for patients with tuberculous meningitis (strong recommendation, moderate certainty in evidence)	Our updated systematic review found a mortality benefit from the use of adjuvant corticosteroids.	No subgroup consideration by severity of TB meningitis or HIV status.	Kumaravelu S et al. Tuber Lung Dis 1994 Chotmongkol V et al. J Med Assoc Thai 1996 Schoeman JF et al. Pediatrics 1997 Malhotra HS et al. Ann Trop Med Parasitol 2009 Thwaites GE et al. N Engl J Med 2004	Mortality Death or severe disability Relapse Adverse events

⁶ American Thoracic Society/United States Centers for Disease Control and Prevention/Infectious Diseases Society of America, the European Respiratory Society.

Appendix 3. Risk of bias assessment Donovan (2023)

Unique ID	Donovan et. al. 2023	Study ID	DOI:10.1056/NEJMoa2216218	Assessor	JT
Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Adjunctive dexamethasone	Comparator	Placebo	Source	Journal article(s)
Outcome	Mortality	Results	HR 0.85	Weight	1
Domain	Signalling question		Response		Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?		Y	Randomization computer-generated using randomly permuted blocks of 4 and 6. Randomization of participants performed using trained clinical staff, with 24-hour availability using Web-based software.	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N		
	Risk of bias judgement		Low		
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?		N		
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N		
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA		
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA		
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y		
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA		

	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Death of any cause - objective
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	Not specifically stated
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	Death of any cause - objective
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	