The neurocritical care of tuberculous meningitis

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Tuberculous meningitis is the most severe form of tuberculosis and often causes critical illness with high mortality. Two primary management objectives are reducing intracranial pressure, and optimising cerebral perfusion, while killing the bacteria and controlling intracerebral inflammation. However, the evidence base guiding the care of critically ill patients with tuberculous meningitis is poor and many patients do not have access to neurocritical care units. Invasive intracranial pressure monitoring is often unavailable and although new non-invasive monitoring techniques show promise, further evidence for their use is required. Optimal management regimens of neurological complications (eg, hydrocephalus and paradoxical reactions) and of hyponatraemia, which frequently accompanies tuberculous meningitis, remain to be elucidated. Advances in the field of tuberculous meningitis predominantly focus on diagnosis, inflammatory processes, and antituberculosis chemotherapy. However, clinical trials are required to provide robust evidence guiding the most effective supportive, therapeutic, and neurosurgical interventions for tuberculous meningitis that will improve morbidity and mortality.

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Introduction

Mycobacterium tuberculosis is responsible for approximately 10 million new cases of tuberculosis and 1·3 million deaths annually.[1] Tuberculous meningitis is the most severe form of the disease, killing or severely disabling around 50% of affected patients (panel 1).[8] Tuberculous meningitis disproportionately affects children and those with HIV infection.[9] Clinical onset of tuberculous meningitis is indolent and diagnosis is challenging.[10] Treatment of the disease is lengthy and optimal drug regimens are uncertain. Thick obstructing intracerebral exudates and inflammatory lesions result in raised intracranial pressure, which leads to clinical neurological deterioration, coma, and death.

Advances in the field of tuberculous meningitis include standardisation of tuberculous meningitis clinical research methods (such as collection of datasets and outcome reporting),[11] improved diagnosis,[12] increased understanding of host genetic influence on intracerebral inflammation and survival,[5,13] and identification of first-line antituberculosis treatment regimens.[14,15] Yet, critical illness caused by tuberculous meningitis is an area that requires further research. No guidelines exist for the management of critical illness associated with tuberculous meningitis, and the evidence base for treatment is poor. Studies of critically ill patients with tuberculous meningitis are largely retrospective, observational, and contain small patient numbers,[16–19] with paediatric data particularly scarce.[20] Patient outcomes in those admitted to critical care units are extremely poor, with studies predominantly involving adults showing 40–53% mortality, and neurological disability is common in survivors.[16,19] Severe tuberculous meningitis presents specific clinical challenges, in particular the detection and management of raised intracranial pressure and brain ischaemia.[7] Further research to optimise supportive care and neurosurgical interventions is required to improve functional outcomes of patients with tuberculous meningitis.[21]

In this Review, we focus on aspects relevant to the neurocritical care of patients with tuberculous meningitis, with general diagnosis and treatment reviewed elsewhere.[7] We start by discussing causes of critical illness, focusing on causes that occur earliest and those which contribute most to mortality and morbidity. We then describe complications in disease progression, including those arising from treatment. We then discuss supportive management, followed by medical, and then surgical management. We conclude by suggesting future research directions and proposing clinical trials that are required to improve outcomes from critical illness arising from the disease.

Causes of critical illness in tuberculous meningitis

Raised intracranial pressure

Coma in tuberculous meningitis is associated with raised intracranial pressure.[7] A sustained intracranial pressure of more than 20 mm Hg is considered abnormal in adults,[22] although pressure changes have not been correlated with prognosis in patients with tuberculous meningitis and the true incidence of raised intracranial pressure in patients with tuberculous meningitis is uncertain. The reduction of cerebral blood flow in conditions of raised intracranial pressure, after limits of compensatory changes are reached, is an unproven mechanism in the disease. The normal intracranial pressure range in children is lower than in adults and depends on age.[23] Hydrocephalus results from CSF blockage at either the basal cistern or absorptive arachnoid granulations (so-called communicating hydrocephalus), or at the cerebral aqueduct or fourth ventricle outlet (non-communicating hydrocephalus),[8,24] and is the most common cause of raised intracranial pressure in patients with tuberculous meningitis.[7] In two studies of adolescents (older than age 14 years) and adults with tuberculous meningitis in India, 109 (52%) of 209 patients and 52 (65%) of 80 patients had baseline MRI images consistent with hydrocephalus.[25,26] Most patients (70–80%) have communicating hydrocephalus.[8] The two types of hydrocephalus increase intracranial pressure and manifest clinically with headache, reduced consciousness or focal neurological deficits, or both. Cerebral oedema[8] and tuberculoma formation[27] could also elevate intracranial pressure in patients with tuberculous

Panel 1: Pathophysiology of tuberculous meningitis

Tuberculous meningitis results from the haematogenous dissemination of *Mycobacterium tuberculosis* to the brain, followed by granuloma rupture and bacterial inoculation into the subarachnoid space.[2] An insidious onset of non-specific prodromal symptoms followed by a slowly progressive meningitis makes diagnosis challenging, with a wide range of differential diagnosis, especially in patients with HIV co-infection.[3] Delayed diagnosis and treatment lead to poor outcomes,[4] and inflammatory pathways are not completely understood. In patients with HIV co-infection, mortality is associated with higher CSF neutrophil counts,[5] yet how neutrophils drive inflammation in tuberculous meningitis is unclear.[6] Intracerebral inflammation is thought to contribute to the poor prognosis associated with tuberculous meningitis.[5] Inflammatory pathways and adjunctive anti-inflammatory therapies have been reviewed elsewhere.[7]

meningitis. Severe ischaemic strokes can cause brain shift and raise intracranial pressure,[28] although such events are not well described for patients with tuberculous meningitis. Seizures,[29] fever, impaired ventilation, and hyponatraemia, which are symWptoms frequently observed in tuberculous meningitis, might raise intracranial pressure to a critical level, resulting in brain injury.[7]

Cerebral infarction

Cerebral infarction is the main cause of long-term neurological disability in patients with tuberculous meningitis.[7] The exact pathophysiology of cerebral infarction associated with tuberculous meningitis is uncertain, although inflammation and necrosis secondary to surrounding basal exudate are thought to contribute to blood vessel pathology.[8,30] The lateral and medial lenticulostriate arteries are most commonly affected,[31] with resulting basal ganglia infarcts, although subcortical white matter infarcts have also been reported in patients with tuberculous meningitis.[32] Vasculitis is common, vasospasm is uncommon, and complete vessel occlusion of major arteries is unusual, but has been reported in patients with tuberculous meningitis.[8,32] Two MRI studies in adults with tuberculous meningitis showed cerebral infarction in 40 (35%) of 114 patients[30] and 34 (67%) of 51 patients.[31] A systematic review of six studies including 843 children with tuberculous meningitis showed that cerebral infarction was present in 255 children at admission.[9] Impaired cerebral perfusion leads to ischaemia, cerebral infarction, and raised intracranial pressure.[7] Hemiplegia is the most common clinical consequence of cerebral infarction due to tuberculous meningitis.[8] The range of neurological complications resulting from cerebral infarction associated with tuberculous meningitis has not been studied in detail over the past 10 years, and the effect of irreversible neurological disability on feeding, pneumonia, pressure damage, and thrombosis remains unknown.

Tuberculoma

A tuberculoma is the result of granulomatous inflammation forming space-occupying brain lesions, after metastatic seeding of *M tuberculosis* to the CNS.[27] Tuberculomas are the most common cause of paradoxical reactions in HIV-negative patients with tuberculous meningitis.[33] A systematic review[9] of seven studies including 1056 children with tuberculous meningitis showed that tuberculomas were present in 112 children at admission, compared with 15 (13%) of 114 HIV negative adults with tuberculous meningitis in a randomised controlled trial (RCT),[30] indicating that they play a role in both paediatric and adult cases of tuberculous meningitis.[33] Tuberculomas might exert local mass effect on brain tissue, causing compression of cerebral ventricles, leading to headache, vomiting, decreased consciousness, focal neurological signs, and seizures.[27] Tuberculomas can have a severe effect on outcome and might cause severe disability.

Hyponatraemia

Hyponatraemia can develop at any time during treatment of tuberculous meningitis. Hyponatraemia is classified as profound when sodium falls below 125 mmol/L.[34] In one study of adults and children with tuberculous meningitis, 34 (45%) of 76 individuals had hyponatraemia, and 8 (11%) patients had sodium values below 120 mmol/L.[35] Cerebral salt wasting and the syndrome of inappropriate antidiuretic hormone secretion are considered the most likely causes of hyponatraemia in patients with tuberculous meningitis and could overlap;[35] yet the mechanism of hyponatraemia remains poorly understood. In cerebral salt wasting, renal sodium loss could be mediated by natriuretic peptides, whereas in the syndrome of inappropriate antidiuretic hormone secretion, vasopressin secretion occurs independently of serum osmolality or circulating volume.[34] Diagnosis is confounded by varying definitions of cerebral salt wasting and the syndrome of inappropriate antidiuretic hormone secretion and similarity of electrolytes and osmolality values.[35] Hyponatraemia occurs with brain injury[36] and contributes to raised intracranial pressure. Hyponatraemia worsens cerebral oedema, with acute sodium changes particularly harmful for patients.[34] Hyponatraemia causes headache and confusion (seizures and coma when severe)[34] and predicts increased mortality in patients with HIV and tuberculous meningitis.[37]

Paradoxical reactions

Paradoxical reactions are when worsening signs and symptoms of tuberculosis occur despite effective antituberculosis chemotherapy.[38] These reactions are commonly considered an exuberant inflammatory response to dead or dying bacteria; their pathogenesis is poorly understood.[38] In a study of patients with tuberculous meningitis in India (mean age 30 years), 44 (31%) of 141 patients developed a paradoxical reaction.[39] These

reactions usually occur after 2–4 months of antituberculosis chemotherapy.[33] Paradoxical reactions contribute to critical illness of patients with tuberculous meningitis, with clinical features including headache, altered vision, and seizures.[39] Neuroimaging findings include enhancing basal exudates, new or worsening tuberculomas, and optochiasmatic or spinal arachnoiditis.[39] Paradoxical changes might cause mass effect and obstruct CSF,[33] raising intracranial pressure. Clinical spinal disease is common and might be overlooked and is often revealed after commencing antituberculous chemotherapy. High CSF protein concentrations indicate a greater likelihood of development.[40] Lumbosacral disease is most common,[40] and urinary retention is often the first presenting symptom.

Drugs

Critical illness can result from or be exacerbated by side-effects of antituberculosis chemotherapy and interactions with other drugs (table 1). Drug-induced liver injury is the most common drug-associated adverse event of antituberculosis chemotherapy,[11] with severe symptoms such as vomiting and abdominal pain. Drug reactions affecting neurological status might confound monitoring of patients with tuberculous meningitis. Antituberculosis chemotherapy such as fluoroquinolones[15,46] and isoniazid[7] can increase seizure risk, and both isoniazid and fluoroquinolone treatments might cause psychiatric disorders.

Antituberculosis drug resistance

Tuberculosis caused by *M tuberculosis* that is resistant to first-line antituberculosis drugs is becoming increasingly common worldwide[1] and increases the risk of treatment failure and death. Tuberculous meningitis caused by bacteria resistant to at least rifampicin and isoniazid (ie, multi-drug resistance) is mostly fatal unless second-line drugs are administered early.[47] Prevalence of multidrug resistance in tuberculous meningitis is about 4% in Europe[48] and 12% in China.[49] Mono-isoniazid resistance is more common (nine [6%] of 142 cases in the European study[48]) and is associated with worse outcomes, although its effect on treatment response is less than that of multidrug resistance.[47] The low sensitivity of current molecular diagnostic tests, which can detect *M tuberculosis* and drug resistance (eg, GeneXpert) in CSF, and the 4–8 weeks taken to obtain in-vitro drug susceptibility testing information, means that determining whether drug resistance is causing or contributing to critical illness caused by tuberculous meningitis is extremely challenging.

Young children and individuals with HIV co-infection

Specific risks apply to young children and individuals with HIV. Intracerebral inflammation is increased in individuals with HIV and tuberculous meningitis.[13] Immune reconstitution inflammatory syndrome (IRIS) might develop, presenting as new or worsening neurological symptoms after the introduction of antiretroviral therapy.[50] Neurological manifestations of IRIS include meningitis, brain tuberculoma, brain abscess, radiculomyelitis, and spinal epidural abscess.[51] The effect of HIV co-infection on the pharmacokinetics of first-line antituberculosis chemotherapy is uncertain; a systematic review of 27 studies was unable to conclude a clear effect.[52] Antiretroviral therapy is complicated by rifampicin's induction of cytochrome P450 enzymes,[53] and drug-induced liver injury could be more common in patients with HIV. Miliary tuberculosis[54] (in which widespread dissemination of *M tuberculosis* occurs) and opportunistic infections in HIV co-infection could complicate critical illness further. Very young children (younger than age 1 year) are highly susceptible to *M tuberculosis*, and might present acutely and deteriorate rapidly.[7] Hydrocephalus is particularly common in children, affecting 931 of 1088 children with tuberculous meningitis in a systematic review of nine studies.[9]

Monitoring of critically ill patients with tuberculous meningitis

The continuous monitoring of physiological variables (temperature, respiratory rate, pulse, and blood pressure) should be the standard of care in critical illness, although this is probably hard to achieve in resource-limited settings. In this Review, we focus on additional monitoring specific to tuberculous meningitis, and discuss the most basic (and most available) non-invasive monitoring methods first, followed by the invasive techniques (table 2).

Clinical assessment and basic bedside monitoring

Clinical assessment and basic bedside monitoring can sometimes be the only available monitoring techniques in some resource-limited settings. The Glasgow Coma Scale is easy to learn, reliable with training, and recognised internationally.[55] In children younger than age 5 years, in whom verbal and motor abilities are less developed, a modified Glasgow Coma Scale might be more suitable. The use of the Glasgow Coma Scale to monitor treatment response might be confounded by intubation, sedative drugs, and pre-existing neurological conditions (such as dementia or psychiatric disorders).[55] The UK Medical Research Council tuberculous meningitis grade combines the Glasgow Coma Scale and focal neurological signs to categorise disease severity.[7] A high tuberculous meningitis grade at presentation predicts mortality regardless of HIV status.[37] EEG monitoring is recommended in critically ill individuals with encephalitis who are comatose,[60] although the role of this tool in monitoring of critically ill patients with tuberculous meningitis is unclear.

For more on **GeneXpert** see https://www.cdc.gov/tb/publications/factsheets/pdf/xpertmtb-rifassayfactsheet_final.pdf

Non-invasive intracranial pressure monitoring

Transcranial Doppler ultrasound uses a low frequency transducer, placed on the scalp, to determine cerebral blood flow velocity in the basal arteries of the brain, with

	Therapeutic role in tuberculous meningitis	Primary adverse effect	Drug interactions	Additional adverse effects
Rifampicin	First-line antituberculosis therapy	Induces cytochrome 3A4 enzyme[41]	Antiretroviral therapy drugs (including non-nucleoside reverse transcriptase inhibitors and protease inhibitors), reduces serum concentrations; benzodiazepines, substrates for cytochrome 3A4	Drug-induced liver injury; hypersensitivity including Stevens-Johnson syndrome; renal failure; adrenal insufficiency; haemolysis; cytopenia
Isoniazid	First-line antituberculosis therapy	Inhibits cytochrome 3A4 enzyme[42]	Phenytoin, higher serum phenytoin concentrations in slow acetylators;[43] benzodiazepines, substrates for cytochrome 3A4	Drug-induced liver injury; seizures; psychiatric disorders; toxic epidermal necrolysis; Stevens-Johnson syndrome; pancreatitis; haemolysis; cytopenia
Pyrazinamide	First-line antituberculosis therapy	Drug induced liver injury[41]	No interactions relevant to critically ill patients with tuberculous meningitis	Hypersensitivity, including urticaria
Ethambutol hydrochloride	First-line antituberculosis therapy	Ocular toxicity difficult to detect in comatose patients[7]	No interactions relevant to critically ill patients with tuberculous meningitis	Hypersensitivity, including Stevens-Johnson syndrome; thrombocytopenia; leucopenia; renal failure
Fluoroquinolones (eg, levofloxacin, moxifloxacin hydrochloride, gatifloxacin)	Second-line antituberculosis therapy	Lowers seizure threshold[15]	No interactions relevant to critically ill patients with tuberculous meningitis	Drug-induced liver injury; seizures; psychiatric disorders; QT prolongation; toxic epidermal necrolysis; Stevens-Johnson syndrome; haemolysis; cytopenia; renal failure
Corticosteroids (eg, dexamethasone)	Adjunctive antiinflammatory drug	Associated with an increased risk of gastrointestinal bleeding in patients admitted to hospital[44]	Aspirin, adverse effect of corticosteroids overlaps with treatment effect of aspirin	Adrenal insufficiency on discontinuation; psychosis; infections
Aspirin	Anti-platelet and antithrombotic agent	Increased gastrointestinal bleeding tendencies established	Corticosteroids, treatment effect of aspirin overlaps with adverse effect of corticosteroids	Hypersensitivity
Acetazolamide	Reduces CSF production	Might cause hyponatraemia, or exacerbate hypotraemia of tuberculosis meningitis[45]	Overlapping treatment effect profile with fludrocortisone; increased metabolic acidosis and neurological effects with concomitant aspirin; interactions with anti-convulsants	Electrolyte imbalance; renal failure; extensive adverse effects and drug interactions

Table 1: **Drugs commonly used during management of tuberculous meningitis**

intracranial pressure possibly inferred from changes in the pulsatility index.[61] Transcranial Doppler ultrasound has been used to detect vasculopathy in patients with tuberculous meningitis,[56] although its value in quantifying intracranial pressure is uncertain given that changes in partial pressure of carbon dioxide or blood pressure could alter blood flow and pulsatility index, independently of changes in intracranial pressure.[57] A study of 20 children from South Africa showed that pulsatility index could not reliably predict intracranial pressure in children with tuberculous meningitis.[62]

Optic nerve sheath diameter ultrasound is a potentially quick, easy, and safe method for early intracranial pressure detection. The optic nerve is surrounded by a dural sheath that distends in its retrobulbar segment under elevated intracranial pressure. Optic nerve sheath appearances can be recorded and distension measured (figure 1). In patients with tuberculous meningitis, higher optic nerve sheath diameter measurements have been associated with raised intracranial pressure.[58] No data yet exist to support the use of optic nerve sheath diameter measurement in guiding management, measuring treatment response, or improving outcomes in patients with tuberculous meningitis.

Lumbar puncture

Lumbar puncture and CSF analysis are essential for diagnosis of tuberculous meningitis and can be used to assess treatment response, provide opening pressure measurement, and enabling air encephalography. CSF opening pressure is elevated in approximately half of adult tuberculous meningitis cases,[63] although no evidence yet supports opening pressure as a predictor of intracranial pressure or outcome in patients with tuberculous meningitis. Low pretreatment leucocyte numbers and CSF glucose concentrations have been associated with death from tuberculous meningitis,[5] and CSF glucose concentrations rise with successful treatment. However, the value of repeated assessments of CSF opening pressure, glucose concentrations, and leucocyte numbers in defining clinical management and prognosis has not yet been studied.

	Advantages	Disadvantages
Non-invasive		
Glasgow Coma Scale	Well known internationally; generally reproducible; easy to learn; and effective for regular assessment[55]	Broad tool for assessment; unlikely to identify subtle changes in clinical status; influenced by reversible (drugs such as sedatives) and irreversible factors (cranial nerve palsies) so sensitivity will change with time; cannot be applied to children younger than age 5 years[55]
CT brain imaging	Identifies hydrocephalus and large mass lesions; available at most large centres; fast procedure	Role in identifying raised intracranial pressure uncertain; might not identify subtle changes in intracranial pressure; often requires contrast; radiation exposure
MRI brain imaging	Likely to identify intracranial cause of neurological deterioration in patients with tuberculous meningitis; good sensitivity for detecting pathological features of tuberculous meningitis; can detect acute infarcts with diffusion weighted imaging; multiple imaging sequences available allowing targeted detection of specific pathologies	Role in identifying raised intracranial pressure uncertain; time consuming; might be unavailable, or MRI machine could be located off site with patient transfer to machine time consuming and high risk of patient deterioration during transit; might require anaesthesia in young patients
Transcranial Doppler ultrasound	Safe procedure	Value in quantifying intracranial pressure is uncertain, but useful to detect vasculopathy in patients with tuberculous meningitis;[56] only measures cerebral blood flow in major vessels in Circle of Willis, which might change (via changes in partial pressure of carbon dioxide or mean arterial pressure) independently of intracranial pressure;[57] user dependent
Optic nerve sheath diameter ultrasound	Ultrasound machines available at many centres; fast and safe procedure	Requires knowledge of normal population values for comparison; not for continuous monitoring; role yet to be defined in management, but a study of 25 patients with tuberculous meningitis showed promising results[58]
Invasive		
Lumbar puncture	Single pressure measurement (opening pressure) well recognised; equipment widely available; allows CSF drainage; allows air encephalogram to be performed	Association with intracranial pressure changes uncertain; continuous pressure measurement available only at specialist centres
Intraventricular catheters, intraparenchymal pressure transducers, subarachnoid bolts, and epidural transducers	Gold standard for intracranial pressure monitoring; continuous monitoring; allows rapid detection of intracranial pressure changes; ventricular catheters allow CSF drainage	Risks of infection and bleeding;[59] available only at specialist centres; costly

Table 2: **Methods of intracranial pressure monitoring in patients with tuberculous meningitis**

Invasive intracranial monitoring devices

Gold standard intracranial pressure monitoring is invasive and can be done at intraventricular, intraparenchymal, and epidural sites.[59] Haemorrhage and infection are rare risks of intracranial device insertion, and devices should not be inserted in individuals with coagulopathy or at sites of local infection.[64] Intraventricular access allows CSF drainage, sampling, and drug administration.[59] Descriptions of intracranial pressure monitoring in patients with tuberculous meningitis are scarce, and whether intracranial pressure monitoring guides treatment regimen or improves outcomes is uncertain.

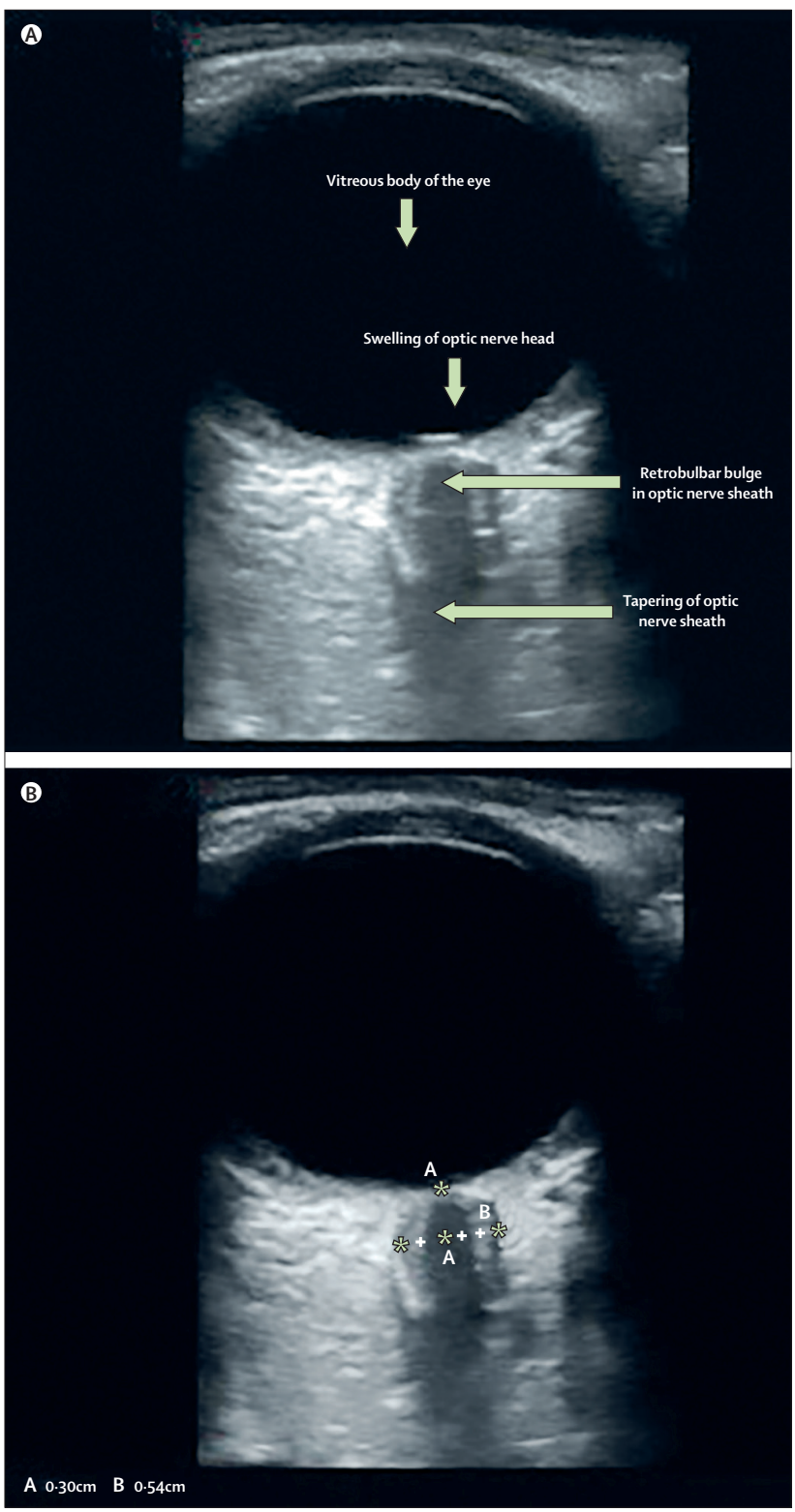
Biomarkers of brain injury

Biomarkers of neuronal injury offer a potential future approach to quantifying and monitoring brain pathology. Brain pathologies result in leakage of proteins into the CSF where they can be measured, or into the bloodstream through an impaired blood–brain barrier.[65] A study of blood–brain barrier function and CSF biomarkers of CNS injury in 66 adults and children with brain infections in Laos found blood–brain barrier leakage and higher amounts of glial fibrillary acidic protein in the 11 adults with tuberculous meningitis than was observed in the patients with other brain infections (except bacterial meningitis).[66] An increasing concentration of CSF biomarkers of neuronal and glial injury over time was associated with worse outcome in a study of 44 paediatric patients with tuberculous meningitis and hydrocephalus in South Africa.[67] Biomarkers represent a potential future method to monitor treatment response and predict outcome; however, further research is required to define optimal concentration ranges of biomarkers for clinical use.

Brain imaging

Brain imaging allows identification of the causes (hydrocephalus, tuberculous masses, cerebral oedema) and consequences (brain shift and ischaemia) of raised intracranial pressure. Baseline brain imaging can alter immediate management if hydrocephalus is found, and follow-up brain imaging is recommended for patients with worsening symptoms.[7] No evidence supports routine follow-up brain imaging in patients who recover back to neurological baseline from tuberculous meningitis. Brain CT can identify dilated ventricles, mass effects, infarctions, and inflammatory exudates. The detrimental effects of brain irradiation from CT during brain injury remain

unknown. Brain MRI has no radiation risks and provides higher resolution of *M tuberculosis*-associated brain pathology than does CT, although it is expensive, time consuming, and might require transfer of a critically ill patient to a hospital with MRI.[68,69] By contrast, enhanced fluid attenuated inversion recovery MRI, removal of CSF enhancement (and removal of enhancement of normal vessels and meninges) might show inflammation and leptomeningeal changes more clearly than does CT.[70,71] Retrospective data show that both CT and MRI have a role in detecting brain pathoogy associated with tuberculous meningitis.[72] In a study of 26 adults and children with tuberculous meningitis, magnetic resonance angiography identified blood vessel abnormalities in 11 (42%) of 26 patients,[73] suggesting a future role of this imaging technique in monitoring of tuberculous meningitis.



Management of critically ill patients with tuberculous meningitis

This section on management of critical illness starts with supportive management, followed by medical, and then surgical management (panel 2).

General patient management

Supportive care is critical in tuberculous meningitis, yet few data exist to guide management. With control of intracranial pressure a priority, supportive care aims to optimise patient position and parameters such as temperature, haemoglobin, and glucose concentrations, and avoid complications of prolonged critical illness such as ventilator associated pneumonia and pressure area damage (panel 3). Fever is associated with worse outcomes in patients with severe neurological injury of multiple causes,[75] and an increased 1-year mortality in HIV-negative individuals with tuberculous meningitis.[5] Cerebral metabolic rate and oxygen demand fall with body temperature,[76] and a role for therapeutic hypothermia in neuroprotection has been explored. RCTs showed that therapeutic hypothermia was associated with increased mortality in patients with severe bacterial meningitis,[77] and worse functional outcomes in patients with traumatic brain injury;[78] however, no trials have investigated therapeutic hypothermia in patients with tuberculous meningitis.

Figure 1: **Use of optic nerve sheath diameter ultrasound in critically ill patients with tuberculous meningitis**

Optic nerve sheath diameter ultrasound is a simple, non-invasive tool that shows potential to screen individuals with tuberculous meningitis for raised intracranial pressure.[57] (A) Optic nerve sheath diameter ultrasound image of the left eye from an adult patient with Medical Research Council grade 2 tuberculous meningitis (GCS 11–14, or GCS 15 with focal neurological signs) and raised intracranial pressure. This image was taken at diagnosis of tuberculous meningitis, on the first day of antituberculosis chemotherapy. At the posterior aspect of the globe, a short narrow horizontal line represents swelling of the head of the optic nerve. Retrobulbar distension of the optic nerve sheath can be seen, with a subsequent tapering of the optic nerve sheath proximally. (B) Identical to (A) with the addition of measuring calipers, showing retrobulbar distension of the optic nerve sheath measured at 0·3 cm from the posterior aspect of the globe of the eye (A-A calipers), and the diameter of the optic nerve sheath (caliper B, diameter 0·54 cm).

Raised intracranial pressure contributes to poor outcome in patients with tuberculous meningitis. Intracranial pressure reduction strategies derive from evidence acquired in other causes of brain injury. We summarise potential strategies for optimising intracranial pressure and preserving brain perfusion in critically ill individuals with tuberculous meningitis (figure 2). Supportive therapies include optimisation of patient position for CSF and cerebral venous drainage, avoidance of hyperthermia and hypotension, control of seizures, and appropriate mechanical ventilation. Drug therapies include acetazolamide for reducing CSF production, adjunctive anti-inflammatory therapy, and antituberculosis chemotherapy. Furthermore, sodium management, hyperosmolar therapy, and neurosurgical strategies (endoscopic third ventriculostomy [ETV] and ventriculoperitoneal [VP] shunting) are also potential treatment strategies.

Airway protection and respiratory failure

In two studies, 53 (70%) of 76 adults and children[16] and 63 (70%) of 90 adults[19] with tuberculous meningitis, admitted to an intensive care unit, required mechanical ventilation. However, optimal ventilation strategies in patients with tuberculous meningitis are unknown. Neuromuscular blockade could allow more efficient control of oxygenation, hyperventilation, and positive end-expiratory pressure, and limit coughing, with the overall result of avoiding surges of intracranial pressure; but no data support its routine use in patients with traumatic brain injury[79] or those with tuberculous meningitis. Hypocarbia and hypercarbia have detrimental effects on cerebral blood flow and intracranial pressure in patients with tuberculous meningitis.[7] No evidence supports the use of hyperventilation for intracranial pressure management in patients with tuberculous meningitis.

Antituberculosis chemotherapy

The use of antituberculosis chemotherapy in patients with tuberculous meningitis has been reviewed elsewhere[7] and only aspects relevant to critically ill patients with tuberculous meningitis are discussed in this Review. Rifampicin, isoniazid, pyrazinamide, and ethambutol are first-line agents for drug-susceptible tuberculosis,[7] with 9–12 month regimens common for patients with tuberculous meningitis.[8] Prompt treatment and avoidance of therapy interruptions are essential to reduce mortality from tuberculous meningitis.[7] Optimal drug doses and administration routes are unknown, especially in critically ill patients, although some evidence has shown that high rifampicin doses (>10 mg/kg, normal dose is 10 mg/kg per day, up to a maximum of 600 mg per day) administered intravenously might improve outcomes.[14] Severely ill individuals who are unable to swallow can receive crushed antituberculosis medications via an enteral feeding tube, yet no data exist confirming that this approach achieves adequate intracerebral drug concentrations. Intravenous preparations might be preferable, if available, although evidence is scarce, and no intravenous pyrazinamide preparation exists. Interruptions to first-line antituberculosis chemotherapy could be necessary if drug-induced liver injury occurs, although the transaminase thresholds for stopping drugs, and the timing of their reintroduction, have not yet been defined by RCTs.

Anti-inflammatory treatment

Adjunctive corticosteroids, given from the start of antituberculosis drug treatment, reduce mortality from tuberculous meningitis, at least in the short term (less than 2 years after treatment initiated).[80] Their benefit in HIV co-infection is uncertain and is the objective of an ongoing RCT in Vietnam and Indonesia (NCT03092817).[81] The optimal dose and administration route, and whether prednisolone and dexamethasone are equally effective, remain unknown. Correct use of corticosteroids following the start of antituberculosis drug treatment in the management of complications causing neurological

Panel 2: Case study

A 30-year-old man was admitted to a hospital in Ho Chi Minh City, Vietnam, with a 2-week history of fever, headache, and meningism. He had no relevant past medical history. Glasgow Coma Scale score was 15, and the only abnormal neurological sign was a right sixth cranial nerve palsy. Serum sodium was 117 mmol/L and liver function tests were normal. An HIV test was positive, CD4 count was 17 cells per µL, and a chest x-ray was normal. CSF analysis revealed 304 white blood cells (73% neutrophils), protein was 2·01 g/L, glucose was 0·72 mmol/L (paired serum glucose was 4·75 mmol/L), and lactate was 7·7 mmol/L. Acid-fast bacilli were seen on CSF smear microscopy and a CSF GeneXpert test was negative. CT (appendix) and MRI brain imaging with contrast were normal. Tuberculous meningitis was diagnosed and first-line oral antituberculosis chemotherapy was initiated (rifampicin, isoniazid, pyrazinamide, and ethambutol, at weight appropriate doses). Adjunctive dexamethasone was used, initially at 0·4 mg/kg per day, with weekly tapering. Reduced serum osmolality, inappropriately high urine osmolality, elevated urinary sodium, and hypovolaemia were consistent with cerebral salt wasting, and hypertonic saline was administered to correct circulating volume and serum sodium concentration. Antiretroviral therapy was not immediately started because of the risk of neurological immune reconstitution inflammatory syndrome.

2 weeks after starting antituberculosis chemotherapy, the patient's condition had improved. The cranial nerve palsy had resolved, serum sodium had recovered to 130 mmols/L with correction of hypovolaemia, and hypertonic saline therapy had been stopped. A decision was made to commence antiretroviral therapy (tenofovir, lamivudine, and efavirenz). After 5 days, the patient developed a headache and began vomiting. Glasgow Coma Scale score remained at 15. Brain CT with contrast did not reveal focal lesions, although cerebral ventricles had slightly increased in size (appendix). After 5 days, the Glasgow Coma Scale score acutely fell to 11 (eyes open to speech, inappropriate words, localising motor response). MRI brain imaging with contrast showed substantially enlarged cerebral ventricles (appendix) with a tuberculoma compressing the fourth ventricle outlet. Antituberculosis chemotherapy was administered via a nasogastric tube, and high dose intravenous dexamethasone was initiated. A decision was made in conjunction with the patient's family and neurosurgical team not to proceed with neurosurgical intervention. The following day, the Glasgow Coma Score fell to 7 and the patient underwent endotracheal intubation and mechanical ventilation. Supportive care and medical therapy were continued. 2 days later, the patient had a cardiac arrest and died.

See **Online** for appendix

Panel 3: **Approaches and evidence gaps in the supportive care of critically ill patients with tuberculous meningitis**

Infection control and reducing potential in-hospital *Mycobacterium tuberculosis* transmission
- Respiratory isolation might be required in patients with concomitant pulmonary tuberculosis
- Respiratory isolation in critical care is challenging when patients require constant monitoring from staff
- The effect of endotracheal intubation and a closed ventilation circuit on tuberculosis transmission is uncertain, given that periodic breaks to this closed circuit to allow suction might induce coughing

Head-of-bed elevation to reduce intracranial pressure
- Elevating the head end of a bed is known to aid venous drainage and shifts CSF extracranially, but might also lower mean arterial pressure
- Optimal head-of-bed elevation in patients with tuberculous meningitis has not been studied

Maintaining normal glucose concentrations
- Hyperglycaemia and hypoglycaemia adversely affect the brain during critical illness; however, optimal glucose control is not known[74]

Treating anaemia to ensure optimal tissue oxygenation
- Haemoglobin is important for optimal oxygen delivery in patients at risk of ischaemia, and optimal transfusion thresholds have not been determined in patients with tuberculous meningitis

Controlling and reducing fever
- Whether treating fever in patients with tuberculous meningitis improves outcomes is not known
- No randomised controlled trials have yet described therapeutic hypothermia in patients with tuberculous meningitis

Preventing deep vein thrombosis
- The role of deep vein thrombosis prophylaxis in critically ill patients with tuberculous meningitis, in which corticosteroids and aspirin might add to the gastrointestinal bleeding risk, has not been studied
- The effect of head-of-bed elevation or general patient positioning in patients with tuberculous meningitis on deep vein thrombosis has not been studied

Protecting pressure areas
- The effect of head-of-bed elevation or general patient positioning on pressure area damage in patients with tuberculous meningitis has not been studied

Ventilator-associated pneumonia prevention
- Mechanical ventilation is common in critical care tuberculous meningitis[19]
- Almost a quarter of patients with tuberculous meningitis who had mechanical ventilation developed ventilator-associated pneumonia[29]
- Ventilator-associated pneumonia prevention strategies are uncertain in patients with tuberculous meningitis

Optimising nutrition
- Tuberculosis is a catabolic illness, yet no nutritional guideline exists specifically for tuberculous meningitis
- Alternative drug administration routes can be considered when an oral route is unavailable in unconscious patients

deterioration and critical illness is unclear. Despite weak evidence, corticosteroids are often used as rescue therapy for raised intracranial pressure as they can reduce cerebral oedema. They are often used in the treatment of neurological deterioration caused by expanding brain tuberculomas[33] and for immune reconstitution inflammatory syndrome in patients with HIV.[50] Occasionally, tuberculomas do not respond to corticosteroids, with persistence or progression of symptoms associated with tuberculomas despite therapy.[7] Case reports and small case series suggest adjunctive thalidomide, infliximab, and interferon gamma might be effective in this circumstance.[8] Adjunctive aspirin given with dexamethasone might reduce brain infarcts and improve mortality, and phase 3 trials are planned to assess the effect of adjunctive aspirin administered with dexamethasone on brain infarcts and mortality.[29]

Seizure management

Data regarding the cause and timing of seizures in patients with tuberculous meningitis is scarce, and their incidence appears to vary substantially between populations. A study of 817 Vietnamese adults with tuberculous meningitis showed that seizures occurred in 11 (3%) of 409 patients receiving standard antituberculosis chemotherapy.[15] Seizures were also reported in 8% of 515 HIV-negative individuals and 13% of 93 HIV-positive individuals (all older than age 14 years) with tuberculous meningitis in Indonesia.[6] Conversely, a study of Indian adults with tuberculous meningitis showed seizures in 27 (34%) of 79 patients, and abnormal EEG changes were observed in 17 (85%) of 20 patients who had seizures and EEG tests.[78] Early-onset seizures were associated with cerebral oedema and meningeal irritation, whereas late-onset seizures were associated with hydrocephalus, cerebral infarction, and tuberculomas in patients with tuberculous meningitis.[78] Seizure risk can be increased by fluoroquinolone coadministration.[15,46] The optimum treatment of seizures in patients with tuberculous meningitis has not been studied. Therapy is complicated when cytochrome P450 induction and inhibition alters concentrations of drugs metabolised by these

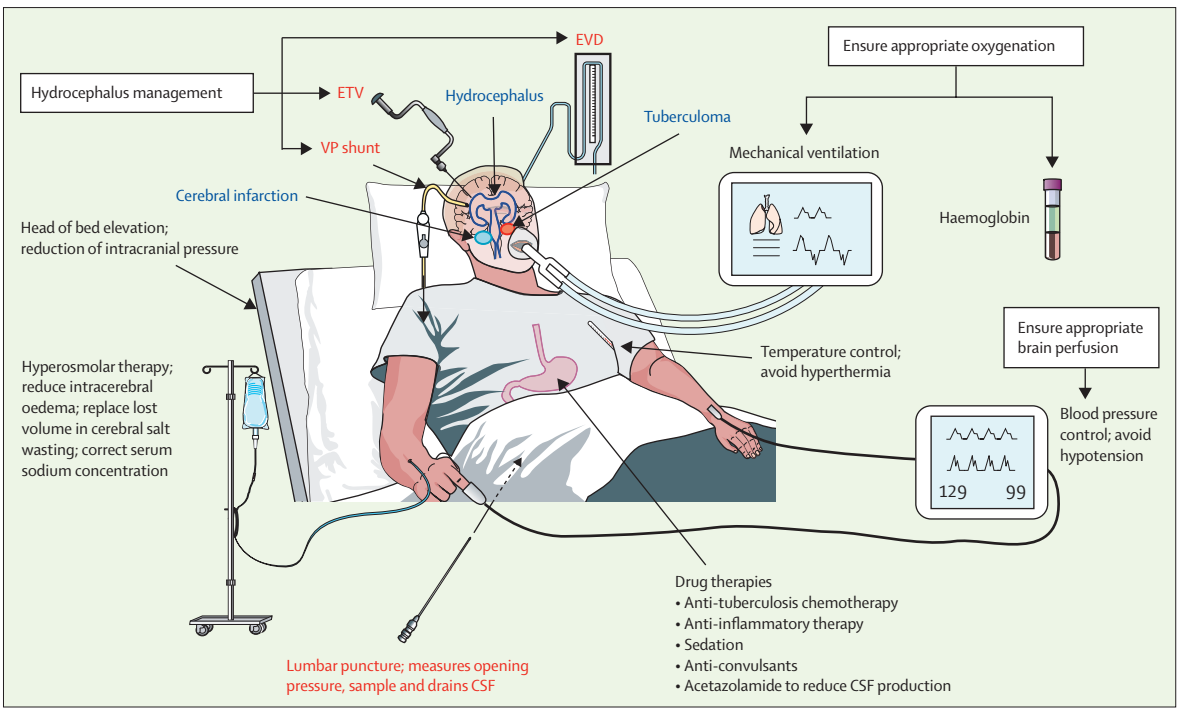


Figure 2: **Potential strategies for management of intracranial pressure and maintenance of brain perfusion in critically ill individuals with tuberculous meningitis** Avoiding and reducing high intracranial pressure, and preserving brain perfusion and oxygenation in critically ill individuals with tuberculous meningitis is important. Little evidence exists specific to tuberculous meningitis; however, the strategies in this figure show the multiple potential ways in which the problem of raised intracranial pressure and impaired brain perfusion can be approached. Surgical interventions labelled in red, disease processes labelled in blue, and other interventions labelled in black. EVD=external ventricular drainage. ETV=endoscopic third ventriculostomy. VP=ventriculoperitoneal.

enzymes, and levetiracetam might be preferred to prevent interactions with rifampicin in patients with seizures.[82]

Hyponatraemia and hyperosmolar therapy

Hyponatraemia commonly accompanies critical illness resulting from tuberculous meningitis, and cerebral salt wasting and syndrome of inappropriate antidiuretic hormone secretion are considered the most likely causes.[35] An RCT compared intravenous and oral sodium supplementation with or without fludrocortisone (0·1–0·4 mg/day) in the treatment of 37 Indian adults with hyponatraemia (<135 mEq/L) caused by cerebral salt wasting associated with tuberculous meningitis.[83] Fludrocortisone (combined with intravenous and oral salt supplementation) was significantly associated with faster correction of plasma sodium than intravenous and oral salt supplementation alone (4 days *vs* 15 days), but did not influence mortality or disability at 6 months. Fludrocortisone was associated with severe hypokalaemia and hypertension in two patients with hyponatraemia, necessitating its discontinuation.[79] For syndrome of inappropriate antidiuretic hormone secretion, clinical practice guidelines recommend fluid restriction as first-line treatment,[34] although this approach has not been investigated in patients with tuberculous meningitis. Distinguishing the cause of hyponatraemia in patients with tuberculous meningitis is difficult,[35] and fluid restriction in a critically ill patient with cerebral salt wasting is potentially harmful because these patients are often profoundly hypovolaemic. Assessment of intravascular fluid status can guide therapy, with hypovolaemia expected in patients with cerebral salt wasting, and euvolaemia expected in patients with syndrome of inappropriate antidiuretic hormone secretion.[34]

Meta-analyses of studies in patients with traumatic brain injury suggest mannitol could have a detrimental effect on mortality when compared with hypertonic saline (four studies),[84] or no benefit of one intervention over the other (six studies).[85] Hypertonic saline might reduce intracranial pressure faster, to a greater extent, and for longer than does mannitol; however, the choice of agent requires individual patient consideration.[86] Case reports describe use of mannitol and hypertonic saline in patients with tuberculous meningitis,[87,88] but no comparative clinical trials exist. Mannitol can promote hypovolaemia (reducing cerebral perfusion pressure) through dehydration, and the osmotic gradient reversal upon stopping mannitol is potentially harmful. Osmotic properties of hypertonic saline mean it is less likely to cross the blood–brain barrier than is mannitol,[86] which reduces the ability of hypertonic saline to exacerbate raised intracranial pressure. Rapid correction of hyponatraemia could result in central pontine myelinolysis, which reduces the ability of and would result in worsening of clinical neurological state.[34]

Hydrocephalus

Differentiation of communicating from non-communicating hydrocephalus is important, yet difficult with conventional brain imaging techniques such as CT and MRI. Air encephalography shows whether intrathecally injected air can pass into the lateral ventricles of the brain,[7] yet is rarely done. Acetazolamide reduces CSF production,[45] and could have value in hydrocephalus treatment, but no recent trials of medical treatment of communicating hydrocephalus, with acetazolamide or other therapy, have been done. Thus, optimal drug therapy for communicating hydrocephalus is unknown.

Urgent neurosurgical intervention relieves high intracranial pressure in non-communicating hydrocephalus, and could be tried for communicating hydrocephalus in cases for which medical therapy is ineffective. The most commonly used surgical procedures are external ventricular drainage (EVD), ETV, and VP shunting, described in detail elsewhere.[89] EVD can temporarily relieve acutely raised CSF pressure in patients who might not require long-term hydrocephalus treatment. ETV is an endoscopic procedure that connects obstructed CSF in the ventricular system to the pre-pontine cistern through a stoma, allowing access to possibly normal CSF absorption areas of the brain.[90] ETV is technically more difficult in patients with acute tuberculous meningitis than in other causes of hydrocephalus because of the increased exudate in the basal cisterns, and outcomes can improve when the procedure is done at a later stage during disease progression.[90]

ETV and VP shunting carry a substantial risk of bleeding and infection,[91] and are only available in specialist centres. An RCT comparing ETV versus VP shunting in 48 children (≤18 years) with hydrocephalus associated with tuberculous meningitis in India showed that ETV was successful in ten (42%) of 24 patients, and VP shunting successful in 13 (54%) of 24 patients.[90] Although no significant difference in success was observed between these two surgical techniques, the timing of the procedure (days of anti-tuberculosis chemotherapy received) must be considered along with procedural success and risks of the procedure after the relevant number of days of antituberculosis treatment. ETV and VP shunting were compared in an observational study of 52 children (<18 years)[91] with hydrocephalus associated with tuberculous meningitis in India. ETV was successful in 17 (65%) of 26 patients and VP shunting successful in 16 (62%) if 26 patients. Unsuccessful cases of both techniques were linked to disease severity, emphasising the challenges of surgically managing severe cases of tuberculous meningitis.[91] An age of younger than 5 years was significantly associated with VP shunt failure.[91] A systematic review of 19 studies including 1038 patients with hydrocephalus associated with tuberculous meningitis concluded that high-quality data in adults for these techniques are scarce.[92] Long-term outcomes in hydrocephalus associated with tuberculous meningitis are worse in individuals with HIV,[93] although better outcomes are suggested in those receiving antiretroviral therapy.[94] Decision making between medical treatment of hydrocephalus, EVD, ETV, and VP shunting remains challenging and controversial.

Conclusions and future research

The management of critically ill patients with tuberculous meningitis is difficult. Conventional triggers for intensive care unit admission (such as reduced Glasgow Coma Scale score) might occur too late in the disease process, and for tuberculous meningitis prognosis quickly worsens once coma develops. Coma is often the result of raised intracranial pressure due to hydrocephalus, infarction, or tuberculoma mass effect.[7] A management priority is to monitor and safely reduce intracranial pressure, preserving brain perfusion while antituberculosis chemotherapy takes effect. The high mortality and morbidity associated with tuberculous meningitis might result from the disease itself, its complications, or its treatment, all of which can contribute to critical illness. Complications (eg, tuberculomas) could be present at diagnosis,[9,30] or develop after beginning antituberculosis chemotherapy.[33] RCTs are required to provide an evidence base for the management of critically ill patients with tuberculous meningitis. The benefit of therapies that are effective in other conditions such as hypertonic saline[22] remain to be proven in patients with tuberculous meningitis. The development of a staircase approach to manage intracranial pressure in patients with tuberculous meningitis, similar to that proposed for those with traumatic brain injury,[22] would be valuable.

Hydrocephalus, hyponatraemia, and supportive management are crucial areas to target for future research. The distinction between communicating and non-communicating hydrocephalus is essential to guide therapy. Future research should investigate the use of air encephalograms to make this distinction, whether this practice is safe, affects therapy, and improves outcomes are other aspects of further investigation. Paediatric studies[90,91] have reported varying success with ETV and VP shunting for treatment of hydrocephalus. RCTs of acetazolamide with or without frusemide in the treatment of communicating hydrocephalus are required. An improved understanding of hyponatraemia's pathophysiology is important to guide care of patients with tuberculous meningitis. The effects on patient outcome of treating hyponatraemia, or further sodium reduction after correction are not known. No evidence supports fluid restriction for syndrome of inappropriate antidiuretic hormone secretion associated with tuberculous meningitis. For individuals receiving hypertonic saline, the optimum saline concentration, total daily dose and volume, and duration of therapy are unknown. Clinical parameters to guide therapy—extracellular or intravascular volume, serum sodium, or other parameters—are uncertain. These could be assessed in future clinical

trials, in which hypertonic saline is administered to volume or sodium targets, and serum sodium, intracranial pressure, and neurological outcome are endpoints. The potential benefit and harm of fludrocortisone was shown in a small study[83] and a larger trial is needed.

Evidence for supportive care specific to patients with tuberculous meningitis is weak. Optimal infection control strategies, nutrition, and pressure area care are unknown, and further study is warranted. Head-of-bed elevation angles should be studied as this practice reduces intracranial pressure and less gastric secretions move into lungs, which can cause ventilator-associated pneumonia. Study endpoints could include pressure area damage (sacral skin and tissue that ulcerates when patients are bedbound for long periods), ventilator-associated pneumonia, and neurological outcomes (neurological disability and mortality). Furthermore, the effect of seizure prophylaxis and thromboprophylaxis upon drug interactions, seizures, venous thromboembolism, and gastrointestinal bleeding needs to be assessed in prospective studies. A supportive tuberculous meningitis care bundle containing supportive strategies to follow and therapies to administer could be created and studied. Ward round checklists specific to patients with tuberculous meningitis could ensure daily review and improvements in all aspects of care.

Anti-inflammatory therapy is widely used in patients with tuberculous meningitis, yet the optimal dose and duration is not known for adults or children.[2,7,8] RCTs of corticosteroid therapy are required for both paradoxical reactions and IRIS to provide strong evidence to support their use in these conditions, and to guide dosing and treatment duration. The optimal dose and duration of corticosteroids in patients with tuberculous meningitis is not known for adults or children. Additionally, the effect of tapering therapy on adrenal function remains unknown.

Mortality prediction in patients with tuberculous meningitis is improving,[5,37] and could identify high-risk individuals requiring intensive monitoring. For example, in a retrospective study of brain infection in a critical care unit, in which 36 (47%) of 76 patients had tuberculous meningitis, duration of hospital stay or mechanical ventilation predicted mortality.[16] Early identification of complications associated with tuberculous meningitis through intensive monitoring can allow earlier therapy and improve outcomes. Non-invasive intracranial pressure monitoring has shown promise as a tool for the identification of raised intracranial pressure in patients with tuberculous meningitis;[58] however, robust evidence that techniques such as optic nerve sheath diameter ultrasound detect raised intracranial pressure earlier, lead to appropriate interventions, and then improve outcomes, is required. A future trial design could compare standard care with care in which optic nerve sheath diameter ultrasound is used. A diameter value over a set threshold would lead to brain imaging followed by appropriate therapy on the basis of imaging findings, with neurological disability and mortality recorded as outcomes. Preliminary research monitoring (such as 18F-fluorodeoxyglucose PET, jugular venous saturation monitoring, and interstitial fluid sampling; appendix) show promise for the future, and further data regarding their role in monitoring of patients with tuberculous meningitis should be collected.

Search strategy and selection criteria

We searched PubMed for human studies published in any language between Jan 1, 2013, and Jan 14, 2019, using the search terms: "neurocritical care" (variations: "neuro critical care", "neurointensive care", "neuro intensive care", "critical care", "intensive care") or "tuberculous meningitis" (variations: "tuberculosis meningitis", "TB meningitis", "TBM"), plus each one of the following search terms: "admission", "clinical trials", "monitoring", "transcranial Doppler ultrasound", "TCD ultrasound", "optic nerve sheath diameter ultrasound", "ONSD ultrasound", "head of bed elevation", "nutrition", "infection control", "anti-tuberculosis chemotherapy", "antitubercular chemotherapy", "antiretroviral therapy", "ART", "corticosteroids", "anti-inflammatory", "aspirin", "sedatives", "anticonvulsants", "hyperthermia", "hypothermia", "seizure", "mechanical ventilation", "tracheostomy", "hyponatraemia", "hyperosmolar therapy", "hypertonic saline", "mannitol", "fludrocortisone", "acetazolamide", "hydrocephalus", "cerebral infarction", "stroke", "cerebrovascular accident", "CVA", "cerebral ischaemia", "tuberculoma", "immune reconstitution inflammatory syndrome", "IRIS", "paradoxical reaction", "HIV co-infection", "brain imaging", "computed tomography", "CT", "magnetic resonance imaging", "MRI", "electroencephalogram", "EEG", "neuromonitoring", "positron emission tomography imaging", "PET imaging", "18F-FDG PET", "jugular venous saturation monitoring", "brain tissue oxygen tension monitoring", "PbtO2", "near infra-red spectroscopy", "biomarkers of brain injury", "intracerebral microdialysis", "transcranial cerebral oximetry", "lumbar puncture", "opening pressure", "severe", "critical", "coma", or "standardisation". A separate search of PubMed was done using the search terms "neurocritical care" (variations: "neuro critical care", "neurointensive care", "neuro intensive care", "critical care", "intensive care") and "tuberculous meningitis" (variations: "tuberculosis meningitis", "TB meningitis", "TBM") only. Relevant references of selected papers were also included. The final list of references was based on relevance to the topics covered in this Review.

Contributors

GET and JD defined the concept and scope of the Review, with discussion with AF and UR. JD did the literature review and wrote the first draft of the manuscript. JD, AF, DI, NHP, UR, and GET reviewed and revised the manuscript drafts and agreed on the final manuscript for submission.

Declaration of interests

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