A clinical practice guideline for tuberculous meningitis

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Tuberculous meningitis is the most severe form of tuberculosis, causing death or disability in around half of those affected. There are no up-to-date international guidelines defining its optimal management. Therefore, the Tuberculous Meningitis International Research Consortium conducted a systematic review of available evidence to address key management questions and to develop practice guidance. The consortium includes representatives from India, Indonesia, South Africa, Uganda, Viet Nam, Australia, the Netherlands, the UK, and the USA. Questions were developed using the Population, Intervention, Comparator, Outcome (PICO) format for tuberculous meningitis diagnosis, anti-tuberculosis chemotherapy, adjunctive anti-inflammatory therapy, and neurocritical and neurosurgical care. A Grading of Recommendations, Assessment, Development and Evaluations approach was used to assess the certainty (or quality) of evidence and establish the direction and strength of recommendations for each PICO-based question. We provide evidence-based recommendations for the optimal treatment and diagnosis of tuberculous meningitis, alongside expert opinion. We expose substantial knowledge and evidence gaps, thereby highlighting current research priorities.

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Introduction

An estimated 10·8 million people develop tuberculosis globally each year,[1] of whom 2–5% have tuberculous meningitis.[2–4] Young children and people who are immunosuppressed, including those living with HIV, are at a particularly high risk of the disease and the associated poor outcomes.[5]

Tuberculous meningitis develops following dissemination of *Mycobacterium tuberculosis* from the lungs to the brain and has a clinical course that is usually insidious, with typical features of headache, neck stiffness, and fever, that develops in days to weeks. In untreated cases, neurological deficits develop, consciousness declines, which results in death.[5] Even with the best available treatment, 20–50% of patients die.[6–10] Early diagnosis and treatment, before the onset of coma, substantially reduces death and disability,[11] yet the best diagnostics and most effective treatments are not well defined. Therefore, we conducted a systematic review of the available evidence to address a series of predefined, crucial clinical questions, to produce authoritative international practice guidelines for the management of tuberculous meningitis.

No international clinical practice guideline exists for tuberculous meningitis. Previous national guidelines by the United Kingdom British Infection Society for CNS tuberculosis in adults and children, published in 2009, have not been updated.[12] Tuberculosis treatment guidelines from WHO[13–15] and jointly from the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of America (IDSA)[16,17] include limited recommendations on CNS tuberculosis management. Up-to-date, evidence-based practice guidelines are required to help physicians globally provide the best care to adults and children with tuberculous meningitis.

We provide guidance for the diagnosis and management of tuberculous meningitis in children and adults, including people living with HIV. We provide some review of other CNS tuberculous complications, including isolated brain tuberculomas, spinal cord tuberculosis, and tuberculous brain abscesses. We sought to make recommendations using the best available evidence, providing an assessment

Key messages

- Diagnosing tuberculous meningitis is difficult; no single test excludes tuberculous meningitis and anti-tuberculosis treatment is often needed based on compatible clinical features alone
- Xpert Ultra or Xpert PCR tests, in addition to mycobacterial culture, are strongly recommended as diagnostic tests for tuberculous meningitis
- There is insufficient evidence to recommend greater than a dose of 10 mg/kg per day of rifampicin in adults at present; however, limited data suggest a dose greater than 20 mg/kg per day is safe, and the results of on-going phase 3 trials investigating greater doses (35 mg/kg per day) are awaited
- Corticosteroids reduce mortality in tuberculous meningitis without HIV co-infection, and are strongly recommended as an adjunctive therapy
- In the absence of an effective alternative adjunctive therapy for HIV-associated tuberculous meningitis and given their safety and potential effectiveness, corticosteroids are recommended for use in HIV-associated tuberculous meningitis on a case-by-case basis
- Tuberculous meningitis leads to critical illness with unique neurocritical and neurosurgical considerations, yet there is little evidence guiding management strategies for these complications

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of the strength and certainty of our recommendations. However, the recommendations are to guide and do not mandate treatment approaches. Clinicians should continue to exercise their own judgment based upon the individual characteristics of their patients.

The guideline is written for health-care workers responsible for tuberculous meningitis management anywhere in the world. We recognise that not all diagnostic tests, treatments, and management strategies are available in all settings, and decisions should be individualised by the treating clinician according to available resources.

Methods

The Tuberculous Meningitis International Research Consortium identified the need for tuberculous meningitis practice guidelines in October, 2020. A writing group was convened from within the multidisciplinary and global consortium to define its scope, target audience, and methods.

Four working groups addressed key questions concerning diagnosis, anti-tuberculosis chemotherapy, adjunctive therapy, and neurocritical and neurosurgical care. Individuals were assigned to working groups (four to six members per group) based on expertise and experience, ensuring adult and paediatric expertise within each group. A Guideline Steering Group provided oversight. Working groups were supported by a librarian and methodologist.

The key questions were developed using the Population, Intervention, Comparator, Outcome (PICO) format. Final questions, with recommendations, are given in panels 1–4. A GRADE[18] approach was used to assess certainty (or quality) of evidence and establish the direction and strength of recommendations. Data for PICO questions were summarised and presented in the appendix (pp 3–18, 19–25). The following domains were assessed: risk of bias (using a standard approach to applying signalling questions), indirectness, inconsistency, imprecision, and other considerations (eg, publication bias). Risk of bias assessment was performed using the appropriate tools—eg, Quality Assessment of Diagnostic Accuracy Studies 2 for diagnostic studies and revised Cochrane risk-of-bias tool for randomised controlled trials (RCTs).[19,20] Certainty assessment was performed by one individual from the respective working group, with certainty downgrading or upgrading conducted in line with the GRADE approach.[21]

For each PICO question, the certainty of evidence (high, moderate, weak, or very weak) and the strength of recommendation (strong or weak, and for or against) were stated.[18] Justifications for recommendation strengths are given in the accompanying narrative. Draft recommendations were developed and approved in guideline group meetings. Wider consultations with global tuberculous meningitis experts (approximately 120 people) occurred during Tuberculous Meningitis International Research Consortium Meetings (Oxford, UK in September, 2023, and Bali, Indonesia in November, 2024). An evaluation of patient values and preferences was not performed.

Recognising the need to provide practical guidance, even when evidence is scarce or absent, we also provide expert-opinion-based good practice points and figures (figures 1 and 2) summarising suggested diagnostic and therapeutic approaches.

PICO questions for the diagnosis of tuberculous meningitis

Recommendations are shown in panel 1, with evidence synthesis in the appendix (pp 3–13). A uniform case definition was created in 2010 as a research tool for tuberculous meningitis classification, defining definite, probable, possible, and not having tuberculous meningitis.[24] Developed as a standardised approach to classifying tuberculous meningitis diagnosis in research, it is now used as a standard against which diagnostic tests are assessed.

How accurate are CSF microscopy and biochemistry for diagnosing tuberculous meningitis?

We found no studies directly addressing this question. The tuberculous meningitis lumbar cerebrospinal fluid (CSF) profile typically includes a moderate lymphocytic pleocytosis, elevated protein, low glucose (<50% plasma concentration), and moderately elevated lactate (5–10 mmol/L).[25] However, none of these parameters is specific enough individually, or in combination, for definitive diagnosis. Nevertheless, CSF analysis is an essential part of the tuberculous meningitis diagnostic workup, providing supporting evidence for tuberculous meningitis diagnosis[26] and an opportunity to detect *M tuberculosis* or identify other causes of meningoencephalitis.

How accurate are microbiological and molecular tests for diagnosing tuberculous meningitis?

The challenge in detecting *M tuberculosis* within CSF is the very low bacterial numbers, limiting the sensitivity of all currently available tests. Technician skill, large CSF volumes, and optimal processing can improve diagnostic yields.[27–29]

In most settings, CSF Ziehl–Neelsen (ZN) smear testing is insensitive (<30%), and provides little advantage compared with GeneXpert Xpert MTB/RIF (Xpert) or Xpert MTB/RIF Ultra (Ultra) tests (GeneXpert, Cepheid Sunnyvale, CA USA; appendix pp 3–4).[29] Xpert and Ultra are PCR-based tests that provide rapid results and detect mutations associated with rifampicin resistance. Ultra PCR's lower limit of detection enhances its sensitivity, making it the test of choice, when available.[26] Both Xpert and Ultra PCR tests showed high specificity (appendix pp 5–8), although neither test can rule out tuberculous meningitis. These tests should, when possible, be

Panel 1: Population, Intervention, Comparator, Outcome (PICO) questions for the diagnosis of tuberculous meningitis

How accurate are CSF microscopy and biochemistry for diagnosing tuberculous meningitis?

- Population: all individuals in hospital being evaluated for tuberculous meningitis
- Intervention: CSF cell microscopy, biochemistry, and lactate
- Comparators: (1) definite or probable tuberculous meningitis, and (2) positive CSF mycobacterial culture
- Outcome: true positive, false positive, true negative, and false negative
- Conclusion: insufficient evidence to recommend for or against use

How accurate are microbiological and molecular tests for diagnosing tuberculous meningitis?

- Population: all individuals in hospital being evaluated for tuberculous meningitis
- Intervention: each of Ziehl–Neelsen smear microscopy, Xpert or Xpert Ultra PCR test, mycobacterial culture (eg, mycobacteria growth indicator tube, Lowenstein–Jensen, or microscopic observation drug susceptibility assay), and Alere–Lipoarabinomannan (AlereLAM)
- Comparators: (1) definite or probable tuberculous meningitis, and (2) positive CSF mycobacterial culture
- Outcome: true positive, false positive, true negative, and false negative
- Conclusions:
    - Ziehl–Neelsen smear microscopy: low certainty of evidence for test accuracy, weak recommendation for use in diagnosis of tuberculous meningitis
    - Xpert PCR: high certainty of evidence for test accuracy, strong recommendation for use in diagnosis of tuberculous meningitis, in addition to mycobacterial culture
    - Xpert Ultra PCR: moderate certainty of evidence for test accuracy, strong recommendation for use in diagnosis of tuberculous meningitis, in addition to mycobacterial culture
    - Mycobacterial culture: moderate certainty of evidence, strong recommendation for use in diagnosis of tuberculous meningitis, ideally in combination with Xpert or Xpert Ultra PCR
    - AlereLAM: insufficient evidence to recommend for or against use

How accurate is adenosine deaminase (ADA) for diagnosing tuberculous meningitis?

- Population: all individuals in hospital being evaluated for tuberculous meningitis
- Intervention: ADA
- Comparators: (1) definite or probable tuberculous meningitis, and (2) positive CSF mycobacterial culture
- Outcome: true positive, false positive, true negative, and false negative
- Conclusion: very low certainty of evidence for test accuracy, weak recommendation for use in the diagnosis of tuberculous meningitis

How accurate is neuroimaging for diagnosing tuberculous meningitis?

- Population: all individuals in hospital being evaluated for tuberculous meningitis or other CNS tuberculosis (eg, spinal tuberculosis and tuberculomas)
- Intervention: CT or MRI brain (with or without contrast)
- Comparators: (1) definite or probable tuberculous meningitis, and (2) positive CSF mycobacterial culture
- Outcome: true positive, false positive, true negative, and false negative
- Conclusion: insufficient evidence to recommend for or against neuroimaging use as a diagnostic tool for tuberculous meningitis, but neuroimaging might demonstrate features that increase the likelihood of a diagnosis of tuberculous meningitis; neuroimaging has an important role in identifying intracerebral mass lesions and ensuring lumbar puncture safety (see figure 1); baseline neuroimaging is recommended

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See **Online** for appendix

combined with mycobacterial culture, enabling subsequent extended drug susceptibility tests (appendix p 9). The accuracy of Xpert and Ultra PCR tests for detecting rifampicin resistance is reduced when bacterial numbers are very low.[30] The Alere-Lipoarabinomannan (AlereLAM) test (Abbott Determine TB-LAM antigen, Lake Bluff, IL, USA) identifies *M tuberculosis* cell wall components by lateral flow. There is insufficient evidence to recommend for or against using the AlereLAM test on CSF (appendix pp 10–11).

How accurate is ADA for diagnosing tuberculous meningitis?

Adenosine deaminase (ADA) accuracy assessment is limited by variable assays with uncertain positive test cutoffs, and lack of gold standard comparators (appendix pp 12–13). Elevated CSF ADA concentrations are not specific for tuberculous meningitis. While evidence certainty is very low, ADA measurement is relatively inexpensive, and elevated concentrations might prompt use of better tests (eg, Ultra PCR). Measurement of CSF ADA should not replace Xpert or Ultra PCR tests or culture.

How accurate is neuroimaging for diagnosing tuberculous meningitis?

We found no studies directly assessing this question. However, brain imaging, with CT or MRI, enables assessment of the incidence and evolution of

Panel 2: Population, Intervention, Comparator, Outcome (PICO) questions for anti-tuberculosis chemotherapy

Does increasing the rifampicin dose reduce mortality in adults with tuberculous meningitis versus a standard 10 mg/kg per day dose?

- Population: adults in hospital requiring treatment for tuberculous meningitis
- Intervention: rifampicin dose greater than 10 mg/kg per day, given orally or parenterally
- Comparators: rifampicin dose of 10 mg/kg per day, given orally or parenterally
- Outcome: mortality
- Conclusion: moderate quality of evidence, does not support increased dose of rifampicin at 15 mg/kg per day and higher*

Does rifampicin dose greater than 20 mg/kg per day reduce mortality in adults with tuberculous meningitis versus a standard 10 mg/kg per day dose?

- Population: adults in hospital requiring treatment for tuberculous meningitis
- Intervention: rifampicin dose of greater than 20 mg/kg per day, given orally or parenterally
- Comparators: rifampicin dose of 10 mg/kg per day, given orally or parenterally
- Outcome: mortality
- Conclusion: insufficient evidence to recommend for or against rifampicin dose of 20 mg/kg per day and higher*

Does an adjunctive fluoroquinolone reduce mortality from tuberculous meningitis in adults versus no fluoroquinolone?

- Population: adults in hospital requiring treatment for tuberculous meningitis
- Intervention: adjunctive fluoroquinolone
- Comparators: standard anti-tuberculosis chemotherapy
- Outcome: mortality
- Conclusions: high quality of evidence; in adults with fully drug-susceptible *Mycobacterium tuberculosis*, strong recommendation against adding a fluoroquinolone to the tuberculosis regimen or using a fluoroquinolone in place of another drug in the regimen; for individuals with a high probability of tuberculous meningitis caused by isoniazid-resistant bacteria, strong recommendation for adding a fluoroquinolone to the regimen or using a fluoroquinolone in place of isoniazid

Does adjunctive linezolid reduce mortality from tuberculous meningitis in adults versus no linezolid?

- Population: adults in hospital requiring treatment for tuberculous meningitis
- Intervention: adjunctive linezolid
- Comparators: standard anti-tuberculosis chemotherapy
- Outcome: mortality
- Conclusion: insufficient evidence to make recommendation, for or against use of linezolid

Does higher dosing, or alternative administration routes, of other tuberculosis drugs reduce mortality in adults caused by tuberculous meningitis?

- Population: adults in hospital requiring treatment for tuberculous meningitis
- Intervention: change in dose and route of administration, or addition or substitution of any other tuberculosis drugs
- Comparators: standard anti-tuberculosis chemotherapy
- Outcome: mortality
- Conclusion: insufficient evidence to make recommendation, for or against higher dosing or alternative administration routes, or other tuberculosis drugs

Is treatment duration less than 12 months effective against tuberculous meningitis in adults?

- Population: adults in hospital requiring treatment for tuberculous meningitis
- Intervention: anti-tuberculosis chemotherapy duration of less than 12 months
- Comparators: standard anti-tuberculosis chemotherapy duration of 12 months
- Outcome: mortality
- Conclusion: insufficient evidence to make a recommendation, for or against less than 12 months of anti-tuberculosis chemotherapy

What is the optimal treatment for childhood tuberculous meningitis?

- Population: children in hospital requiring treatment for tuberculous meningitis
- Intervention: 6 months of high-dose isoniazid, high-dose rifampicin, pyrazinamide, and ethionamide ($6H_{15–20}R_{20–30}Z_{40}Eto_{20}$)
- Comparators: standard anti-tuberculosis chemotherapy
- Outcome: mortality
- Conclusion: insufficient evidence to make a recommendation for or against the shorter regimen; either the 6-month $6H_{15–20}R_{20–30}Z_{40}Eto_{20}$ intensive regimen or the standard 12-month regimen can be used†

*Trial results from HARVEST (ISRCTN15668391, reporting in 2025) and INTENSE-TBM (NCT04145258, reporting in 2026) should provide definitive data. †Standard antibiotic dosing achieves subtherapeutic levels in children; please see narrative under the PICO questions for anti-tuberculosis chemotherapy recommendations.

common tuberculous meningitis complications (eg, hydrocephalus, tuberculomas, and infarctions) before and after the start of tuberculous meningitis treatment.[31] For these purposes, baseline brain imaging is recommended.

Good practice points

CSF volume

We recommend sampling 6 mL or more of CSF for dedicated *M tuberculosis* testing.[27] Larger CSF volumes are a strong predictor of positive ZN stain, *M tuberculosis* culture, and Xpert PCR.[28,32] CSF should be centrifuged at 3000 g for 20 min, with the cell pellet used for mycobacterial tests.[27,32,33]

Children and adults living with HIV

Our recommendations apply to all age groups and people living with HIV. Only one study evaluated Ultra PCR tests in children, reporting 50% sensitivity,[34] lower than adult studies (approximately 65%), probably reflecting lower CSF volumes from children. ZN staining, mycobacterial culture, and Xpert and Ultra PCR tests have higher sensitivity in people living with HIV, possibly due to higher bacillary loads.[35–37]

Diagnostic approach and empirical therapy

No single negative test can rule out tuberculous meningitis. Combining CSF ZN smear, Xpert or Ultra PCR, and mycobacterial culture might increase diagnostic yields.[35,37] Repeated testing of CSF can increase diagnostic yields. Consistent neuroimaging features—eg, hydrocephalus, basal exudates, infarcts, or tuberculomas—increases the probability of a diagnosis of tuberculous meningitis,[31,38,39] as does *M tuberculosis* identification outside of the CNS. Testing of sputum for *M tuberculosis* is recommended given that pulmonary tuberculosis is present in around 50% of cases of tuberculous meningitis.[9,10] Nevertheless, given the limited sensitivity of available tests and the fatal consequences of delayed treatment, many patients (30–50%) must start treatment empirically,[6,9,10,40] based on clinical suspicion alone. A diagnostic approach to tuberculous meningitis, based on evidence and expert opinion, is presented in figure 1.

PICO questions for anti-tuberculosis chemotherapy

Recommendations are shown in panel 2, with evidence synthesis in the appendix (pp 14–18). Anti-tuberculosis drug regimens for tuberculous meningitis treatment are based on those developed for pulmonary tuberculosis and do not account for the need to achieve therapeutic concentrations within the CNS.[41] Tuberculous meningitis caused by bacteria resistant to first-line drugs (rifampicin and isoniazid) is an increasing therapeutic challenge, with few data describing the CNS activity and effectiveness of drugs recently approved and highly effective for multidrug resistant pulmonary tuberculosis treatment.[42–45] Recent animal and clinical studies using PET imaging with radio-labelled antibiotics have provided insights on CSF and brain distribution, and the activity of these drugs.[46–49]

Does increasing the rifampicin dose reduce mortality in adults with tuberculous meningitis versus a standard 10 mg/kg per day dose?

Standard 10 mg/kg per day rifampicin dosing results in very low CSF concentrations or exposures.[9,50] Rifampicin was undetectable in CSF in two-thirds of patients with tuberculous meningitis as reported in two studies that used the standard dose.[7,51] Higher rifampicin doses or exposures increase bacterial killing in pulmonary tuberculosis,[52] and 35 mg/kg per day has been safely used in adults and children with pulmonary tuberculosis and tuberculous meningitis.[53–56]

Four phase 2 trials and one phase 3 trial have investigated higher rifampicin doses for tuberculous meningitis (appendix pp 14–15). Across these five studies, three studies

Panel 3: Population, Intervention, Comparator, Outcome (PICO) questions for adjunctive therapy

Should corticosteroids be used as an adjunctive therapy in patients with tuberculous meningitis?

- Population: adults and children with tuberculous meningitis
- Intervention: anti-tuberculosis chemotherapy with adjunctive corticosteroids
- Comparators: anti-tuberculosis chemotherapy without adjunctive corticosteroids
- Outcome: mortality and morbidity
- Conclusions: high certainty of evidence, strong recommendation for use in individuals without HIV; high certainty of evidence, weak recommendation for use in people living with HIV so the decision to use should be made on a case-by-case basis

What is the optimal timing of antiretroviral therapy for CNS tuberculosis?

- Population: adults and children with tuberculous meningitis
- Intervention: immediate antiretroviral therapy (within 7 days of commencing anti-tuberculosis treatment)
- Comparators: deferred antiretroviral therapy initiation (after 2 months of anti-tuberculosis treatment)
- Outcome: mortality and morbidity
- Conclusion: high certainty of evidence, weak recommendation to defer initiating antiretroviral therapy 4–8 weeks after starting anti-tuberculosis treatment

What other adjunctive therapies can be considered for the management of tuberculous meningitis?

- Population: adults and children with tuberculous meningitis
- Intervention: adjunctive aspirin, thalidomide, infliximab, cyclophosphamide, anakinra, or interferon-γ
- Comparators: anti-tuberculosis chemotherapy without the aforementioned adjunctive agents
- Outcome: mortality and morbidity
- Conclusion: insufficient evidence to make a recommendation for or against adjunctive aspirin, thalidomide, infliximab, cyclophosphamide, anakinra, or interferon-γ; decision to initiate these treatments should be made on a case-by-case basis considering factors discussed in the guideline

Panel 4: **Population, Intervention, Comparator, Outcome (PICO) questions for neurocritical and neurosurgical care**

Should active management (medical or surgical) or standard of care be used in individuals with tuberculous meningitis with hydrocephalus or raised intracranial pressure?

- Population: adults or children (with or without HIV) in hospital with tuberculous meningitis and hydrocephalus or raised intracranial pressure
- Intervention: active medical (repeated lumbar punctures with diuretics) or surgical management (or a combination)
- Comparators: standard WHO therapy (ie, the current treatment regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol given daily for the first 2 months, followed by isoniazid and rifampicin given daily for an additional 10 months, that was established in 1995 and excludes streptomycin as first-line therapy)
- Outcome: mortality and morbidity, radiological outcome, and complications (including treatment failure)
- Conclusion: insufficient evidence to make a recommendation, for or against active medical or surgical management of hydrocephalus or raised intracranial pressure

Should a ventriculoperitoneal shunt or endoscopic third ventriculostomy be used for the surgical management of hydrocephalus in patients with tuberculous meningitis?

- Population: adults or children (with or without HIV) in hospital with tuberculous meningitis and hydrocephalus or raised intracranial pressure
- Intervention: surgical management of hydrocephalus by ventriculoperitoneal shunt
- Comparators: surgical management of hydrocephalus by endoscopic third ventriculostomy
- Outcome: mortality, morbidity, radiological outcome, and complications (including treatment failure)
- Conclusion: insufficient evidence to recommend ventriculoperitoneal shunt over endoscopic third ventriculostomy if surgical intervention is required; discretion of the treating clinician is required

Should surgical management of tuberculomas with or without tuberculous meningitis occur at time of diagnosis or after medical treatment failure?

- Population: adults or children (with or without HIV) in hospital with tuberculomas (with or without tuberculous meningitis)
- Intervention: surgical management of tuberculomas at diagnosis
- Comparators: surgical management after failure of standard WHO therapies
- Outcome: mortality, morbidity, radiological outcome, and complications (including treatment failure)
- Conclusion: insufficient evidence to make a recommendation for or against surgical management of tuberculomas at diagnosis or after medical treatment failure

Should surgical management of tuberculous abscesses with or without tuberculous meningitis occur at time of diagnosis or after medical treatment failure?

- Population: adults or children (with or without HIV) in hospital with tuberculous abscesses (with or without tuberculous meningitis)
- Intervention: surgical management of tuberculous abscesses at diagnosis
- Comparators: surgical management after failure of standard WHO therapies
- Outcome: mortality, morbidity, radiological outcome, and complications (including treatment failure)
- Conclusion: insufficient evidence to make a recommendation for or against surgical management of tuberculous abscesses at diagnosis or after medical treatment failure

Should the management of hyponatremia in patients with tuberculous meningitis be based on aetiology?

- Population: adults or children (with or without HIV) in hospital with tuberculous meningitis and hyponatraemia
- Intervention: treatment of hyponatremia tailored by aetiology (cerebral salt-wasting syndrome or syndrome of inappropriate antidiuretic hormone secretion)
- Comparators: treatment of hyponatremia not tailored by aetiology (cerebral salt-wasting syndrome or syndrome of inappropriate antidiuretic hormone secretion)
- Outcome: mortality, morbidity, and complications (including treatment failure)
- Conclusion: insufficient evidence to make a recommendation for or against treatment of hyponatremia tailored by aetiology

Should all patients with tuberculous meningitis be assessed for clinical and subclinical seizures?

- Population: adults or children (with or without HIV) in hospital with tuberculous meningitis
- Intervention: assessed for clinical and subclinical seizures by electroencephalogram
- Comparators: not assessed for clinical and subclinical seizures by electroencephalogram
- Outcome: mortality and morbidity
- Conclusion: insufficient evidence to make a recommendation for or against assessment for clinical and subclinical seizures

did not have mortality as their primary outcomes or used high-dose rifampicin with other interventions (eg, linezolid and aspirin).[43,51,57] The duration (2–8 weeks) and doses (15–35 mg/kg per day) of rifampicin varied, but higher rifampicin doses were not associated with reduced tuberculous meningitis mortality (odds ratio 0·91, 95% CI 0·56–1·46). However, these data are dominated by a large (817 adults) phase 3 trial investigating 15 mg/kg per day rifampicin, which might not have resulted in sufficiently high CSF exposures.[9,50] We therefore examined

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the benefit of rifampicin doses higher than 20 mg/kg per day, including lower dose intravenous administration that achieved equivalent exposures. Data were limited and a mortality benefit was not observed, although a dose higher than 20 mg/kg per day was safe.

Two active phase 3 trials are investigating 35 mg/kg per day of rifampicin in adults with tuberculous meningitis. Later in 2025, the HARVEST trial (ISRCTN15668391) will report results, followed by the INTENSE-TBM trial (NCT04145258) that will report results in 2026. The results of these trials might provide definitive data to address this particular PICO question.

Does an adjunctive fluoroquinolone or linezolid reduce mortality in adults caused by tuberculous meningitis?

Five RCTs have evaluated the addition of fluoroquinolones to standard rifampicin-based regimens for tuberculous meningitis (appendix p 16). Three studied levofloxacin, one moxifloxacin, and one levofloxacin, ciprofloxacin, and gatifloxacin together. Taken together, the addition of a fluoroquinolone to the regimen was not associated with significantly reduced mortality (odds ratio 0·86, 95% CI 0·51–1·45). However, post-hoc analysis of the 2016 Viet Nam trial[9] found that rifampicin at 15 mg/kg per day with levofloxacin (as the fifth drug) reduced mortality in adults with tuberculous meningitis caused by isoniazid-resistant bacteria (hazard ratio 0·34, 95% CI 0·15–0·76, p=0·01).[58]

WHO endorsed linezolid for multidrug-resistant pulmonary tuberculosis treatment in 2019.[14] Data investigating linezolid use for tuberculous meningitis treatment are limited to three small phase 2 trials (appendix p 17),[42,43,59] which did not establish its benefit in presumed drug-sensitive tuberculous meningitis. Linezolid might, however, have a role in treating multidrug-resistant tuberculous meningitis, given its favourable CNS pharmacokinetic and bactericidal activity.[60]

Does higher dosing, or alternative administration routes, of other tuberculosis drugs reduce mortality in adults caused by tuberculous meningitis?

Only one study has addressed this question: a phase 2 trial of higher-dose intravenous isoniazid (500 mg per day) and ethambutol (2 g per day) with rifampicin and pyrazinamide in 54 adults (appendix p 18).[61] Pharmacokinetic analysis of the 2016 Viet Nam trial found a strong association between high CSF isoniazid concentrations, slow acetylator status, and reduced case fatality.[50] A 6-month regimen with high doses of rifampicin, isoniazid, pyrazinamide (RHZ), and ethionamide has produced excellent outcomes in South African children (see question 5), but has not been studied in adults.

Intrathecal administration, usually of aminoglycosides, were used in the early years of anti-tuberculosis chemotherapy,[62] but became uncommon once RHZ became available. Intrathecal administration has some recent proponents,[63,64] although there are no comparative trials and data are insufficient to make a recommendation.

Is treatment duration less than 12 months effective against tuberculous meningitis in adults?

There were no trials comparing anti-tuberculosis chemotherapy for less than 12 months versus 12 months or longer. In 2016, a meta-analysis of 19 observational studies concluded that in all cohorts, most deaths occurred in the first 6 months and that relapse was uncommon in all participants irrespective of the regimen. No inferences regarding optimal treatment duration could be made.[65] WHO currently recommends treating adult tuberculous meningitis with 12 months of anti-tuberculosis drugs; there is no evidence supporting a different recommendation. Additionally, there is no substantive evidence to support longer durations of anti-tuberculosis chemotherapy for tuberculous meningitis (than for pulmonary tuberculosis) in terms of better outcomes.

What is the optimal treatment for childhood tuberculous meningitis?

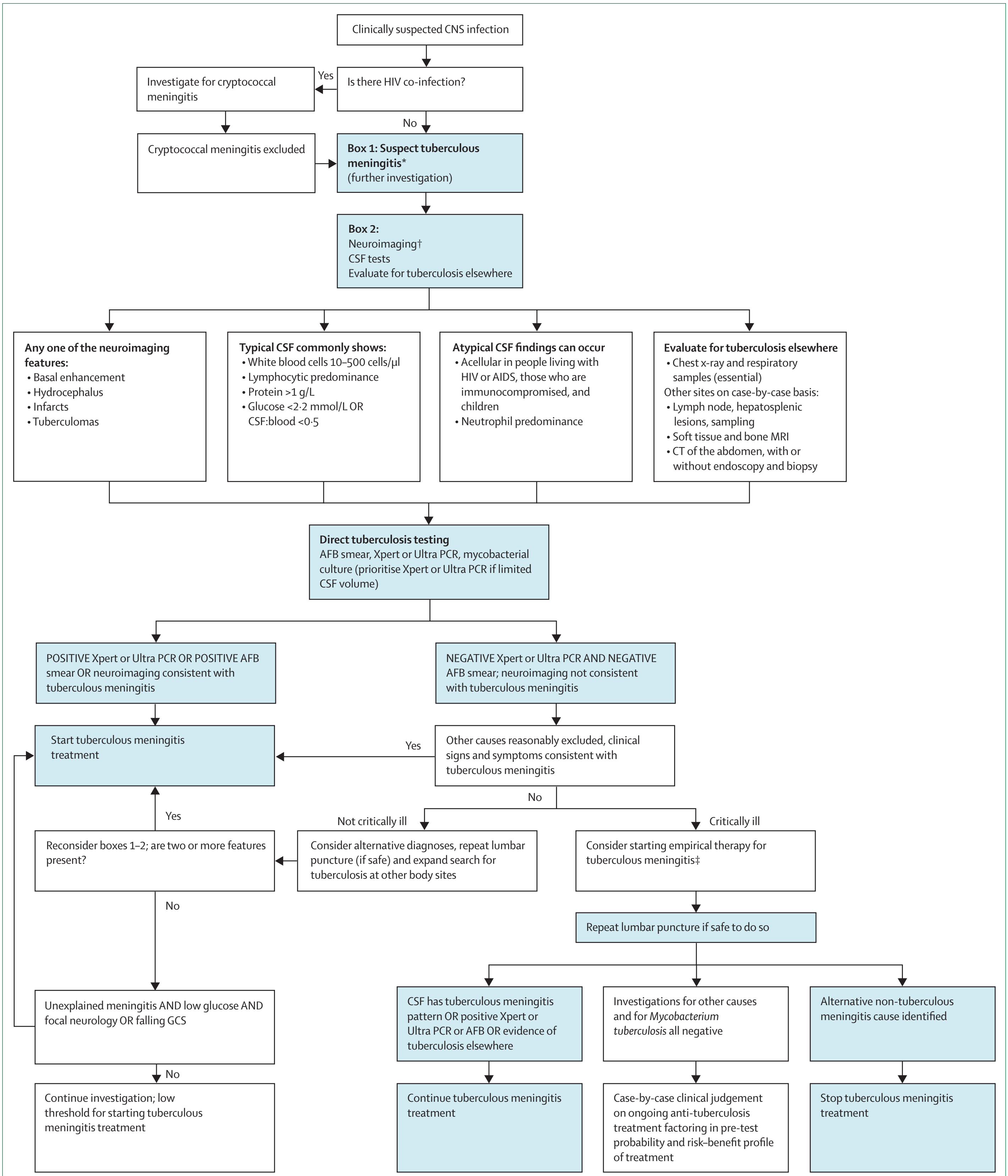
Due to the non-linear effect of weight on clearance, young children, particularly those younger than 2 years, have lower drug exposures when given the same dose (mg/kg) as older children, adolescents, and adults.[66] Rifampicin up to 35 mg/kg per day is safe in children, and in one study, doses of up to 65–70 mg/kg rifampicin were needed to reach the target exposure.[54] Additionally, a small phase 2 RCT of children with tuberculous meningitis reported better neurocognitive outcomes in those receiving regimens containing high-dose (30 mg/kg per day) rifampicin.[67] For more than 30 years, children with tuberculous meningitis in South Africa have been treated with 6 months of higher doses of RHZ and ethionamide, with excellent outcomes.[68] A recent systematic review informed the 2022 WHO child and adolescent tuberculosis guidelines;[69] no clinical trials were identified but seven observational studies provided evidence that were graded as low quality. For children and adolescents aged 19 years or younger with drug-susceptible tuberculous meningitis, WHO recently recommended that a 6-month regimen (isoniazid 15–20 mg/kg per day, rifampicin 22·5–30 mg/kg per day, and pyrazinamide 35–45 mg/kg per day, and the substitution of ethambutol with ethionamide at 17·5–22·5 mg/kg per day) can be used instead of the 12-month standard regimen.[70]

Results of the SURE trial (ISRCTN40829906),[71] an RCT comparing a 6-month intensive regimen to the 12-month standard for childhood tuberculous meningitis, should be available by the end of 2025.

Good practice points

Drug-resistant tuberculous meningitis

Mortality from tuberculous meningitis caused by bacteria resistant to rifampicin and isoniazid


Clinically suspected CNS infection
Is there HIV co-infection?
Yes
Investigate for cryptococcal meningitis
Cryptococcal meningitis excluded
No
Box 1: Suspect tuberculous meningitis* (further investigation)
Box 2: Neuroimaging† CSF tests Evaluate for tuberculosis elsewhere
Any one of the neuroimaging features: • Basal enhancement • Hydrocephalus • Infarcts • Tuberculomas
Typical CSF commonly shows: • White blood cells 10–500 cells/μl • Lymphocytic predominance • Protein >1 g/L • Glucose <2·2 mmol/L OR CSF:blood <0·5
Atypical CSF findings can occur • Acellular in people living with HIV or AIDS, those who are immunocompromised, and children • Neutrophil predominance
Evaluate for tuberculosis elsewhere • Chest x-ray and respiratory samples (essential) Other sites on case-by-case basis: • Lymph node, hepatosplenic lesions, sampling • Soft tissue and bone MRI • CT of the abdomen, with or without endoscopy and biopsy
Direct tuberculosis testing AFB smear, Xpert or Ultra PCR, mycobacterial culture (prioritise Xpert or Ultra PCR if limited CSF volume)
POSITIVE Xpert or Ultra PCR OR POSITIVE AFB smear OR neuroimaging consistent with tuberculous meningitis
NEGATIVE Xpert or Ultra PCR AND NEGATIVE AFB smear; neuroimaging not consistent with tuberculous meningitis
Start tuberculous meningitis treatment
Yes
Other causes reasonably excluded, clinical signs and symptoms consistent with tuberculous meningitis
No
Not critically ill
Critically ill
Yes
Reconsider boxes 1–2; are two or more features present?
Consider alternative diagnoses, repeat lumbar puncture (if safe) and expand search for tuberculosis at other body sites
Consider starting empirical therapy for tuberculous meningitis‡
No
Repeat lumbar puncture if safe to do so
Unexplained meningitis AND low glucose AND focal neurology OR falling GCS
CSF has tuberculous meningitis pattern OR positive Xpert or Ultra PCR or AFB OR evidence of tuberculosis elsewhere
Investigations for other causes and for Mycobacterium tuberculosis all negative
Alternative non-tuberculous meningitis cause identified
No
Continue investigation; low threshold for starting tuberculous meningitis treatment
Continue tuberculous meningitis treatment
Case-by-case clinical judgement on ongoing anti-tuberculosis treatment factoring in pre-test probability and risk–benefit profile of treatment
Stop tuberculous meningitis treatment

(multidrug-resistant tuberculous meningitis) exceeds 70%.[58,72] Poor outcomes are driven by delayed detection of resistance and initiation of second-line anti-tuberculosis treatment, compounded by the uncertain effectiveness of second-line drugs in tuberculous meningitis. Currently, there are no RCTs informing guidance.

Early rifampicin resistance detection is crucial for outcomes. Therefore, Xpert or Ultra PCR testing of CSF and other specimens, if extra-neural tuberculosis is suspected, are strongly encouraged in all patients with tuberculous meningitis. Clinical deterioration after the start of anti-tuberculosis treatment is an unreliable indicator of multidrug-resistant tuberculous meningitis as it is more commonly caused by hydrocephalus, infarcts, or other inflammatory complications (eg, tuberculomas).

Without trials, the selection of second-line drugs is based upon their predicted activity within the CNS (appendix p 19). CSF pharmacokinetic data assist drug selection, although CSF concentrations of some drugs do not correlate well with brain concentrations. For example, rifampicin, delamanid, pretomanid, and bedaquiline achieve much higher concentrations in the brain than CSF.[46–48,73] Employing therapeutic drug monitoring to address low exposure in plasma or serum could help to optimise CNS concentration.[74]

The bedaquiline, pretomanid, and linezolid (BPaL) regimen is highly effective for multidrug-resistant pulmonary tuberculosis,[75] but has not been evaluated in patients with multidrug-resistant tuberculous meningitis. In animal models of tuberculous meningitis, the BPaL regimen is inferior to the standard tuberculosis regimen,[46] with no additive effective of bedaquiline.[49] Excellent activity was however noted in animal studies with PaZ-based regimens.[49] Whether bedaquiline achieves sufficient CNS exposure to be effective is uncertain; however, more than 50% of patients with tuberculous meningitis have concurrent pulmonary tuberculosis,[9] for which bedaquiline will be highly effective.

Figure 1: **Diagnostic approach for suspected tuberculous meningitis in children and adults**
Boxes shaded in blue represent evidence-based recommendations. Boxes without shading represent consensus recommendations drawn from collective expert opinion and expertise. In people living with HIV or AIDS, cryptococcal meningitis can present similarly to tuberculous meningitis and should be excluded in the first instance as cryptococcal antigen testing is highly sensitive.[22] Large volumes of CSF are recommended. Diagnostic tests performed will depend on local availability; however, multiple tuberculosis testing where available should be performed. Where rapid diagnostic testing or neuroimaging is consistent, anti-tuberculosis therapy for tuberculous meningitis should be commenced. While mycobacterial culture does not return rapid results, it remains an important diagnostic test to perform. When rapid diagnostic testing is negative and neuroimaging is not suggestive of tuberculous meningitis, a decision to start treatment should be made on degree of clinical suspicion, repeated evaluations, neurological deterioration, and active exclusion of other possible causes. For box 1, suspected tuberculous meningitis* refers to risk factors, symptoms, and signs that are suggestive. Compatible symptoms and signs include more than 5 days of fever with any of: headache, vomiting, neck stiffness, poor appetite or poor weight gain (young children), cough, or cranial nerve palsy. In the absence of HIV co-infection, a potential diagnosis of cryptococcal meningitis should still be considered. For box 2, mass lesions and raised intracranial pressure can develop as part of CNS tuberculosis (tuberculoma or tuberculous abscess) or from an alternative diagnosis (eg, brain tumour or bacterial abscess); as such, in patients being evaluated for tuberculous meningitis there may be contraindications to lumbar puncture due to the risk of cerebral herniation. Obtaining neuroimaging before lumbar puncture can delay treatment initiation;[23] therefore, clinical discretion should be used on a case-by-case basis. Modality of neuroimaging† depends on availability. CT is often accessible and, using contrast, can detect hydrocephalus, basal exudates, large infarcts, and tuberculomas. MRI is more sensitive at detecting small and evolving infarcts, particularly in the brainstem. Strongly consider starting empirical therapy in conjunction with treatment for alternative causes in patients who are critically unwell. Repeating CSF analysis with tuberculosis testing can provide valuable guidance when deciding between tuberculous meningitis or other CNS infections. In the absence of a perfect test to diagnose tuberculous meningitis, clinical judgement on whether to initiate or continue anti-tuberculosis treatment should consider all aspects of the case, including epidemiological, clinical, laboratory, and imaging features where available. Specialist input should be also sought. AFB=acid-fast bacilli. CSF=cerebrospinal fluid. GCS=Glasgow Coma Scale. *Risk factors other than HIV include immunosuppression, malnutrition, travel or residence in a tuberculosis-endemic region, young age, and contact with infectious tuberculosis in the last 1–2 years. †Neuroimaging should be performed before lumbar puncture (to exclude the risk of herniation) if this is possible, and lumbar puncture should only be performed when it is safe to do so. ‡Differentiating tuberculous meningitis from other meningitides in high incidence tuberculosis settings can be challenging.

Adverse drug effects

Pyrazinamide, isoniazid, and rifampicin can all cause drug-induced liver injury, the most common reason for treatment interruption and drug substitution. However, unlike in pulmonary tuberculosis, stopping anti-tuberculosis drugs is an independent risk factor for death from tuberculous meningitis.[76–78] Therefore, clinicians should weigh carefully the risks of discontinuing of anti-tuberculosis therapy with the severity of drug-induced liver injury.

Little evidence exists to guide clinicians, although the ACT HIV[10,78] and LAST ACT[77] (NCT03100786) tuberculous meningitis trials randomly assigned participants who developed drug-induced liver injury to three strategies: replace RHZ with a fluoroquinolone and an aminoglycoside, withdraw pyrazinamide and monitor aminotransferases, or continue all drugs unless amino-transferases rise by more than ten times the upper limit of normal. Results are anticipated by the end of 2025.

Reintroduction of first-line drugs can be considered once liver function normalises, either stepwise or all at once, at a full dose, or an escalating dose. There is insufficient evidence to support one approach instead of another, or the order of the drugs to be reintroduced.[79]

Drug–drug interactions are an essential consideration for the treatment of tuberculosis. Rifampicin induces the hepatic metabolism of various drugs, including antiretroviral therapies. The most up-to-date information on drug interactions are listed on the HIV Drug Interactions tracker.

For the **HIV Drug Interactions tracker** see https://www.hiv-druginteractions.org/checker

PICO questions for adjunctive therapy

Recommendations are given in panel 3, with evidence synthesis in the appendix (pp 21–24). Outcomes from tuberculous meningitis are strongly associated with dysregulated inflammatory responses.[80] However, these

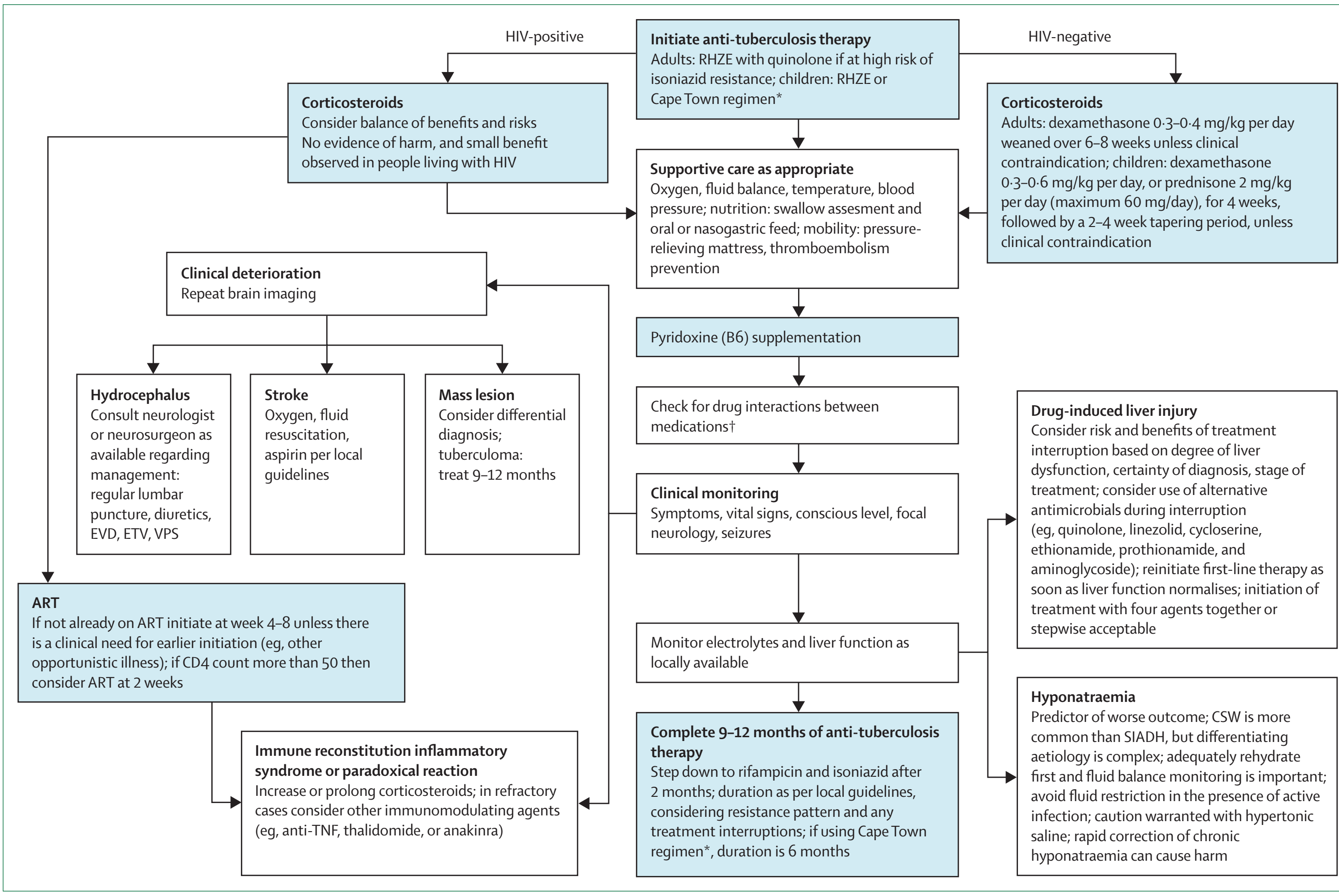


Figure 2: **Summary of the treatment and follow-up of adults and children, with or without HIV, with tuberculous meningitis**
Boxes shaded in blue represent evidence-based recommendations while boxes without shading represent consensus recommendations drawn from collective expert opinion and expertise. ART=antiretroviral therapy. CSW=cerebral salt-wasting syndrome. EVD=external ventricular drain. ETV=endoscopic third ventriculostomy. RHZE=rifampicin and isoniazid and pyrazinamide with ethambutol. SIADH=syndrome of inappropriate antidiuretic hormone secretion. TNF=tumour necrosis factor. VPS=ventriculoperitoneal shunt. *The Cape Town regimen is also recommended by WHO for the treatment of drug-susceptible tuberculous meningitis in children and is of 6-months duration, with elevated doses of isoniazid (15–20 mg/kg per day), rifampicin (22·5–30 mg/kg per day), and pyrazinamide (35–45 mg/kg per day), and the substitution of ethambutol with ethionamide (17·5–22·5 mg/kg per day). †Drug interactions can be seen in the HIV Drug Interactions tracker and the Medscape Drug Interaction Checker.

For more on the **Medscape Drug Interaction Checker** see https://reference.medscape.com/drug-interactionchecker

responses vary substantially between individuals. For example, people living with HIV and tuberculous meningitis have higher concentrations of inflammatory markers but lower numbers of leucocytes, compared with patients with tuberculous meningitis without HIV.[40,81]

Adjunctive corticosteroids have been given to control tuberculous meningitis-associated inflammation ever since anti-tuberculosis drugs became available to treat tuberculous meningitis.[82] The challenge, however, has been recognising the heterogeneity in inflammatory responses and identifying patients who benefit most from corticosteroids or, more recently, better targeted adjunctive therapies.

Should corticosteroids be used as an adjunctive therapy in patients with tuberculous meningitis?

Corticosteroids are recommended by WHO and ATS/CDC/IDSA for everyone with tuberculous meningitis, regardless of severity.[16,83] The results of two large (n=1065) and seven smaller (n=585) RCTs support these and our recommendations (appendix pp 21–22). Corticosteroids reduced case fatality, especially in children and adults without HIV.[84] 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. One large RCT, published 3 months after the updated literature search (July 23, 2023), was included given its relevance.[10] 520 adults with HIV-associated tuberculous meningitis were enrolled; dexamethasone was associated with a non-significant survival benefit (hazard ratio 0·85, 95% CI 0·66–1·10). Disability and the incidence of immune reconstitution inflammatory syndrome (IRIS) were not reduced by dexamethasone. Despite most participants being profoundly immune suppressed (52% with CD4 <50 cells/mm³), dexamethasone did not increase the number of adverse events.

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.

What is the optimal timing of antiretroviral therapy for CNS tuberculosis?

Clinical trials for people living with HIV with pulmonary tuberculosis have shown clear mortality benefits for patients with CD4 counts lower than 50 cells per mm³ who initiate antiretroviral therapy within 2 weeks of starting anti-tuberculosis treatment, albeit with increased risk of IRIS.[85–87] One RCT was conducted for people living with HIV with tuberculous meningitis (median CD4 count 41 cells per mm³) comparing antiretroviral therapy initiation within 7 days of anti-tuberculosis treatment or at 2 months. No difference in 9-month survival between the groups was found (appendix p 23).[88] This finding was similar for all CD4 counts. More grade 4 laboratory events were observed in the immediate antiretroviral therapy group, but there was no increase in neurological events.

These limited data inform our weak recommendation to defer antiretroviral therapy for 4–8 weeks after starting tuberculosis treatment, which is in agreement with WHO and other guidelines.[89–92] A range of time to start antiretroviral therapy has been given based on expert opinion and clinicians should decide to start therapy based on individual patient factors considering CD4 count (if available), other opportunistic infections, neuroimaging, and tuberculous meningitis-IRIS risk factors (eg, CSF ZN or culture positivity or CSF neutrophil pleocytosis).[93]

What other adjunctive therapies can be considered for the management of tuberculous meningitis?

Several small phase 2 studies in adults and children suggest aspirin, added to corticosteroids, can reduce the incidence of brain infarcts and death (appendix p 24). However, the trials are too small and heterogeneous to be definitive and a recommendation to use aspirin routinely cannot be given. The SURE (ISRCTN40829906) and INTENSE-TBM (NCT04145258) trials, investigating adjunctive aspirin in children and adults, respectively, will provide high-quality data from the end of 2025.

Observational studies in South African children have suggested that adjunctive thalidomide (2–5 mg/kg per day) was safe and effective in treating tuberculous mass lesions and optochiasmatic arachnoiditis.[94,95] A trial of higher dose thalidomide (24 mg/kg per day) was terminated early due to adverse effects and mortality in the thalidomide group.[96] No additional trials have been reported. Teratogenicity and other adverse events have restricted thalidomide's use as an adjunctive agent.

Case series have suggested that biological agents targeting TNF (eg, infliximab or adalimumab) can help treat tuberculomas and optochiasmatic arachnoiditis.[97,98] A retrospective cohort study in India reported adjunctive infliximab (10 mg/kg for one to three doses, 4 weeks apart) was safe and effective in treating severe inflammatory complications of tuberculous meningitis.[99] The active TIMPANI trial (NCT05590455) is investigating adjunctive adalimumab in adults with tuberculous meningitis and HIV.

Good practice points

Paradoxical reactions and IRIS

Adjunctive anti-inflammatory therapies (eg, corticosteroids) are usually given with anti-tuberculosis drugs at the start of treatment. However, in around 20% of patients with tuberculous meningitis (>30% of people living with HIV), inflammatory intracerebral complications occur. These complications typically arise after 20–60 days of treatment, but can occur many months later. Often called 'paradoxical reactions', they can occur despite effective anti-tuberculosis treatment. In the context of people living with HIV starting antiretroviral therapy, they can meet the criteria for IRIS,[100] although the clinical and imaging characteristic are similar, regardless of HIV status.

The management of these inflammatory complications has not been subject to trials. Expert opinion recommends using high-dose corticosteroids initially (eg, dexamethasone at 0·4 mg/kg per day), tapering slowly according to symptom resolution. If corticosteroids do not control symptoms, then small case-series and case reports have described the use of anti-TNF biologicals (eg, infliximab),[99] thalidomide,[101] or anakinra.[102,103]

Adjuvant interferon-γ treatment has been described in refractory CNS tuberculosis,[104] and cyclophosphamide treatment described in CNS vasculitis.[105,106] Data are too limited to make recommendations concerning their use (appendix p 35).

PICO questions for the neurocritical and neurosurgical care

Recommendations are shown in panel 4, with evidence synthesis in the appendix (p 25). Tuberculous meningitis causes critical illness with unique neurocritical and neurosurgical considerations. Raised intracranial pressure can fatally compress brain tissue and cause ischaemia. Cerebral infarction is common (>65%) and predictive of poor outcomes.[107] Key management concerns relate to controlling raised intracranial pressure, whether from oedema, hydrocephalus, or mass lesions (eg, tuberculomas or tuberculous abscess), and ameliorating cerebral ischaemia from raised intracranial pressure and vasculitis.[108]

Should active management (medical or surgical) or standard of care be used in individuals with tuberculous meningitis with hydrocephalus or raised intracranial pressure?

Hydrocephalus occurs in 50–90% of patients. Management varies from monitoring without intervention, to medical (regular lumbar punctures or diuretics) and neurosurgical (lumbar or external ventricular drain, endoscopic third ventriculostomy, or ventriculoperitoneal shunt) interventions;[107,109–112] however, no studies have directly compared these approaches. A lack of standardised definitions and management approaches preclude evidence-based recommendations.

Should a ventriculoperitoneal shunt or endoscopic third ventriculostomy be used for the surgical management of hydrocephalus in patients with tuberculous meningitis?

Two single-centre RCTs have compared ventriculoperitoneal shunt with endoscopic third ventriculostomy,[113,114] and although both studies showed the benefit of surgery, mortality and success rates were similar between the interventions (appendix p 25). These procedures should be considered on a case-by-case basis; recommending one procedure instead of the other cannot be made based on the available data.

Should surgical management of tuberculomas with or without tuberculous meningitis occur at time of diagnosis or after medical treatment failure; and should surgical management of tuberculous abscesses with or without tuberculous meningitis occur at time of diagnosis or after medical treatment failure?

No studies directly address these two PICO questions. Surgery can be necessary, but no studies have compared the timing of surgery for tuberculomas or tuberculous abscesses. There was heterogeneity in diagnosis, surgical techniques (eg, biopsy *vs* debulking *vs* full resection), lesion location, duration of follow-up, and assessment of resolution or treatment failure. Evidence-based recommendations cannot be made. Consortium members have reviewed the management of intracranial tuberculous mass lesions elsewhere.[115]

Should the management of hyponatremia in patients with tuberculous meningitis be based on aetiology?

Hyponatremia can cause cerebral oedema, raised intracranial pressure, and infarction.[108,116–118] Studies suggest that hyponatremia is more commonly caused by cerebral salt-wasting syndrome than syndrome of inappropriate antidiuretic hormone secretion, although their discrimination is difficult and diagnostic criteria vary.[118,119] Whether outcomes are improved by management tailored to the cause of hyponatremia is uncertain. There are insufficient data to make recommendations concerning optimal management of tuberculous meningitis-associated hyponatraemia.

Should all patients with tuberculous meningitis be assessed for clinical and subclinical seizures?

Seizures can occur due to raised intracranial pressure, tuberculomas, and ischaemia, and can increase cerebral oxygen consumption to increasing the risk of a metabolic crisis and infarction.[120,121] The pooled incidence of electroencephalogram-confirmed seizures was 25% from five descriptive studies, with seizures more common in children than adults.[122–126] Seizures are associated with increased mortality and morbidity.[121,123] We found no studies directly addressing the PICO question; therefore, we were unable to provide recommendations.

Good practice points

Supportive care and checklists

A comprehensive assessment proforma and an accompanying priorities checklist for patients with tuberculous meningitis were proposed in 2019, by consortium members.[127] The proforma outlines what should be asked, checked, or tested at initial evaluation, and daily inpatient reviews are conducted to assist

Search strategy and selection criteria

Literature searches were conducted for each Population, Intervention, Comparator, Outcome (PICO) question using keywords and controlled vocabulary. OVID MEDLINE, Embase, Cochrane CENTRAL, Global Health, and Global Index Medicus were searched from inception until July 24, 2023, followed by a final screening for new literature on March 11, 2025 (appendix p 34). Search strategies for MEDLINE are provided in the appendix (pp 26–32). A total of 35 143 records were retrieved, with 7380 records screened for relevance after duplicate removal. Non-English language articles and conference abstracts were excluded. For diagnostic questions, we only included test accuracy studies. For anti-tuberculosis chemotherapy, only data from phase 2 and 3 randomised controlled trials using standard WHO recommended therapy as the comparator were considered for adults. Pharmacokinetic studies not reporting a mortality endpoint were excluded. An up-to-date systematic review and meta-analysis of anti-tuberculosis chemotherapy in children directly informed recommendations; a literature review was not repeated. For optimal antiretroviral therapy timing, only randomised controlled trials were included. For neurocritical and neurosurgical care, a standard WHO therapy comparator included only studies after 1995, when streptomycin was phased out as a first-line drug (ensuring recommendations were relevant to current treatment). For all questions, abstracts were independently assessed by two reviewers from working groups and relevant abstracts were shortlisted for full text review. When the reviewers did not agree on abstract inclusion, consensus was reached after discussion. Full texts of included studies were retrieved and independently assessed for eligibility by two reviewers. Data extracted from eligible studies was tabulated and quality assessed. Full text data extraction was performed by one group member, with data from a random sample of 10% of studies cross-checked by another group member. Only English language articles were included; studies from high-burden countries not published in English were not included. Quality assessment was performed by an individual researcher from each working group (rather than two independent researchers).

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supportive clinical care for patients. The checklist offers a useful and easy reminder of important issues to review during a time-critical period of acute patient deterioration. A global survey showed that many centres (>90%) have the resources to apply these approaches.[127,128] Figure 2 provides an evidence-based and expert opinion overview of tuberculous meningitis treatment.

Conclusion

In conclusion, we present a clinical practice guideline for the diagnosis and management of tuberculous meningitis in children and adults, written for health-care workers anywhere in the world. We expose substantial knowledge and evidence gaps and thereby highlight current research priorities.

Contributors

AGD, AF, AvL, CMU, ER, EWT, FCC, FVC, GET, J-WCA, JD, JH, JAS, JES, NCB, REA, RBR, RS, RJW, RvC, STA, SD, SKJ, UKM, and UKR were responsible for reviewing and editing. AGD, EWT, FCC, FVC, GET, JD, JH, JES, NCB, RS, SKJ, and UKR wrote the original draft. AGD, AvL, AM, CMU, EWT, FCC, FVC, GS, J-WCA, JD, JH, JAS, JES, KED, NCB, REA, RBR, RS, RvT, STA, SD, SKJ, UKR, and VS were responsible for data curation, formal analysis, investigation. FVC, JD, JH, and NCB did the visualisation. The Review was conceptualised by GET, JD, and RJW, and ER, GET, and JD were responsible for the methodology. The Review was supervised by AF, DG, DM, GET, KED, RvC, RJW, and UKM. ER provided the resources and SP designed the searches and gave library support and curated the data. JD was the administrator and led the project. AGD and RS co-led the adjunctive therapy group while AvL, AM, JES, RvT, and STA were in the group. EWT and UKR co-led the neurocritical and neurosurgical care group while AF and GS were in the group. FVC and JAS co-led the anti-TB chemotherapy group while CMU, FCC, J-WCA, KED, REA, and SKJ were in the group. JD and JH co-led the diagnosis group while NCB, RBR, SD, and VS were in the group. AF, DG, DM, GET, KED, RvC, RJW, and UKM were in the steering group. Working group membership signifies a role in article review, data extraction, and subgroup recommendation formulation. All authors approved the final manuscript.

Declaration of interests

AGD was supported by a Wellcome clinical PhD fellowship (award number 175479) and a Crick clinical postdoctoral fellowship (via Meningitis Now) for the duration of this project. The funders had no influence on the content of the work. AF received grants from a Wellcome Trust Discovery Grant and South African NRF SARChI Chair Neurosciences, unrelated to this publication, and is the President-elect for the International Society for Pediatric Neurosurgery and is the President of the Society of Neurosurgeons of South Africa. AvL received funding from the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (R01AI145781 and R01AI165721). DM received funding from the UK Medical Research Council and US NIH. FCC received funding from the NIH (R21TW011035, T32NS131126, and R01NS126086) and received medicolegal consulting fees. FVC declares institutional grants from Wellcome and Janssen and Viiv; is on the data and safety monitoring board for the SaDAPT and DOLPHIN3 (NCT03249181) trials; and has a trial steering committee membership for the ILANA (NCT05294159) study. JES received an NIH R21 grant (1R21NS134516-01) for investigating cerebrovascular flow in tuberculous meningitis. NCB received funding from the NIH (NINDS K23 NS110470 and NIAID R01 AI170158). RBR declares funding from the National Institute for Health and Care Research (NIHR; academic clinical lectureship CL-2018-20-001), and is a named inventor for Prostanoid receptor modulators to treat non-tuberculous mycobacterial infections (WO2024/069179A1). RJW received institutional grants from Wellcome, Cancer Research UK, Medical Research Council, NIH, and NIHR; and support for attending meetings or travel from Wellcome (refunded to institution) and the Gates Foundation (refund of personal costs). RvC is on the data and safety monitoring board for two randomised controlled trials on tuberculous meningitis (no payments received). SKJ received an institutional grant from the US NIH. The other authors declare no competing interests.

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