Tuberculous meningitis: progress and remaining questions

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Tuberculous meningitis is a devastating brain infection that is caused by *Mycobacterium tuberculosis* and is notoriously difficult to diagnose and treat. New technologies characterising the transcriptome, proteome, and metabolome have identified new molecules and pathways associated with tuberculous meningitis severity and poor outcomes that could offer novel diagnostic and therapeutic targets. The next-generation GeneXpert MTB/RIF Ultra assay, when used on CSF, offers diagnostic sensitivity for tuberculous meningitis of approximately 70%, although it is not widely available and a negative result cannot rule out tuberculous meningitis. Small trials indicate that clinical outcomes might be improved with increased doses of rifampicin, the addition of linezolid or fluoroquinolones to standard antituberculosis therapy, or treatment with adjunctive aspirin combined with corticosteroids. Large phase 3 clinical trials are underway worldwide to address these and other questions concerning the optimal management of tuberculous meningitis; these studies also form a platform for studying pathogenesis and identifying novel diagnostic and treatment strategies, by allowing the implementation of new genomic, transcriptomic, proteomic, and metabolomic technologies in nested substudies.

Introduction

Tuberculosis affects 10 million people globally each year,[1] of which an estimated 2–5% have tuberculous meningitis.[2] The true incidence of tuberculous meningitis is unknown; however, tuberculous meningitis is the leading cause of bacterial brain infections in settings with a high tuberculosis burden, disproportionately affecting young children and individuals with HIV.[3] Here, we review advances made in the past 7 years concerning the pathogenesis, diagnosis, and treatment of tuberculous meningitis, emphasising areas of uncertainty and updating Reviews published in *The Lancet Neurology* in 2005 and 2013.[4,5] This Review focuses mainly on adult tuberculous meningitis and briefly emphasises novel research advances in paediatric tuberculous meningitis, including important clinical trials on its management. Management recommendations and research published before July 1, 2015, are discussed elsewhere and are not included.[6]

Global burden of tuberculous meningitis

In retrospective region-specific studies, 0·3–4·9% of all people with tuberculosis have tuberculous meningitis (appendix p 1). Applying these proportions to the WHO global estimate of 10 million tuberculosis cases suggests that 30 000–490 000 people are diagnosed with tuberculous meningitis each year. The variable geographical distribution of key tuberculous meningitis risk factors—eg, prevalence of pulmonary tuberculosis, age, and HIV infection—probably contributes to regional variation in incidence of the disease. Furthermore, global shortages in Bacillus Calmette-Guérin vaccine, which reduces the risk of tuberculous meningitis in young children, have been linked to rising tuberculous meningitis cases in settings with a high tuberculosis burden.[7] Tuberculous meningitis is likely to be substantially under-reported, given the difficulties confirming microbiological diagnosis and inadequate surveillance.

See Online for appendix

Pathogenesis

Brain injury and death

Inflammation and damage of brain tissue (ie, encephalitis) and the meninges (ie, meningitis) in patients with tuberculous meningitis is predominantly driven by an aberrant host-immune response, triggered by *Mycobacterium tuberculosis* (*M tuberculosis*) invading the CNS. Although *M tuberculosis* causes direct damage to microglia, neurons, and astrocytes through antigen recognition,[8] the host-immune response ultimately determines the nature of disease.

Investigations of biomarkers of neuronal excitotoxicity and cerebral damage have advanced understanding of brain injury associated with tuberculous meningitis. Concentrations of S100B, ENO2, and GFAP were significantly higher in the ventricular CSF of 23 children with tuberculous meningitis-associated hydrocephalus compared with in 11 healthy controls.[9] In seven children with tuberculous meningitis-associated hydrocephalus who died, markers of cerebral injury increased over time, whereas inflammatory markers decreased,[9] suggesting that brain injury mechanisms might be independent from inflammation.

Other molecules might play a role in pathogenesis. Specialised proresolving mediators counter-regulate the production of proinflammatory mediators to promote repair and regeneration of damaged tissues.[10] Increased concentrations of specialised proresolving mediators in the CSF have been associated with reduced severity of disease and improved chance of survival from tuberculous meningitis.[11] These molecules might represent a novel therapeutic target: a phase 2 trial of adjunctive aspirin in adults with tuberculous meningitis reported upregulation of specialised proresolving mediators in CSF and improved survival for patients taking aspirin and dexamethasone compared with placebo and dexamethasone.[11,12]

Immune-mediated tissue destruction in patients with tuberculous meningitis is characterised by a disequilibrium of proinflammatory and anti-inflammatory

cytokines.[13] Neurological events in adults with tuberculous meningitis have been associated with high pretreatment CSF neutrophil counts, cytokine concentrations, and mycobacterial load.[14] A study of 692 Vietnamese adults with tuberculous meningitis reported that death was associated with an attenuated inflammatory response at the start of treatment when compared with survivors,[14,15] which challenges the dogma that only excessive inflammation is associated with death or long-term disability in patients with tuberculous meningitis.[14,15]

Heterogeneity of intracerebral inflammatory response can be partly explained by the *LTA4H* gene, which encodes an enzyme that balances the activities of proinflammatory and anti-inflammatory eicosanoids.[14,15] A prospective study of 764 Vietnamese adults with tuberculous meningitis who were HIV-negative and treated with dexamethasone reported that presence of inflammatory markers in CSF and fatality rates were predicted by *LTA4H* genotype (fatality in 3 [7%] of 42 patients with TT genotype [ie, high inflammatory variant], 40 [21%] of 187 patients with CT genotype [ie, intermediate inflammatory variant], and 39 [19%] of 209 patients with CC genotype [ie, low inflammatory variant]).[15] These findings support the possibility of personalising adjunctive dexamethasone treatment on the basis of *LTA4H* genotype. However, in a study of 427 Indonesian adults with tuberculous meningitis, *LTA4H* variants were not associated with mortality.[16] Addressing these conflicting findings, a Bayesian analysis of both datasets suggested that the TT genotype confers survival benefit in both Vietnamese and Indonesian populations, but the effect might be modified in patients with severe disease, in whom other factors, such as HIV co-infection and Glasgow Coma Scale score, might have a greater influence on outcome than in patients with less severe disease.[17] Whether *LTA4H* genotype could be used clinically to define adjunctive treatment in patients with tuberculous meningitis will depend on the results of an ongoing large randomised controlled trial (NCT03100786) of adjunctive dexamethasone stratified by *LTA4H* genotype.[18]

Other factors can modulate the intracerebral inflammatory response. Data suggest that co-infection with the widely distributed helminth *Strongyloides stercoralis* (*S stercoralis*) can result in reduced concentrations of proinflammatory cytokines in the CSF before treatment and reduced neurological complications by 3 months in adults with tuberculous meningitis.[8] Mechanisms of immunomodulation are uncertain, but *S stercoralis*-induced T-helper-2-cell immune responses could inhibit proinflammatory T-helper-1-cell responses.

Advancing understanding of pathogenesis with new technology

The era of omics (eg, genomics, transcriptomics, proteomics, and metabolomics[8,19]) has allowed new insights into the pathophysiology of tuberculous meningitis. In South Africa, peripheral blood transcriptional responses in 33 people with tuberculous meningitis who were HIV-positive[19] showed more abundant neutrophil-associated transcripts in the 16 people who had immune reconstitution inflammatory syndrome (IRIS) than in those who did not. The inflammatory signal preceded antituberculosis therapy and the onset of tuberculous meningitis-associated IRIS by several weeks, raising the possibility of identifying people at highest risk of IRIS at the start of treatment and providing pre-emptive anti-inflammatory therapy.

Similarly, transcriptional responses by use of RNA sequencing showed distinct immune responses between different CNS compartments in 15 children with tuberculous meningitis compared with 24 healthy controls who had similar immune responses between compartments.[20] Whole blood analysis showed an increase in inflammasome activation and decreased T-cell activation, whereas ventricular CSF transcripts suggested neuronal excitotoxicity and cerebral damage, and lumbar CSF transcripts suggested protein translation and cytokine signalling in children with tuberculous meingitis.

Different pathological states occur simultaneously in the same host, exemplified in dynamic [^{11}C]-rifampicin PET imaging of rabbits with experimentally induced tuberculous meningitis.[21] Radiolabelled imaging allows visual representation of drug tissue penetration, an important consideration when drugs need to cross the blood–brain and blood–CSF barrier. [^{11}C]-rifampicin PET exposures were spatially heterogeneous and variable within brain lesions, and temporal changes in drug exposures occurred over the duration of treatment for tuberculous meningitis, suggesting that this imaging method could be used to assess and optimise the drug therapy of tuberculosis brain lesions.[21] Drug-labelled PET imaging has allowed nuanced characterisation of neuropathological features in tuberculous meningitis in humans.[21]

CSF metabolome analysis on 33 Indonesian adults with tuberculous meningitis who were HIV-negative identified that high tryptophan concentrations in CSF were associated with significantly higher mortality.[22] 11 genetic loci were identified that predicted both tryptophan concentrations in CSF and survival. These findings need validation in a different population but might offer new therapeutic targets for host-directed therapy.

Diagnosis

Diagnostic tests for tuberculous meningitis

Confirming a diagnosis of tuberculous meningitis is challenging because it requires detection of *M tuberculosis* in CSF (table 1). CSF Ziehl-Neelsen staining and microscopy is rapid, inexpensive, and can be performed in many laboratories with few resources. However, a study of 618 individuals with tuberculous meningitis in Vietnam, South Africa, and Indonesia reported that its

	Confirms tuberculous meningitis?*	Principle	Strengths	Limitations	Sensitivity for tuberculous meningitis diagnosis*
Ziehl-Neelsen smear microscopy	Yes†	*M tuberculosis* cell-wall staining	Quick—performed in approximately 30 min; widely available; little equipment required	Poor sensitivity; requires laboratory experience to conduct and interpret	Approximately 10–50%,[23] rarely exceeds 50%[24,25]
GeneXpert MTB/RIF	Yes	*M tuberculosis* DNA identification	Quick—performed in approximately 2 h; offers rifampicin susceptibility if positive	Cannot exclude tuberculous meningitis when negative	Approximately 20–60%[23–28]
GeneXpert MTB/RIF Ultra	Yes	*M tuberculosis* DNA identification	Higher sensitivity than GeneXpert MTB/RIF	Insufficient sensitivity to exclude tuberculous meningitis when negative; not widely available worldwide	44–77% (against individual centre standards of tuberculous meningitis)[24,26,27,29–31]
Loop-mediated isothermal amplification	Yes	*M tuberculosis* DNA identification	Quick—performed in <1 h; can be read by the naked eye	Cannot identify rifampicin resistance	76% (95% CI 56–89; pooled estimate from a meta-analysis of four studies)[32]
Truenat‡	Yes	*M tuberculosis* DNA identification	Preliminary data suggested similar diagnostic accuracy to GeneXpert MTB/RIF for sputum and suspected pulmonary tuberculosis;[33] first study for tuberculous meningitis diagnosis published in 2021 suggested that sensitivity was similar to GeneXpert MTB/RIF Ultra[33]	Single study describing use in patients with tuberculous meningitis	79–86%[33]
Metagenomic next generation sequencing	Yes	*M tuberculosis* DNA identification	Huge potential if technical and analytical challenges can be overcome	Challenging interpretation; expensive; scarce availability	78–84%[34,35]
Lipoarabinomannan	Yes	*M tuberculosis* cell-wall identification	CSF or urine testing is possible; future generations of this test might show improved performance	Low sensitivity	22–33%[36,37]
MGIT	Yes	*M tuberculosis* culture	Allows drug-susceptibility testing	Expensive and slow; requires specialised laboratory facilities	Approximately 25–70%[23–28]
Microscopic observation drug susceptibility testing	Yes	*M tuberculosis* culture	Allows drug susceptibility testing	Labour intensive; faster than MGIT but still too slow to define tuberculous meningitis therapy	Diagnostically equivalent to MGIT[38]
Interferon-γ release assay	No	Immune response to *M tuberculosis*	Based on host response, so overcomes challenges of detecting low bacterial concentrations in CSF	Cannot confirm tuberculous meningitis; can be false negative in active disease; can be indeterminate in immunosuppression; not confirmatory—88% specific in meta-analysis of six studies[39] and 88% specific in meta-analysis of 16 studies for T-SPOT.*TB*[40]	77% (95% CI 69–84; pooled estimate for meta-analysis of six studies);[39] 76% (95% CI 72–80; pooled estimate for meta-analysis for T-SPOT)[40]
Adenosine deaminase	No	Enzyme elevated in patients with tuberculosis and other diseases	Relatively cheap to measure, although variable assays and diagnostic cutoff values	Adenosine deaminase cutoff values uncertain; not confirmatory—91% pooled specificity (95% CI 87–93; meta-analysis of 20 studies);[41] study had substantial heterogeneity and variable cutoff values (cutoff values ranging 6–16 IU/L, 14 of 20 studies used a low cutoff of ≤10 IU/L)	89% (95% CI 84–92; pooled estimate from meta-analysis of 20 studies)[41]

MGIT=mycobacteria growth indicator tube. *M tuberculosis=Mycobacterium tuberculosis*. *Diagnostic sensitivities vary by reference standard used, and individual studies should be reviewed for a full range. Comparison of an index test (eg, GeneXpert MTB/RIF) against more accurate reference standards (eg, against a mycobacterial culture standard [ie, confirmed tuberculous meningitis] rather than against clinical standard [ie, probable tuberculous meningitis]) increases index-test sensitivity, probably through selection of a reference standard with higher bacillary load, in which the index test is more likely to return a positive result than with a lower bacillary load. Specificities of confirmatory tests generally approach 100%, although accurate assessment of specificity of such tests is challenging given that a positive confirmatory test result can rarely be considered a false positive when no other gold-standard comparator test exists. *A confirmatory test detects the presence of *M tuberculosis* in CSF or brain tissue and thus confirms the diagnosis of tuberculous meningitis. †Although non-tuberculous mycobacteria and other bacteria can identify as positive by Ziehl-Neelsen smear microscopy, the presence of these organisms in CSF is sufficiently low to justify calling this test confirmatory. ‡Truenat MTB and Truenat MTB Plus are semi-automated chip-based molecular assays.[42] All confirmatory tests are expected to be highly specific (approaching 100%), although true values are uncertain as a positive test is unlikely to be classified as false positive.

Table 1: **Diagnostic tests for tuberculous meningitis**

sensitivity was generally poor (ie, approximately 30%) and was not improved by adaptations to enhance staining of intracellular bacteria.[23]

PCR-based tests, such as GeneXpert MTB/RIF and GeneXpert MTB/RIF Ultra (Cepheid, Sunnyvale, CA, USA), are rapid and offer identification of rifampicin resistance. Although these tests are useful when positive, the negative predictive values of GeneXpert MTB/RIF and GeneXpert MTB/RIF Ultra are insufficient to rule out tuberculous meningitis.[24] Many other diagnostic tests for tuberculous meningitis exist (table 1), but most research activity in the past 5 years has focused on

GeneXpert MTB/RIF. Large-volume CSF sampling and meticulous processing steps are essential to optimise the performance of smear, culture, and nucleic acid amplification tests. Searching for *M tuberculosis* outside of the CNS (eg, in respiratory samples, such as bronchoalveolar lavage) in people who have relevant neurological symptoms (eg, headache with fever) can also aid diagnosis of tuberculous meningitis.[43]

GeneXpert MTB/RIF Ultra is recommended by WHO as the initial test for extrapulmonary tuberculosis in adults and children,[44] although it is still not widely available in low-income and middle-income countries. The performance of GeneXpert MTB/RIF Ultra for diagnosis of patients with tuberculous meningitis has been assessed in two large[17,24] and many smaller[27,29–31] studies. A prospective randomised study of 205 Vietnamese adults with meningitis (31 [15%] HIV-positive) found that the diagnostic sensitivity of GeneXpert MTB/RIF Ultra was 47·2% (95% CI 34·4–60·3; 25 of 53 patients with *M tuberculosis* were correctly identified) and that of GeneXpert MTB/RIF was 39·6% (27·6–53·1; 21 of 53 patients with *M tuberculosis* were correctly identified; p=0·56 for the comparison of sensitivity between tests), compared against a reference standard of definite, probable, or possible tuberculous meningitis.[24] A study of 204 Ugandan adults (196 [96%] of patients were HIV-positive) with meningitis reported that the sensitivity of GeneXpert MTB/RIF Ultra was 76·5% (95% CI 62·5–87·2; 39 of 51 patients with *M tuberculosis* correctly identified) and that of GeneXpert MTB/RIF was 55·6% (44·0–70·4; 25 of 45 patients with *M tuberculosis* correctly identified; p=0·001 for the comparison of sensitivity between tests), compared against a reference standard of definite or probable tuberculous meningitis.[26] CSF-sampling volume and processing, host and bacillary factors, and variable reference standards could explain the different findings.[28]

Alternative diagnostic platforms to GeneXpert MTB/RIF are emerging (table 2), such as loop-mediated isothermal amplification (LAMP), a test-tube-based DNA amplification technique (TB-LAMP; Eiken Chemical Company, Tokyo, Japan).[47] A meta-analysis of LAMP performance for diagnosis of patients with extrapulmonary tuberculosis reported pooled sensitivity of 76% (95% CI 68–85) and specificity of 99% (96–100) for the identification of *M tuberculosis* in CSF against a composite reference standard (four studies, with a total of 727 patients from China and India).[32] Importantly, however, LAMP tests do not identify rifampicin resistance.

In a study of 108 individuals with definite or probable tuberculous meningitis in India, the semiautomated chip-based PCR assay Truenat MTB (TruPlus, Molbio Diagnostics, Goa, India) showed similar performance to GeneXpert MTB/RIF Ultra for the diagnosis of patients with tuberculous meningitis against a reference standard of definite or probable tuberculous meningitis. Truplus identified 85 [79%] patients with tuberculous meningitis, whereas GeneXpert MTB/RIF Ultra identified 73 [68%] patients with tuberculous meningitis; p=0·059).[33]

Tests for detecting drug-resistant *M tuberculosis*

The ability of GeneXpert MTB/RIF and GeneXpert MTB/RIF Ultra to simultaneously detect *M tuberculosis* and rifampicin resistance enables the identification of patients with tuberculous meningitis that is likely to be multidrug resistant (ie, resistant to at least isoniazid and rifampicin) and the start of life-saving, second-line, antituberculosis drugs. Before these tests, multidrug-resistant tuberculous meningitis was almost always fatal, because the diagnosis came too late through culture and phenotypic drug-susceptibility testing to prompt timely changes to the antituberculosis regimen. Other assays are available (table 1), but all (including GeneXpert MTB/RIF Ultra[48]) have decreased sensitivity when bacterial numbers are low.

Compared with rifampicin resistance, the mechanisms for resistance to other tuberculosis drugs, such as isoniazid, are more complex and not fully understood. As such, the rapid detection of resistance to isoniazid, fluoroquinolone, and aminoglycoside by molecular methods is difficult and an important research priority. Line-probe assays (eg, genotype MTBDR [Hain Life-Science, Nehren, Germany]) can detect both rifampicin and isoniazid resistance, but sensitivity is low from clinical specimens with small numbers of bacteria (table 2).[45] The new GeneXpert MTB/XDR assay detects resistance to isoniazid, fluoroquinolones, and aminoglycosides,[42] but has yet to be evaluated for patients with tuberculous meningitis. A novel CSF diagnostic tool for antimicrobial resistance, combining metagenomic next-generation sequencing with finding low-abundance sequences by hybridisation enrichment, offers promise for detecting multidrug-resistant tuberculous meningitis by identifying multiple antimicrobial resistance mutations, although further clinical data are required to establish its performance.[46]

Future role for novel diagnostic tests

The detection of urinary tuberculosis lipoarabinomannan (ie, a cell-wall component of *M tuberculosis*)[49] offers promise as an inexpensive and convenient point-of-care test. When performed on CSF from 59 adults with HIV and suspected tuberculous meningitis, the first generation lipoarabinomannan test performed poorly on sensitivity (24%, 95% CI 7–50; 4 of 17 patients with tuberculous meningitis correctly identified) and specificity (95%, 84–99; 40 of 42 patients without tuberculous meningitis correctly identified) when compared with the definite or probable tuberculous meningitis reference standard.[36] In a study of 550 patients with suspected tuberculous meningitis from Zambia, 474 (86%) of whom were HIV-positive, sensitivity to detect CSF lipoarabinomannan was 22% and specificity was

	Principle	Drug resistance detected	Strengths	Limitations	Sensitivity for drug resistance in tuberculous meningitis (phenotypic drug-susceptibility testing as reference standard)
GeneXpert MTB/RIF	Genotypic: single-copy gene mutation	Rifampicin	Quick—performed in 2 h	Detects rifampicin resistance only; does not detect isoniazid resistance	92–97%[24,26,27]
GeneXpert MTB/RIF Ultra	Genotypic: single-copy gene mutation	Rifampicin	Quick—performed in 2 h; able to detect trace results in CSF (ie, true positives)	Detects rifampicin resistance only; does not detect isoniazid resistance	92–97%[24,26,27]
GeneXpert MTB/XDR	Genotypic: multiple-copy gene mutations	Fluoroquinolone; isoniazid; amikacin, kanamycin	Quick—performed in 2 h; detects multidrug-resistant tuberculous meningitis or extensively drug-resistant tuberculous meningitis when used as follow-on from GeneXpert MTB/RIF	Requires upgrade of GeneXpert module; no published data on performance in patients with tuberculous meningitis	Unknown
Line probe assay	Genotypic: multiple-copy gene mutations	GenoType MTBDR*plus*: rifampicin and isoniazid; GenoType MTBDR*sl*: fluoroquinolone and amikacin; Genoscholar NTM+MDRTB II: rifampicin and isoniazid	Quick and accurate when used on cultured bacteria—results in 1 day; detect resistance to second-line agents; detect low-level and high-level isoniazid resistance	Low yield on direct CSF; limited to prominent target DNA sequences associated with resistance	Few data; 55%[45]
Genome sequencing	Genotypic: full genome	All current first-line and second-line drugs	Complete drug-susceptibility profile within 1–2 days	Expensive—expertise and extensive training required; DNA sequences associated with resistance not yet known for new and repurposed drugs; performed from cultures, not yet directly from CSF	Unknown[34,46]
Mycobacteria growth indicator tube	Phenotypic: culture based	All drugs, including new and repurposed drugs	Gold standard for resistance testing; initial test for new and repurposed drugs	Slow (ie, 2–6 weeks) to result; labour intensive; requires skilled staff and laboratory	100% (eg, bedaquiline, delamanid, pretomanid, linezolid, clofazimine)

Table 2: **Diagnostic tests for drug-resistant tuberculous meningitis**

94% compared with a diagnosis made with CSF culture.[37] The next-generation SILVAMP TB lipoarabinomannan assay (FujiLAM, Fujifilm, Tokyo, Japan) detects concentrations 30 times lower than the conventional lipoarabinomannan assay and is 35% more sensitive in detecting tuberculosis in adults with HIV.[50] One prospective cohort study of 101 Ugandan adults (of whom 95 participants were HIV-positive) showed that the sensitivity of FujiLAM on CSF was similar to GeneXpert MTB/RIF Ultra (52%, 95% CI 38–65, 30 of 58 participants with tuberculous meningitis correctly identified *vs* 55%, 42–68, 32 of 58 participants correctly identified) against a reference standard of definite or probable tuberculous meningitis.[51] Whether FujiLAM has sufficient sensitivity to assist in the diagnosis of patients with tuberculous meningitis is uncertain.

Metagenomic next-generation sequencing offers a novel option for untargeted pathogen detection in CSF. A retrospective study of 23 patients from China with definite, probable, or possible tuberculous meningitis reported that Torrent NGS platform (BGISEQ, BGI, Tianjin, China) detected *M tuberculosis* DNA sequences in 18 (78%) of these individuals.[34] Another study of 45 individuals with definite, probable, or possible tuberculous meningitis, reported metagenomic next-generation sequencing sensitivity of 84% (95% CI 70–93; 38 of 45 patients with *M tuberculosis* correctly identified) and specificity of 100% (52–100, 6 of 6 patients without *M tuberculosis* correctly identified).[35] These preliminary results are encouraging, but costs and insufficient availability reduce the applicability of this technique.

In a South African study of 47 children diagnosed with tuberculous meningitis, a biosignature of three markers (adipsin, amyloid β42, and IL10) gave 83% (95% CI 61–95) diagnostic sensitivity and 75% (53–90) diagnostic specificity.[52] A Chinese study reported 28 differentially expressed microRNAs in patients with tuberculous meningitis compared with patients who had viral meningitis, suggesting possible diagnostic use.[53] Emerging technologies to characterise the transcriptome, metabolome, and proteome of patients with tuberculous meningitis are likely to identify new molecules and pathways that might become novel diagnostic and therapeutic targets.

Predictors of tuberculous meningitis outcomes

The accurate and early identification of patients at highest risk of complications and death from tuberculous meningitis can help to target resources and treatment to those most in need. The three Medical Research Council grades have been used to categorise tuberculous meningitis severity for nearly 75 years, and the system

strongly predicts death (appendix p 2). Investigators from India suggested creating a new fourth grade, which would define patients at the highest risk of death by deep coma and need for mechanical ventilation.[54] A new prognostic model, developed from studies of 1699 Vietnamese adults with tuberculous meningitis, predicted outcome more accurately than did the Medical Research Council grade or Glasgow Coma Scale score.[55] Accuracy of predictions of poor prognosis and death were improved by a subsequent dynamic prediction model, which was developed from pretreatment and post-treatment data (ie, Glasgow Coma Scale score and serial plasma sodium concentration) from 1048 Vietnamese adults with tuberculous meningitis.[56] These models could be used as clinical tools to identify people with tuberculous meningitis who require critical illness care.

Quantitative measurements of bacillary loads, by use of cycle threshold values, have been shown to predict outcomes. High CSF bacillary load, measured with GeneXpert MTB/RIF, was associated with disease severity and new neurological events in 692 Vietnamese adults with tuberculous meningitis who were HIV-negative.[14] Cycle threshold values for GeneXpert MTB/RIF Ultra in 102 Ugandan adults with tuberculous meningitis who were HIV-positive predicted mortality: low cycle threshold values (ie, high bacillary loads) were associated with a two-fold increase in mortality (57%) compared with high cycle threshold values (ie, low bacillary load; 25%) cycle threshold values.[57] These results raise the possibility of using GeneXpert MTB/RIF cycle threshold values to identify patients at greatest risk of death and who would benefit from additional supportive care.

Little is known about neurocognitive outcomes in the long term following tuberculous meningitis. A study reported worse neurocognitive outcomes in people with HIV-associated tuberculous meningitis than in controls who were HIV-negative,[58] emphasising the potential value of targeted neurorehabilitation in management of tuberculous meningitis.

Management

International guidelines

WHO guidelines for the treatment of drug-susceptible tuberculosis were updated in 2017.[59] They, and other current guidelines, largely focus on pulmonary tuberculosis and recommend similar antituberculosis drug regimens for tuberculous meningitis treatment, albeit with longer durations (table 3).[59,65] British Infection Society guidelines for the diagnosis and treatment of CNS tuberculosis in adults and children were published in 2009 and have not been updated.[66]

The evidence base supporting recommended antituberculosis chemotherapy regimens (ie, drugs, doses, and durations) for patients with tuberculous meningitis is weak due to scarcity of evidence. Recommendations for the treatment of patients with drug-susceptible tuberculous meningitis generally include four drugs (ie, rifampicin, isoniazid, pyrazinamide, and ethambutol) at standard doses for at least 2 months, followed by rifampicin and isoniazid for a further 10 months.[61,65] In August, 2021, WHO issued a rapid communication suggesting that a 6-month intensified regimen for patients with tuberculous meningitis could be used as an alternative to the standard 12 months in children and adolescents,[67] although supporting evidence for this statement from randomised controlled trials is scarce. Although 2010 WHO tuberculosis treatment guidelines[65] recommended that streptomycin should replace ethambutol for treatment of patients with tuberculous meningitis, in practice the side-effects of streptomycin and drug resistance have reduced its use.

Rifampicin is considered a crucial drug in patients with tuberculous meningitis, yet its poor CNS penetration and multiple drug interactions present challenges. Heemskerk and colleagues compared an intensified antituberculosis regimen containing higher dose rifampicin (15 mg/kg per day) and levofloxacin (20 mg/kg per day) for the first 8 weeks of treatment with a standard regimen (10 mg/kg per day rifampicin) in 817 Vietnamese adults with tuberculous meningitis.[68] The group receiving intensified treatment did not have reduced mortality at 9 months.[68]

A phase 2 study of 60 adults with tuberculous meningitis in Indonesia showed that, compared with 10 mg/kg rifampicin per day, 30 mg/kg per day increased plasma and CSF rifampicin concentrations without increasing adverse events.[69] Pharmacokinetic analyses of rifampicin use in 133 Indonesian adults suggested that high rifampicin exposure reduced the risk of death and predicted that doses higher than 30 mg/kg per day might further improve survival.[70] A phase 2, open-label trial of Ugandan adults with suspected tuberculous meningitis showed that high-dose intravenous rifampicin (20 mg/kg/day; geometric mean CSF concentrations 1·74 mg/L) and oral rifampicin (35 mg/kg/day; geometric mean CSF concentrations 2·17 mg/L) were safe and resulted in 6-fold and 8-fold higher CSF concentrations than the standard dose (10 mg/kg/day; geometric mean CSF concentrations 0·27 mg/L), which resulted in subtherapeutic CSF concentrations for 16 (89%) of 18 patients with tuberculous meningitis.[71] Pharmacokinetic studies in the same population showed that rifampicin concentrations in plasma were higher when patients were dosed orally at 35 mg/kg per day than when dosed intravenously at 20 mg/kg per day, supporting further evaluation of high-dose oral rifampicin.[72] Phase 3 trials of high-dose (ie, 30–35 mg/kg) rifampicin are ongoing (ISRCTN15668391, NCT02958709, NCT04021121, NCT04145258, ISRCTN40829906, NCT03927313; table 3).

Metabolism of isoniazid includes acetylation by NAT2, with polymorphism in the *NAT2* gene resulting in fast or slow acetylator phenotypes.[73] Fast acetylation reduces

blood and CSF isoniazid exposures and can impair treatment responses. In a subgroup of participants with tuberculous meningitis (n=237) from Heemskerk and colleagues' intensified antituberculosis treatment trial,[68] low isoniazid exposure predicted death and was linked to the fast acetylator phenotype (ie, 28 of 38 deaths were in fast acetylators).[74] A *NAT2*-stratified trial of higher isoniazid doses (ie, 600 mg per day *vs* 300 mg per day) in patients with tuberculous meningitis is being conducted in China (NCT03787940).

The fluoroquinolones, particularly levofloxacin and moxifloxacin, achieve high CSF exposures after standard oral doses and might improve outcomes. However, aside from the benefit of levofloxacin in people with isoniazid-resistant tuberculous meningitis,[68] there are no clinical trial data to indicate that fluoroquinolones improve survival in people with drug-sensitive tuberculous meningitis.[75] Similarly, linezolid penetrates the CNS well (although co-administration with rifampicin can reduce exposure[76]) and rapidly,[77] yet clinical trial data are scarce. Randomised controlled trials evaluating levofloxacin and linezolid for treatment of patients with tuberculous meningitis are ongoing (NCT04145258, NCT02958709, NCT04021121, NCT03537495, NCT04145258, NCT03927313).

Treatment adherence is an important consideration in management of tuberculosis and is more likely to be an issue with the long regimens used for patients with tuberculous meningitis. Adherence has not been comprehensively studied, but the SURE trial (ISRCTN40829906) evaluating shortened, intensified antituberculosis and anti-inflammatory therapy will address this gap (table 4).

Tuberculous meningitis caused by drug-resistant bacteria

Drug-resistant tuberculous meningitis is difficult to diagnose and optimal therapy is unknown. Isoniazid resistance is common (ie, 20–30% of cases in some settings) and impairs treatment responses in patients with tuberculous meningitis, especially in individuals with HIV.[78] Trials comparing different regimens for isoniazid-resistant tuberculous meningitis have not been conducted, but Heemskerk and colleagues' trial comparing the standard antituberculosis regimen with an intensified regimen of 15 mg/kg rifampicin and

	Guideline focus	Anti-tuberculosis chemotherapy for patients with tuberculous meningitis: main recommendations	Adjunctive therapy or antiretroviral therapy: main recommendations
WHO (2020)[60]	WHO-consolidated guidelines on drug-resistant tuberculosis treatment	Long duration regimens for multidrug-resistant tuberculosis also apply to extrapulmonary disease; treatment of multidrug-resistant tuberculous meningitis is guided by drug-susceptibility testing of the infecting strain; treatment of multidrug-resistant tuberculous meningitis is guided by knowledge of which drugs cross the blood–brain barrier; CNS penetration of individuals agents is discussed	No information
American Thoracic Society, US Centers for Disease Control and Prevention, European Respiratory Society, Infectious Diseases Society of America (2019)[61]	Treatment of drug-resistant tuberculosis	Use of prothionamide and ethionamide in treatment of patients with tuberculous meningitis	Optimal approach to starting antiretroviral therapy in patients with tuberculous meningitis is uncertain[62]
WHO (2017)[59]	Guidelines for treatment of drug-susceptible tuberculosis and patient care—2017 update	In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used	Immediate antiretroviral therapy was significantly associated with more severe adverse events than was initiation of antiretroviral therapy 2 months after the start of tuberculosis treatment[62]
American Thoracic Society, US Centers for Disease Control and Prevention, Infectious Diseases Society of America (2016)[63]	Clinical practice guidelines: treatment of drug-susceptible tuberculosis	Initial therapy is rifampicin, isoniazid, pyrazinamide, and ethambutol—after 2 months of these four drugs, if *Mycobacterium tuberculosis* strain is known or presumed to be susceptible, continue just rifampicin and isoniazid for an additional 7–10 months; optimal duration of chemotherapy is not defined; repeat lumbar punctures should be considered to monitor changes in CSF parameters	Adjunctive corticosteroid therapy with dexamethasone or prednisolone is recommended, tapered over 6–8 weeks

British Infection Society guidelines for the diagnosis and management of tuberculous meningitis were published in 2009.[64] The guidelines listed include the management of patients with tuberculous meningitis, published in the past 5 years. The guidelines are listed in date order, with the most recent first.

Table 3: **International guidelines published since 2015 containing recommendations for the management of patients with tuberculous meningitis, by supporting organisation**

	Registry number	Study population with clinical tuberculous meningitis	Trial type	Setting	Planned sample size
Anti-tuberculosis chemotherapy					
Optimizing antituberculosis therapy in adults with tuberculous meningitis	NCT03787940	Aged 18–65 years	*NAT2*-stratified, randomised, parallel group trial of high-dose isoniazid	China	676
HARVEST	ISRCTN15668391	Aged ≥18 years	Randomised, double-blind, placebo-controlled, phase 3 trial of high-dose rifampicin	Indonesia, South Africa, and Uganda	500
TBM-KIDS	NCT02958709	Aged ≥6 months to <12 years and weight >6 kg	Randomised, open-label, phase 2 trial of high-dose rifampicin and levofloxacin	India and Malawi	120
ALTER	NCT04021121	Aged >18 years	Randomised, open-label, phase 2 trial of high-dose rifampicin and linezolid	Uganda	60
SIMPLE	NCT03537495	Aged ≥18 years	Randomised, open-label, phase 2 trial of high-dose rifampicin and linezolid	Indonesia	36
Adjunctive therapy					
LAST ACT	NCT03100786	Aged ≥18 years without HIV infection	*LTA4H*-stratified, randomised, double-blind, placebo-controlled, phase 3 trial of adjunctive dexamethasone	Vietnam	720
ACT HIV	NCT03092817	Aged ≥18 years with HIV co-infection	Randomised, double-blind, placebo-controlled, phase 3 trial of adjunctive dexamethasone	Vietnam and Indonesia	520
A study for evaluation of utility of indomethacin in tuberculous meningitis in patients	CTRI/2018/02/011722	Any age without HIV infection	Randomised, open-label trial of standard of care plus indomethacin versus standard of care	India	300
Anti-tuberculosis chemotherapy plus adjunctive therapy					
INTENSE-TBM	NCT04145258	Aged ≥15 years	Randomised, placebo-controlled, phase 3, 2 × 2 factorial trial of high-dose rifampicin, linezolid, and aspirin	Ivory Coast, Madagascar, South Africa, and Uganda	768
SURE	ISRCTN40829906	Aged >28 days and <15 years and weight ≥3 kg	Factorial, randomised, phase 3 trial of 6-month intensified tuberculosis-drug regimen and aspirin	India, Uganda, Vietnam, Zambia, and Zimbabwe	400
LASER-TBM	NCT03927313	Aged ≥18 years with HIV co-infection	Randomised, parallel group, multiarm, phase 2a trial of high-dose rifampicin, linezolid, and aspirin	South Africa	100

We searched ClinicalTrials.gov, the ISRCTN registry, and the WHO International Clinical Trials Registry platform for clinical trials in patients with tuberculous meningitis that have either started recruitment or are registered but have not yet started recruitment. Trials are listed in three subsections, then by trial sample size with the largest first. Data correct to Nov 1, 2021. People with and without HIV were included in the population unless otherwise specified.

Table 4: **Planned or ongoing clinical trials evaluating anti-tuberculosis drug regimens and adjunctive therapies**

20 mg/kg levofloxacin for the first 2 months in Vietnam reported that the intensified regimen benefited only participants with isoniazid-resistant tuberculous meningitis (n=86).[78]

Multidrug resistant-tuberculous meningitis is still associated with unacceptably high mortality[78] owing to the absence of a standardised treatment approach and few drug options that adequately penetrate the blood–brain barrier.[79] CNS pharmacokinetic data on the new antituberculosis drugs delamanid, bedaquiline, and pretomanid are scarce. Studies on experimentally induced tuberculous meningitis in rabbits showed that, although delamanid concentrations were markedly lower in CSF than in plasma, they were five-fold higher in brain tissue (9 h after drug administration, mean plasma delamanid concentrations of 96·4 ng/mL *vs* mean brain tissue concentrations of 549·0 ng/mL).[80] Similarly, in rats, pretomanid showed early drug penetration into the rat brain compared with penetration into the lung.[81,82] Little is known about the role of bedaquiline, a highly protein-bound drug, in the treatment of patients with multidrug resistant-tuberculous meningitis.[83] Undetectable CSF concentrations were reported in one human study with tuberculous meningitis,[83] although these findings are complicated by the propensity for bedaquiline to adsorb to plastic during CSF collection and assaying.[84]

Improved understanding of the role of new tuberculosis drugs in patients with multidrug resistant-tuberculous meningitis could be provided through non-invasive dynamic PET imaging and animal models.[21] Studies using whole-body PET, as seen first with rifampicin, have shown detectable concentrations of bedaquiline and linezolid in brains of mice infected

with *M tuberculosis*.[85,86] In the absence of clinical trials, dynamic PET imaging with radiolabelled drugs and through preclinical models could guide future tuberculous meningitis studies[87] and optimal drug regimens for patients with multidrug-resistant tuberculous meningitis.

Host-directed anti-inflammatory drugs

A systematic review of nine randomised controlled trials, including 1337 participants, reported that adjunctive corticosteroids reduced deaths from tuberculous meningitis by almost a quarter (risk ratio 0·75, 95% CI 0·65–0·87)[88] but had no effect on disabling neurological deficits. The mechanism by which corticosteroids confer benefit, and their optimum starting dose or tapering regimen, are still unknown. Whether their beneficial therapeutic effect depends on *LTA4H* genotype and HIV status are important unanswered questions and are the focus of two ongoing trials (NCT03100786, NCT03092817; table 4).

Aspirin acts by irreversibly inhibiting the cyclo-oxygenase pathways of arachidonic acid metabolism and the production of prostanoids involved in inflammation and thrombosis.[12] Anti-inflammatory effects occur at high doses by inhibition of proinflammatory prostaglandins and by triggering the production of specialised proresolving mediators. A phase 2, placebo-controlled trial of adjunctive aspirin in 120 adults with tuberculous meningitis who were HIV-negative suggested that aspirin could reduce brain infarcts and death, especially at a high dose (ie, 1000 mg/day).[12] Aspirin was associated with dose-dependent inhibition of prostanoids and upregulation of specialised proresolving mediators in CSF.[11] Phase 3 trials are now being conducted in adults (NCT04145258, NCT03927313) and children (ISRCTN40829906) to define the role of aspirin in the treatment of patients with tuberculous meningitis.

Immunomodulatory treatment with thalidomide (a TNF inhibitor) has been studied in animals and humans with tuberculous meningitis, with contrasting results.[89] Although thalidomide reduced neuroinflammation and dramatically improved survival in rabbit models of tuberculous meningitis, high dose (ie, 24 mg/kg/day) was associated with increased mortality in the only trial in children with tuberculous meningitis.[90] No further clinical trials of thalidomide have been conducted, but case series have renewed interest in the drug. Thalidomide has been prescribed safely at much lower doses (ie, 3–5mg/kg/day) in 38 South African children with CNS tuberculosis-related complications.[91] Thalidomide appeared to cause clinical and radiological improvement in 16 South African children with progressive tuberculosis cerebral pseudoabscesses[92] and five English adults who had favourable outcomes.[93] Further clinical trials are required to define the role of adjuvant thalidomide in the treatment of patients with tuberculous meningitis.

Infliximab, a selective TNF inhibitor, has been used in adults and children with tuberculous meningitis. Case series have reported that infliximab used as a so-called rescue adjuvant therapy for refractory paradoxical reactions, or tuberculous meningitis-associated vasculopathy, improved clinical outcomes.[93,94] Anakinra (an interleukin-1 inhibitor) has also been used to control tuberculous meningitis-associated paradoxical inflammation.[95] Clinical trials are required to investigate how and when biological agents should be used in the treatment of patients with tuberculous meningitis, while carefully monitoring for aggravation of disease.

HIV co-infection

Initiation of antiretroviral therapy (ART) in patients with tuberculous meningitis is guided by studies published around 10 years ago.[62,96] Drug interactions with rifampicin complicate choice and dose of ART,[64,97] and the timing of ART initiation in individuals with tuberculous meningitis who are ART naive is a challenging clinical issue. The primary risk of early ART initiation is intracerebral IRIS, which occurs after the start of ART in up to 50% of those with tuberculous meningitis and incurs substantial morbidity and mortality.[96] A trial indicated that prednisone given with ART could prevent tuberculosis-associated IRIS,[98] although people with tuberculous meningitis were excluded. Whether corticosteroids prevent and treat tuberculous meningitis-associated IRIS is an important unanswered question.

Only one trial has examined whether to start ART immediately after initiation of antituberculosis drugs during treatment of patients with tuberculous meningitis or to defer for up to 2 months.[62] Immediate commencement of ART was associated with more grade 4 adverse events than was ART given after 2 months, but there was no overall benefit associated with either strategy when compared with each other.[62] A pharmacokinetic substudy in 85 participants reported that ART did not influence tuberculosis drug pharmacokinetics.[99]

Critical illness

The neurocritical care of patients with tuberculous meningitis and management of the common complications (figure) has been reviewed by Donovan and colleagues.[104] A subsequent international survey from 43 countries (with 222 responses) showed substantial variation in supportive care and scarcity of available data to guide the management of critical illness caused by tuberculous meningitis.[105] Attempts to improve care of patients with tuberculous meningitis have included the development of checklists that provide comprehensive tailored proformas for inpatient and critical care assessments, with an additional checklist for acutely deteriorating patients.[106] Studies are required

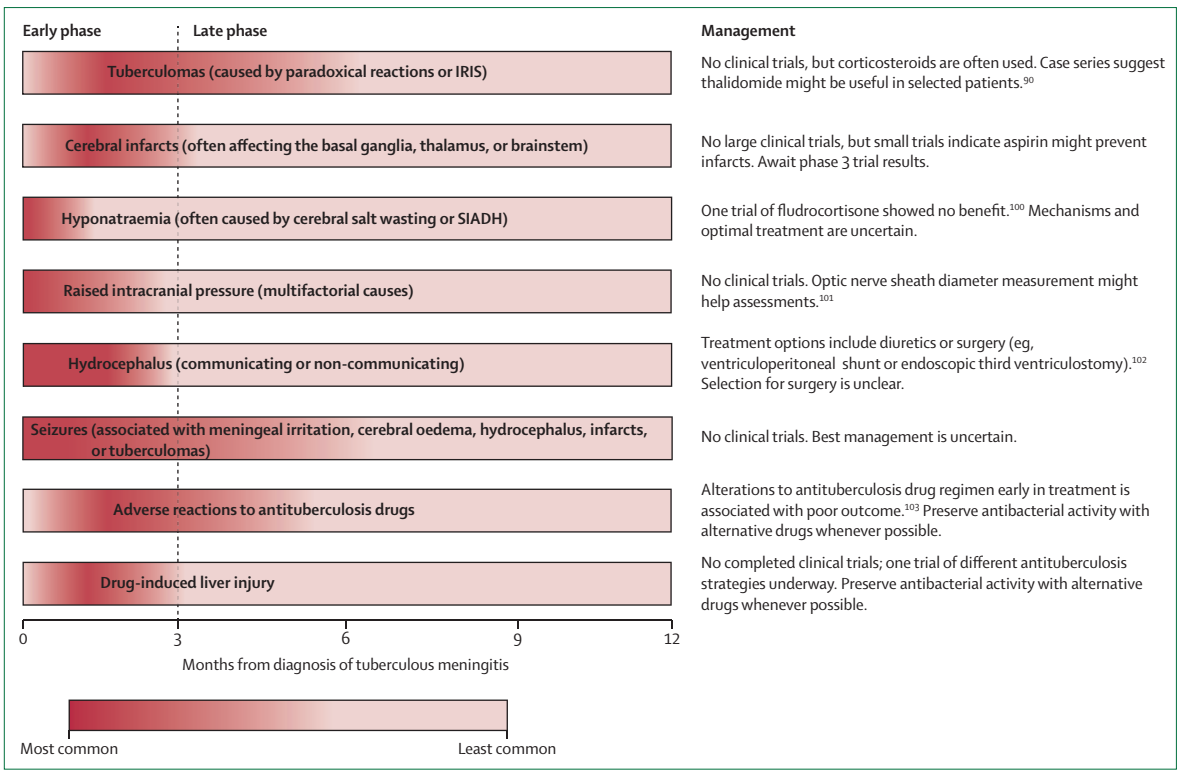

Figure: **Timeline of complications in patients with tuberculous meningitis and evidence for their management**
Early complications occur while the patient is in critical care and during the first 3 months from diagnosis, when most tuberculous meningitis deaths occur; late complications are defined as occurring beyond 3 months. Tuberculous meningitis complications can present at diagnosis and most occur in the early phase. Management of these complications is varied with scarce supporting evidence. In the past 5 years, few clinical trials have been designed to address these areas. IRIS=immune reconstitution inflammatory syndrome. SIADH=syndrome of inappropriate antidiuretic hormone.

to show whether checklists improve clinical outcomes in patients with tuberculous meningitis.

Hydrocephalus is a common complication of tuberculous meningitis, and ventriculoperitoneal shunt insertion and endoscopic third ventriculostomy are often considered. A systematic review and meta-analysis of ventriculoperitoneal shunt insertion in adults with HIV (including three studies and 75 patients) reported 12-month survival of only 33·3%.[107] A systematic review and meta-analysis of endoscopic third ventriculostomy in patients with tuberculous meningitis (including eight studies and 174 patients) estimated that endoscopic third ventriculostomy had a 59% pooled success rate and a 15% complication rate.[102] How patients should be selected for either procedure, the precise timing, and the benefit of surgical shunting are uncertain.

Ultrasound measurement of diameter of the optic nerve sheath, which distends under the influence of raised intracranial pressure, might have a role in the management of patients with tuberculous meningitis. Optic nerve sheath diameter was measured 267 times during the treatment of 107 Vietnamese adults with tuberculous meningitis; higher pretreatment optic nerve sheath diameter was associated with more severe disease and abnormal brain imaging.[101] Further studies are required to define how optic nerve sheath diameter measurements can be used to improve clinical outcomes.

Conclusions and future directions

Major advances in management of patients with tuberculous meningitis are anticipated following the completion of trials evaluating antituberculosis drugs and adjunctive therapy (table 4). Within 5 years, evidence should suggest whether survival from tuberculous meningitis is improved by high doses of rifampicin (ie, 30–35mg/kg) or the addition of levofloxacin or linezolid to treatment regimens. New data should also show whether adjunctive dexamethasone should be used only in people with specific *LTA4H* genotypes, and whether dexamethasone improves outcomes in adults with tuberculous meningitis who are HIV-positive. Uncertainty concerning the use of adjunctive aspirin should be resolved by completion of trials in adults and children. New upcoming treatment options for both drug-susceptible and drug-resistant tuberculosis are expected, with an increasing number of drugs in the clinical development phase.[108] However, studies are limited to patients with pulmonary tuberculosis and yet to include patients with tuberculous meningitis.

Panel: Important unanswered questions in tuberculous meningitis

Burden of disease
- How many adults and children have tuberculous meningitis globally?
- What are the mortality rates of tuberculous meningitis in adults and children in low-income and middle income settings and high-income settings?

Understanding pathogenesis
- What are the underlying mechanisms of cerebral infarctions, tuberculomas, and hydrocephalus?
- How is intracerebral inflammation regulated and controlled by corticosteroids?
- How is pathogenesis different between people with or without HIV?*
- What are the mechanisms of brain injury and their relation to neuroinflammation?*

Diagnosis
- How can we improve sensitivity of pathogen-based testing to improve diagnosis of patients with tuberculous meningitis?
- Does host response-based testing (eg, biomarkers) have a role in diagnosis?*
- What is the role of new point-of-care testing (eg, lipoarabinomannan) in diagnosis?*
- How can we improve detection of drug-resistant tuberculous meningitis, including isoniazid-resistant tuberculous meningitis?
- Which diagnostic test could be used to monitor treatment response in patients with tuberculous meningitis with or without brain abscesses?*

Drug therapy
- What is the optimal dose of rifampicin in the treatment of patients with tuberculous meningitis?

Antimicrobial therapy
- Should fast metabolisers of isoniazid receive higher doses of isoniazid than slow or intermediate metabolisers?*
- Should linezolid or fluoroquinolones be used as alternative fourth antituberculosis drugs to ethambutol?
- Can duration of tuberculous meningitis therapy be shortened?
- What second-line drug combination (ie, dose and duration) improves outcome in patients with drug-resistant tuberculous meningitis?*

Adjuvant therapy
- Should dexamethasone use be stratified by HIV status and *LTA4H* ?
- Does high-dose aspirin have a role in improving mortality and neurodisability?*
- Do thalidomide and biological agents improve outcomes and CNS complications?
- What is the optimal dose and duration of corticosteroid therapy and weaning?

Complications
- Can blood biomarkers be used clinically to predict the development of immune reconstitution inflammatory syndrome or paradoxical reactions?
- What is the best treatment regimen for managing immune reconstitution inflammatory syndrome or paradoxical reactions?
- How can raised intracranial pressure be detected and monitored in low-resource settings?
- What is the optimum management of patients with hydrocephalus (eg, ventricular shunting *vs* diuretic therapy)?
- Does aspirin reduce the development of cerebral infarcts in patients with tuberculous meningitis?
- What causes tuberculous meningitis-associated hyponatraemia and how is it best managed?
- Should patients with brain abscesses and CNS tuberculomas be managed differently to patients with tuberculous meningitis?*

Outcomes
- Can advanced technology (eg, artificial intelligence or machine learning) be used as a tool to improve prediction of treatment responses and outcomes?*

*New questions since the 2013 *Lancet Neurology* Review.[5] Other questions were posed in the previous review but remain unanswered.

Many of the ongoing trials provide a platform for substudies on pathogenesis and diagnostics. Nested multi-omic studies will increase understanding of the immunopathology of tuberculous meningitis, its regulation by host genotype, and novel host-directed therapies that target brain injury and specific inflammatory mediators. The next 5 years are likely to include the exploration and validation of new signatures and biomarkers in blood and CSF and the generation of new diagnostic tests. Their potential role, in combination with current pathogen-based tests, is likely to be an important future contribution to improving survival from tuberculous meningitis.

Brain MRI features that predict future outcome and treatment response are poorly defined. Tools based on artificial intelligence and machine learning are being developed to enable an unbiased and automated assessment of brain images and provide guidance to clinicians on treatment response and outcomes. Artificial intelligence and machine learning, particularly when applied to digital brain imaging, have been implemented to devise diagnostic, complication prediction, and outcome prediction systems for neurodegenerative disorders, demyelinating disorders of the brain, and acute ischaemic strokes.[109,110] Machine learning in tuberculous meningitis is likely to assist in

Search strategy and selection criteria

We searched PubMed using each of the search terms "tuberculous meningitis", "TB meningitis", "TBM", "Tuberculosis", and "meningeal", with each of "prevention", "pathology", "pathophysiology", "diagnosis", "treatment", "management, "drug-resistant", "multidrug-resistant", "bedaquiline", "delamanid", and "pretomanid", for articles published between July 1, 2015, and Nov 1, 2021. We identified additional articles through relevant references of selected papers. Only publications in English were reviewed. The final reference list was selected on the basis of originality and relevance to the broad scope of this Review.

diagnosis and individualised treatment decisions in the future.

Lastly, non-invasive [^{11}C]-rifampicin-labelled PET imaging has been used to successfully track antibiotic penetration into and concentrations in infected brain lesions of rabbits with experimentally induced tuberculous meningitis.[21] If this technique can be applied to humans, it could allow clinicians to tailor antibiotic regimens to patients who are at risk of not responding to treatment or those who require optimised or prolonged antituberculosis therapy.

Substantial progress had been made in the past 5 years, with better molecular diagnostic tests than previously available, and better understanding of disease mechanisms and how antituberculosis drugs and anti-inflammatory agents might improve outcomes. Many important questions exist concerning the optimal management of patients with tuberculous meningitis (panel), but there are more clinical trials ongoing or planned to address these questions than at any time in history. Notable advances are anticipated in the coming 5 years, which should alleviate the effects of this devastating infectious disease.

Contributors

GET, JH, and JD conceptualised the manuscript. JH and JD conducted the literature search and wrote the first draft of the manuscript, which was subsequently reviewed and revised by all authors before submission for publication.

Declaration of interests

We declare no competing interests.

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