Tuberculous meningitis: advances in diagnosis and treatment

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Abstract

Introduction: Tuberculous meningitis (TBM) is the most severe form of infection caused by Mycobacterium tuberculosis, causing death or disability in more than half of those affected. The aim of this review is to examine recent advances in our understanding of TBM, focussing on the diagnosis and treatment of this devastating condition.

Sources of data: Papers on TBM published between 1891 and 2014 and indexed in the NCBI Pubmed. The following search terms were used: TBM, diagnosis, treatment and outcome.

Areas of agreement: The diagnosis of TBM remains difficult as its presentation is non-specific and may mimic other causes of chronic meningoencephalitis. Rapid recognition of TBM is crucial, however, as delays in initiating treatment are associated with poor outcome. The laboratory diagnosis of TBM is hampered by the low sensitivity of cerebrospinal fluid microscopy and the slow growth of M. tuberculosis in conventional culture systems. The current therapy of TBM is based on the treatment of pulmonary tuberculosis, which may not be ideal. The combination of TBM and HIV infection poses additional management challenges because of the need to treat both infections and the complications associated with them.

Areas of controversy: The pathogenesis of TBM remains incompletely understood limiting the development of interventions to improve outcome. The optimal therapy of TBM has not been established in clinical trials, and increasing antimicrobial resistance threatens successful treatment of this condition. The use of adjunctive anti-inflammatory agents remains controversial, and their mechanism of action remains incompletely understood.
The role of surgical intervention is uncertain and may not be available in areas where TBM is common.

**Growing points:** Laboratory methods to improve the rapid diagnosis of TBM are urgently required. Clinical trials of examining the use of high-dose rifampicin and/or fluoroquinolones are likely to report in the near future.

**Areas timely for developing research:** The use of biomarkers to improve the rapid diagnosis of TBM warrants further investigation. The role of novel anti-tuberculosis drugs, such as bedaquiline and PA-824, in the treatment of TBM remains to be explored. Human genetic polymorphisms may explain the heterogeneity of response to anti-inflammatory therapies and could potentially be used to tailor therapy.

**Key words:** tuberculosis, meningitis, tuberculous meningitis, diagnosis, treatment

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**Introduction**

Tuberculous meningitis (TBM) is the most frequent form of central nervous system (CNS) tuberculosis.\(^1\) CNS disease accounts for only 5% of all cases of extra-pulmonary tuberculosis and peak incidence is in children under 4 years of age.\(^2\) However, the number of adults presenting with TBM has increased as a result of the HIV epidemic. The presenting clinical features and CSF features of TBM have been extensively described\(^3\)–\(^9\) and are summarized in Table 1. The classic presentation is with a subacute meningitic illness, which can be difficult to distinguish from other causes of meningoencephalitis. Once the neurological symptoms of advanced disease are present (e.g. coma, seizures, raised intracranial pressure and hemiparesis), the diagnosis is apparent but the prognosis is poor. TBM is classified into three grades of severity according to the British Medical Research Council TBM grade.\(^10\) Grade 1 TBM is defined as a Glasgow coma score (GCS) of 15 with no focal neurology, Grade 2 TBM as a GCS of 15 with a focal neurological deficit, or a GCS of 11–14 and Grade 3 TBM is defined as a GCS of ≤10. The importance of this classification system is that it enables stratification of patients and is useful to predict prognosis.

Unusual neurological presentations of TBM may result in diagnostic difficulty.\(^11\)–\(^13\) Movement disorders may occur after infarction of the basal ganglia and present with tremor, chorea, ballismus or myoclonus.\(^14\) Some children may present with ‘tuberculous encephalopathy’ with disseminated tuberculosis but without clinical or CSF evidence of meningitis.\(^12,13\) TBM with spinal involvement, which presents as paraplegia, occurs in <10% of cases.\(^10\) Vertebral tuberculosis (Pott’s disease) accounts for about a quarter of patients with spinal TBM and may be associated with paravertebral abscess or a gibbus. Extra-dural cord tuberculomas account for over 60% of cases of non-osseous paraplegia, although tuberculomas may occur in any part of the cord.\(^15\) Tuberculous radiculomyelitis rarely occurs in TBM and is characterized by subacute paraparesis, radicular pain and bladder dysfunction.\(^16\)

TBM can also cause metabolic complications, the commonest of which, hyponatraemia, affects >50% of patients with the disease.\(^3\) A ‘cerebral salt-wasting syndrome’ associated with TBM and attributed to a renal tubular defect.\(^17\) The discovery of a syndrome of inappropriate antidiuretic hormone as a cause of hyponatraemia led to speculation of a similar mechanism causing TBM-associated hyponatraemia.\(^18\) However, many patients with TBM-associated hyponatraemia have low plasma volumes and persistent natriuresis despite normal concentrations of antidiuretic hormone (ADH).\(^19\) Although a role for ADH has not been excluded, ‘hyponatraemic natriuretic syndrome’ is probably a better term for this condition. Despite these investigations, the best method of correcting the plasma sodium
concentration remains unknown; sodium and fluid replacement is probably indicated in hypovolaemic hyponatraemia, whereas fluid restriction may be more appropriate in those who are euvoalaemic. There is anecdotal evidence to suggest that fludrocortisone replacement therapy and demeclocycline may also be useful.

Pathogenesis of TBM

The first description of TBM dates back to 1836 when six cases of acute hydrocephalus in children characterized by ‘an inflammation of the meninges, with the deposit of tubercular matter in the form of granulations, or cheesy matter’ were described in the Lancet. The author concluded that the children had died of ‘tubercular meningitis’, a disease similar in nature to other previously described conditions characterized by tubercles, such as tubercular peritonitis. The microbiological cause of tuberculosis was not identified until 1882 when Robert Koch stained and cultured the bacterium that caused tuberculosis and subsequently became known as Mycobacterium tuberculosis. Fifty years later, two pathologists Rich and McCordock demonstrated, using a series of experiments in rabbits and post-mortem findings in children, that TBM was caused by release of M. tuberculosis bacilli into the meningeal space from focal sub-pial or sub-ependymal lesions, which were most commonly located in the Sylvian fissure. Three pathological processes account for the commonly observed neurological deficits: the exudate may obstruct CSF flow resulting in hydrocephalus; granulomas can coalesce to form tuberculomas or abscesses resulting in focal neurological signs and an obliterator vasculitis can cause infarction and stroke syndromes. More recently, a study examining the radiological features of TBM showed that the most common abnormalities seen on cerebral magnetic resonance imaging (MRI) were basal meningeal enhancement and hydrocephalus. Tuberculomas developed in 74% of patients during the course of TB treatment and the basal ganglia were the most common site of infarction.

Table 1 Clinical features of tuberculous meningitis in children and adults

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Clinical findings</th>
<th>CSF findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children Early symptoms are non-specific and include fever, cough, vomiting, malaise and weight loss.</td>
<td>Apathy, irritability, meningitis, reduced level of consciousness, bulging anterior fontanelle (infants), VI cranial nerve palsy, optic atrophy, abnormal movements and focal neurological signs, e.g. hemiplegia</td>
<td>Usually clear and colourless, raised white cell count (0.5–1×10⁹/l) with neutrophils and lymphocytes</td>
</tr>
<tr>
<td>Duration of symptoms &gt;6 days Seizures more common in children than in adults</td>
<td></td>
<td>Raised protein (0.5–2.5 g/l)</td>
</tr>
<tr>
<td>Adults Prodomal period with low-grade fever, malaise, weight loss followed by gradual onset of headache (1–2 weeks). Worsening headache, vomiting, confusion, coma.</td>
<td>Neck stiffness, confusion, coma Cranial nerve palsies—VI, III, IV Focal neurological signs, e.g. monoplegia, hemiplegia, paraplegia</td>
<td>High opening pressure &gt;25 cm</td>
</tr>
<tr>
<td>Duration of symptoms ≥6 days</td>
<td>Urinary retention</td>
<td>Raised white cell count (0.05–1×10⁹/l) with neutrophils and lymphocytes</td>
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<tr>
<td></td>
<td></td>
<td>Raised protein (0.5–2.5 g/l)</td>
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<tr>
<td></td>
<td></td>
<td>CSF to plasma glucose ratio &lt;0.5 in 95% of cases</td>
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The numbers and types of white cells in the CSF may help to differentiate TM from other meningitides, but little is known of their role in disease pathogenesis. Typically, the CSF shows a high CSF white cell count, which is predominantly lymphocytic, with a high protein and low CSF to blood glucose ratio. However, total CSF white cell count can be normal in those with TBM and depressed cell-mediated immunity, such as the elderly and HIV-infected individuals. A low
CSF cell count has also been associated with poor outcome. Neutrophils can predominate, especially early in the disease, and a high proportion of neutrophils in the CSF has been associated with an increased likelihood of a bacteriological diagnosis and improved survival. Thus, neutrophils may play a role in the pathogenesis of TBM. The kinetics of the lymphocyte response are probably also important, particularly the roles of different lymphocyte subsets.

Although TBM is associated with inflammation in the CNS, there is conflicting evidence on the role of tumour necrosis factor (TNF)-α in the pathogenesis of TBM. The release of \textit{M. tuberculosis} into the subarachnoid space results in a local T lymphocyte-dependent response, characterized by caseating granulomatous inflammation. In pulmonary tuberculosis, TNF-α is thought to be important in granuloma formation. Studies of acute bacterial meningitis showed that CSF concentrations of TNF-α correlated with disease severity, and study in a rabbit model of TBM found that high CSF concentrations were associated with a worse outcome. In humans, however, TNF-α concentrations were not correlated with disease severity or outcome. Treatment with antibiotics and thalidomide (a TNF-α antagonist) improved survival and neurological outcome in rabbits. Preliminary research in humans found that thalidomide was safe and well tolerated, but a clinical trial of adjunctive thalidomide in children with TBM was stopped early because of lack of benefit and an excess number of adverse events in the thalidomide arm.

The role of other inflammatory mediators in the pathogenesis of TBM has also been explored. Thwaites and colleagues measured concentrations of pro- and anti-inflammatory cytokines in serial blood and CSF samples from 21 Vietnamese adults with TBM. CSF concentrations of soluble TNF-α receptors, matrix metalloprotein-9 (MMP-9) and its tissue inhibitor were measured, and blood–brain barrier permeability was assessed. Pre-treatment CSF concentrations of lactate, IL-8 and IFN-γ were high and then decreased rapidly during treatment, but significant immune activation and blood–brain barrier dysfunction were still apparent after 2-month treatment. Death was associated with high CSF

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose in children</th>
<th>Dose in adults</th>
<th>Duration</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>10–20 mg/kg/day</td>
<td>450 mg (weight &lt;50 kg)</td>
<td>12 months</td>
<td>Orange, discoloration of bodily fluids, hepatitis, gastrointestinal symptoms, headache, drowsiness, hepatitis, peripheral neuropathy</td>
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<td></td>
<td>(maximum 600 mg/day)</td>
<td>600 mg (weight &lt;50 kg)</td>
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<tr>
<td>Isoniazid</td>
<td>15–30 mg/kg/day</td>
<td>1.5 g (weight &lt;50 kg)</td>
<td>2 months</td>
<td>Hepatitis, red/green colour blindness, peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td>(maximum 500 mg/day)</td>
<td>2 g (weight &lt;50 kg)</td>
<td></td>
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<tr>
<td>Pyrazinamide</td>
<td>15–20 mg/kg/day</td>
<td>15 mg/kg (weight &lt;50 kg)</td>
<td>2 months</td>
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<tr>
<td></td>
<td>(maximum 2 g/day)</td>
<td>2 g (weight &lt;50 kg)</td>
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<tr>
<td>Ethambutol</td>
<td>15–20 mg/kg/day</td>
<td>15 mg/kg (weight &lt;50 kg)</td>
<td>2 months</td>
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<tr>
<td></td>
<td>(maximum 1 g/day)</td>
<td>2 g (weight &lt;50 kg)</td>
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concentrations of lactate, low numbers of white blood cells, in particular neutrophils, and low CSF glucose levels. A second study examined the relationship between pre-treatment intracerebral and peripheral immune responses and outcome in Vietnamese adults. Baseline CSF IL-6 concentrations were independently associated with severe disease at presentation. Surprisingly, however, elevated CSF inflammatory cytokines were not associated with death or disability in HIV-negative TBM patients. HIV infection attenuated multiple cerebrospinal fluid inflammatory indices. Low CSF IFN-γ concentrations were independently associated with death in HIV-positive but not in HIV-negative individuals. A third study examined CSF inflammatory markers in patients enrolled in a study of adjunctive corticosteroids in TBM. Prolonged inflammatory responses were detected in all TBM patients irrespective of treatment assignment (placebo or dexamethasone). Dexamethasone significantly modulated acute cerebrospinal fluid protein concentrations and marginally reduced IFN-γ concentrations but did not affect immunological and routine biochemical indices of inflammation or peripheral blood monocyte and T-cell responses to M. tuberculosis antigens.

Host and pathogen genetics in TBM

The findings reported above challenged previous assumptions about anti-inflammatory effects of corticosteroids in this disease. A potential explanation for this came from studies of mycobacterial infections in a zebrafish model. A polymorphism in the leukotriene A4 hydrolase (LTA4H) gene, which controls the balance of pro-inflammatory and anti-inflammatory eicosanoids, was found to influence susceptibility of zebrafish to Mycobacterium marinum infection and humans to tuberculosis. Furthermore, in humans with TBM, the polymorphism was associated with inflammatory cell recruitment, patient survival and response to adjunctive corticosteroids. These findings provide a possible explanation for the failure to find a mechanism by which corticosteroids improved survival in TBM and suggest the possibility of using host-directed therapies tailored to patient LTA4H genotypes.

A number of studies have sought to investigate the potential role of host genetic factors in the immunopathogenesis of TBM. Hawn and colleagues hypothesized that polymorphisms in toll-interleukin 1 receptor domain containing adaptor protein (TIRAP), an adaptor protein that mediates signals from toll-like receptors activated by mycobacteria, were associated with susceptibility to tuberculosis. They found that the TIRAP single-nucleotide polymorphism (SNP) C558T was associated with increased susceptibility to TB. Subgroup analysis revealed that SNP 558TT was more strongly associated with susceptibility to meningeal TB than to pulmonary TB. The 558TT genotype was associated with decreased whole-blood interleukin-6 production (compared with the 558CC genotype), suggesting that TIRAP influences disease susceptibility by modulating the inflammatory response. A second study examined the influence of polymorphisms in toll-like receptor 2 (TLR2) on bacterial dissemination and the development of TBM. The TLR2 genotype 597CC was associated with increased susceptibility to TB and was more strongly associated with meningeal than pulmonary TB. This association was strongest in patients with TBM and miliary TB. Furthermore, the association increased with increasing disease severity, indicated by TBM grade. These results demonstrate a strong association of TLR2 SNP T597C with the development of TBM and miliary TB and suggest that TLR2 influences the dissemination of M. tuberculosis.

A third study compared host and bacterial genotype in Vietnamese adults with TBM and pulmonary tuberculosis. The host genotype of tuberculosis cases was also compared with the genotype of cord blood controls from the same population. Isolates of M. tuberculosis were genotyped by large sequence polymorphisms. The hosts were defined by polymorphisms in genes encoding TIRAP and TLR-2. The study found a significant protective association between the Euro-American lineage of M. tuberculosis and pulmonary (rather than meningeal tuberculosis), suggesting these strains were less capable of extra-pulmonary dissemination than others in the study population. It also found that individuals with TLR-2 T597C allele were more likely to have tuberculosis caused by the East-Asian/Beijing genotype.
than other individuals, thus providing evidence that *M. tuberculosis* genotype influenced disease phenotype and that there was a significant interaction between host and bacterial genotypes and the development of tuberculosis.

**Laboratory diagnosis of TBM**

The laboratory diagnosis of TBM is summarised in Table 2. Despite being developed over 100 years ago, the acid-fast smear remains the most commonly used method to diagnose TB. A fixed smear of a clinical specimen (e.g. sputum) is covered with carbol fuschin, heated and decolourized with acid-alcohol before being counterstained with methylene blue. Mycobacteria appear as red, slightly bent, beaded rods, 2–4 μm in length and 0.2–0.5 μm wide. An estimated 10,000 organisms are required for a smear positivity resulting in poor sensitivity of this test, particularly in paucibacillary disease. Fluorescent microscopy is more sensitive and has a higher throughput than light microscopy, but the equipment and bulbs are more expensive.48 The development of light-emitting diode (LED) fluorescent microscopy has overcome some of these issues49,50 and is now recommended by the World Health Organisation.51 In TBM, early studies reported extremely high sensitivity rates for smear microscopy,52,53 but these have proved difficult to reproduce in routine laboratories.54 Thwaites and colleagues33 identified a number of factors associated with improved diagnostic rates such as culture of a large volume (>5 ml) of CSF and examination of the slide for 30 min. A recent study from China reported increased sensitivity with pre-treatment of CSF leukocytes with triton prior to ZN staining.55

The microscopic observation drug-susceptibility assay (MODS) is a liquid culture assay that uses Middlebrook 7H9 broth culture and an inverted microscope to detect mycobacterial growth.56 This technique has been evaluated in a number of studies and has been found to be useful for the diagnosis of tuberculosis and the detection of drug resistance, in a number of settings.57 It has also been evaluated for the diagnosis of TBM and was found to be more sensitive than CSF smear, and more rapid than conventional TB culture (with a median time to positivity of 6 days), although drug susceptibility testing was not performed in this study.58

Nucleic acid amplification tests (NAAT) can detect fewer than 10 organisms that can be used to identify *M. tuberculosis* in clinical specimens or cultures. The polymerase chain reaction (PCR) is the most common methodology, but alternatives include real-time PCR, isothermal, strain displacement or transcription-mediated amplification and ligase chain reaction.59 The literature on NAATs has been extensively reviewed, and has shown that the specificity of NAATs is high but sensitivity is variable.59,60 Sensitivity is highest in smear-positive respiratory samples and lower in smear-negative samples and in non-respiratory disease. Thus, a negative result does not rule out the diagnosis of TB in these situations.

Recently, line-probe assays (LPAs) and the Xpert MTB/RIF (Cepheid, Sunnyvale, USA) have been formally endorsed by the World Health Organisation and are now in routine use in middle- and high-income countries. The two LPAs—INNO-LiPA Rif. TB (Innogenetics, Gent, Belgium) and Genotype MTBDRplus (Hain LifescienceGmbH, Nehren Germany)—are currently available for the detection of *M. tuberculosis* in clinical specimens and culture isolates. They are based on PCR of specific fragments of the *M. tuberculosis* genome followed by hybridization of PCR products to oligonucleotide probes immobilized on membranes. A single study from China has evaluated the use of the Genotype MTBDRplus assay in the diagnosis of TBM and found it to be useful in the rapid diagnosis of drug-resistant tuberculosis.61

The Xpert MTB/RIF is a fully automated RT–PCR based assay for the detection of *M. tuberculosis* and rifampicin resistance in clinical specimens. In sputum smear-positive samples, studies have reported sensitivities ranging from 93 to 98% and specificities if 83–99%.62 The introduction of Xpert MTB/RIF assays has increased the confirmation rate in patients with suspected TB in high-burden countries such as India, Uganda and South Africa.63 One of the key concerns about rolling out this technology in areas with a low prevalence of rifampicin resistance, however, is the low positive predictive value of the test, which means that most resistant results will
be false positives. Several studies have evaluated the use of Xpert MTB/RIF for the diagnosis of TBM.\textsuperscript{64} A South African study of 204 patients (87% HIV infected) found that the sensitivity of Xpert MTB/RIF was higher than that of smear microscopy (62 versus 12%; \(P = 0.001\)), and for centrifuged compared with non-centrifuged specimens.\textsuperscript{64} A Vietnamese study of 182 patients found that the sensitivity of Xpert MTB/RIF was slightly higher than smear microscopy (59.3 versus 51.8%).\textsuperscript{65} There was one false-positive result (giving a specificity of 99.5%) and four cases of rifampicin resistance, three of which were confirmed to be multidrug resistant by phenotypic tests. A third study compared the Xpert MTB/RIF assay with the Roche Amplicor assay and found similar rates of sensitivity and specificity.\textsuperscript{66}

Interferon-\(\gamma\) release assays (IGRAs) for the diagnosis of active and latent TB have been extensively reviewed.\textsuperscript{67,68} While IGRAs have been shown to be of limited value in the diagnosis of pulmonary TB,\textsuperscript{69} their application to site-specific lymphocytes may be of diagnostic benefit.\textsuperscript{70} Several recent studies have examined the utility of CSF IGRAs and found variable sensitivity, a high rate of indeterminate results and a requirement for large volumes of CSF.\textsuperscript{71–74}

Over the past 30 years, a number of studies have investigated the detection of antibodies to \textit{M. tuberculosis} or its antigens within the CSF. While many of these looked promising in preliminary studies, they have failed to be translated into routine clinical care. Two recent studies have reported interesting results. The first study used a real-time quantitative PCR and ELISA to detect a panel of \textit{M. tuberculosis} antigens (GlcB, HspX, MPT51, Ag85B and PstS1) in 532 Indian children with TBM.\textsuperscript{75} In patients with definite TB, sensitivity and specificity were 100 and 96–97\%, respectively, and in those with probable/possible TB, the sensitivity and specificity were 98\%. The combination of PCR with GlcB and HspX ELISAs accurately detected all patients with TBM with 90\% specificity. A second study used a polyvalent rabbit IgG to \textit{M. tuberculosis} to stain antigen-specific CSF leucocytes.\textsuperscript{76} A diagnostic evaluation of 393 CSF samples revealed a sensitivity of 73.5 and a specificity of 90.7\%.

Given the low sensitivity of standard diagnostic methods, attempts have been made to investigate biomarkers to diagnose TBM. Cerebrospinal fluid lactate levels have been used as a diagnostic marker for central nervous system infections. Lactate is produced by bacterial anaerobic metabolism, and increased CSF levels have been reported in patients with bacterial meningitis\textsuperscript{77–81} and TBM.\textsuperscript{32} Clinical experience in Vietnam suggests that CSF lactate levels of 5–10 mmol/l support a diagnosis of TBM, and that high initial levels are associated with death.\textsuperscript{32} However, this marker has not been formally validated as a diagnostic test for TBM.

The adenosine deaminase (ADA) activity test is a rapid test that has been used for the diagnosis of the pleural, peritoneal and pericardial forms of tuberculosis. A systematic review of 522 studies of ADA values in TBM cases and controls (diagnosed with other types of meningitis) has been reported.\textsuperscript{82} Out of a total of 522 studies, 13 studies (380 patients with TBM) were included in the meta-analysis. The sensitivity, specificity and diagnostic odds ratios (DOR) were calculated based on arbitrary ADA cut-off values from 1 to 10 U/l. ADA values from 1 to 4 U/l (sensitivity >93\% and specificity <80\%) helped to exclude TBM; values between 4 and 8 U/l were insufficient to confirm or exclude the diagnosis of TBM (\(P = 0.07\)), and values >8 U/l (sensitivity <59\% and specificity >96\%) improved the diagnosis of TBM (\(P < 0.001\)). None of the cut-off values could be used to discriminate between TBM and bacterial meningitis. In conclusion, ADA cannot distinguish between bacterial meningitis and TBM, but using ranges of ADA values could be important to improve TBM diagnosis, particularly after bacterial meningitis has been ruled out. However, the different methods used to measure ADA and the heterogeneity of data limit the diagnostic use of this test.

A recent study evaluated the performance of number of diagnostic tests in 506 patients in with microbiologically confirmed TBM in Albania, Croatia, Denmark, Egypt, France, Hungary, Iraq, Italy, Macedonia, Romania, Serbia, Slovenia, Syria and Turkey between 2000 and 2012.\textsuperscript{83} The study included the following tests: Ziehl Neelsen stain (ZN), CSF \textit{M. tuberculosis} polymerase chain reaction assay (CSF PCR), CSF automated culture system (CSF ACS) and Lowenstein Jensen (LJ) culture,
IGRA and ADA activity. The sensitivities of the tests were as follows: IGRA 90.2%, ACS 81.8%, LJ culture 72.7%, ADA 29.9% and ZN 27.3%. CSF ACS was superior to CSF LJ culture and CSF PCR (< 0.05 for both), and CSF LJ culture was also superior to CSF PCR (< 0.05). The combination CSF LJ and CSF ACS was superior to using these tests alone (< 0.05). However, because of the delays incurred by culture-based methods, the combined use of non-culture tests could contribute to early diagnosis. The authors concluded that diagnostic approach to TBM should be individualized according to the technical capacities of medical institutions, particularly in those with poor resources.

A study by Kataria and colleagues performed proteomic analysis and two-dimensional electrophoresis on the CSF of patients with and without TBM. They identified 11 human proteins and 8 mycobacterial proteins as possible diagnostic markers. One human protein, arachidonate 5-lipoxygenase (ALOX-5), was validated in a second experiment and differentiated TBM from fungal meningitis. ALOX-5 is an enzyme in the metabolic pathway of leukotriene B4 and lipoxin and has been shown to have a role in the pathogenesis of TBM in mice. Genetic studies in humans have also shown higher susceptibility to pulmonary tuberculosis in ALOX+ variants.

**Treatment of TBM**

The modern era of tuberculosis treatment began in 1948 with the demonstration of the efficacy of streptomycin in the treatment of pulmonary tuberculosis. This was followed by the introduction of isoniazid in 1952 and rifampicin in 1971, which revolutionized the treatment of TB. Over the next few years, a number of clinical trials, using combinations of antituberculosis drugs, were conducted by the British Medical Research Council. Combination therapy enabled the duration of treatment to be reduced from 2 years, prior to rifampicin, to 6 months with rifampicin, isoniazid and pyrazinamide.

In contrast to pulmonary TB, the optimal therapy of TBM has not been determined in clinical trials. Current guidelines recommend a 2-month initiation phase with four drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) followed by a 10-month continuation phase of two drugs (rifampicin and isoniazid) (Table 3). In some settings such as South Africa and Vietnam, shorter continuation phases of 4 to 7 months are recommended. The treatment of drug-resistant TBM has likewise not been systematically investigated in clinical trials, and detailed recommendations are beyond the scope of this review. A prospective study of 180 Vietnamese adults with TBM found resistance to at least one drug in 40% of patients and resistance to rifampicin and isoniazid (multidrug resistance) in 5.6% of patients. Resistance to isoniazid and/or streptomycin was associated with slower clearance of bacteria from the CSF, but there were no differences in outcome. Multidrug resistance was independently associated with HIV infection and was strongly predictive of death (relative risk 11.63, 95% confidence interval 5.21–26.32). A larger retrospective study conducted in the USA between 1993 and 2005 included 1896 patients with a clinical diagnosis of TBM and positive cultures from any site. Six per cent of patients had isoniazid-resistant cultures on initial susceptibility testing. Among 1614 patients with positive cerebrospinal fluid cultures, a significant unadjusted association was found between initial isoniazid resistance and subsequent death (odds ratio 1.61, 1.08–2.40). This association increased after adjustment for age, race, sex, and HIV status (odds ratio 2.07, 1.30–3.29).

Two recent studies have investigated the role of intensified therapy for TBM. The first was randomized controlled trial with three parallel arms that compared the effect of adding a fluoroquinolone (ciprofloxacin, levofloxacin or gatifloxacin) with standard therapy in 61 Vietnamese adults with TBM. The CSF penetration was greater for levofloxacin than gatifloxacin or ciprofloxacin. Surprisingly, worse outcomes were recorded in patients with lower and higher fluoroquinolone exposures, than those with intermediate exposures. Those with high exposures were older and tended to have more severe disease, which may have resulted in greater blood–brain barrier breakdown. A second study conducted in Indonesia investigated the use of high (600 mg) or standard (450 mg) dose rifampicin and high (800 mg) or standard (400 mg) dose moxifloxacin in 60 Indonesian adults with TBM. High-dose rifampicin resulted in an increase...
<table>
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<th>Principles of test</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>CSF smear</td>
<td>CSF sample (10 ml) centrifuged and deposit stained with Ziehl Neelsen stain or fluorescent stain and visualized under a light or fluorescence microscopy</td>
<td>Universally available, quick, inexpensive</td>
<td>Low sensitivity in routine diagnostic laboratories</td>
</tr>
<tr>
<td>CSF culture</td>
<td>CSF inoculated into liquid culture media (e.g. Mycobacterial Growth Indicator Tube, Becton Dickinson) and incubated for 42 days. Growth detected by fluorescence resulting from consumption of oxygen by mycobacteria.</td>
<td>Faster and more sensitive than solid culture—median time to detection 10–14 days; ability to perform first-line drug susceptibility testing</td>
<td>Only available at reference laboratory level rather than district/peripheral level. Requires containment Level 3 facilities and laboratory expertise</td>
</tr>
<tr>
<td>MODS culture</td>
<td>CSF deposit inoculated into a microtitre plate and incubated. Growth examined using an inverted microscope.</td>
<td>More sensitive than CSF smear and faster than commercial liquid/solid culture; ability to perform first-line drug susceptibility testing</td>
<td>Requires a containment Level 3 laboratory and laboratory expertise</td>
</tr>
<tr>
<td>Line probe assays</td>
<td>DNA strip test than can detect Mycobacterium tuberculosis and most common genetic mutations conferring resistance to certain antituberculosis drugs.</td>
<td>Ability to detect M. tuberculosis and drug resistance in sputum specimens or cultured isolates published on TBM</td>
<td>Expensive. Requires a containment Level 3 laboratory and laboratory expertise including PCR. Only one study</td>
</tr>
<tr>
<td>GeneXpert RIF/TB</td>
<td>Automated cartridge-based system for sputum processing, DNA extraction and amplification, detection of M. tuberculosis and rifampicin resistance.</td>
<td>Ability to detect M. tuberculosis and drug resistance in sputum and other clinical specimens. Can be used in a district-level laboratory</td>
<td>Disadvantages: Expensive. High false positivity rate in areas with low prevalence of rifampicin resistance</td>
</tr>
<tr>
<td>Interferon-γ release assays</td>
<td>Whole-blood tests that detect immune responses to a panel of M. tuberculosis antigens.</td>
<td>Used for diagnosis of latent TB; results available within 24 h; not affected by BCG vaccination</td>
<td>Not recommended for diagnosis of active TB disease. Requires large volumes of CSF for diagnosis of TBM and sensitivity variable</td>
</tr>
<tr>
<td>Antigen detection</td>
<td>Detection of lipoarabinomannan (LAM) antigen in urine.</td>
<td>Rapid, point-of-care test that can be conducted at community level. Currently being validated for diagnosis of pulmonary TB</td>
<td>No data in TBM patients. Two recent studies looking at other M. tuberculosis antigens in CSF (see text for details)</td>
</tr>
<tr>
<td>Biomarkers</td>
<td>Proteomic analysis of CSF samples.</td>
<td>Potential novel diagnostic test</td>
<td>Currently experimental—a single study has identified ALOX-5 as a potential biomarker (see text for details)</td>
</tr>
</tbody>
</table>
in plasma and CSF levels and was associated with reduced mortality (65 versus 35%). A large randomized controlled trial of high-dose rifampicin and levofloxacin versus standard therapy is underway in Vietnam and expected to report soon.98

**HIV-associated TBM**

HIV-associated TBM often presents in patients with advanced HIV infection and is associated with a high mortality.99 The treatment of this condition is complicated by the need to treat both conditions simultaneously, with the attendant drug interactions and toxicities, and the risk of immune reconstitution inflammatory syndrome (IRIS), a potentially fatal condition.100 A number of studies have examined the optimal timing of initiation of antiretroviral therapy (ART) in HIV-associated tuberculosis.101–104 Most of these were conducted in patients with pulmonary tuberculosis and found that early initiation of ART was beneficial, particularly in those with low CD4 counts, but it was associated with an increased risk of IRIS. In contrast, a study of immediate versus deferred in 253 Vietnamese adults with HIV-associated TBM found that early ART did not reduce mortality or time to new AIDS events or death.105 Furthermore, there was an increased frequency of severe adverse events in the immediate ART arm, suggesting that it may be better to defer initiation of ART for 2 months in this setting. Of note, all patients received adjunctive corticosteroids during the first 6–8 weeks of the study, which may have prevented the development of IRIS.

The risk of TBM-associated IRIS remains a major clinical concern. The clinical predictors of its development were studied in a cohort of patients with HIV-associated TBM who started ART 2 weeks after commencing TB treatment.106 16/34 patients developed TBM-IRIS, a median of 14 days after commencing ART; the most common presentations were worsening headache and fever. Factors associated with the development of TBM-IRIS included longer duration of illness, the presence of extra-neural TB, higher CSF neutrophil counts and a positive CSF culture for *M. tuberculosis*. The combination of high CSF TNF-α and low interferon-γ concentrations at baseline were predictive of the development of TBM-IRIS.

**Adjunctive anti-inflammatory therapies**

Over the past 60 years, a number of studies have investigated the use of adjunctive corticosteroids in the treatment of TBM.10,107–112 The largest trial in 545 Vietnamese adults showed a reduction in mortality but not in neurological disability in patients treated with dexamethasone, compared with placebo.10 A parallel immunological study showed that prolonged inflammatory responses were detected in all TBM patients, regardless of their treatment allocation.42 The CSF response was characterized by a leukocytosis (predominantly CD3+ CD4+ T cells that were phenotypically distinct from those in the peripheral blood), elevated concentrations of inflammatory and anti-inflammatory cytokines and chemokines, and evidence of prolonged blood–brain barrier dysfunction. Although dexamethasone significantly reduced CSF protein concentrations and marginally reduced IFN-γ concentrations, all other immunological and routine biochemical indices of inflammation in the CSF were unaffected. The peripheral blood monocyte and T cell responses to *M. tuberculosis* antigens were also unaffected. Thus, dexamethasone did not appear to improve survival from TBM by attenuating immunological mediators of inflammation in the CSF, nor by suppressing peripheral T cell responses to mycobacterial antigens, challenging previously held views of the pathogenesis of TBM. A study that looked at the long-term outcome recruited to the Vietnamese study found that adjunctive dexamethasone appeared to improve the survival in patients with TBM, until at least 2 years of follow-up, but failed to demonstrate a 5-year survival benefit.113

Two recent studies have examined the possible benefits of aspirin in TBM treatment. The first study was a randomized controlled trial of aspirin versus placebo in 118 Indian adults.114 Aspirin was associated with a non-significant reduction in stroke at 3 months, and a significant reduction in mortality (21.7 versus 43.4%, *P* = 0.02). The effects of aspirin are difficult to interpret, however, as prednisolone was also given to some patients such as those with
severe disease at baseline, or those whose clinical condition worsened during treatment. The second study was a randomized controlled trial with three parallel arms (low- and high-dose aspirin and placebo) in 146 South African children. Aspirin had no impact on morbidity (hemiparesis and developmental outcome) or mortality. Aspirin was well tolerated, but one death occurred and was probably related to aspirin. Outcomes in the high-dose aspirin group compared favourably with the other treatment groups despite younger age and more severe neurological involvement.

**Conclusions**

Despite advances in our understanding TBM over the past few years, it remains the most lethal form of tuberculosis. The best way to improve survival is by rapid accurate diagnosis and prompt initiation of therapy. The current rapid diagnostic methods for TBM are inadequate but some recent developments have shown promise. These include methods to improve the sensitivity of smear microscopy, the development of automated nucleic acid amplification platforms and the use of novel biomarkers to diagnose TBM, and these warrant further investigation. The optimal antimicrobial treatment regimen for TBM has not been established in clinical trials, and current guidelines are extrapolated from treatment regimens for pulmonary tuberculosis. Ongoing trials of intensified therapy with rifampicin and fluoroquinolones are going some way towards addressing this deficiency. However, the role of other agents with good CSF penetration (such as linezolid) or novel antituberculosis agents (such as bedaquiline and PA-824) warrants investigation. Adjunctive corticosteroids appear to improve survival in HIV-negative patients with TBM, but the mechanism by which they exert their beneficial effects are poorly understood. The role of other adjunctive therapies such as thalidomide and aspirin remain controversial, although the latter may augment the response to corticosteroids. Recent studies have suggested that LTA4H genotype may module response to corticosteroids and offers the prospect of targeted immunomodulatory therapies based on patient genotype in the future. HIV-associated TBM remains a devastating condition with a dismal prognosis, and strategies to improve outcome are urgently required. The benefit of adjunctive corticosteroids in HIV-infected patients has not been established and is unlikely to be investigated in a large clinical trial. The advances in diagnosis and treatment described in this review highlight the many challenges that clinicians face in managing this condition and a number of opportunities for research.

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**Conflict of Interest statement**

The authors have no potential conflicts of interest.

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