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Abstract: Tuberculous meningitis (TBM) is the most devastating form of tuberculosis (TB) and often causes critical illness with high mortality. A primary management objective is reducing intracranial pressure (ICP), and optimising cerebral perfusion, whilst killing the bacteria and controlling intra-cerebral inflammation. However, the evidence base guiding the care of critically ill patients with TBM is poor and many patients do not have access to neurocritical care units. Invasive ICP monitoring is often unavailable; whilst new non-invasive monitoring techniques show promise, further evidence for their use is required. Optimal management of neurological complications, and of hyponatraemia, which frequently accompanies TBM, is not known. The best supportive care remains uncertain. Recent advances in the field of TBM predominantly focus upon diagnosis, inflammatory processes and anti-TB chemotherapy. Clinical trials are required to provide robust evidence guiding the most effective supportive, therapeutic and neurosurgical interventions in TBM, with proven benefits for morbidity and mortality.

## The neurocritical care of tuberculous meningitis

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## Abstract

Tuberculous meningitis (TBM) is the most devastating form of tuberculosis (TB) and often causes critical illness with high mortality. A primary management objective is reducing intracranial pressure (ICP), and optimising cerebral perfusion, whilst killing the bacteria and controlling intra-cerebral inflammation. However, the evidence base guiding the care of critically ill patients with TBM is poor and many patients do not have access to neurocritical care units. Invasive ICP monitoring is often unavailable; whilst new non-invasive monitoring techniques show promise, further evidence for their use is required. Optimal management of neurological complications, and of hyponatraemia, which frequently accompanies TBM, is not known. The best supportive care remains uncertain. Recent advances in the field of TBM predominantly focus upon diagnosis, inflammatory processes and anti-TB chemotherapy. Clinical trials are required to provide robust evidence guiding the most effective supportive, therapeutic and neurosurgical interventions in TBM, with proven benefits for morbidity and mortality.

## Search strategy and selection criteria

References for this review were identified by searches of PubMed using the following 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”);

“admission”, “clinical trials”, “monitoring”, “transcranial Doppler ultrasound”, “TCD ultrasound”, “optic nerve sheath diameter ultrasound”, “ONSD ultrasound”, “head of bed elevation”, “nutrition”, “infection control”, “antituberculosis chemotherapy”, “antitubercular chemotherapy”, “antiretroviral therapy”, “ART”, “corticosteroids”, “antiinflammatory”, “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”, “PbtO<sub>2</sub>”, “near infra-red spectroscopy”, “biomarkers of brain injury”, “intracerebral microdialysis”, “transcranial cerebral oximetry”, “lumbar puncture”, “opening pressure”, “severe”, “critical”, “coma”, “standardisation”.

In addition a separate search of PubMed was conducted using the 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.

No language restrictions were applied. The PubMed filter for studies in humans was applied. A separate search using the “clinical trials” filter was also performed. The final list of references was based on relevance to the topic; the neurocritical care management of TBM, as required for this review. Relevant references of selected papers were also included. Only references from 1<sup>st</sup> January 2013 onwards were included. The search was performed on 14<sup>th</sup> January 2019.

## Glossary of abbreviations

ART: antiretroviral therapy; BBB: blood brain barrier; CNS: central nervous system; CSF: cerebrospinal fluid; CSW: cerebral salt wasting; CT: computed tomography; DILI: drug-induced liver injury; ETV: endoscopic third ventriculostomy; EVD: external ventricular drainage; FDG: fluorodeoxyglucose; FLAIR: fluid attenuated inversion recovery; GCS: Glasgow coma score; GFAP: glial fibrillary acidic protein; HIV: human immunodeficiency virus; ICP: intracranial pressure; ICU: intensive care; IRIS: immune reconstitution inflammatory syndrome; LP: lumbar puncture; MRC: Medical Research Council; MRI: magnetic resonance imaging; *Mtb*: *Mycobacterium tuberculosis*; NSE: neuron-specific enolase; ONSD: optic nerve sheath diameter; PbtO2: brain tissue oxygen tension monitoring; PET: positron emission tomography; SIADH: syndrome of inappropriate diuretic hormone secretion; TB: tuberculosis; TBI: traumatic brain injury; TBM: tuberculous meningitis; TCD: transcranial Doppler; VP: ventriculoperitoneal

## Introduction

*Mycobacterium tuberculosis* (*Mtb*) is responsible for approximately 10 million new cases of tuberculosis (TB) annually and 1.3 million deaths.<sup>1</sup> Tuberculous meningitis (TBM) is the most severe form of the disease, killing or severely disabling half of those affected (**panel 1**).<sup>2</sup> Clinical onset of TBM is indolent and diagnosis is challenging.<sup>9</sup> Treatment is lengthy and optimal drug regimens are uncertain. Thick obstructing intracerebral exudates and inflammatory lesions result in raised intracranial pressure (ICP). TBM disproportionately affects children and those with human immunodeficiency virus (HIV) infection.<sup>10</sup>

Recent advances include standardisation of TBM clinical research methods,<sup>11</sup> improved diagnosis,<sup>12</sup> increased understanding of host genetic influence upon intracerebral inflammation and survival,<sup>6,13</sup> and identification of improved first line anti-TB treatment regimens.<sup>14,15</sup> Yet critical illness caused by TBM remains under-researched. No guidelines exist for the management of TBM-associated critical illness and the evidence base for treatment is poor. Studies of critically ill patients with TBM are largely retrospective, observational, and contain small patient numbers,<sup>16–19</sup> with paediatric data especially scarce.<sup>20</sup> Patient outcomes in those admitted to critical care units are extremely poor, with studies predominantly involving adults reporting 40–53% mortality, and neurological disability common in survivors.<sup>16,19</sup> Severe TBM presents specific clinical challenges, in particular the detection and management of raised ICP and brain ischaemia. Further research to optimise supportive care and neurosurgical interventions is required.<sup>21</sup>

Here we review the neurocritical care of TBM of adults and children, discussing causes of critical illness, their management, and the existing evidence base for best practice. Specifically we review the monitoring and management of raised ICP, hydrocephalus, and hyponatraemia, and supportive care strategies aimed at controlling ICP and improving outcomes. We focus on aspects relevant to the neurocritical care of TBM, with general diagnosis and treatment reviewed elsewhere.<sup>8</sup> 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 later complications 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 caused by TBM.

## Causes of critical illness in TBM

### *Raised ICP*

Coma in TBM is associated with raised ICP.<sup>8</sup> ICP >20mmHg is considered abnormal in adults,<sup>22</sup> although pressures have not been correlated with prognosis in TBM, and the true incidence of raised ICP is uncertain. The reduction of cerebral blood flow in the face of raised ICP, after limits of compensatory changes are reached, is an unproven mechanism in TBM. Hydrocephalus results from CSF blockage at either the basal cistern or absorptive arachnoid granulations (communicating), or at the cerebral aqueduct or fourth ventricle outlet (non-communicating),<sup>2,23</sup> and is the commonest cause of raised ICP in TBM.<sup>8</sup> Communicating hydrocephalus causes 70-80% of cases.<sup>2</sup> In two studies of adolescents (>14 years) and adults with TBM in India, 52% (109/209) and 65% (52/80) had baseline images consistent with hydrocephalus.<sup>24,25</sup> Both forms increase ICP and manifest clinically with headache, reduced consciousness and/or focal neurological deficits. Cerebral oedema<sup>8</sup> and tuberculoma formation<sup>26</sup> may elevate ICP in TBM. Massive ischaemic strokes cause brain shift and raise ICP,<sup>27</sup> although such events are not well described in TBM. Seizures,<sup>28</sup> fever, impaired ventilation, and hyponatraemia may also cause or contribute to raised ICP.<sup>8</sup>

### *Cerebral infarction*

Cerebral infarction is the main cause of long term neurological disability in TBM.<sup>8</sup> The exact pathophysiology of TBM-associated cerebral infarction is uncertain, although inflammation and necrosis secondary to surrounding basal exudate are thought to contribute to vessel pathology.<sup>2,29</sup> The lateral and medial lenticulostriate arteries are most frequently affected,<sup>30</sup> with resulting basal ganglia infarcts, although subcortical white matter infarcts have also been described.<sup>31</sup> Vasculitis is common, vasospasm is uncommon, and complete vessel occlusion of major arteries is unusual, but reported.<sup>2,31</sup> Magnetic resonance imaging (MRI) studies in adults with TBM revealed cerebral infarction in 35-67% (40/114 vs. 34/51, respectively) at admission.<sup>29,30</sup> In a systematic review of children with TBM, cerebral infarction affected 27% at admission (6 studies, 843 patients included).<sup>10</sup> Impaired cerebral perfusion leads to ischaemia, infarction and raised ICP.<sup>8</sup> Hemiplegia is the most common clinical consequence of TBM-associated infarction.<sup>2</sup> The range of clinical disease resulting from TBM-cerebral infarction has not been recently studied, and the impact of irreversible neurological disability on feeding, pneumonia, pressure damage and thrombosis is unknown.

### *Tuberculomas*

A tuberculoma is the result of granulomatous inflammation forming space-occupying brain lesions, after metastatic seeding of *Mtb* to the central nervous system (CNS).<sup>26</sup> Tuberculomas are the commonest cause of paradoxical reactions in HIV negative TBM.<sup>32</sup> In a systematic review of children with TBM, tuberculoma affected 11% at admission (7 studies, 1056 patients included),<sup>10</sup> compared with 13% (15/114) in an adult study.<sup>29</sup> Tuberculomas may exert local mass effect on brain tissue, causing compression of cerebral ventricles, leading to headache, vomiting, decreased consciousness, focal neurological signs, and/or seizures.<sup>26</sup> Tuberculomas can have a devastating clinical effect and may result in severe disability.<sup>32</sup>

### **Hyponatraemia**

Hyponatraemia may develop at any time during treatment. Hyponatraemia is classified as profound when sodium falls below 125mmols/L.<sup>33</sup> In one study of adults and children with TBM 45% of 76 individuals had hyponatraemia, with sodium values below 120mmols/L in 11% of individuals.<sup>34</sup> Cerebral salt wasting (CSW) and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) are considered the most likely causes of hyponatraemia in TBM and may overlap,<sup>34</sup> yet the mechanism of hyponatraemia remains poorly understood. In CSW renal sodium loss may be mediated by natriuretic peptides, whereas in SIADH secretion of vasopressin occurs independently of serum osmolality or circulating volume.<sup>33</sup> Diagnosis is confounded as CSW and SIADH definitions vary, and electrolytes and osmolality values are often similar.<sup>34</sup> Hyponatraemia occurs with brain injury,<sup>35</sup> and contributes to raised ICP. It worsens cerebral oedema, with acute sodium changes especially dangerous.<sup>33</sup> Hyponatraemia causes headache and confusion, and when severe, seizures and coma,<sup>33</sup> and predicts increased mortality in HIV co-infected individuals with TBM.<sup>36</sup>

### **Paradoxical reactions**

Paradoxical reactions are when worsening signs and symptoms of TB occur despite effective anti-TB chemotherapy.<sup>37</sup> Commonly considered an exuberant inflammatory response to dead or dying bacteria, their pathogenesis is poorly understood.<sup>37</sup> In a study of 141 patients in India (mean age 30 years), 44 (31%) developed a paradoxical reaction.<sup>38</sup> Paradoxical reactions usually occur after 2-4 months of anti-TB chemotherapy.<sup>32</sup> Paradoxical reactions contribute to critical illness of TBM, with clinical features including headache, altered vision, and seizures.<sup>38</sup> Neuroimaging findings include enhancing basal exudates, new or worsening tuberculomas, and optochiasmatic or spinal arachnoiditis.<sup>38</sup> Paradoxical changes may cause mass effect and obstruct CSF,<sup>32</sup> raising ICP. Clinical spinal disease is often revealed



after commencing anti-TB chemotherapy, with high CSF protein indicating a greater likelihood.<sup>39</sup> Lumbosacral disease is most common,<sup>39</sup> and urinary retention may be the first presenting sign.

## Drugs

Critical illness may result from or be exacerbated by side effects anti-TB chemotherapy and interactions with other drugs (**table 1**). Drug-induced liver injury (DILI) is the most common drug-associated adverse event<sup>11</sup> and may be severe. Drug reactions affecting neurological status may confound monitoring of TBM. Fluoroquinolones<sup>15,42</sup> and isoniazid may increase seizure risk, whilst both isoniazid and fluoroquinolones may cause psychiatric disorders.

## Anti-tuberculosis drug resistance

TB caused by *Mtb* resistance to first-line anti-TB drugs is becoming increasingly common worldwide<sup>1</sup> and increases the risk of treatment failure and death. TBM caused by bacteria resistant to at least rifampicin and isoniazid (multi-drug resistance) is almost always fatal unless second-line drugs are given early.<sup>43</sup> Published rates of multi-drug resistance in TBM range from 4-12%, in Europe<sup>44</sup> and China,<sup>45</sup> respectively. Mono-isoniazid resistance is more common (6%, 9/142 in the European study<sup>44</sup>) and is associated with worse outcomes from TBM, although its impact on treatment response is less than multi-drug resistance.<sup>43</sup> The low sensitivity of current molecular diagnostic tests which can detect *Mtb* and drug resistance (e.g. 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 TBM is extremely challenging.

## Young children and individuals with HIV co-infection

Specific risks apply to young children and those with HIV co-infection. Intracerebral inflammation is increased in HIV co-infected individuals with TBM.<sup>13</sup> Neurological immune reconstitution inflammatory syndrome (IRIS) may develop, presenting as new or worsening neurological signs after the introduction of anti-retroviral therapy (ART).<sup>46</sup> Neurological manifestations of IRIS include meningitis, brain tuberculoma, brain abscess, radiculomyelitis, and spinal epidural abscess.<sup>47</sup> The effect of HIV co-infection on pharmacokinetics of first line anti-TB chemotherapy is uncertain; a systematic review of 27 studies was unable to conclude a clear effect.<sup>48</sup> ART is complicated by rifampicin's induction of cytochrome P450 enzymes,<sup>49</sup> and DILI may be more common in HIV co-infection. Miliary TB<sup>50</sup> and

opportunistic infections in HIV co-infection, may complicate critical illness further. Very young children are highly susceptible to *Mtb*, and may present acutely and deteriorate rapidly.<sup>8</sup> Hydrocephalus is particularly common in children, affecting 86% in a large systematic review of 9 studies and 1088 patients.<sup>10</sup>

## Monitoring critically ill patients with TBM

The continuous monitoring of physiological variables (temperature, respiratory rate, pulse, and blood pressure) is standard of care in critical illness, although may be hard to achieve in resource limited settings. Here, we focus on additional monitoring specific to TBM, summarising the various methods in **table 2**. Monitoring is ordered with the least invasive first. Within the non-invasive techniques the most basic (and most available) are listed first.

### *Clinical assessment and basic bedside monitoring*

Clinical assessment and basic bed side monitoring may be the only available monitoring techniques in some resource-limited settings. GCS is easy to learn, reliable with training, and recognised internationally.<sup>51</sup> In children under 5 years of age, where verbal and motor abilities are less developed, a modified GCS may be more suitable. The use of GCS to monitor treatment response may be confounded by intubation, sedative drugs, and pre-existing neurological conditions.<sup>51</sup> The Medical Research Council (MRC) TBM grade combines GCS and focal neurological signs to categorise disease severity. High TBM grade at presentation predicts mortality regardless of HIV status.<sup>36</sup> Electroencephalogram monitoring is recommended in critically ill individuals with encephalitis who are comatose,<sup>56</sup> although the role of this tool in TBM is unclear.

### *Non-invasive ICP monitoring*

Transcranial Doppler (TCD) ultrasound uses a low frequency transducer, placed on the scalp, to determine cerebral blood flow velocity in the basal arteries of the brain, with ICP possibly inferred from changes in the pulsatility index.<sup>57</sup> TCD has been used to detect vasculopathy in TBM,<sup>52</sup> although its value in quantifying ICP is uncertain given that changes in PaCO<sub>2</sub> or blood pressure may alter blood flow and measured pulsatility index, independently of changes in ICP.<sup>53</sup> A study of 20 South African children suggested pulsatility index could not reliably predict ICP in TBM.<sup>58</sup> TCD is user-dependent and challenging to conduct continuously.

Optic nerve sheath diameter (ONSD) ultrasound represents a potentially quick, easy and safe method for early ICP detection. The optic nerve is surrounded by a dural sheath that distends in its retrobulbar segment under elevated ICP. ONSD appearances can be recorded, and distension measured (**figure 1**). In TBM higher ONSD measurements have been associated with raised ICP.<sup>54</sup> No data yet exists to support the use of ONSD measurement in guiding management, measuring treatment response, or improving outcomes in TBM.

### *Lumbar puncture*

Lumbar puncture (LP) and CSF analysis is essential for TBM diagnosis and may assess treatment response, providing opening pressure as an ICP surrogate, and allowing air encephalography. CSF opening pressure is elevated in approximately half of adult TBM cases,<sup>59</sup> although evidence supporting opening pressure as a predictor of ICP or outcome in TBM is absent. Low pre-treatment leucocyte numbers and CSF glucose concentrations have been associated with death from TBM<sup>6</sup> and glucose rises with successful treatment. However, the value of repeated assessments of CSF opening pressure, glucose, and leucocyte numbers in defining clinical management and prognosis has not been studied.

### *Invasive ICP monitoring devices*

Gold standard ICP monitoring is invasive and can be performed at intraventricular, intraparenchymal, and epidural sites.<sup>55</sup> Haemorrhage and infection are rare risks of intracranial device insertion, and monitors should not be inserted in individuals with coagulopathy or at sites of local infection.<sup>60</sup> Intraventricular access allows CSF drainage, sampling and drug administration.<sup>55</sup> Descriptions of ICP monitoring in TBM are scarce, and whether ICP monitoring dictates therapy 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 a leaky blood brain barrier (BBB).<sup>61</sup> A study of BBB function and CSF biomarkers of CNS injury in 66 adult and child brain infections in Laos found BBB leakage and glial fibrillary acidic protein (GFAP) levels to be higher in adult TBM (n=11) than in other brain infections except bacterial meningitis.<sup>62</sup> An increasing trend of CSF biomarkers of neuronal and glial injury was

associated with worse outcome in a study of 44 paediatric patients with TBM and hydrocephalus in South Africa.<sup>63</sup> Biomarkers represent a potential future method to monitor treatment response and predict outcome, however further research is required to define levels 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 ICP. Baseline imaging may alter immediate management if hydrocephalus is found, and repeat imaging is recommended for patients who deteriorate.<sup>8</sup> No evidence supports routine repeat brain imaging in patients who recover uneventfully from TBM. Brain CT can identify dilated ventricles, mass effects, infarctions, and inflammatory exudates. The detrimental effect of brain irradiation from CT during brain injury is unknown. Brain MRI has no radiation risks and provides greater resolution of *Mtb*-associated brain pathology than CT, although it is expensive, time consuming and may require transfer of a critically ill patient.<sup>64,65</sup> In contrast enhanced fluid attenuated inversion recovery (FLAIR) MRI, removal of CSF enhancement, and that of normal vessels and meninges, may show inflammation and leptomeningeal changes more clearly.<sup>66 67</sup> Retrospective data shows both CT and MRI have a role in detecting TBM-associated complications.<sup>68</sup> In study of 26 adults and children with TBM, magnetic resonance angiography abnormalities were present in 42% (11/26),<sup>69</sup> suggesting a greater future role for this imaging modality in TBM.

### **Management of critically ill patients with TBM**

The section on management of critical illness begins with supportive management, followed by medical and then surgical management. An example of critical illness caused by TBM is shown in **panel 2**.

#### **General patient management**

Supportive care is critical in TBM, yet few data exist to guide management. With control of ICP a priority, supportive care aims to optimise patient position, and parameters such as temperature, haemoglobin, and glucose, and avoid complications of prolonged critical illness. Approach and evidence gaps in the supportive care of TBM are described in **panel 3**. Fever is associated with worse outcomes in severe neurological injury,<sup>71</sup> and an increased 1-year mortality in HIV-uninfected TBM.<sup>6</sup> Cerebral metabolic rate and oxygen demand fall with body temperature.<sup>72</sup> Randomised trials have associated therapeutic

hypothermia with excess mortality in severe bacterial meningitis,<sup>73</sup> and worse functional outcomes in traumatic brain injury (TBI),<sup>74</sup> however no trials have investigated therapeutic hypothermia in TBM.

Raised ICP contributes to poor outcome in TBM. ICP reduction strategies derive from evidence acquired in other causes of brain injury. **Figure 2** summarises potential strategies for optimising ICP and preserving brain perfusion in critically ill individuals with TBM. 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 reduction of CSF production, adjunctive anti-inflammatory therapy, and anti-TB chemotherapy. Sodium management, hyperosmolar therapy and neurosurgical strategies (endoscopic third ventriculostomy [ETV] and ventriculoperitoneal [VP] shunting) are also discussed.

### *Airway protection and respiratory failure*

In two studies, 70% (53/76 adults and children vs. 63/90 adults, respectively) of those admitted to an intensive care unit (ICU) with TBM required mechanical ventilation.<sup>16,19</sup> Optimal ventilation strategies in TBM are unknown. Neuromuscular blockade may allow tighter control of oxygenation, hyperventilation and positive end-expiratory pressure, and limit coughing, with the overall result of avoiding surges of ICP; but no data supports its routine use in TBI,<sup>75</sup> let alone TBM. Hypocarbica and hypercarbica have detrimental effects on cerebral blood flow and ICP.<sup>8</sup> No evidence supports hyperventilation for ICP management in TBM.

### *Anti-tuberculosis chemotherapy*

The anti-TB chemotherapy of TBM has been reviewed elsewhere<sup>8</sup> and only aspects relevant to critically ill patients will be discussed here. Rifampicin, isoniazid, pyrazinamide and ethambutol are recommended first line agents for drug susceptible TB<sup>8</sup> with 9-12 month regimens common for TBM.<sup>2</sup> Prompt treatment and avoidance of therapy interruptions are essential to avoiding deaths from TBM.<sup>8</sup> Optimal drug doses and administration routes are unknown, especially in the critically ill, although there is some evidence that higher rifampicin doses (>10mg/kg) given intravenously may improve outcomes.<sup>14</sup> Severely ill individuals unable to swallow may receive crushed anti-TB medications via an enteral feeding tube yet no data confirming that this approach achieves adequate intracerebral drug concentrations. Intravenous preparations may be preferable, if available, although evidence is scarce and no intravenous pyrazinamide preparation exists. Interruptions to first-line chemotherapy may be necessary if DILI

occurs, although the transaminase thresholds for stopping drugs, and the timing of their reintroductions, have never been defined by randomised trials.

### *Anti-inflammatory treatment*

Adjunctive corticosteroids, given from the start of anti-TB drug treatment, reduce mortality from TBM, at least in the short term.<sup>76</sup> Their benefit in HIV co-infection is uncertain and is the subject of an ongoing randomised controlled trial in Vietnam and Indonesia (NCT03092817).<sup>77</sup> The optimal dose and administration route, and whether prednisolone and dexamethasone are equally effective, is unknown. It is also unclear how corticosteroids should be used after the start of anti-TB drugs in the management of complications causing neurological deterioration and critical illness. Despite minimal evidence, corticosteroids are often used as rescue therapy for raised ICP as they may reduce cerebral oedema. They are often used in the treatment of neurological deterioration caused by expanding brain tuberculomas<sup>32</sup> and for neurological IRIS in HIV co-infected patients, with observational evidence of benefit.<sup>46</sup> Occasionally tuberculomas do not respond to corticosteroids, with persistence or progression of symptoms despite therapy.<sup>8</sup> Case reports and small case series suggest adjunctive thalidomide, infliximab, and interferon-gamma may be effective in this circumstance.<sup>8</sup> There is evidence that adjunctive aspirin, given with dexamethasone, may reduce brain infarcts and improve survival, and phase III trials are planned.<sup>29</sup>

### *Seizure management*

Little published data exists regarding the aetiology and timing of seizures in TBM and their incidence appears to vary substantially between populations. A study of 817 Vietnamese adults with TBM reported seizures in 3% (11/409) receiving standard anti-TB chemotherapy.<sup>15</sup> Seizures were reported in 8% of 515 HIV uninfected, and 13% of 93 HIV co-infected, individuals (age>14 years) with TBM in Indonesia.<sup>6</sup> Conversely, a study of 79 Indian adults with TBM reported seizures in 34%, with abnormal electroencephalogram changes in 85% (17/20).<sup>78</sup> Early-onset seizures were associated with cerebral oedema and meningeal irritation, whereas late onset seizures were associated with hydrocephalus, cerebral infarction, and tuberculomas.<sup>78</sup> Seizure risk may be increased by fluoroquinolone co-administration.<sup>15,42</sup> The optimum treatment of seizures in TBM has not been studied. Therapy is complicated when cytochrome P450 induction and inhibition alters concentrations of drugs metabolised by these enzymes, and levetiracetam may be preferred to prevent interactions with rifampicin.<sup>78</sup>

### *Hyponatraemia and Hyperosmolar therapy*

Hyponatraemia commonly accompanies critical illness caused by TBM, and CSW and SIADH are considered the most likely causes.<sup>34</sup> A trial compared intravenous and oral sodium supplementation with or without fludrocortisone (0.1-0.4mg/day) in the treatment 37 Indian adults with hyponatraemia (<135 mEq/L) caused by TBM-associated CSW.<sup>79</sup> Fludrocortisone was associated with faster correction of plasma sodium (4 vs. 15 days;  $p=0.004$ ), but did not influence survival or disability at 6 months. Fludrocortisone was associated with severe hypokalemia and hypertension in 2 patients, necessitating its discontinuation. In SIADH, clinical practice guidelines recommend fluid restriction as first line treatment,<sup>33</sup> although this approach has not been investigated in TBM. Distinguishing the cause of hyponatraemia in TBM is difficult however,<sup>34</sup> and fluid restriction in a critically ill patient with CSW is potentially dangerous. Assessment of intravascular fluid status may guide therapy, with hypovolaemia expected in CSW and euvolaemia expected in SIADH.<sup>33</sup>

Meta-analyses in TBI suggest mannitol may have a detrimental effect on mortality when compared to hypertonic saline (4 studies),<sup>80</sup> or no benefit of one intervention over the other (6 studies).<sup>81</sup> Hypertonic saline may lower ICP faster, further, and for longer than mannitol; however, the choice of agent requires individual patient considerations.<sup>82</sup> Case reports describe mannitol and hypertonic saline use in TBM<sup>83,84</sup> however no comparative clinical trials exist. Mannitol may promote hypovolaemia (reducing cerebral perfusion pressure) through dehydration, and osmotic gradient reversal upon stopping mannitol is potentially harmful. Osmotic properties of hypertonic saline mean it is less likely to cross the BBB than mannitol.<sup>82</sup> Rapid correction of hyponatraemia may result in central pontine myelinolysis.<sup>33</sup>

### *Hydrocephalus*

Differentiating communicating from non-communicating hydrocephalus is important yet difficult with conventional brain imaging. Air encephalography demonstrates whether intrathecally injected air can pass into the lateral ventricles of the brain,<sup>8</sup> yet is rarely performed. Acetazolamide reduces CSF production,<sup>41</sup> and may have value in hydrocephalus treatment, but no recent trials of medical treatment of communicating hydrocephalus, with acetazolamide or other therapy, have been performed. Optimal drug therapy for communicating hydrocephalus is unknown.

Urgent neurosurgical intervention relieves high ICP in non-communicating hydrocephalus. The most commonly used surgical procedures are external ventricular drainage (EVD), ETV and VP shunting,

described in detail elsewhere.<sup>85</sup> EVD can temporarily relieve acutely raised CSF pressure in patients who may 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.<sup>86</sup> ETV is technically more difficult in acute TBM compared to other causes of hydrocephalus due to the increased exudate in the basal cisterns, and outcomes may improve when performed later in the illness.<sup>86</sup>

ETV and VP shunting carry significant risk,<sup>87</sup> and are only available in specialist centres. A randomised comparison of ETV versus VP shunting in 48 children (age $\leq$ 18 years) with TBM-associated hydrocephalus in India reported ETV was successful in 42% (10/24) cases and VP shunting in 54% (13/24) cases.<sup>86</sup> Success rates of ETV and VP shunting in an observational study of 52 children (age $<$ 18 years) with TBM-associated hydrocephalus, also in India, were 65 and 62% respectively, with failure of both techniques linked to disease severity.<sup>87</sup> Age  $<$ 5 years was significantly associated with VP shunt failure.<sup>87</sup> A systematic review of 19 studies and 1038 patients concluded that there is little high quality data in adults.<sup>88</sup> Long term outcomes in TBM-associated hydrocephalus are worse in HIV co-infected individuals,<sup>89</sup> although better outcomes are suggested in those receiving ART.<sup>90</sup> 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 individuals with TBM is difficult. Conventional triggers for ICU admission may prove too late in TBM, where prognosis worsens quickly once coma develops. Coma is often the result of raised ICP, due to hydrocephalus, infarction, or tuberculoma mass effect. A management priority is to monitor and safely reduce ICP, preserving brain perfusion whilst anti-TB chemotherapy takes effect. The high mortality and morbidity associated with TBM may result from the disease itself, its complications, or its treatment, all of which can contribute to critical illness. Complications may be present at diagnosis, or develop after beginning anti-TB chemotherapy. Randomised controlled clinical trials are urgently required to provide an evidence base for the management of critically ill TBM patients, for whom there is extremely limited evidence to guide management. The benefit of therapies that are effective in other conditions must be proven in TBM, rather than assumed. The development of a staircase approach to raised ICP management in TBM, similar to that proposed<sup>22</sup> for TBI would be



valuable. Hydrocephalus, hyponatraemia and supportive management are critical areas to target for future research.

The distinction between communicating and non-communicating hydrocephalus is vital to guide correct therapy. Future research could study routine use of air encephalograms in making this distinction, whether this practice is safe, affects therapy, and improves outcomes. Paediatric studies<sup>86,87</sup> have reported varying success with ETV and VP shunting. Future trials of acetazolamide with or without frusemide in the treatment of communicating hydrocephalus are required. An improved understanding of hyponatraemia pathophysiology is important to guide future care. The effects on patient outcome of correcting hyponatraemia, or further sodium reduction after correction are not known. No evidence supports fluid restriction for TBM-associated SIADH. 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. Potential future clinical trials could compare hypertonic saline strengths for the treatment of CSW, with serum sodium, ICP and neurological outcome as endpoints. Hypertonic therapy could be administered to a volume target or sodium target. The potential benefit and harm of fludrocortisone was shown in a small study<sup>79</sup> and a larger trial is needed.

Supportive care has almost no evidence base specific to TBM. Optimal infection control strategies, nutrition, and pressure area care are unknown. Head-of-bed elevation angles could be studied, with ventilator-associated pneumonia, pressure damage, and neurological outcomes as endpoints. The effect of seizure prophylaxis and thromboprophylaxis upon drug interactions, seizures, venous thromboembolism and gastrointestinal bleeding could be assessed in prospective studies. A supportive TBM care bundle could be created and studied. Ward round checklists specific to TBM may ensure daily review and improvements in all aspects of care.

Anti-inflammatory therapy is widely used in TBM. Randomised trials of corticosteroid therapy are required for both paradoxical reactions and neurological IRIS. The optimal dosing and duration of corticosteroids in TBM is not known for adults or children, nor is the effect of tapering therapy on adrenal function. Mortality prediction in TBM is improving,<sup>6,36</sup> and may identify high-risk individuals requiring intensive monitoring. In a retrospective study of brain infection in critical care, where 47% (36/76) patients had TBM, duration of hospital stay or mechanical ventilation predicted mortality.<sup>16</sup> Mortality predictors specific to TBM in critical care are required. Early identification of TBM-associated

complications through intensive monitoring may allow earlier therapy and improve outcomes. Non-invasive ICP monitoring has shown promise in TBM,<sup>54</sup> but evidence that techniques such as ONSD detect raised ICP earlier, lead to appropriate interventions, and then improve outcomes is required. A future trial design could compare standard care with care where ONSD ultrasound is utilised, with an ONSD value over a set threshold triggering brain imaging and appropriate therapy based upon imaging findings, with outcome as an endpoint. Preliminary research monitoring (such as 18F-fluorodeoxyglucose [FDG], positron emission tomography [PET], jugular venous saturation monitoring and interstitial fluid sampling) (**appendix 1**) show promise for the future and further data regarding their role in TBM monitoring should be collected.

TBM continues to devastate patients globally, largely through severe neurological complications resulting from uncontrolled inflammation and raised ICP. The neurocritical care of TBM is vastly under researched and future studies are urgently required to further understand and effectively manage this lethal disease.

### **Authors' contributions**

GT and JD defined the concept and scope of the article, with discussion with AJ and UR. JD conducted the literature review and wrote the first draft of the manuscript. JD, AF, DI, NP, UR and GT reviewed and revised the manuscript drafts and agreed on the final manuscript for submission.

### **Conflicts of interest**

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## Panel 1: Pathophysiology

TBM results from the haematogenous dissemination of *Mtb* to the brain, followed by granuloma rupture and bacterial inoculation into the subarachnoid space.<sup>3</sup> An insidious onset of non-specific prodromal symptoms followed by a slowly progressive meningitis makes diagnosis challenging, with a wide differential especially in HIV co-infection.<sup>4</sup> Delayed diagnosis and treatment lead to poor outcomes.<sup>5</sup> Inflammatory pathways are not completely understood. In HIV co-infection, mortality is associated with higher CSF neutrophil counts,<sup>6</sup> yet how neutrophils drive inflammation in TBM is unclear.<sup>7</sup> Intracerebral inflammation is thought to contribute to the poor prognosis associated with TBM.<sup>6</sup> Inflammatory pathways and adjunctive anti-inflammatory therapies have been reviewed elsewhere.<sup>8</sup>

## Panel 2: Case study: Critical illness caused by TBM

A 30 year old male was admitted to hospital with 2-week history of fever, headache and meningism. There was no significant past medical history. GCS was 15, and the only abnormal neurological clinical sign was a right 6<sup>th</sup> cranial nerve palsy. Serum sodium was 117mmol/L and liver function tests were normal. An HIV test was positive, and CD4 count was 17cells/ $\mu$ L. A chest X-ray was normal. CSF analysis revealed 304 WBC (73% neutrophils), protein 2.01g, glucose 0.72mmol/L (paired serum glucose 4.75mmol/L), and lactate 7.7mmol/L. AFB were seen on CSF smear microscopy and a CSF GeneXpert test was negative. CT ([appendix 2, image A](#)) and MRI brain imaging with contrast were normal. A diagnosis of TBM was made and first line oral anti-TB chemotherapy was started (rifampicin, isoniazid, pyrazinamide and ethambutol, at weight appropriate doses). Adjunctive dexamethasone was used, initially at 0.4mg/kg/day, with weekly tapering. Reduced serum osmolality, inappropriately elevated urine osmolality, elevated urinary sodium and hypovolaemia were consistent with CSW and hypertonic saline was administered to correct volume and sodium. ART was not immediately started due to the risk of neurological IRIS.

Two weeks after starting anti-TB chemotherapy the patient's condition had improved. The cranial nerve palsy had resolved, serum sodium had recovered to 130mmols/L with correction of hypovolaemia, and hypertonic saline therapy had been stopped. A decision was made to commence ART (tenofovir, lamivudine and efavirenz). After five days the patient developed a headache and began vomiting. GCS remained at 15. CT brain imaging ([appendix 2, image B](#)) with contrast did not reveal focal lesions although cerebral ventricles had slightly increased in size. After 5 further days the GCS acutely fell to 11 (E3, V3, M5). MRI brain with contrast showed substantially enlarged cerebral ventricles ([appendix 2, image C](#)) with a tuberculoma compressing the fourth ventricle outlet. Anti-TB chemotherapy was administered via NG tube, and high dose intravenous dexamethasone was started. A decision was made in conjunction with the patient's family and neurosurgical team to not proceed with neurosurgical intervention. The following day the GCS fell to 7 and the patient underwent endotracheal intubation and mechanical ventilation. Supportive care and medical therapy were continued. Two days later the patient had a cardiac arrest and died.

AFB: acid-fast bacilli; ART: antiretroviral therapy; CSF: cerebrospinal fluid; CSW: cerebral salt wasting; CT: computed tomography; E: eye opening; GCS: Glasgow coma score; HIV: human immunodeficiency virus;

IRIS: immune reconstitution inflammatory syndrome; M: motor response; MRI: magnetic resonance imaging; NG: nasogastric tube; TB: tuberculosis; TBM: tuberculous meningitis; V: verbal response; WBC: white blood cells

### Panel 3: Approaches and evidence gaps in the supportive care of TBM

Infection control and reducing potential in-hospital <i>Mtb</i> transmission	<ul style="list-style-type: none"> <li>• Respiratory isolation may be required in those with concomitant pulmonary TB.</li> <li>• Respiratory isolation in critical care is challenging when high patient visibility is required.</li> <li>• The effect of endotracheal intubation and a closed ventilation circuit on TB transmission is uncertain, given periodic breaks to this closed circuit to allow suction may induce coughing.</li> </ul>
Head-of-bed elevation to reduce ICP	<ul style="list-style-type: none"> <li>• Elevating the head end of a bed aids venous drainage and shifts CSF extracranially, but may also lower mean arterial pressure</li> <li>• The effect of head-of-bed elevation in TBM has not been studied. An optimal elevation is unknown.</li> </ul>
Maintaining normal glucose concentrations	<ul style="list-style-type: none"> <li>• Hyperglycaemia and hypoglycaemia adversely affect the brain during critical illness, however optimal glucose control is not known.<sup>70</sup></li> </ul>
Treating anaemia to ensure optimal tissue oxygenation	<ul style="list-style-type: none"> <li>• Haemoglobin is important for optimal oxygen delivery in patients at risk of ischaemia, and optimal transfusion thresholds have not been determined in TBM.</li> </ul>
Controlling and reducing fever	<ul style="list-style-type: none"> <li>• It is not known if treating fever in TBM improves outcomes.</li> <li>• No trials describe therapeutic hypothermia in TBM.</li> </ul>
Deep vein thrombosis prevention	<ul style="list-style-type: none"> <li>• The role of deep vein thrombosis prophylaxis in critically ill individuals with TBM, where corticosteroids and aspirin may add to gastrointestinal bleeding risk, has not been studied.</li> <li>• The effect of head-of-bed elevation or general patient positioning in TBM on deep vein thrombosis has not been studied.</li> </ul>
Protecting pressure areas	<ul style="list-style-type: none"> <li>• The effect of head-of-bed elevation or general patient positioning in TBM on pressure area damage has not been studied.</li> </ul>
Ventilator-associated pneumonia prevention	<ul style="list-style-type: none"> <li>• Mechanical ventilation common in critical care TBM (70% in a study by <i>Cantier et al</i>).<sup>19</sup> Almost one quarter of mechanically ventilated TBM patients developed ventilator-associated pneumonia in a study by <i>Misra</i></li> </ul>

	<i>et al.</i> <sup>28</sup> <ul style="list-style-type: none"> <li>• Ventilator-associated pneumonia prevention strategies uncertain in TBM</li> </ul>
Optimising nutrition	<ul style="list-style-type: none"> <li>• TB is a catabolic illness yet no nutritional guideline exists specifically for TBM.</li> <li>• Alternative drug administration routes are considered when an oral route is unavailable in unconscious patients.</li> </ul>

TB: tuberculosis; TBM: tuberculous meningitis

## The neurocritical care of tuberculous meningitis

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## Abstract

Tuberculous meningitis (TBM) is the most devastating form of tuberculosis (TB) and often causes critical illness with high mortality. A primary management objective is reducing intracranial pressure (ICP), and optimising cerebral perfusion, whilst killing the bacteria and controlling intra-cerebral inflammation. However, the evidence base guiding the care of critically ill patients with TBM is poor and many patients do not have access to neurocritical care units. Invasive ICP monitoring is often unavailable; whilst new non-invasive monitoring techniques show promise, further evidence for their use is required. Optimal management of neurological complications, and of hyponatraemia, which frequently accompanies TBM, is not known. The best supportive care remains uncertain. Recent advances in the field of TBM predominantly focus upon diagnosis, inflammatory processes and anti-TB chemotherapy. Clinical trials are required to provide robust evidence guiding the most effective supportive, therapeutic and neurosurgical interventions in TBM, with proven benefits for morbidity and mortality.

## Search strategy and selection criteria

References for this review were identified by searches of PubMed using the following 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”);

“admission”, “clinical trials”, “monitoring”, “transcranial Doppler ultrasound”, “TCD ultrasound”, “optic nerve sheath diameter ultrasound”, “ONSD ultrasound”, “head of bed elevation”, “nutrition”, “infection control”, “antituberculosis chemotherapy”, “antitubercular chemotherapy”, “antiretroviral therapy”, “ART”, “corticosteroids”, “antiinflammatory”, “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”, “standardisation”.

In addition a separate search of PubMed was conducted using the 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.

No language restrictions were applied. The PubMed filter for studies in humans was applied. A separate search using the “clinical trials” filter was also performed. The final list of references was based on relevance to the topic; the neurocritical care management of TBM, as required for this review. Relevant references of selected papers were also included. Only references from 1<sup>st</sup> January 2013 onwards were included. The search was performed on 14<sup>th</sup> January 2019.

## Glossary of abbreviations

ART: antiretroviral therapy; BBB: blood brain barrier; CNS: central nervous system; CSF: cerebrospinal fluid; CSW: cerebral salt wasting; CT: computed tomography; DILI: drug-induced liver injury; ETV: endoscopic third ventriculostomy; EVD: external ventricular drainage; FDG: fluorodeoxyglucose; FLAIR: fluid attenuated inversion recovery; GCS: Glasgow coma score; GFAP: glial fibrillary acidic protein; HIV: human immunodeficiency virus; ICP: intracranial pressure; ICU: intensive care; IRIS: immune reconstitution inflammatory syndrome; LP: lumbar puncture; MRC: Medical Research Council; MRI: magnetic resonance imaging; *Mtb*: *Mycobacterium tuberculosis*; NSE: neuron-specific enolase; ONSD: optic nerve sheath diameter; PbtO2: brain tissue oxygen tension monitoring; PET: positron emission tomography; SIADH: syndrome of inappropriate diuretic hormone secretion; TB: tuberculosis; TBI: traumatic brain injury; TBM: tuberculous meningitis; TCD: transcranial Doppler; VP: ventriculoperitoneal

## Introduction

*Mycobacterium tuberculosis* (*Mtb*) is responsible for approximately 10 million new cases of tuberculosis (TB) annually and 1.3 million deaths.<sup>1</sup> Tuberculous meningitis (TBM) is the most severe form of the disease, killing or severely disabling half of those affected (**panel 1**).<sup>2</sup>

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Clinical onset of TBM is indolent and diagnosis is challenging.<sup>9</sup> Treatment is lengthy and optimal drug regimens are uncertain. Thick obstructing intracerebral exudates and inflammatory lesions result in raised intracranial pressure (ICP). TBM disproportionately affects children and those with human immunodeficiency virus (HIV) infection.<sup>10</sup>

Recent advances include standardisation of TBM clinical research methods,<sup>11</sup> improved diagnosis,<sup>12</sup> increased understanding of host genetic influence upon intracerebral inflammation and survival,<sup>6,13</sup> and identification of improved first line anti-TB treatment regimens.<sup>14,15</sup> Yet critical illness caused by TBM remains under-researched. No guidelines exist for the management of TBM-associated critical illness and the evidence base for treatment is poor. Studies of critically ill patients with TBM are largely retrospective, observational, and contain small patient numbers,<sup>16–19</sup> with paediatric data especially scarce.<sup>20</sup> Patient outcomes in those admitted to critical care units are extremely poor, with studies predominantly involving adults reporting 40–53% mortality, and neurological disability common in survivors.<sup>16,19</sup> Severe TBM presents specific clinical challenges, in particular the detection and management of raised ICP and brain ischaemia. Further research to optimise supportive care and neurosurgical interventions is required.<sup>21</sup>

Here we review the neurocritical care of TBM of adults and children, discussing causes of critical illness, their management, and the existing evidence base for best practice. Specifically we review the monitoring and management of raised ICP, hydrocephalus, and hyponatraemia, and supportive care strategies aimed at controlling ICP and improving outcomes. We focus on aspects relevant to the neurocritical care of TBM, with general diagnosis and treatment reviewed elsewhere.<sup>8</sup> 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 later complications 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 caused by TBM.

## Causes of critical illness in TBM

### *Raised ICP*

Coma in TBM is associated with raised ICP.<sup>8</sup> ICP >20mmHg is considered abnormal in adults,<sup>22</sup> although pressures have not been correlated with prognosis in TBM, and the true incidence of raised ICP is uncertain. The reduction of cerebral blood flow in the face of raised ICP, after limits of compensatory changes are reached, is an unproven mechanism in TBM. Hydrocephalus results from CSF blockage at either the basal cistern or absorptive arachnoid granulations (communicating), or at the cerebral aqueduct or fourth ventricle outlet (non-communicating),<sup>2,23</sup> and is the commonest cause of raised ICP in TBM.<sup>8</sup> Communicating hydrocephalus causes 70-80% of cases.<sup>2</sup> In two studies of adolescents (>14 years) and adults with TBM in India, 52% (109/209) and 65% (52/80) had baseline images consistent with hydrocephalus.<sup>24,25</sup> Both forms increase ICP and manifest clinically with headache, reduced consciousness and/or focal neurological deficits. Cerebral oedema<sup>8</sup> and tuberculoma formation<sup>26</sup> may elevate ICP in TBM. Massive ischaemic strokes cause brain shift and raise ICP,<sup>27</sup> although such events are not well described in TBM. Seizures,<sup>28</sup> fever, impaired ventilation, and hyponatraemia may also cause or contribute to raised ICP.<sup>8</sup>

### *Cerebral infarction*

Cerebral infarction is the main cause of long term neurological disability in TBM.<sup>8</sup> The exact pathophysiology of TBM-associated cerebral infarction is uncertain, although inflammation and necrosis secondary to surrounding basal exudate are thought to contribute to vessel pathology.<sup>2,29</sup> The lateral and medial lenticulostriate arteries are most frequently affected,<sup>30</sup> with resulting basal ganglia infarcts, although subcortical white matter infarcts have also been described.<sup>31</sup> Vasculitis is common, vasospasm is uncommon, and complete vessel occlusion of major arteries is unusual, but reported.<sup>2,31</sup> Magnetic resonance imaging (MRI) studies in adults with TBM revealed cerebral infarction in 35-67% (40/114 vs. 34/51, respectively) at admission.<sup>29,30</sup> In a systematic review of children with TBM, cerebral infarction affected 27% at admission (6 studies, 843 patients included).<sup>10</sup> Impaired cerebral perfusion leads to ischaemia, infarction and raised ICP.<sup>8</sup> Hemiplegia is the most common clinical consequence of TBM-associated infarction.<sup>2</sup> The range of clinical disease resulting from TBM-cerebral infarction has not been

recently studied, and the impact of irreversible neurological disability on feeding, pneumonia, pressure damage and thrombosis is unknown.

### **Tuberculomas**

A tuberculoma is the result of granulomatous inflammation forming space-occupying brain lesions, after metastatic seeding of *Mtb* to the central nervous system (CNS).<sup>26</sup> Tuberculomas are the commonest cause of paradoxical reactions in HIV negative TBM.<sup>32</sup> In a systematic review of children with TBM, tuberculoma affected 11% at admission (7 studies, 1056 patients included),<sup>10</sup> compared with 13% (15/114) in an adult study.<sup>29</sup> Tuberculomas may exert local mass effect on brain tissue, causing compression of cerebral ventricles, leading to headache, vomiting, decreased consciousness, focal neurological signs, and/or seizures.<sup>26</sup> Tuberculomas can have a devastating clinical effect and may result in severe disability.<sup>32</sup>

### **Hyponatraemia**

Hyponatraemia may develop at any time during treatment. Hyponatraemia is classified as profound when sodium falls below 125mmols/L.<sup>33</sup> In one study of adults and children with TBM 45% of 76 individuals had hyponatraemia, with sodium values below 120mmols/L in 11% of individuals.<sup>34</sup> Cerebral salt wasting (CSW) and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) are considered the most likely causes of hyponatraemia in TBM and may overlap;<sup>34</sup> yet the mechanism of hyponatraemia remains poorly understood. In CSW renal sodium loss may be mediated by natriuretic peptides, whereas in SIADH secretion of vasopressin occurs independently of serum osmolality or circulating volume.<sup>33</sup> Diagnosis is confounded as CSW and SIADH definitions vary, and electrolytes and osmolality values are often similar.<sup>34</sup> Hyponatraemia occurs with brain injury,<sup>35</sup> and contributes to raised ICP. It worsens cerebral oedema, with acute sodium changes especially dangerous.<sup>33</sup> Hyponatraemia causes headache and confusion, and when severe, seizures and coma,<sup>33</sup> and predicts increased mortality in HIV co-infected individuals with TBM.<sup>36</sup>

### **Paradoxical reactions**

Paradoxical reactions are when worsening signs and symptoms of TB occur despite effective anti-TB chemotherapy.<sup>37</sup> Commonly considered an exuberant inflammatory response to dead or dying bacteria, their pathogenesis is poorly understood.<sup>37</sup> In a study of 141 patients in India (mean age 30 years), 44

(31%) developed a paradoxical reaction.<sup>38</sup> Paradoxical reactions usually occur after 2-4 months of anti-TB chemotherapy.<sup>32</sup> Paradoxical reactions contribute to critical illness of TBM, with clinical features including headache, altered vision, and seizures.<sup>38</sup> Neuroimaging findings include enhancing basal exudates, new or worsening tuberculomas, and optochiasmatic or spinal arachnoiditis.<sup>38</sup> Paradoxical changes may cause mass effect and obstruct CSF,<sup>32</sup> raising ICP. Clinical spinal disease is often revealed after commencing anti-TB chemotherapy, with high CSF protein indicating a greater likelihood.<sup>39</sup> Lumbosacral disease is most common,<sup>39</sup> and urinary retention may be the first presenting sign.

## Drugs

Critical illness may result from or be exacerbated by side effects anti-TB chemotherapy and interactions with other drugs (table 1).

**Table 1: Drugs commonly used during TBM management**

Drug	Role in TBM	Main adverse drug effect/side effect	Additional drugs affected	Additional side/adverse effects
Rifampicin	First line ATT	–Inducer of cytochrome 3A4 enzyme	–Reduction in serum levels of anti-retroviral therapy including NNRTIs and PIs –Benzodiazepines; substrates for cytochrome 3A4	DILI, hypersensitivity including SJS, renal failure, adrenal insufficiency, haemolysis, cytopenia
Isoniazid	First line ATT	–Inhibitor of cytochrome 3A4	–Phenytoin; higher serum phenytoin levels in slow acetylators <sup>40</sup> –Benzodiazepines; substrates for	DILI, seizures, psychiatric disorders, TEN, SJS, pancreatitis, haemolysis, cytopenia

			cytochrome 3A4	
Pyrazinamide	First line-ATT			DILI, hypersensitivity including urticarial
Ethambutol	First line-ATT	Ocular toxicity difficult to detect in comatose patient		Ocular toxicity, hypersensitivity including SJS, thrombocytopenia, leucopenia, renal failure
Fluoroquinolones (e.g. levofloxacin, moxifloxacin, gatifloxacin)	ATT (second line agents)	–Lowers seizure threshold, demonstrated in higher dose rifampicin plus levofloxacin arm of TBM trial <sup>45</sup>		DILI, seizures, psychiatric disorders, QT prolongation, TEN, SJS, haemolysis, cytopenia, renal failure
Corticosteroids (e.g. dexamethasone)	Adjunctive anti-inflammatory drug	Gastrointestinal bleeding risk higher in critically ill patients	Aspirin; overlapping side effect profile	Adrenal insufficiency on discontinuation, gastrointestinal bleeding, psychosis, infections
Aspirin	Anti-platelet / anti-thrombotic agent	Gastrointestinal bleeding risk higher in critically ill patients	Corticosteroids; overlapping side effect profile	Gastrointestinal bleeding, hypersensitivity reactions
Acetazolamide	–Reduction of CSF production <sup>44</sup>	May cause hyponatraemia in a condition where hyponatremia is common and hazardous	–Overlapping treatment effect profile with fludrocortisone –Increased metabolic acidosis and neurological effects with concomitant aspirin, interactions with anti-convulsants	–Electrolyte imbalance, renal failure –Extensive side effects and drug interactions, covered elsewhere

Critical illness may result from or be exacerbated by side effects anti-TB chemotherapy and interactions with other drugs (table 1).



~~ATT: anti tuberculosis therapy; ART: anti-retroviral therapy; CCR5: C chemokine receptor 5; CSF: cerebrospinal fluid; DILI: drug induced liver injury; INIs: integrase inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors; PIs: protease inhibitors; SJS: Stevens Johnson syndrome; TBM: tuberculous meningitis; TEN: toxic epidermal necrolysis~~

Drug-induced liver injury (DILI) is the most common drug-associated adverse event<sup>11</sup> and may be severe. Drug reactions affecting neurological status may confound monitoring of TBM. Fluoroquinolones<sup>15,42</sup> and isoniazid may increase seizure risk, whilst both isoniazid and fluoroquinolones may cause psychiatric disorders.

### **Anti-tuberculosis drug resistance**

TB caused by *Mtb* resistance to first-line anti-TB drugs is becoming increasingly common worldwide<sup>1</sup> and increases the risk of treatment failure and death. TBM caused by bacteria resistant to at least rifampicin and isoniazid (multi-drug resistance) is almost always fatal unless second-line drugs are given early.<sup>43</sup> Published rates of multi-drug resistance in TBM range from 4-12%, in Europe<sup>44</sup> and China,<sup>45</sup> respectively. Mono-isoniazid resistance is more common (6%, 9/142 in the European study<sup>44</sup>) and is associated with worse outcomes from TBM, although its impact on treatment response is less than multi-drug resistance.<sup>43</sup> The low sensitivity of current molecular diagnostic tests which can detect *Mtb* and drug resistance (e.g. 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 TBM is extremely challenging.

### **Young children and individuals with HIV co-infection**

Specific risks apply to young children and those with HIV co-infection. Intracerebral inflammation is increased in HIV co-infected individuals with TBM.<sup>13</sup> Neurological immune reconstitution inflammatory syndrome (IRIS) may develop, presenting as new or worsening neurological signs after the introduction of anti-retroviral therapy (ART).<sup>46</sup> Neurological manifestations of IRIS include meningitis, brain tuberculoma, brain abscess, radiculomyelitis, and spinal epidural abscess.<sup>47</sup> The effect of HIV co-infection on pharmacokinetics of first line anti-TB chemotherapy is uncertain; a systematic review of 27 studies was unable to conclude a clear effect.<sup>48</sup> ART is complicated by rifampicin's induction of cytochrome P450 enzymes,<sup>49</sup> and DILI may be more common in HIV co-infection. Miliary TB<sup>50</sup> and opportunistic infections in HIV co-infection, may complicate critical illness further. Very young children are highly susceptible to *Mtb*, and may present acutely and deteriorate rapidly.<sup>8</sup> Hydrocephalus is particularly common in children, affecting 86% in a large systematic review of 9 studies and 1088 patients.<sup>10</sup>

### **Monitoring critically ill patients with TBM**

The continuous monitoring of physiological variables (temperature, respiratory rate, pulse, and blood pressure) is standard of care in critical illness, although may be hard to achieve in resource-limited settings. Here, we focus on additional monitoring specific to TBM, summarising the various methods in **table 2**.

**Table 2: The advantages and disadvantages of different methods of intracranial pressure monitoring in TBM**

Monitoring method	Advantages	Disadvantages
<b>Non-invasive:</b> Clinical assessment of GCS	<ul style="list-style-type: none"> <li>Well known internationally, generally reproducible, easy to learn, and effective for regular assessment<sup>54</sup></li> </ul>	<ul style="list-style-type: none"> <li>Broad tool for assessment</li> <li>Unlikely to identify subtle changes in clinical status</li> <li>Influenced by reversible and irreversible factors so sensitivity will change with time</li> <li>Cannot be applied to children of all ages<sup>54</sup></li> </ul>
CT brain imaging	<ul style="list-style-type: none"> <li>Identifies hydrocephalus and large mass lesions</li> <li>Available at most large centres</li> <li>Quick to perform</li> </ul>	<ul style="list-style-type: none"> <li>Role in identifying raised ICP uncertain</li> <li>May not identify subtle changes</li> <li>Often requires contrast</li> <li>Radiation exposure</li> </ul>
MRI brain imaging	<ul style="list-style-type: none"> <li>Likely to identify intracranial cause of neurological deterioration in TBM</li> <li>Good sensitivity for detecting pathological features of TBM</li> <li>Can detect acute infarcts with DWI</li> </ul>	<ul style="list-style-type: none"> <li>Role in identifying raised ICP uncertain</li> <li>Time consuming</li> <li>May be unavailable, or MRI machine may be located off site with patient transfer high risk</li> </ul>

	<ul style="list-style-type: none"> <li>Multiple imaging sequences</li> </ul>	<ul style="list-style-type: none"> <li>May requires anaesthesia in young patients</li> </ul>
Transcranial Doppler ultrasound	<ul style="list-style-type: none"> <li>Use described in the diagnosis and monitoring of TBM vasculopathy<sup>52</sup></li> <li>Safe to perform</li> </ul>	<ul style="list-style-type: none"> <li>Only measures cerebral blood flow in major vessels in Circle of Willis, which may change (via changes in PaCO<sub>2</sub> or mean arterial pressure) independently of ICP<sup>53</sup></li> <li>User dependent</li> <li>Not for continuous use</li> <li>Requires a specific machine</li> </ul>
Optic nerve sheath diameter ultrasound	<ul style="list-style-type: none"> <li>Use in TBM for the detection of raised ICP described in small studies<sup>54</sup></li> <li>Ultrasound machines available at many centres</li> <li>Fast</li> <li>Safe to perform</li> </ul>	<ul style="list-style-type: none"> <li>Requires knowledge of normal population values for comparison</li> <li>Not a continuous monitor</li> <li>Role yet to be defined in management</li> </ul>
<b>Invasive:</b> Lumbar puncture	<ul style="list-style-type: none"> <li>Single non continuous pressure measurement (opening pressure) well recognised and equipment widely available</li> <li>Allows CSF drainage</li> <li>Allows air encephalogram to be performed</li> </ul>	<ul style="list-style-type: none"> <li>Uncertain correlation with ICP</li> <li>Continuous pressure measurement available only at specialist centres</li> </ul>
Intraventricular catheters, intraparenchymal pressure transducers, subarachnoid bolts and epidural transducers	<ul style="list-style-type: none"> <li>Gold standard for ICP monitoring</li> <li>Continuous monitoring</li> <li>Allows rapid detection of ICP changes</li> </ul>	<ul style="list-style-type: none"> <li>Risks of infection and bleeding<sup>55</sup></li> <li>Available only at specialist centres</li> <li>Costly</li> </ul>

	<del>Ventricular catheters allow CSF drainage</del>	
<p><u>The continuous monitoring of physiological variables (temperature, respiratory rate, pulse, and blood pressure) is standard of care in critical illness, although may be hard to achieve in resource limited settings. Here, we focus on additional monitoring specific to TBM, summarising the various methods in <a href="#">table 2</a>.</u></p> <p><del>CSF: cerebrospinal fluid; CT: computed tomography; DWI: diffusion-weighted imaging; GCS: Glasgow coma score; ICP: intracranial pressure; MRI: magnetic resonance imaging; TCD: transcranial Doppler; TBM: tuberculous meningitis</del></p>		

Monitoring is ordered with the least invasive first. Within the non-invasive techniques the most basic (and most available) are listed first.

#### ***Clinical assessment and basic bedside monitoring***

Clinical assessment and basic bed side monitoring may be the only available monitoring techniques in some resource-limited settings. GCS is easy to learn, reliable with training, and recognised internationally.<sup>51</sup> In children under 5 years of age, where verbal and motor abilities are less developed, a modified GCS may be more suitable. The use of GCS to monitor treatment response may be confounded

by intubation, sedative drugs, and pre-existing neurological conditions.<sup>51</sup> The Medical Research Council (MRC) TBM grade combines GCS and focal neurological signs to categorise disease severity. High TBM grade at presentation predicts mortality regardless of HIV status.<sup>36</sup> Electroencephalogram monitoring is recommended in critically ill individuals with encephalitis who are comatose,<sup>56</sup> although the role of this tool in TBM is unclear.

### *Non-invasive ICP monitoring*

Transcranial Doppler (TCD) ultrasound uses a low frequency transducer, placed on the scalp, to determine cerebral blood flow velocity in the basal arteries of the brain, with ICP possibly inferred from changes in the pulsatility index.<sup>57</sup> TCD has been used to detect vasculopathy in TBM,<sup>52</sup> although its value in quantifying ICP is uncertain given that changes in PaCO<sub>2</sub> or blood pressure may alter blood flow and measured pulsatility index, independently of changes in ICP.<sup>53</sup> A study of 20 South African children suggested pulsatility index could not reliably predict ICP in TBM.<sup>58</sup> TCD is user-dependent and challenging to conduct continuously.

Optic nerve sheath diameter (ONSD) ultrasound represents a potentially quick, easy and safe method for early ICP detection. The optic nerve is surrounded by a dural sheath that distends in its retrobulbar segment under elevated ICP. ONSD appearances can be recorded, and distension measured (**figure 1**). In TBM higher ONSD measurements have been associated with raised ICP.<sup>54</sup> No data yet exists to support the use of ONSD measurement in guiding management, measuring treatment response, or improving outcomes in TBM.

### *Lumbar puncture*

Lumbar puncture (LP) and CSF analysis is essential for TBM diagnosis and may assess treatment response, providing opening pressure as an ICP surrogate, and allowing air encephalography. CSF opening pressure is elevated in approximately half of adult TBM cases,<sup>59</sup> although evidence supporting opening pressure as a predictor of ICP or outcome in TBM is absent. Low pre-treatment leucocyte numbers and CSF glucose concentrations have been associated with death from TBM<sup>6</sup> and glucose rises with successful treatment. However, the value of repeated assessments of CSF opening pressure, glucose, and leucocyte numbers in defining clinical management and prognosis has not been studied.

### *Invasive ICP monitoring devices*

Gold standard ICP monitoring is invasive and can be performed at intraventricular, intraparenchymal, and epidural sites.<sup>55</sup> Haemorrhage and infection are rare risks of intracranial device insertion, and monitors should not be inserted in individuals with coagulopathy or at sites of local infection.<sup>60</sup> Intraventricular access allows CSF drainage, sampling and drug administration.<sup>55</sup> Descriptions of ICP monitoring in TBM are scarce, and whether ICP monitoring dictates therapy 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 a leaky blood brain barrier (BBB).<sup>61</sup> A study of BBB function and CSF biomarkers of CNS injury in 66 adult and child brain infections in Laos found BBB leakage and glial fibrillary acidic protein (GFAP) levels to be higher in adult TBM (n=11) than in other brain infections except bacterial meningitis.<sup>62</sup> An increasing trend of CSF biomarkers of neuronal and glial injury was associated with worse outcome in a study of 44 paediatric patients with TBM and hydrocephalus in South Africa.<sup>63</sup> Biomarkers represent a potential future method to monitor treatment response and predict outcome, however further research is required to define levels 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 ICP. Baseline imaging may alter immediate management if hydrocephalus is found, and repeat imaging is recommended for patients who deteriorate.<sup>8</sup> No evidence supports routine repeat brain imaging in patients who recover uneventfully from TBM. Brain CT can identify dilated ventricles, mass effects, infarctions, and inflammatory exudates. The detrimental effect of brain irradiation from CT during brain injury is unknown. Brain MRI has no radiation risks and provides greater resolution of *Mtb*-associated brain pathology than CT, although it is expensive, time consuming and may require transfer of a critically ill patient.<sup>64,65</sup> In contrast enhanced fluid attenuated inversion recovery (FLAIR) MRI, removal of CSF enhancement, and that of normal vessels and meninges, may show inflammation and leptomeningeal changes more clearly.<sup>66 67</sup> Retrospective data shows both CT and MRI have a role in detecting TBM-associated complications.<sup>68</sup> In study of 26 adults and children with TBM, magnetic resonance angiography abnormalities were present in 42% (11/26),<sup>69</sup> suggesting a greater future role for this imaging modality in TBM.

## Management of critically ill patients with TBM

The section on management of critical illness begins with supportive management, followed by medical and then surgical management. An example of critical illness caused by TBM is shown in **panel 32**.

### *General patient management*

Supportive care is critical in TBM, yet few data exist to guide management. With control of ICP a priority, supportive care aims to optimise patient position, and parameters such as temperature, haemoglobin, and glucose, and avoid complications of prolonged critical illness. Approach and evidence gaps in the supportive care of TBM are described in **panel 32**. Fever is associated with worse outcomes in severe neurological injury,<sup>71</sup> and an increased 1-year mortality in HIV-uninfected TBM.<sup>6</sup> Cerebral metabolic rate and oxygen demand fall with body temperature.<sup>72</sup> Randomised trials have associated therapeutic hypothermia with excess mortality in severe bacterial meningitis,<sup>73</sup> and worse functional outcomes in traumatic brain injury (TBI),<sup>74</sup> however no trials have investigated therapeutic hypothermia in TBM.

Raised ICP contributes to poor outcome in TBM. ICP reduction strategies derive from evidence acquired in other causes of brain injury. **Figure 2** summarises potential strategies for optimising ICP and preserving brain perfusion in critically ill individuals with TBM. 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 reduction of CSF production, adjunctive anti-inflammatory therapy, and anti-TB chemotherapy. Sodium management, hyperosmolar therapy and neurosurgical strategies (endoscopic third ventriculostomy [ETV] and ventriculoperitoneal [VP] shunting) are also discussed.

### *Airway protection and respiratory failure*

In two studies, 70% (53/76 adults and children vs. 63/90 adults, respectively) of those admitted to an intensive care unit (ICU) with TBM required mechanical ventilation.<sup>16,19</sup> Optimal ventilation strategies in TBM are unknown. Neuromuscular blockade may allow tighter control of oxygenation, hyperventilation and positive end-expiratory pressure, and limit coughing, with the overall result of avoiding surges of ICP; but no data supports its routine use in TBI,<sup>75</sup> let alone TBM. Hypocarbica and hypercarbia have detrimental effects on cerebral blood flow and ICP.<sup>8</sup> No evidence supports hyperventilation for ICP management in TBM.



### *Anti-tuberculosis chemotherapy*

The anti-TB chemotherapy of TBM has been reviewed elsewhere<sup>8</sup> and only aspects relevant to critically ill patients will be discussed here. Rifampicin, isoniazid, pyrazinamide and ethambutol are recommended first line agents for drug susceptible TB<sup>8</sup> with 9-12 month regimens common for TBM.<sup>2</sup> Prompt treatment and avoidance of therapy interruptions are essential to avoiding deaths from TBM.<sup>8</sup> Optimal drug doses and administration routes are unknown, especially in the critically ill, although there is some evidence that higher rifampicin doses (>10mg/kg) given intravenously may improve outcomes.<sup>14</sup> Severely ill individuals unable to swallow may receive crushed anti-TB medications via an enteral feeding tube yet no data confirming that this approach achieves adequate intracerebral drug concentrations. Intravenous preparations may be preferable, if available, although evidence is scarce and no intravenous pyrazinamide preparation exists. Interruptions to first-line chemotherapy may be necessary if DILI occurs, although the transaminase thresholds for stopping drugs, and the timing of their reintroductions, have never been defined by randomised trials.

### *Anti-inflammatory treatment*

Adjunctive corticosteroids, given from the start of anti-TB drug treatment, reduce mortality from TBM, at least in the short term.<sup>76</sup> Their benefit in HIV co-infection is uncertain and is the subject of an ongoing randomised controlled trial in Vietnam and Indonesia (NCT03092817).<sup>77</sup> The optimal dose and administration route, and whether prednisolone and dexamethasone are equally effective, is unknown. It is also unclear how corticosteroids should be used after the start of anti-TB drugs in the management of complications causing neurological deterioration and critical illness. Despite minimal evidence, corticosteroids are often used as rescue therapy for raised ICP as they may reduce cerebral oedema. They are often used in the treatment of neurological deterioration caused by expanding brain tuberculomas<sup>32</sup> and for neurological IRIS in HIV co-infected patients, with observational evidence of benefit.<sup>46</sup> Occasionally tuberculomas do not respond to corticosteroids, with persistence or progression of symptoms despite therapy.<sup>8</sup> Case reports and small case series suggest adjunctive thalidomide, infliximab, and interferon-gamma may be effective in this circumstance.<sup>8</sup> There is evidence that adjunctive aspirin, given with dexamethasone, may reduce brain infarcts and improve survival, and phase III trials are planned.<sup>29</sup>

### *Seizure management*

Little published data exists regarding the aetiology and timing of seizures in TBM and their incidence appears to vary substantially between populations. A study of 817 Vietnamese adults with TBM reported seizures in 3% (11/409) receiving standard anti-TB chemotherapy.<sup>15</sup> Seizures were reported in 8% of 515 HIV uninfected, and 13% of 93 HIV co-infected, individuals (age>14 years) with TBM in Indonesia.<sup>6</sup> Conversely, a study of 79 Indian adults with TBM reported seizures in 34%, with abnormal electroencephalogram changes in 85% (17/20).<sup>78</sup> Early-onset seizures were associated with cerebral oedema and meningeal irritation, whereas late onset seizures were associated with hydrocephalus, cerebral infarction, and tuberculomas.<sup>78</sup> Seizure risk may be increased by fluoroquinolone co-administration.<sup>15,42</sup> The optimum treatment of seizures in TBM has not been studied. Therapy is complicated when cytochrome P450 induction and inhibition alters concentrations of drugs metabolised by these enzymes, and levetiracetam may be preferred to prevent interactions with rifampicin.<sup>78</sup>

#### ***Hyponatraemia and Hyperosmolar therapy***

Hyponatraemia commonly accompanies critical illness caused by TBM, and CSW and SIADH are considered the most likely causes.<sup>34</sup> A trial compared intravenous and oral sodium supplementation with or without fludrocortisone (0.1-0.4mg/day) in the treatment 37 Indian adults with hyponatraemia (<135 mEq/L) caused by TBM-associated CSW.<sup>79</sup> Fludrocortisone was associated with faster correction of plasma sodium (4 vs. 15 days; p=0.004), but did not influence survival or disability at 6 months. Fludrocortisone was associated with severe hypokalemia and hypertension in 2 patients, necessitating its discontinuation. In SIADH, clinical practice guidelines recommend fluid restriction as first line treatment,<sup>33</sup> although this approach has not been investigated in TBM. Distinguishing the cause of hyponatraemia in TBM is difficult however,<sup>34</sup> and fluid restriction in a critically ill patient with CSW is potentially dangerous. Assessment of intravascular fluid status may guide therapy, with hypovolaemia expected in CSW and euvolaemia expected in SIADH.<sup>33</sup>

Meta-analyses in TBI suggest mannitol may have a detrimental effect on mortality when compared to hypertonic saline (4 studies),<sup>80</sup> or no benefit of one intervention over the other (6 studies).<sup>81</sup> Hypertonic saline may lower ICP faster, further, and for longer than mannitol; however, the choice of agent requires individual patient considerations.<sup>82</sup> Case reports describe mannitol and hypertonic saline use in TBM<sup>83,84</sup> however no comparative clinical trials exist. Mannitol may promote hypovolaemia (reducing cerebral perfusion pressure) through dehydration, and osmotic gradient reversal upon stopping mannitol is

potentially harmful. Osmotic properties of hypertonic saline mean it is less likely to cross the BBB than mannitol.<sup>82</sup> Rapid correction of hyponatraemia may result in central pontine myelinolysis.<sup>33</sup>

### Hydrocephalus

Differentiating communicating from non-communicating hydrocephalus is important yet difficult with conventional brain imaging. Air encephalography demonstrates whether intrathecally injected air can pass into the lateral ventricles of the brain,<sup>8</sup> yet is rarely performed. Acetazolamide reduces CSF production,<sup>41</sup> and may have value in hydrocephalus treatment, but no recent trials of medical treatment of communicating hydrocephalus, with acetazolamide or other therapy, have been performed. Optimal drug therapy for communicating hydrocephalus is unknown.

Urgent neurosurgical intervention relieves high ICP in non-communicating hydrocephalus. The most commonly used surgical procedures are external ventricular drainage (EVD), ETV and VP shunting, described in detail elsewhere.<sup>85</sup> EVD can temporarily relieve acutely raised CSF pressure in patients who may 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.<sup>86</sup> ETV is technically more difficult in acute TBM compared to other causes of hydrocephalus due to the increased exudate in the basal cisterns, and outcomes may improve when performed later in the illness.<sup>86</sup>

ETV and VP shunting carry significant risk,<sup>87</sup> and are only available in specialist centres. A randomised comparison of ETV versus VP shunting in 48 children (age $\leq$ 18 years) with TBM-associated hydrocephalus in India reported ETV was successful in 42% (10/24) cases and VP shunting in 54% (13/24) cases.<sup>86</sup> Success rates of ETV and VP shunting in an observational study of 52 children (age $<$ 18 years) with TBM-associated hydrocephalus, also in India, were 65 and 62% respectively, with failure of both techniques linked to disease severity.<sup>87</sup> Age  $<$ 5 years was significantly associated with VP shunt failure.<sup>87</sup> A systematic review of 19 studies and 1038 patients concluded that there is little high quality data in adults.<sup>88</sup> Long term outcomes in TBM-associated hydrocephalus are worse in HIV co-infected individuals,<sup>89</sup> although better outcomes are suggested in those receiving ART.<sup>90</sup> 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 individuals with TBM is difficult. Conventional triggers for ICU admission may prove too late in TBM, where prognosis worsens quickly once coma develops. Coma is often the result of raised ICP, due to hydrocephalus, infarction, or tuberculoma mass effect. A management priority is to monitor and safely reduce ICP, preserving brain perfusion whilst anti-TB chemotherapy takes effect. The high mortality and morbidity associated with TBM may result from the disease itself, its complications, or its treatment, all of which can contribute to critical illness. Complications may be present at diagnosis, or develop after beginning anti-TB chemotherapy. Randomised controlled clinical trials are urgently required to provide an evidence base for the management of critically ill TBM patients, for whom there is extremely limited evidence to guide management. The benefit of therapies that are effective in other conditions must be proven in TBM, rather than assumed. The development of a staircase approach to raised ICP management in TBM, similar to that proposed<sup>22</sup> for TBI would be valuable. Hydrocephalus, hyponatraemia and supportive management are critical areas to target for future research.

The distinction between communicating and non-communicating hydrocephalus is vital to guide correct therapy. Future research could study routine use of air encephalograms in making this distinction, whether this practice is safe, affects therapy, and improves outcomes. Paediatric studies<sup>86,87</sup> have reported varying success with ETV and VP shunting. Future trials of acetazolamide with or without furosemide in the treatment of communicating hydrocephalus are required. An improved understanding of hyponatraemia pathophysiology is important to guide future care. The effects on patient outcome of correcting hyponatraemia, or further sodium reduction after correction are not known. No evidence supports fluid restriction for TBM-associated SIADH. 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. Potential future clinical trials could compare hypertonic saline strengths for the treatment of CSW, with serum sodium, ICP and neurological outcome as endpoints. Hypertonic therapy could be administered to a volume target or sodium target. The potential benefit and harm of fludrocortisone was shown in a small study<sup>79</sup> and a larger trial is needed.

Supportive care has almost no evidence base specific to TBM. Optimal infection control strategies, nutrition, and pressure area care are unknown. Head-of-bed elevation angles could be studied, with ventilator-associated pneumonia, pressure damage, and neurological outcomes as endpoints. The effect of seizure prophylaxis and thromboprophylaxis upon drug interactions, seizures, venous

thromboembolism and gastrointestinal bleeding could be assessed in prospective studies. A supportive TBM care bundle could be created and studied. Ward round checklists specific to TBM may ensure daily review and improvements in all aspects of care.

Anti-inflammatory therapy is widely used in TBM. Randomised trials of corticosteroid therapy are required for both paradoxical reactions and neurological IRIS. The optimal dosing and duration of corticosteroids in TBM is not known for adults or children, nor is the effect of tapering therapy on adrenal function. Mortality prediction in TBM is improving,<sup>6,36</sup> and may identify high-risk individuals requiring intensive monitoring. In a retrospective study of brain infection in critical care, where 47% (36/76) patients had TBM, duration of hospital stay or mechanical ventilation predicted mortality.<sup>16</sup> Mortality predictors specific to TBM in critical care are required. Early identification of TBM-associated complications through intensive monitoring may allow earlier therapy and improve outcomes. Non-invasive ICP monitoring has shown promise in TBM,<sup>54</sup> but evidence that techniques such as ONSD detect raised ICP earlier, lead to appropriate interventions, and then improve outcomes is required. A future trial design could compare standard care with care where ONSD ultrasound is utilised, with an ONSD value over a set threshold triggering brain imaging and appropriate therapy based upon imaging findings, with outcome as an endpoint. Preliminary research monitoring (such as 18F-fluorodeoxyglucose [FDG], positron emission tomography [PET], jugular venous saturation monitoring and interstitial fluid sampling) (**appendix 1**) show promise for the future and further data regarding their role in TBM monitoring should be collected.

TBM continues to devastate patients globally, largely through severe neurological complications resulting from uncontrolled inflammation and raised ICP. The neurocritical care of TBM is vastly under researched and future studies are urgently required to further understand and effectively manage this lethal disease.

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### Authors' contributions

GT and JD defined the concept and scope of the article, with discussion with AJ and UR. JD conducted the literature review and wrote the first draft of the manuscript. JD, AF, DI, NP, UR and GT reviewed and revised the manuscript drafts and agreed on the final manuscript for submission.

### Conflicts of interest

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### **Panel 1: Pathophysiology**

TBM results from the haematogenous dissemination of *Mtb* to the brain, followed by granuloma rupture and bacterial inoculation into the subarachnoid space.<sup>3</sup> An insidious onset of non-specific prodromal symptoms followed by a slowly progressive meningitis makes diagnosis challenging, with a wide differential especially in HIV co-infection.<sup>4</sup> Delayed diagnosis and treatment lead to poor outcomes.<sup>5</sup> Inflammatory pathways are not completely understood. In HIV co-infection, mortality is associated with higher CSF neutrophil counts,<sup>6</sup> yet how neutrophils drive inflammation in TBM is unclear.<sup>7</sup> Intracerebral inflammation is thought to contribute to the poor prognosis associated with TBM.<sup>6</sup> Inflammatory pathways and adjunctive anti-inflammatory therapies have been reviewed elsewhere.<sup>8</sup>

### **Panel 2: Case study: Critical illness caused by TBM**

A 30 year old male was admitted to hospital with 2-week history of fever, headache and meningism. There was no significant past medical history. GCS was 15, and the only abnormal neurological clinical sign was a right 6<sup>th</sup> cranial nerve palsy. Serum sodium was 117mmol/L and liver function tests were normal. An HIV test was positive, and CD4 count was 17cells/ $\mu$ L. A chest X-ray was normal. CSF analysis revealed 304 WBC (73% neutrophils), protein 2.01g, glucose 0.72mmol/L (paired serum glucose 4.75mmol/L), and lactate 7.7mmol/L. AFB were seen on CSF smear microscopy and a CSF GeneXpert test was negative. CT (appendix 2, image A) and MRI brain imaging with contrast were normal. A diagnosis of TBM was made and first line oral anti-TB chemotherapy was started (rifampicin, isoniazid, pyrazinamide and ethambutol, at weight appropriate doses). Adjunctive dexamethasone was used, initially at 0.4mg/kg/day, with weekly tapering. Reduced serum osmolality, inappropriately elevated urine osmolality, elevated urinary sodium and hypovolaemia were consistent with CSW and hypertonic saline

was administered to correct volume and sodium. ART was not immediately started due to the risk of neurological IRIS.

Two weeks after starting anti-TB chemotherapy the patient's condition had improved. The cranial nerve palsy had resolved, serum sodium had recovered to 130mmols/L with correction of hypovolaemia, and hypertonic saline therapy had been stopped. A decision was made to commence ART (tenofovir, lamivudine and efavirenz). After five days the patient developed a headache and began vomiting. GCS remained at 15. CT brain imaging (appendix 2, image B) with contrast did not reveal focal lesions although cerebral ventricles had slightly increased in size. After 5 further days the GCS acutely fell to 11 (E3, V3, M5). MRI brain with contrast showed substantially enlarged cerebral ventricles (appendix 2, image C) with a tuberculoma compressing the fourth ventricle outlet. Anti-TB chemotherapy was administered via NG tube, and high dose intravenous dexamethasone was started. A decision was made in conjunction with the patient's family and neurosurgical team to not proceed with neurosurgical intervention. The following day the GCS fell to 7 and the patient underwent endotracheal intubation and mechanical ventilation. Supportive care and medical therapy were continued. Two days later the patient had a cardiac arrest and died.

AFB: acid-fast bacilli; ART: antiretroviral therapy; CSF: cerebrospinal fluid; CSW: cerebral salt wasting; CT: computed tomography; E: eye opening; GCS: Glasgow coma score; HIV: human immunodeficiency virus; IRIS: immune reconstitution inflammatory syndrome; M: motor response; MRI: magnetic resonance imaging; NG: nasogastric tube; TB: tuberculosis; TBM: tuberculous meningitis; V: verbal response; WBC: white blood cells



**Panel 3: Approaches and evidence gaps in the supportive care of TBM**

<u>Infection control and reducing potential in-hospital <i>Mtb</i> transmission</u>	<ul style="list-style-type: none"><li>• <u>Respiratory isolation may be required in those with concomitant pulmonary TB.</u></li><li>• <u>Respiratory isolation in critical care is challenging when high patient visibility is required.</u></li><li>• <u>The effect of endotracheal intubation and a closed ventilation circuit on TB transmission is uncertain, given periodic breaks to this closed circuit to allow suction may induce coughing.</u></li></ul>
<u>Head-of-bed elevation to reduce ICP</u>	<ul style="list-style-type: none"><li>• <u>Elevating the head end of a bed aids venous drainage and shifts CSF extracranially, but may also lower mean arterial pressure</u></li><li>• <u>The effect of head-of-bed elevation in TBM has not been studied. An</u></li></ul>

	<u>optimal elevation is unknown.</u>
<u>Maintaining normal glucose concentrations</u>	<ul style="list-style-type: none"> <li>• <u>Hyperglycaemia and hypoglycaemia adversely affect the brain during critical illness, however optimal glucose control is not known.<sup>70</sup></u></li> </ul>
<u>Treating anaemia to ensure optimal tissue oxygenation</u>	<ul style="list-style-type: none"> <li>• <u>Haemoglobin is important for optimal oxygen delivery in patients at risk of ischaemia, and optimal transfusion thresholds have not been determined in TBM.</u></li> </ul>
<u>Controlling and reducing fever</u>	<ul style="list-style-type: none"> <li>• <u>It is not known if treating fever in TBM improves outcomes.</u></li> <li>• <u>No trials describe therapeutic hypothermia in TBM.</u></li> </ul>
<u>Deep vein thrombosis prevention</u>	<ul style="list-style-type: none"> <li>• <u>The role of deep vein thrombosis prophylaxis in critically ill individuals with TBM, where corticosteroids and aspirin may add to gastrointestinal bleeding risk, has not been studied.</u></li> <li>• <u>The effect of head-of-bed elevation or general patient positioning in TBM on deep vein thrombosis has not been studied.</u></li> </ul>
<u>Protecting pressure areas</u>	<ul style="list-style-type: none"> <li>• <u>The effect of head-of-bed elevation or general patient positioning in TBM on pressure area damage has not been studied.</u></li> </ul>
<u>Ventilator-associated pneumonia prevention</u>	<ul style="list-style-type: none"> <li>• <u>Mechanical ventilation common in critical care TBM (70% in a study by Cantier et al).<sup>19</sup> Almost one quarter of mechanically ventilated TBM patients developed ventilator-associated pneumonia in a study by Misra et al.<sup>28</sup></u></li> <li>• <u>Ventilator-associated pneumonia prevention strategies uncertain in TBM</u></li> </ul>
<u>Optimising nutrition</u>	<ul style="list-style-type: none"> <li>• <u>TB is a catabolic illness yet no nutritional guideline exists specifically for TBM.</u></li> <li>• <u>Alternative drug administration routes are considered when an oral route is unavailable in unconscious patients.</u></li> </ul>

TB: tuberculosis; TBM: tuberculous meningitis

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#### neurological IRIS:

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Dear Dr Wulff,

Thank you for re-reviewing our manuscript 'The neurocritical care of tuberculous meningitis'. Please find our point by point responses to editorial comments.

Editorial points

1) I have slightly amended your submitted clean version of the manuscript (eg, added the sentences on the order of the sections, removed alternative corresponding author as we can only have one, and added/moved the reference to the panels (eg, panel 1 wasn't referred in the text at all); please use this version. I will follow up this message with the latest Word doc.

**Thank you**

2) We can't have three different reference lists, please merge into one (ie, the reference list in the main list). References need to be numbered in the order in which they first appear in the manuscript. If the references "move" from the body text into tables or figures, please maintain the sequence of citation. Please ensure tables and figures are cited correctly in the body text to prevent the need for renumbering of references should the table and figure citations subsequently move.

**We have done this**

3) Please ensure the order of references is also maintained in the panels; that's not the case currently.

**We have done this**

4) Please remove all references from the "electronic Medicines Compendium (eMC)" as this information on side effects is publicly available. and thus doesn't need to be cited.

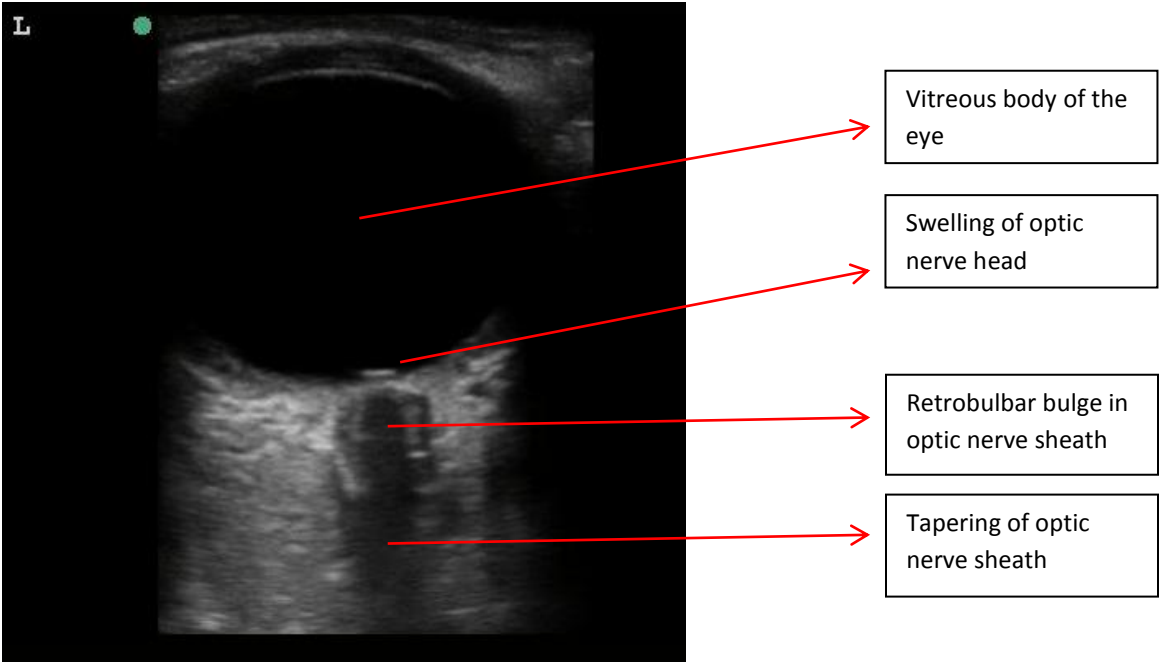
**We have done this**

5) Figure 2: please add the description for the illustrator to the figure legend. Be prepared for additional questions after post-acceptance.

**We have done this**

Figure 1: Images showing the use of optic nerve sheath diameter ultrasound in TBM in critical care

A:



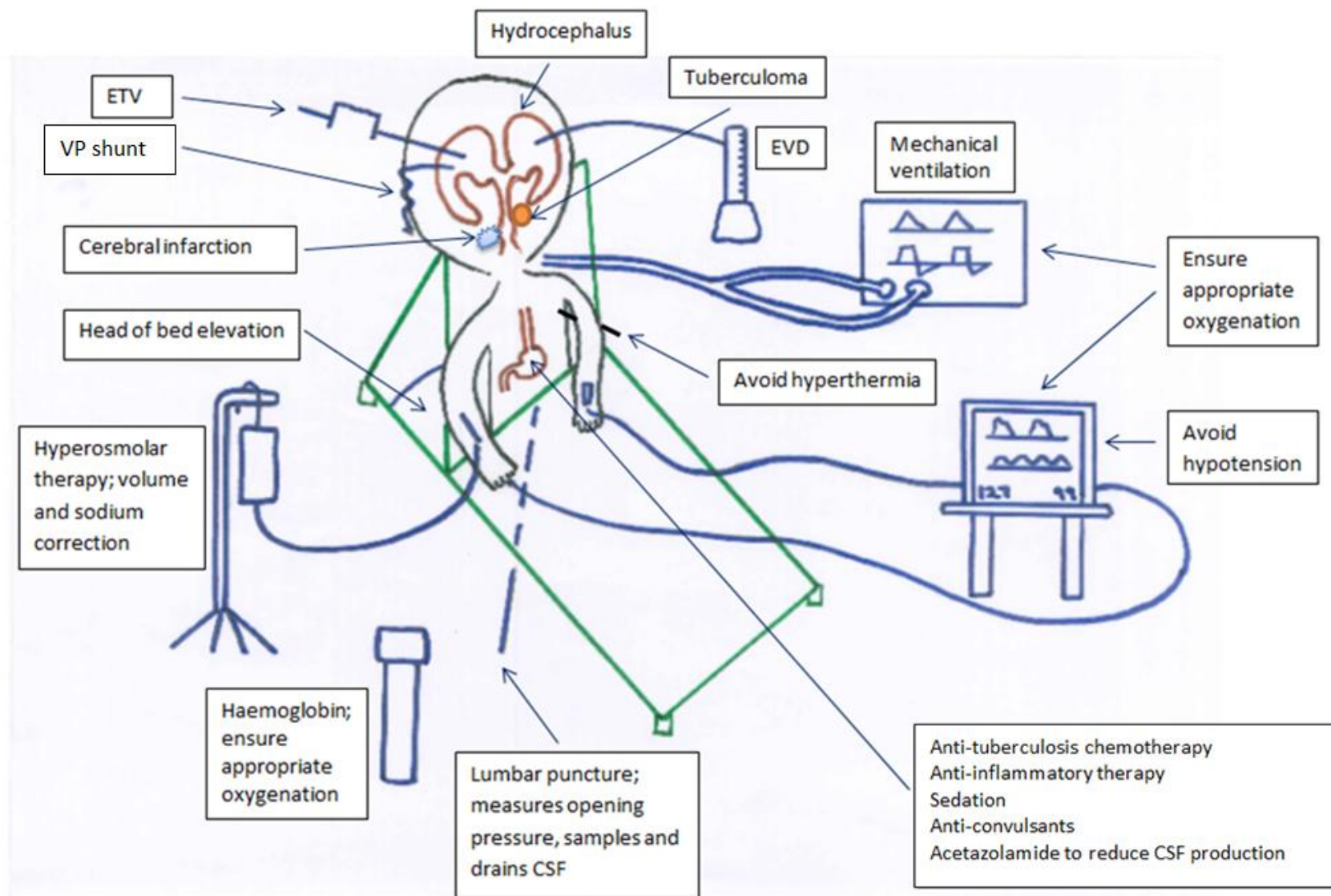
B:





Optic nerve sheath (ONS) ultrasound represents a simple, non-invasive tool which shows potential to screen individuals with TBM for raised ICP.<sup>53</sup> **A:** ONS ultrasound image of the left eye from a patient with grade 2 tuberculous meningitis (TBM) and raised intracranial pressure (ICP). This image was taken at presentation, on the first day of anti-tuberculosis (TB) chemotherapy. At the posterior aspect of the globe, a short narrow horizontal line (labelled) represents swelling of the head of the optic nerve. Retrobulbar distension of the ONS can be seen, with a subsequent tapering of the ONS proximally. **B:** Identical image to image A with the addition of measuring calipers, showing retrobulbar distension of the ONS measured at 0.3cm from the posterior aspect of the globe of the eye (A-A calipers), and the diameter of the ONS (caliper B, diameter 0.54cm).

**Figure 2: Potential strategies for avoiding and reducing high ICP, and preserving brain perfusion and oxygenation, in critically ill individuals with TBM**



CSF: cerebrospinal fluid; ETV: endoscopic third ventriculostomy; EVD: external ventricular drainage; ICP: intracranial pressure; TB: tuberculosis; TBM: tuberculous meningitis; VP: ventriculoperitoneal

### **Description for illustrators:**

This figure represents a patient with TBM who is sat in bed. The head has been deliberately made to appear larger in order to allow the contents/pathology within the brain to be described.

Regarding the equipment: Inside the brain we have drawn the cerebral ventricles which contain fluid. ETV, VP shunt and EVD all insert tubes into this fluid space. ETV is labelling a hand held drill which makes a hole in the skull. This looks like a 'Hudson-Brace drill' in the case of the diagram. The VP shunt shows a 'ventriculoperitoneal catheter' which comes out of a hole in the skull and then lies under the skin. In real life it travels all the way to the abdomen but in the diagram we have ended it near the head, but left an 'arrow head' pointing down to indicate it continues.

Hyperosmolar therapy: This represents a drip stand with a fluid bag (for example saline) hanging from a hook of the stand. An 'intravenous infusion line' connects the bag to a venous cannula in the patient's right forearm.

Haemoglobin: This represents a blood tube, in which blood will be collected to be tested for a 'full blood count'. This tube can be drawn with or without blood in, whichever is easiest.

Lumbar puncture: This represents a procedure where a 'lumbar puncture needle' is inserted into the patient's lower back. Given the figure is facing forward this cannot be seen however we have drawn a dotted line which travels up to patient's midline in the middle of the bed, and shows where the needle would go. We think that drawing a 'lumbar puncture needle' at the position where our dotted line meets the arrow coming from the lumbar puncture text box would work well (alternatively it can be left as we have drawn), plus the dotted line to show where the needle should enter the body.

EVD: This is an 'external ventricular drain', which essentially consists of a collection bag of fluid (at the bottom) and a collection system. The EVD needs to be drawn quite high (at least at the level of the patient's head). Any lower on the diagram and it would look out of place as clinically it cannot be sited too low.

Mechanical ventilation: The box is a 'mechanical ventilator'. Two tubes from this machine merge to a single line tube (as in the diagram) and then connect to the patient's mouth or neck. To avoid the diagram being too crowded at the mouth we did not draw the connection all the way to the mouth but left it just short.

The other box (sat on a table) is a 'patient monitor'. The line coming out its right side (next to '99') is an oxygen saturation probe which clips onto the end of one of the patient's fingers. The line from the left of the machine (next to the '129') connects to a tube in the artery of the left wrist. This is an 'arterial line'. The 99 is the oxygen number, and the 129 is the heart rate (pulse).

Different colours can be used for descriptive labels (Hydrocephalus, Cerebral infarction Tuberculoma), and for potential interventions and strategies (ETV, VP shunt, head of bed elevation, hyperosmolar therapy, lumbar puncture, all contents of the large box in the lower right corner, mechanical ventilation, ensure appropriate oxygenation[both occasions], avoid hypotension, avoid hyperthermia).

Please let us know if any of this is not clear.

Table 1: Drugs commonly used during TBM management

Drug	Role in TBM	Main adverse drug effect/side-effect	Additional drugs affected	Additional side/adverse effects
Rifampicin	First line ATT	- Inducer of cytochrome 3A4 enzyme	- Reduction in serum levels of anti-retroviral therapy including NNRTIs and PIs - Benzodiazepines; substrates for cytochrome 3A4	DILI, hypersensitivity including SJS, renal failure, adrenal insufficiency, haemolysis, cytopenia
Isoniazid	First line ATT	- Inhibitor of cytochrome 3A4	- Phenytoin; higher serum phenytoin levels in slow acetylators <sup>40</sup> - Benzodiazepines; substrates for cytochrome 3A4	DILI, seizures, psychiatric disorders, TEN, SJS, pancreatitis, haemolysis, cytopenia
Pyrazinamide	First line ATT			DILI, hypersensitivity including urticarial
Ethambutol	First line ATT	Ocular toxicity difficult to detect in comatose patient		Ocular toxicity, hypersensitivity including SJS, thrombocytopenia, leucopenia, renal failure
Fluoroquinolones (e.g. levofloxacin, moxifloxacin, gatifloxacin)	ATT (second line agents)	- Lowers seizure threshold, demonstrated in higher dose rifampicin plus levofloxacin arm of TBM trial <sup>15</sup>		DILI, seizures, psychiatric disorders, QT prolongation, TEN, SJS, haemolysis, cytopenia, renal failure
Corticosteroids (e.g. dexamethasone)	Adjunctive anti-inflammatory drug	Gastrointestinal bleeding risk higher in critically ill patients	Aspirin; overlapping side effect profile	Adrenal insufficiency on discontinuation, gastrointestinal bleeding,

				psychosis, infections
Aspirin	Anti-platelet / anti-thrombotic agent	Gastrointestinal bleeding risk higher in critically ill patients	Corticosteroids; overlapping side effect profile	Gastrointestinal bleeding, hypersensitivity reactions
Acetazolamide	- Reduction of CSF production <sup>41</sup>	May cause hyponatraemia in a condition where hyponatremia is common and hazardous	- Overlapping treatment effect profile with fludrocortisone - Increased metabolic acidosis and neurological effects with concomitant aspirin, interactions with anti-convulsants	- Electrolyte imbalance, renal failure - Extensive side effects and drug interactions, covered elsewhere

ATT: anti-tuberculosis therapy; ART: anti-retroviral therapy; CCR5: C chemokine receptor 5; CSF: cerebrospinal fluid; DILI: drug induced liver injury; INIs: integrase inhibitors; NNRTIs: non-nucleoside reverse transcriptase inhibitors; PIs: protease inhibitors; SJS: Stevens-Johnson syndrome; TBM: tuberculous meningitis; TEN: toxic epidermal necrolysis

**Table 2: The advantages and disadvantages of different methods of intracranial pressure monitoring in TBM**

Monitoring method	Advantages	Disadvantages
<b>Non-invasive:</b> Clinical assessment of GCS	<ul style="list-style-type: none"> <li>- Well known internationally, generally reproducible, easy to learn, and effective for regular assessment<sup>51</sup></li> </ul>	<ul style="list-style-type: none"> <li>- Broad tool for assessment</li> <li>- Unlikely to identify subtle changes in clinical status</li> <li>- Influenced by reversible and irreversible factors so sensitivity will change with time</li> <li>- Cannot be applied to children of all ages<sup>51</sup></li> </ul>
CT brain imaging	<ul style="list-style-type: none"> <li>- Identifies hydrocephalus and large mass lesions</li> <li>- Available at most large centres</li> <li>- Quick to perform</li> </ul>	<ul style="list-style-type: none"> <li>- Role in identifying raised ICP uncertain</li> <li>- May not identify subtle changes</li> <li>- Often requires contrast</li> <li>- Radiation exposure</li> </ul>
MRI brain imaging	<ul style="list-style-type: none"> <li>- Likely to identify intracranial cause of neurological deterioration in TBM</li> <li>- Good sensitivity for detecting pathological features of TBM</li> <li>- Can detect acute infarcts with DWI</li> <li>- Multiple imaging sequences</li> </ul>	<ul style="list-style-type: none"> <li>- Role in identifying raised ICP uncertain</li> <li>- Time consuming</li> <li>- May be unavailable, or MRI machine may be located off site with patient transfer high risk</li> <li>- May requires anaesthesia in young patients</li> </ul>
Transcranial Doppler ultrasound	<ul style="list-style-type: none"> <li>- Use described in the diagnosis and monitoring of TBM vasculopathy<sup>52</sup></li> <li>- Safe to perform</li> </ul>	<ul style="list-style-type: none"> <li>- Only measures cerebral blood flow in major vessels in Circle of Willis, which may change (via changes in</li> </ul>

		<p>PaCO<sub>2</sub> or mean arterial pressure) independently of ICP<sup>53</sup></p> <ul style="list-style-type: none"> <li>- User dependent</li> <li>- Not for continuous use</li> <li>- Requires a specific machine</li> </ul>
Optic nerve sheath diameter ultrasound	<ul style="list-style-type: none"> <li>- Use in TBM for the detection of raised ICP described in small studies<sup>54</sup></li> <li>- Ultrasound machines available at many centres</li> <li>- Fast</li> <li>- Safe to perform</li> </ul>	<ul style="list-style-type: none"> <li>- Requires knowledge of normal population values for comparison</li> <li>- Not a continuous monitor</li> <li>- Role yet to be defined in management</li> </ul>
<b>Invasive :</b> Lumbar puncture	<ul style="list-style-type: none"> <li>- Single non-continuous pressure measurement (opening pressure) well recognised and equipment widely available</li> <li>- Allows CSF drainage</li> <li>- Allows air encephalogram to be performed</li> </ul>	<ul style="list-style-type: none"> <li>- Uncertain correlation with ICP</li> <li>- Continuous pressure measurement available only at specialist centres</li> </ul>
Intraventricular catheters, intraparenchymal pressure transducers, subarachnoid bolts and epidural transducers	<ul style="list-style-type: none"> <li>- Gold standard for ICP monitoring</li> <li>- Continuous monitoring</li> <li>- Allows rapid detection of ICP changes</li> <li>- Ventricular catheters allow CSF drainage</li> </ul>	<ul style="list-style-type: none"> <li>- Risks of infection and bleeding<sup>55</sup></li> <li>- Available only at specialist centres</li> <li>- Costly</li> </ul>

CSF: cerebrospinal fluid; CT: computed tomography; DWI: diffusion weighted imaging; GCS: Glasgow coma score; ICP: intracranial pressure; MRI: magnetic resonance imaging; TCD: transcranial Doppler; TBM: tuberculous meningitis



## Appendix

### *Appendix 1 - Preliminary research monitoring techniques*

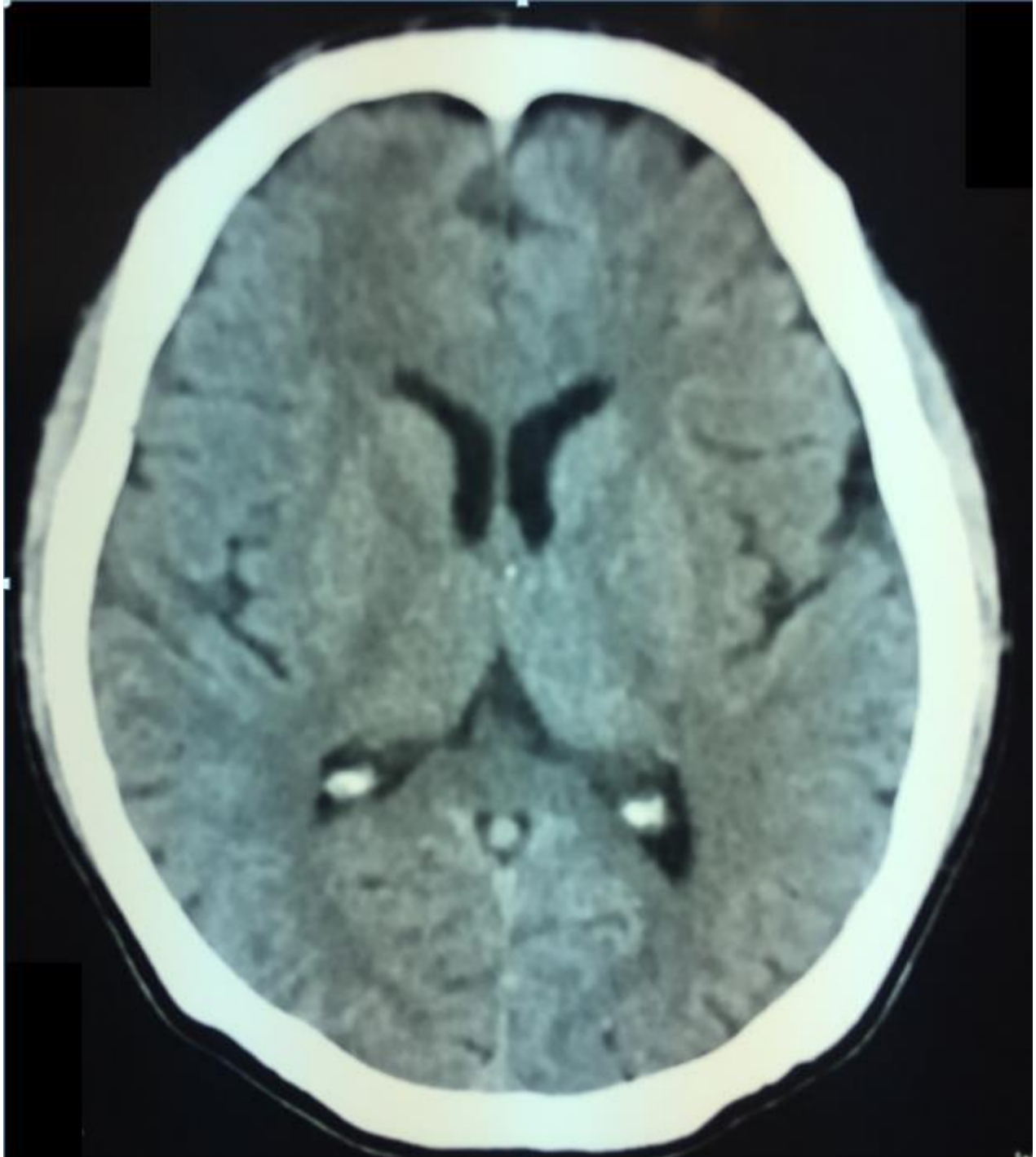
18F-FDG PET may have a role in the detection of brain lesions in TBM,<sup>91</sup> however, this is not commonly available. There are few descriptions of the use of 18F-FDG PET in TBM. In ten individuals with definite TBM (age range 14-55 years), 18F-FDG PET correlated with MRI brain imaging in six cases, revealed additional lesions in one case, and did not detect MRI-detected lesions in three cases.<sup>91</sup>

Measurement of brain oxygenation is an important adjunct to monitoring for individuals with brain injury. Jugular venous saturation monitoring measures the saturation of the venous blood returning to the heart, whereas PbtO<sub>2</sub> offers direct recordings, albeit of a small region of the brain. PbtO<sub>2</sub> correlates with outcome in brain injury, and its use allows ICP targets to be viewed in conjunction with their effect on PbtO<sub>2</sub>.<sup>92</sup>

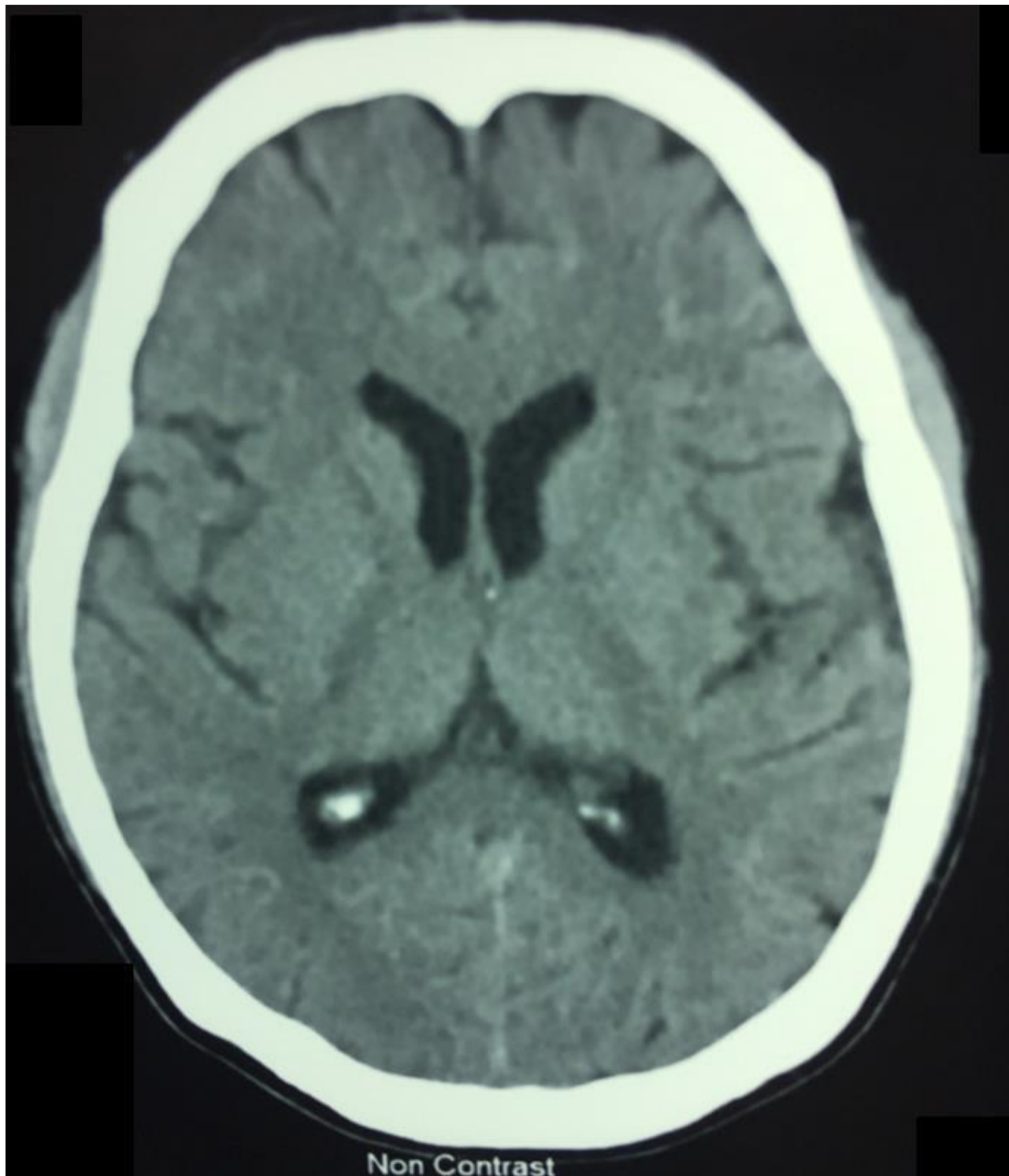
Interstitial fluid sampling via intracerebral microdialysis has been demonstrated in paediatric TBI for the analysis of morphine concentrations,<sup>93</sup> and in theory this technique could be used to measure the CNS delivery of other drugs. No studies describe intracerebral microdialysis in TBM; however the prospect of measuring interstitial drug levels, particularly those of rifampicin, is enticing.

*Appendix 2 – Images from panel 1 (Critical illness caused by TBM: an example)*

**A:** Non-contrast brain CT image taken at baseline showing normal cerebral ventricular size.



**B:** Non-contrast brain CT image taken after worsening of headache and development of vomiting.



C: Brain MRI (T1 weighted, fluid attenuated inversion recovery [FLAIR]) image taken after fall in GCS.

