

International Survey Reveals Opportunities to Improve Tuberculous Meningitis Management and the Need for Standardized Guidelines

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Background. Tuberculous meningitis (TBM) is a medical emergency, yet there are no standardized treatment guidelines for the medical or neurosurgical management of these patients and little data on neurocritical care. We conducted an international survey to understand current medical and neurosurgical TBM management and resource availability to provide baseline data needed for future multicenter trials addressing unanswered clinical research questions and the establishment of standardized guidelines.

Methods. An online survey of 77 questions covering medical and neurosurgical TBM management aimed at clinicians/nurses treating TBM was distributed as an anonymous link through email invitation, international organizations' membership distribution, and direct links on organizational webpages or social media. The survey remained open for 5 months. Data were summarized with frequencies and percentages.

Results. The survey had 222 responses from 43 countries representing 6 continents. Most respondents were from tertiary care facilities, with broad access to medical and neurosurgical resources. There was significant heterogeneity in general supportive care, and TBM-specific management demonstrated considerable divergence from current standard-of-care practices. The lack of standardized guidelines was identified as a major challenge in TBM management. General and neurocritical care were largely absent. Resources for bedside supportive care and noninvasive monitoring were broadly accessible.

Conclusions. These findings suggest that current TBM management could be improved by the establishment of internationally accepted treatment guidelines based on available evidence, and that numerous centers have resources available to participate in future multicenter trials, even for basic interventions, that may further improve patient outcomes globally.

Keywords. international guidelines; neurocritical care; neurosurgery; survey; tuberculous meningitis.

Tuberculous meningitis (TBM) is the most fatal form of tuberculosis (TB) in adult and pediatric patients [1]. Treatment largely focuses on pharmacological intervention, including antibiotics and host-directed therapies. However, patient

outcomes remain poor and treatment regimens are heterogeneous in terms of duration, dosing, and drugs used [2–7]. The treatment of TBM-associated hydrocephalus is also variable with some centers tailoring treatment based on whether the hydrocephalus is communicating, whereas others use surgical intervention uniformly [8, 9]. The evidence base to establish standardized medical and neurosurgical treatment guidelines is limited, and more work is required to establish comprehensive international guidelines.

Little to no investigation into supportive medical management and neurocritical care strategies has been conducted for TBM, despite evidence of ongoing brain injury in patients receiving antibiotic and steroid therapy [10]. Research from other forms of brain injury demonstrates the benefit of neurocritical care to patient outcome [11]. Critical care involves monitoring

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and responding to systemic variables (ie, temperature, nutrition, blood pressure) and cerebral variables (ie, intracranial pressure [ICP] and brain oxygenation), which can affect outcomes [12, 13]. Application of similar critical care measures in TBM could potentially improve outcome, and warrant investigation [14].

We conducted a survey of the current medical and neurosurgical measures available and used internationally. The aim was to establish what practices are currently being used, the degree of heterogeneity thereof, and the availability of resources. To date, this information has not been gathered on a global scale and would be valuable for the establishment of evidence-based guidelines for the acute medical and neurosurgical management of TBM through future multicenter research.

Participant Consent Statement

The survey began with written informed consent, and participants had to electronically indicate their willingness to participate. This survey was approved by the Johns Hopkins Medicine Institutional Review Board (IRB00152756) and the University of Cape Town Scientific and Human Research Ethics Committees (HREC 683/2017).

METHODS

The survey themes and questions were developed based on current management strategies in TBM and piloted by a group within the Tuberculous Meningitis International Research Consortium. The survey was compiled in English using the Qualtrics program (<https://login.qualtrics.com/login>) and was translated into Chinese by collaborators. The survey included 76 questions in 12 sections; the first 2 sections covered demographics and resources, which enabled skip logic to show the participant only questions relevant to their resources. The remaining sections focused on acute medical and neurosurgical management in the first 2 weeks of presentation, including general questions, neuroimaging, laboratory acquisition, and management of hydrocephalus, hyponatremia, oxygenation/ventilation, temperature, nutrition, hemoglobin, blood pressure, and pharmaceuticals. Most questions were closed-ended but allowed participants to “check all that apply.” There were 4 open-ended questions to allow respondents to enter their location and to comment on topics not addressed by previous questions. Open-ended questions were analyzed using qualitative directed content analysis to generate themes, and grouping was reached by consensus by 2 principal investigators [15]. The complete survey can be found in the [Supplementary Material \(Supplementary Text S1\)](#).

Distribution of the survey began on May 1, 2018 and involved a combination of individual email invitations, international organizations’ membership distribution, and direct links on organizational webpages or social media (ie, Twitter) via an anonymous link. The international organizations included the World Federation of Pediatric Intensive and Critical Care

Societies (WFPICCS), World Federation Neurosurgery Society (WFNS), Pediatric Acute Lung Injury and Sepsis Investigators (PALISI)’s Global Health subgroup, International Society for Pediatric Neurosurgery (ISPN), Pediatric Neurocritical Care Research Group (PNCRG), Society of Neurosurgeons of South Africa (SNSA), German Society of Tropical Paediatrics and International Child Health (GTP), American Academy of Pediatrics’ Section on International Child Health (AAP SOICH), Pakistan Neurology Society (PNS), World Federation of Societies of Intensive and Critical Care Medicine (WFICC), and International Child Neurology Association (ICNA). Some authors were also survey respondents. The survey was closed on October 2, 2018.

Data were analyzed using IBM SPSS Statistics (IBM Corporation, Armonk, NY), and figures were made with CorelDRAW (Corel Corporation, Ottawa, CA). Respondent answers were summarized with frequencies and percentages for categorical variables. Partial responses were analyzed if $\geq 75\%$ of questions were completed, but only surveys that were 100% completed had an identified location. Percentages were calculated based on the number of questions answered and applicable to the respondents’ resource availability.

RESULTS

Survey Demographics

The survey was completed by 199 respondents from 43 countries representing 6 continents, with an additional 23 partial responses without a location included. South Africa, India, China, Indonesia, and Pakistan were the countries with the highest survey response ([Figure 1](#) and [Supplementary Table S1](#)). The majority of participants were from tertiary care facilities in urban environments and almost half cared solely for children ([Figure 2](#)). Pediatric neurology (21.6%), neurosurgery (12.2%), adult infectious diseases (11.7%), and adult neurology (10.8%) were the top specialties, with $>90\%$ reporting active involvement in patient care ([Supplementary Table S2](#)). Half of respondents saw >11 patients a year, with 35% seeing >20 annually ([Figure 1](#) and [Supplementary Table S2](#)). Most patients were hospitalized for >10 days. [Supplementary Table S2](#) lists all survey respondent demographics.

Resources Availability and Utilization

[Table 1](#) summarizes the availability and utilization of resources, with detailed information in [Supplementary Material \(Supplementary Tables S3 to S11\)](#). Laboratory studies, including blood, urine, and cerebrospinal fluid (CSF), were available to almost all participant sites and used largely at admission or when clinically indicated ([Table 1](#) and [Supplementary Table S3](#)). Empiric diagnosis (based on clinical presentation, imaging, and/or routine CSF characteristics) was most common in conjunction with culture, Gram stain/acid-fast bacilli smear, or polymerase

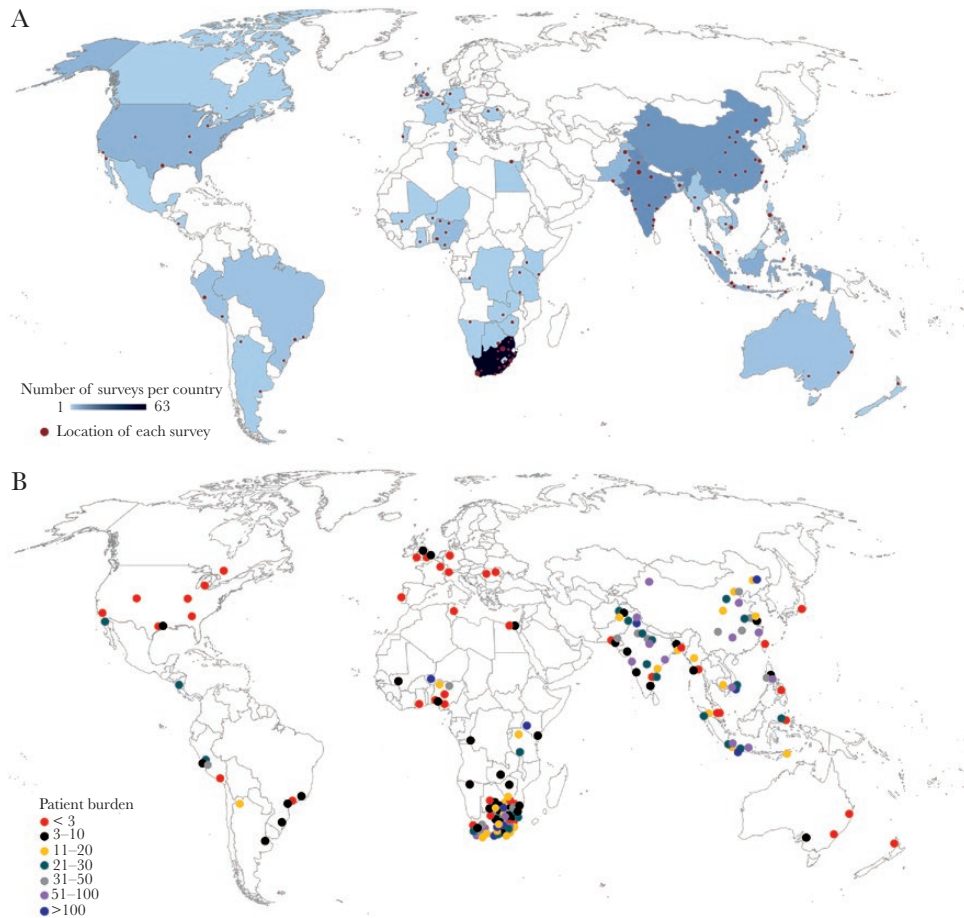


Figure 1. Survey respondent location and their reported patient burden. (A) Map of survey respondents, with red dot indicating location and size corresponding with number of respondents from each city. Darker blue indicates more responses per country. (B) Number of tuberculous meningitis patients per year cared for by respondents.

chain reaction (PCR), with the majority of PCR reported as GeneXpert (98%; Cepheid, Sunnyvale, CA). Neuroimaging was available to 90% of respondents, but admission imaging was performed by only 63%. Access to an intensive care unit (ICU) and to supportive noninvasive monitoring, such as blood pressure, oxygenation (ie, pulse oximetry), and temperature, was common. When ICU care was available, respondents reported high patient to nurse ratios, low ICU admission rates, and barriers to ICU care, most commonly bed shortage ([Supplementary Table S11](#)). Although currently there are no international guidelines available for TBM management, 40.5% of respondents reported access to a protocol for TBM, most commonly an institutional/hospital protocol ([Supplementary Table S12](#)).

Due to the high burden of disease and high survey response rate, a subanalysis of responses from tertiary care centers in China, India, and South Africa was performed for TBM-specific resource availability and utilization ([Table 2](#)). Although access to neuroimaging, ICU care, and neurosurgical management were similar across all 3 countries, South African centers used these resources less. In addition, centers in China (100%) and India (70.6%) more commonly reported managing patients

according to a protocol, whereas this was reported in less than half of South African centers (40.7%).

General Supportive Management

The most common target values in medical management reported by respondents demonstrated significant heterogeneity (see [Supplementary Tables S5](#) for summary and [S6](#) to [S10](#) for complete lists).

Hemodynamics

Blood pressure could be monitored by almost all respondents and was monitored several times per day ([Tables 1](#) and [Supplementary Tables S6](#)). Hypotension was treated with fluid boluses or vasoactive medications, of which dopamine was the most common ([Supplementary Table S6](#)).

Oxygen/Ventilation

Pulse oximetry was more frequently available than end-tidal carbon dioxide (ETCO₂) and used to monitor adequate ventilation ([Tables 1](#) and [Supplementary Table S7](#)). Nasal cannula/prongs were the most common respiratory support devices ([Table 1](#)).

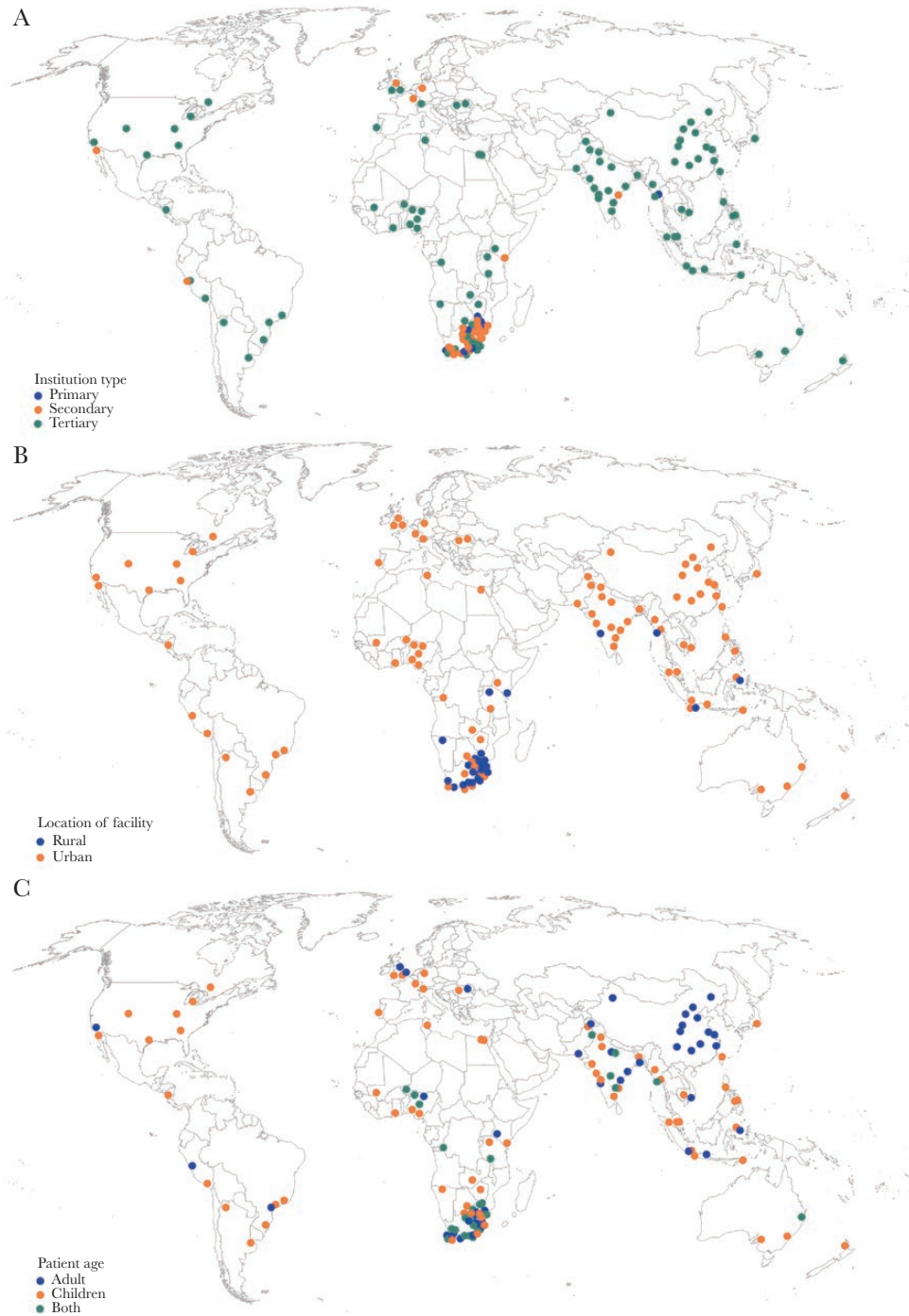


Figure 2. International distribution of respondents. Global maps demonstrating survey respondent distribution by (A) type of facility (primary, secondary, tertiary), (B) location of facility (urban, rural), and (C) patient age (pediatric, adult, both).

Temperature

Temperature was frequently measured, at least every 3–4 hours, by transcutaneous, ear, or oral thermometers (Tables 1 and Supplementary Table S8). Paracetamol and ibuprofen were commonly used to treat hyperpyrexia (Supplementary Table S8).

Nutrition

Nutrition was largely given orally or administered via nasogastric tube. Oral feeding safety was assessed by clinical exam or less commonly by a speech consultant or swallow test (Supplementary Table S9). Glucose levels were monitored daily.

Table 1. Resource Availability and Utilization

Resource	Availability		Utilization	
	Yes (%)	Yes (%)		Frequency
Intensive Care Unit				
Admission	183/222 (82.4)	129/183 (70.5)		
Noninvasive Monitoring				
Blood pressure	217/222 (97.7)		Hourly	Every 4 Hours
Pulse oximetry	214/221 (96.8)		33/217 (15.2)	67/217 (30.9)
End-tidal carbon dioxide	143/219 (65.3)	95/143 (66.4)		
Temperature	216/221 (97.7)		27/216 (12.5)	143/216 (66.2)
Respiratory Support^a				
None (room air)		77/217 (35.5)		
Nasal cannula	211/221 (95.4)	100/211 (47.4)		
High-flow nasal cannula	140/218 (64.2)	10/140 (7.1)		
Continuous positive airway pressure	178/219 (81.3)	2/178 (1.1)		
Bilevel positive airway pressure	153/218 (70.2)	2/153 (1.3)		
Ventilator	192/220 (87.2)	22/192 (11.5)		
Medical Intervention				
Transfusion	213/222 (95.9)	167/213 (78.4)		
Intravenous antibiotic	218/222 (98.2)			
Intravenous antiretroviral	211/222 (95)			
Noninvasive Neuroimaging^a				
All imaging			Admission Only	≥2 Occasions
Computed tomography	203/222 (91.4)	166/203 (81.8)	127/202 (62.9)	124/202 (61.4)
Magnetic resonance imaging	172/222 (77.5)	117/172 (68)		
Cranial ultrasound	148/220 (67.3)	22/148 (14.9)		
Angiography	142/222 (63.9)	14/142 (9.9)		
Ocular ultrasound	74/212 (34.9)			
Noninvasive Neuromonitoring^a				
Near-infrared spectroscopy	38/215 (17.7)			
Transcranial doppler	90/219 (41.1)			
Electroencephalogram	132/220 (60)			
Neurosurgery				
Consult	199/221 (90)			
Neurosurgical Intervention^a				
Ventriculoperitoneal shunt	167/222 (75.2)	Measure ICP		Treat ICP
Lumbar drain	136/220 (61.8)			122/167 (73.1)
Lumbar puncture		156/209 (74.6)		41/136 (30.1)
External ventricular drain	135/220 (61.4)	71/135 (52.9)		79/222 (35.6)
Endoscopic third ventriculostomy	109/217 (50.2)			107/135 (79.3)
				47/179 (26.3)
Invasive Neuromonitoring				
Intraparenchymal intracranial pressure catheter	80/216 (37)			
Partial brain tissue oxygen tension	29/215 (13.5)			
System Resources				
Treatment protocol	90/222 (40.5)			
Any medical record	160/222 (72)			
Electronic medical record	62/222 (27.9)			
Research database	76/222 (34.2)			
Blood Laboratory Tests^a				
All laboratory tests	215/221 (97.2)	Admission		If Clinically Indicated
Basic metabolic profile ^b		107/214 (50)		78/214 (36.4)
Liver function test ^c		103/214 (48.1)		86/214 (40.1)
Kidney function test ^d		109/214 (50.9)		79/214 (36.9)
Complete blood count ^e		117/220 (53.2)		79/220 (35.9)
Blood gas		63/212 (29.7)		128/212 (60.4)
Coagulation ^f		70/214 (32.7)		130/214 (60.7)
Serum osmolality		29/211 (13.7)		127/211 (60.2)
HIV testing				206/222 (92.8)

Table 1. Continued

Resource	Availability	Utilization		
	Yes (%)	Yes (%)	Frequency	
Urine Laboratory Tests ^a		Admission	Clinically Indicated	
All laboratory tests	214/220 (97.2)			
Urine sodium		12/211 (5.6)	131/211 (60.2)	
Urine osmolality		14/212 (6.6)	131/212 (61.8)	
CSF Laboratory Tests ^a		Admission	Every LP	Clinically Indicated
All laboratory tests	215/222 (96.8)			
Protein		141/213 (66.2)	79/213 (37)	66/213 (30.9)
Cell count		140/213 (65.7)	78/213 (36.6)	65/213 (30.5)
Glucose		140/212 (66)	79/212 (37.2)	65/212 (30.6)
Gram stain/culture		143/212 (67.5)	78/212 (36.7)	66/212 (31.1)
TBM Diagnostics ^{a,g}		Admission		
Empiric		142/221 (64.2)		
Culture		133/221 (60.1)		
Gram stain ^h		113/221 (51.1)		
Polymerase chain reaction ⁱ		135/221 (61)		
Interferon gamma release assay		9/221 (4.1)		
Adenosine deaminase		2/221 (0.9)		
Biopsy		1/221 (0.5)		

Abbreviations: CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; ICP, intracranial pressure; LP, lumbar puncture; TBM, tuberculous meningitis.

NOTE: The response “yes” to availability of resource combines respondents that answered “always” and “sometimes” to access. All blank cells reflect data that was not available or applicable, such as frequency of utilization for continuous monitoring (eg, pulse oximetry).

^aMore than 1 response was allowed per question.

^bSodium, potassium, and glucose.

^cAlanine transaminase and aspartate transaminase.

^dCreatinine and blood urea nitrogen.

^eFull blood count, hemoglobin, and platelet.

^fProthrombin time and partial thromboplastin time.

^gOnly utilization, not availability, of TBM diagnostic was surveyed here.

^hGram stain includes acid-fast bacilli smear.

ⁱAll but 4 of the polymerase chain reactions were GeneXpert (Cepheid, Sunnyvale, CA).

Anaemia and Transfusion

Most respondents reported the ability to transfuse TBM patients, although the goal hemoglobin demonstrated heterogeneity across centers (Supplementary Tables S5 and S10).

Tuberculous Meningitis-Specific Management

Tuberculous meningitis-specific patient management was heterogeneous, and some respondents reported divergence from current standard of care as summarized in Table 3.

Pharmaceutical Management

Pharmaceutical management included antibiotics, anti-retrovirals (ARTs), corticosteroids, and other host-directed therapies (Supplementary Table S13). Approximately 70% of respondents used all first-line antibiotics (per the World Health Organization), and over 40% used at least 1 second-line antibiotic, mostly fluoroquinolones [16]. Antibiotic duration was commonly 12 months, and steroid duration was 6 weeks usually with a 1- to 2-week taper. Most respondents waited 2 to 4 weeks after antibiotic initiation before starting ARTs in human immunodeficiency virus (HIV) coinfecting patients; however, 11% did not. Corticosteroids were used by

97% of respondents, although choice of corticosteroid was heterogeneous.

Intracranial Pressure and Hydrocephalus Management

More than 80% of respondents reported measuring ICP, mostly with a lumbar puncture ([LP] Table 1 and Supplementary Table S14). Lumbar punctures were most often repeated when clinically indicated, although only 58.3% recorded opening pressure with each LP. Most respondents tested for communicating hydrocephalus, most commonly using imaging. Air encephalogram and a column test were less commonly used (Supplementary Table S14). Ventriculoperitoneal shunts and external ventricular drains were the most common neurosurgical interventions for elevated ICP (Supplementary Table S14). Medical treatments of raised ICP included raising the head of the bed, seizure control, and hypertonic saline or mannitol, and less commonly temperature control, diuretics, hyperventilation, and frequent LPs (Supplementary Table S14).

Hyponatremia Management

Clinical examination and urine output were used to determine fluid balance (Supplementary Figure S1A). Treatment

Table 2. TBM-Specific Resource Availability and Utilization in Tertiary Centers in China, India, and South Africa

Resource	China	India	South Africa
	Yes (%)	Yes (%)	Yes (%)
Resource Availability			
General			
Intensive care unit	15/16 (93.8)	17/17 (100)	26/27 (96.3)
Treatment protocol	16/16 (100)	12/17 (70.6)	11/27 (40.7)
Noninvasive Neuroimaging ^a			
Computed tomography	16/16 (100)	16/17 (94.1)	26/27 (96.3)
Magnetic resonance imaging	16/16 (100)	16/17 (94.1)	24/27 (88.9)
Neurosurgery ^a			
Neurosurgery consult	15/16 (93.8)	17/17 (100)	26/27 (96.3)
Ventriculoperitoneal shunt	13/16 (81.3)	16/17 (94.1)	23/27 (85.2)
Lumbar drain	13/15 (86.7)*	14/17 (82.4)	18/27 (66.7)
External ventricular drain	15/16 (93.8)	15/17 (88.2)	20/27 (74.1)
Endoscopic third ventriculostomy	10/16 (62.5)	16/17 (94.1)	16/26 (61.5)*
Laboratory Tests			
All blood laboratory tests	16/16 (100)	16/17 (94.1)	26/27 (96.3)
All urine laboratory tests	16/16 (100)	16/17 (94.1)	26/27 (96.3)
All CSF laboratory tests	16/16 (100)	16/17 (94.1)	26/27 (96.3)
Resource Utilization			
Noninvasive Neuroimaging ^a			
Computed tomography	11/16 (68.8)	12/16 (75)	25/26 (96.2)
Magnetic resonance imaging	16/16 (100)	15/16 (93.8)	5/26 (19.2)
TBM Diagnosis ^{a,b}			
Empiric	4/16 (25)	9/17 (52.9)	17/27 (63)
Culture	15/16 (93.8)	7/17 (41.2)	14/27 (51.9)
Gram stain ^c	16/16 (100)	5/17 (29.4)	9/27 (33.3)
Polymerase chain reaction ^d	10/16 (62.5)	10/17 (58.8)	14/27 (51.9)
ICP Monitoring ^a			
External ventricular drain transduced	0/15 (0)*	4/14 (28.6)*	4/26 (15.4)*
Lumbar puncture	15/15 (100)*	12/14 (85.7)*	26/26 (100)*
Intraparenchymal intracranial pressure catheter	0/15 (0)*	5/14 (35.7)*	1/26 (3.8)*
ICP Management ^a			
Ventriculoperitoneal shunt	10/14 (71.4)*	15/17 (88.2)	17/25 (68)*
External ventricular drain	11/14 (78.6)*	15/17 (88.2)	13/25 (52)*
Endoscopic third ventriculostomy	2/14 (14.3)*	7/17 (41.2)	5/25 (20)*
Lumbar drain	8/14 (57.1)*	3/17 (17.6)	2/25 (8)*
Lumbar puncture	8/16 (50)	4/17 (23.5)	16/27 (59.3)
Diuretics	15/16 (93.8)	10/17 (58.8)	12/27 (44.4)
Osmotics	16/16 (100)	17/17 (100.0)	16/27 (59.3)

Abbreviations: CSF, cerebrospinal fluid; ICP, intracranial pressure; TBM, tuberculous meningitis.

NOTE: The availability of resource combines respondents that answered "always" and "sometimes" to access.

^aMore than 1 response was allowed per question.

^bOnly utilization, not availability, of TBM diagnostics.

^cGram stain includes acid-fast bacilli smear.

^dAll but 1 of the polymerase chain reactions were GeneXpert (Cepheid, Sunnyvale, CA).

*Indicates questions for which some responses were missing.

of hyponatremia was most often initiated for serum sodium <130 and hypertonic saline was most commonly used, irrespective of the underlying etiology (Supplementary Figure S1B and C). However, fluid restriction was more common in syndrome of inappropriate antidiuretic hormone ([SIADH] 61.8%) than cerebral salt wasting ([CSW] 31.8%). Rarely, hyponatremia was treated with transfusions, fludrocortisone, or vasopressin/vasopressin receptor analogs (Supplementary Table S15 and Supplementary Figure S1C).

Open-Ended Questions

Three open-ended questions allowed respondents to highlight themes not addressed by the survey, with representative quotes listed in Supplementary Table S16.

"What other imaging, laboratory or clinical parameters do you monitor in TBM patients that were not previously asked about?"—Three themes emerged: (1) neurological clinical exam and neuromonitoring, (2) investigation of extrapulmonary sites, and (3) TB screening of contacts.

Table 3. Clinical Management of TBM*

Clinical Management	Standard of Care	Reference	Survey Results
TBM Diagnosis			
Empiric TBM diagnosis	<ul style="list-style-type: none"> Empiric diagnosis is based on CSF parameters, imaging, clinical exam, and history 	<ul style="list-style-type: none"> As referenced in Panel 1 of Marais et al [29] As referenced in Table 2 of Wilkinson et al [1] 	<ul style="list-style-type: none"> Only ~66% report obtaining CSF studies at admission, but 97% have access to CSF laboratory tests Only 60% report performing a Gram stain, culture or PCR on CSF Only 63% report performing neuroimaging at admission, but 91% have access to CT and 76% to MRI
Antimicrobial Management			
First-line antibiotics	<ul style="list-style-type: none"> First-line antibiotics for drug-susceptible TBM are isoniazid, rifampin, pyrazinamide, and ethambutol 	<ul style="list-style-type: none"> WHO's Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care [30] 	<ul style="list-style-type: none"> Only 78% use all 4 first-line drugs
Antiretroviral (ART) in ART-naïve HIV coinfection	<ul style="list-style-type: none"> In newly diagnosed HIV, TB treatment should be initiated first, followed by ART (strong recommendation, high certainty in the evidence as per WHO) ART should be initiated regardless of CD4 cell count (strong recommendation, high certainty) in the evidence as per WHO) 	<ul style="list-style-type: none"> WHO's Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care [30] Török et al [19] 	<ul style="list-style-type: none"> 11% initiate ART simultaneously with TB treatment instead of waiting until after TB treatment initiation 8% only initiate ART depending on CD4 cell count
Host-Directed Therapy Management			
Corticosteroid initiation	<ul style="list-style-type: none"> Adjuvant corticosteroids are recommended at treatment initiation (strong recommendation, moderate certainty in the evidence) Corticosteroids are recommended regardless of the severity of illness and have decreased mortality in adults and children 	<ul style="list-style-type: none"> WHO's Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care [30] Schoeman et al [31] Thwaites et al [2] 	<ul style="list-style-type: none"> 3% never use corticosteroids
Corticosteroid taper	<ul style="list-style-type: none"> Corticosteroid should be tapered over 6–8 weeks (strong recommendation, moderate certainty in the evidence as per WHO) 	<ul style="list-style-type: none"> WHO's Guidelines for Treatment of Drug-Susceptible Tuberculosis and Patient Care [30] 	<ul style="list-style-type: none"> Only 24% taper corticosteroids over 6–8 weeks
Hydrocephalus Diagnosis			
Hydrocephalus	<ul style="list-style-type: none"> Hydrocephalus increases the risk of poor outcome, especially if undiagnosed 	<ul style="list-style-type: none"> As reviewed by Wen et al [32] 	<ul style="list-style-type: none"> Only 63% perform neuroimaging at admission, 77% during hospitalization, and 61% for ≥2 occasions

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; TB, tuberculosis; TBM, tuberculous meningitis; WHO, World Health Organization. *Clinical management (ie, empiric TBM diagnosis, antimicrobial usage, host-directed therapy management, and hydrocephalus diagnosis) reported by survey respondents compared with current standard of care in literature.

“What other treatments (that were not previously asked about) do you use in patients with TBM?”—The common themes were as follows: (1) additional antimicrobials, (2) other pharmaceutical management, (3) ancillary support (ie, physical/occupational therapy and social work), and (4) supportive technology and/or invasive procedures (ie, biopsy/resection, dialysis, and gastrostomy tube).

“What are the biggest challenges facing your facility in managing patients with TBM?”—Common concerns were as follows: (1) diagnostic challenges, (2) inadequate access to specialized neurosurgical/neurocritical care, (3) general lack of experience and standardized guidelines, (4) management of HIV and comorbidities, (5) antimicrobial management (ie, access, drug delivery/brain penetration, duration of therapy, drug resistance, compliance, and drug toxicities), (6) limited resources (human, physical, and financial), and (7) socioeconomic constraints.

DISCUSSION

The survey had broad global reach with representation from high-burden countries. Two main findings were as follows: (1) notable heterogeneity across all domains of TBM management, including access and utilization of resources, with some respondents diverging from current standards of care; and (2) demonstration of geographic resource availability that could aid in future clinical trials to establish treatment guidelines. Persistent knowledge gaps in medical and neurosurgical care are summarized in [Table 4](#), including clinical trials (both past and ongoing) and required resources to address these questions (see [Supplementary Table S17](#) for expanded version of [Table 4](#)).

Access to Resources

This survey demonstrated that many laboratory tests, neuroimaging, and noninvasive monitoring were broadly accessible. This provides a promising framework for future trials to address unanswered management questions, although trial funding would be needed to compensate for resource limitations. Access to resources alone does not account for all variability in utilization, which was demonstrated by the subanalysis of China, India, and South Africa where South African tertiary centers used ICU care, neuroimaging, and neurosurgery less, possibly due to a higher burden on available resources. It is regrettable that few respondents reported using a research database. Databases that can be shared across centers would be invaluable in the development of evidence-based guidelines, and approaches to standardize data and sample collection for comparison across centers have been published by the Tuberculous Meningitis International Research Consortium [[17](#), [18](#)].

Current Patient Management

Lack of standardized international TBM treatment protocols represents one of the “biggest challenges” in management. National or organizational protocols mentioned did not deal

with supportive management, and few suggested neurosurgical intervention. Furthermore, as demonstrated in [Table 3](#), numerous respondents diverged from current standards of care in terms of diagnosis and clinical management. Despite almost universal access to laboratory investigations, one third of respondents reported not testing CSF on admission. Cerebrospinal fluid is vital to the empiric and laboratory diagnosis of TBM and raises the question of whether there is over- and underdiagnosis of TBM. Likewise, neuroimaging is key to empiric diagnosis and the assessment of hydrocephalus, yet it was used by only 63% of respondents, although it was accessible to 91%. In addition, only 78% of respondents used all 4 first-line antibiotics for drug-susceptible TBM and 3% did not use corticosteroids, although this is the internationally accepted standard of care. Furthermore, 11% of respondents initiated ART simultaneously with antibiotics, even though this is known to increase the risk of an immune reconstitution inflammatory syndrome response in ART-naïve patients [[19](#)]. These departures from the standard of care could be a symptom of the absence of internationally accepted guidelines. It is interesting to note that in the subanalysis of tertiary centers across China, India, and South Africa, China and India reported broader use of treatment protocols and more uniform use of resources. Establishment of clear guidelines for optimal TBM management could improve care now and in the future.

Addressing Unanswered Clinical Research Questions

Pharmaceutical Care

Survey data show heterogeneity in the choice of antibiotics, route of administration, dosage, and duration of treatment. Similarly host-directed therapies were used variably. Numerous studies to address these questions are already underway ([Table 4](#)), and findings suggest that higher doses of rifampicin and intravenous administration may be beneficial [[3](#), [20](#), [21](#)]. Work on corticosteroids aims to understand how they improve mortality and determine whether host-associated characteristics play a role. In HIV-coinfected patients, research on how to optimally incorporate steroids in the treatment regimen is ongoing. New additions to host-directed therapy such as aspirin are being tested, and novel targets are likely to be elucidated by further research [[22](#)].

Neurocritical and Supportive Care

Supportive general and neurocritical care are the standard of care for numerous forms of brain injury [[11–13](#)]. However, it appears rare in TBM despite the high rate of neurological injury, and respondents reported this lack of specialized neurocritical care as one of the biggest challenges to TBM management. Neurocritical care is not limited to the ICU and can include basic, but effective, treatment at ward level. Resources for bedside supportive management and noninvasive monitoring were available in most respondents' centers. Therefore,

Table 4. Outstanding Clinical Research Questions in the Medical and Surgical Management of TBM

Clinical Management	Research Question	Additional Resources ^a	Randomized Controlled Trials ^b
Antimicrobial Management			
Antibiotic choice and dosage	<ul style="list-style-type: none"> • What is the optimal antibiotic regimen for TBM? • What is the optimal dose in adults and children? 	<ul style="list-style-type: none"> • Laboratory <ul style="list-style-type: none"> ◦ Serum and CSF collection ◦ Long-term sample storage ◦ Drug concentration analysis • Pharmaceuticals <ul style="list-style-type: none"> ◦ Antibiotics 	<ul style="list-style-type: none"> • Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ Te Brake et al [20]; Ruslami et al [3]; Dian et al [21]; Heemskerck et al [4] • Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ Optimizing Antituberculosis Therapy in Adults with Tuberculous Meningitis; TBM-KIDS; INTENSE-TBM; LASER-TBM; ALTER; SIMPLE; Harvest Trial—Improving Outcomes from TB Meningitis with High Dose Oral Rifampicin; Is Levofloxacin Better than Rifampicin in the Treatment of Tuberculous Meningitis, a Randomized Control Study; ESCALATE; High Dose Oral and Intravenous Rifampicin for Improved Survival of Adult Tuberculous Meningitis: a Phase II Open-Label Randomised Controlled Trial
Antibiotic duration	<ul style="list-style-type: none"> • What is the optimal treatment duration in adults and children? 	<ul style="list-style-type: none"> • Laboratory <ul style="list-style-type: none"> ◦ As above • Pharmaceuticals <ul style="list-style-type: none"> ◦ Antibiotics 	<ul style="list-style-type: none"> • Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ Reviewed in Jullien et al [33]^c • Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ SURE; Determination of Efficacy of 9 Months, 12 Months and 18 Months of Anti-tubercular Treatment (ATT) for Tuberculous Meningitis (TBM): a Randomized Controlled, Noninferiority Trial
Antibiotic route of administration	<ul style="list-style-type: none"> • What is the optimal route of administration, oral or intravenous? 	<ul style="list-style-type: none"> • Laboratory <ul style="list-style-type: none"> ◦ As above • Pharmaceuticals <ul style="list-style-type: none"> ◦ Antibiotics 	<ul style="list-style-type: none"> • Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ Ruslami et al [3] • Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ LASER-TBM; High Dose Oral and Intravenous Rifampicin for Improved Survival of Adult Tuberculous Meningitis: a Phase II Open-Label Randomised Controlled Trial
Antiretroviral (ART) initiation	<ul style="list-style-type: none"> • What is the optimal timing of ART initiation? 	<ul style="list-style-type: none"> • Laboratory <ul style="list-style-type: none"> ◦ As above • Pharmaceuticals <ul style="list-style-type: none"> ◦ ARTs 	<ul style="list-style-type: none"> • Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ Török et al [19]; Laureillard et al [34]^d • Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ None
Host-Directed Therapy			
Corticosteroid duration	<ul style="list-style-type: none"> • What is the optimal duration of corticosteroid use? 	<ul style="list-style-type: none"> • Laboratory <ul style="list-style-type: none"> ◦ As above • Pharmaceuticals <ul style="list-style-type: none"> ◦ Corticosteroids 	<ul style="list-style-type: none"> • Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ Török et al [35] • Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ Leukotriene A4 Hydrolase Stratified Trial of Adjunctive Corticosteroids for HIV-uninfected Adults with Tuberculous Meningitis; The ACT HIV Trial
Corticosteroids	<ul style="list-style-type: none"> • What is the optimal route of administration, oral or intravenous? 	<ul style="list-style-type: none"> • Laboratory <ul style="list-style-type: none"> ◦ As above • Pharmaceuticals <ul style="list-style-type: none"> ◦ Corticosteroids 	<ul style="list-style-type: none"> • Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ None • Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ Comparison of Regimens of Dexamethasone in Tubercular Meningitis—a Randomized Control Trial
Corticosteroid taper	<ul style="list-style-type: none"> • What is the optimal duration of corticosteroid taper? 	<ul style="list-style-type: none"> • Laboratory <ul style="list-style-type: none"> ◦ As above • Pharmaceuticals <ul style="list-style-type: none"> ◦ Corticosteroids 	<ul style="list-style-type: none"> • Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ None • Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ None
Aspirin	<ul style="list-style-type: none"> • What is the role of aspirin as a host-directed therapy? • What is the optimal dose and duration? 	<ul style="list-style-type: none"> • Laboratory <ul style="list-style-type: none"> ◦ As above • Pharmaceuticals <ul style="list-style-type: none"> ◦ Aspirin 	<ul style="list-style-type: none"> • Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ Mai et al [22]; Schoeman et al [6]^e • Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ INTENSE-TBM; LASER-TBM; SURE
Thalidomide	<ul style="list-style-type: none"> • What is the role of thalidomide as a host-directed therapy? • What is the optimal dose and duration? 	<ul style="list-style-type: none"> • Laboratory <ul style="list-style-type: none"> ◦ As above • Pharmaceuticals <ul style="list-style-type: none"> ◦ Thalidomide 	<ul style="list-style-type: none"> • Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ Schoeman et al [7]^e • Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ None

Table 4. Continued

Clinical Management	Research Question	Additional Resources ^a	Randomized Controlled Trials ^b
Other host-directed therapies	<ul style="list-style-type: none"> What is the role of other host-directed therapies in TBM? 	<ul style="list-style-type: none"> Laboratory <ul style="list-style-type: none"> ◦ As above Pharmaceuticals <ul style="list-style-type: none"> ◦ Other (ie, Indomethacin) 	<ul style="list-style-type: none"> Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ None Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ An Open Label Randomized Study to Evaluate Effectiveness of Indomethacin in Tuberculous Meningitis
Intracranial Pressure (ICP) Management			
ICP management	<ul style="list-style-type: none"> How should ICP be measured? How frequently should ICP be measured? How should ICP be managed? What is the optimal ICP target in TBM? Should the target be age specific? 	<ul style="list-style-type: none"> Neurosurgical Expertise <ul style="list-style-type: none"> ◦ ICP monitoring Neuromonitoring <ul style="list-style-type: none"> ◦ ICP (brain oxygenation) Neuroimaging Equipment <ul style="list-style-type: none"> ◦ Manometer Cardiovascular Monitoring <ul style="list-style-type: none"> ◦ Blood pressure, heart rate Pharmaceuticals <ul style="list-style-type: none"> ◦ Diuretic, sedation/paralytic, antiepileptic, osmotic agent 	<ul style="list-style-type: none"> Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ None Ongoing Study by Clinical Trial Name None
Hydrocephalus diagnosis	<ul style="list-style-type: none"> How should communicating vs non-communicating hydrocephalus be diagnosed? 	<ul style="list-style-type: none"> Neurosurgical Expertise Neuroimaging <ul style="list-style-type: none"> ◦ CT, MRI, X-ray (skull) Equipment <ul style="list-style-type: none"> ◦ Manometer 	<ul style="list-style-type: none"> Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ None Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ None
Hydrocephalus medical and surgical management	<ul style="list-style-type: none"> What should be the standard of care in medical and surgical management of hydrocephalus? What are the indications for medical vs surgical management? 	<ul style="list-style-type: none"> Neurosurgical Expertise <ul style="list-style-type: none"> ◦ Surgical intervention Neuromonitoring <ul style="list-style-type: none"> ◦ ICP monitor Neuroimaging Equipment <ul style="list-style-type: none"> ◦ Manometer Pharmaceuticals <ul style="list-style-type: none"> ◦ Diuretic 	<ul style="list-style-type: none"> Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ None Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ None
Hyponatremia Management			
Hyponatremia diagnosis	<ul style="list-style-type: none"> How should the etiology of hyponatremia be investigated? 	<ul style="list-style-type: none"> Laboratory <ul style="list-style-type: none"> ◦ Electrolytes (serum/urine) Fluid Balance Monitoring <ul style="list-style-type: none"> ◦ Invasive or noninvasive 	<ul style="list-style-type: none"> Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ Misra et al [28]; Misra et al [36]^c Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ None
Hyponatremia management	<ul style="list-style-type: none"> What should be the standard of care in hyponatremia management when etiology is cerebral salt wasting or syndrome of inappropriate antidiuretic hormone? 	<ul style="list-style-type: none"> Laboratory <ul style="list-style-type: none"> ◦ Electrolytes (serum/urine) Fluid Balance Monitoring <ul style="list-style-type: none"> ◦ Invasive or noninvasive Pharmaceuticals <ul style="list-style-type: none"> ◦ Sodium supplementation 	<ul style="list-style-type: none"> Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ Misra et al [37] Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ None
Neurocritical Care Management			
Temperature management	<ul style="list-style-type: none"> How should temperature be monitored and frequency? What is the target temperature and how should temperature be managed? 	<ul style="list-style-type: none"> Temperature Monitoring <ul style="list-style-type: none"> ◦ Continuous or noncontinuous Pharmaceuticals <ul style="list-style-type: none"> ◦ Antimicrobials, corticosteroids, antipyretics 	<ul style="list-style-type: none"> Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ None Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ None
Blood pressure (BP) management	<ul style="list-style-type: none"> How should BP be monitored? What is the target BP? How should BP be managed? 	<ul style="list-style-type: none"> Blood Pressure Monitoring <ul style="list-style-type: none"> ◦ Invasive or noninvasive Neuromonitoring <ul style="list-style-type: none"> ◦ ICP to establish goal CPP Pharmaceuticals <ul style="list-style-type: none"> ◦ Vasopressor 	<ul style="list-style-type: none"> Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ None Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ None

Table 4. Continued

Clinical Management	Research Question	Additional Resources ^a	Randomized Controlled Trials ^b
Respiratory management	<ul style="list-style-type: none"> • How should ventilation/oxygenation be monitored and managed? • What is the target end-tidal carbon dioxide level (ETCO₂)? • What is the target oxygen? 	<ul style="list-style-type: none"> • General Monitoring <ul style="list-style-type: none"> ◦ BP, pulse oximetry • Neuromonitoring <ul style="list-style-type: none"> ◦ Consider brain oxygenation • Equipment <ul style="list-style-type: none"> ◦ Ventilator, nasal cannula, ETCO₂, arterial blood gas • Pharmaceuticals <ul style="list-style-type: none"> ◦ Sedation/paralytics 	<ul style="list-style-type: none"> • Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ None • Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ None
Seizure management	<ul style="list-style-type: none"> • How should seizures be monitored? • How should seizures be managed? 	<ul style="list-style-type: none"> • Noninvasive Monitoring <ul style="list-style-type: none"> ◦ Temperature, EEG • Neuromonitoring • Laboratory <ul style="list-style-type: none"> ◦ Electrolytes (serum) • Pharmaceuticals <ul style="list-style-type: none"> ◦ Antiepileptic 	<ul style="list-style-type: none"> • Past Publications (Clinical Trial Name) <ul style="list-style-type: none"> ◦ None • Ongoing Study by Clinical Trial Name <ul style="list-style-type: none"> ◦ None

Abbreviations: ATT, antitubercular treatment; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; RCT, randomized controlled trial; TBM, tuberculous meningitis.

NOTE: Summary of outstanding questions regarding the medical management of TBM, the necessary resources, and relevant past and ongoing RCTs. Previous clinical trials and their associated publications highlight RCTs and publications since 2010 unless no RCTs exist or only earlier studies are available.

^aAdditional resources are those beyond resources for diagnosis, patient management (general clinical care, monitoring, and staff), trial support.

^bIn [Supplementary Table S17](#), RCT acronyms are spelled out and listed with clinical trial identifier and reflect those registered by the National Institutes of Health's US National Library of Medicine (clinicaltrials.gov) or World Health Organization's International Clinical Trials Registry Platform (<http://apps.who.int/trialsearch/Default.aspx>).

^cNo RCTs available.

^dThis RCT included all patients with TB, including pulmonary and TBM.

^eNo clinical trial identifier available but included due to paucity of data in pediatrics.

basic interventions could be feasible for TBM-endemic settings (Table 4). For example, blood pressure, pulse oximetry, and temperature monitoring are widely available, suggesting that goals to avoid hypotension, hypoxia, and hyperpyrexia could be investigated. Although TBM is often characterized by weight loss and malnutrition affects antibiotic pharmacokinetics, TBM studies investigating early feeding or avoidance of hyperglycemia have not been done despite their ability to improve outcomes in TBI [23, 24]. Data to establish the benefit of simple interventions like these in TBM may require clinical trials in better-resourced environments, but their application would be broadly appropriate. Until a sufficient evidence base for the neurocritical and supportive care of TBM can be established, a checklist may be a beneficial first step [25].

Although 84% of respondents reported measuring ICP, fewer reported how this was done and <50% regularly recorded the opening pressure, suggesting that ICP is not systematically measured (Supplementary Table S14). Given the prevalence of hydrocephalus with associated raised ICP, these data suggest a need for protocols to monitor ICP, including location, frequency of measurement, and treatment thresholds (Table 4) [26]. Medical interventions for raised ICP, such as raising the head of the bed, controlling seizures, and utilizing osmotic agents, were reported by 70%–80% of respondents and could therefore be studied more systematically.

Differentiating between SIADH and CSW as the etiology of hyponatremia is a challenging but important step to implement appropriate intervention due to their divergent treatment (Table 4 and Supplementary Figure 1) [9]. Hypertonic saline may be a suitable treatment for both conditions, and our data demonstrate its frequent use [9]. However, 30% of respondents used fluid restriction even when they did not suspect SIADH. Furthermore, although respondents considered SIADH to be the predominant etiology, recent studies have demonstrated that CSW occurs more frequently in TBM and is associated with severe infarction [27, 28]. Multicenter studies to establish a recommended diagnostic approach for SIADH and CSW, and trial treatment options are needed.

Neurosurgical Care

Currently there is limited evidence for the nature and timing of neurosurgery for TBM hydrocephalus [8]. Consequently, practices are heterogeneous and accurate data on neurosurgical complications and success rates are lacking. The use of shunts or endoscopic third ventriculostomy and the selection of patients most likely to benefit requires multicenter study. Many respondents used imaging to test for hydrocephalus communication, yet there are no data that support the accuracy of imaging in determining this. The relevance, diagnosis, and advantages of medical versus surgical

management of hydrocephalus communication warrant investigation (Table 4) [9].

Limitations

Responses were largely from tertiary centers and may not reflect the rural and primary/secondary setting. However, the data show that most referrals are to tertiary centers. The use of organizational contacts within the TBM field could have contributed to sampling bias, and this likely skewed the data by the high number of respondents from neurosurgery, pediatrics, and South Africa, although wide distribution of the survey was available on social media. This is unlikely to have obscured the heterogeneity of management protocols or resource access, but neurosurgical treatment for hydrocephalus may be overrepresented. In addition, other complications, such as drug-induced liver toxicity or paradoxical reactions, may have revealed similarly heterogeneous management but were beyond the scope of this survey. We were unable to determine the survey hit rate due to the use of an anonymous link and utilization of list-serve distribution. Survey completion was subjective and consistency in intraindividual respondent answers cannot be guaranteed. Due to resource constraints, we were not able to translate this survey into multiple languages. However, English is commonly used by medical professionals worldwide. We were unable to back-translate the Chinese version, but answers were entered directly into the Qualtrics program to maintain response format.

CONCLUSIONS

The management of TBM is highly variable, even with respect to current standard of care, and the use of neurocritical care is limited. Numerous sites have access to important resources to participate in single-center and multicenter clinical trials to establish evidence-based treatment guidelines and investigate the value of supportive medical and neurosurgical measures on patient outcomes. Guidelines based on current evidence could help improve management now, and serve as the framework on which to build.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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