Tuberculous Meningitis: Advance in diagnosis and Treatment Overview

Vijay Kumar Gupta[1*], Sanjeev Attry[1], Nishtha Vashisth[2], Ekata Gupta[2], Karan Marwah[1], Saurabh Bhargav[1], Shilpi Bhargav[2]

[1]Department of Neurosurgery, National Institute of Medical Sciences University and Hospital (NIMS), Jaipur, Rajasthan, INDIA.
[2]Balaji Fertility Hospital, Chomu, Jaipur, Rajasthan, INDIA.
Email: drvijaygupta.neurosurg@gmail.com

Abstract
Tuberculous meningitis (TBM) is a serious meningitic infection commonly found to occur in the developing countries endemic to tuberculosis. Tuberculous meningitis (TBM) is the most common form of central nervous system tuberculosis (TB) and has very high morbidity and mortality. 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. Based on the clinical features alone, the diagnosis of TBM can neither be made nor excluded with certainty. Unfortunately there is still no single diagnostic method that is both sufficiently rapid and sensitive. Most factors found to correlate with poor outcome can be directly traced to the stage of the disease at the time of diagnosis. The only way to reduce the mortality and morbidity is by early diagnosis and timely recognition of complications and institution of the appropriate treatment strategies. 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.
Keywords: breast cancer, Tuberculous meningitis.

***Address for Correspondence:**
Dr. Vijay Kumar Gupta, Department of Neurosurgery, National Institute of Medical Sciences University and Hospital (NIMS), Jaipur, Rajasthan, INDIA.
Email: drvijaygupta.neurosurg@gmail.com

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INTRODUCTION

Tuberculous meningitis (TBM) is the most frequent form of central nervous system (CNS) tuberculosis. Tuberculous meningitis (TBM) is caused by *Mycobacterium tuberculosis* (*M. tuberculosis*). Global burden of tuberculosis is still high, particularly in developing countries; and globally, there were an estimated 9.27 million new cases (139 per 100,000 population) of tuberculosis in 2007, and the number of prevalent cases was 13.7 million (206 per 100,000 population). The incidence of CNS tuberculosis generally reflects the incidence and prevalence of tuberculosis in the community. About 10% of patients who have tuberculosis develop CNS disease. HIV infection predisposes to the development of extra-pulmonary tuberculosis, particularly tuberculous meningitis. With 206 per 100,000 prevalent cases of tuberculosis in 2007 and the projected incidence of cases of CNS tuberculosis being 20.6 per 100,000 population in the year 2007, most of it would be in the high-burden countries. Incidence rates of tuberculous meningitis are age specific and range from 31.5 per 100,000 (<1 year) to 0.7 per 100,000 (10-14 years) in the Western Cape Province, South Africa. The estimated mortality due to tuberculous meningitis in India is 1.5 per 100,000 population. HIV co-infection is associated with higher complication and case fatality rates. The disease occurs when subependymal or subpial tubercles, also known as "Rich foci" seeded during bacillemia of primary infection or disseminated disease, rupture into the subarachnoid space[8]. Individuals with increased risk for TBM include young children with primary TB and patients with immunodeficiency caused by aging, malnutrition, or disorders such as

Table 1: Clinical features of tuberculous meningitis in children and adults

	Symptoms	Clinical findings	CSF findings
Children	Early symptoms are non-specific and include fever, cough, vomiting, malaise and weight loss. Duration of symptoms >6 days Seizures more common in children than in adults	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	Usually clear and colourless, raised white cell count ($0.5–1 \times 10^9$/l) with neutrophils and Lymphocytes Raised protein (0.5–2.5 g/l) CSF to plasma glucose ratio <0.5 in 95% of cases
Adults	Prodromal period with low-grade fever, malaise, weight loss followed by gradual onset of headache (1–2 weeks). Worsening headache, vomiting, confusion, coma. Duration of symptoms ≥6 days	Neck stiffness, confusion, coma Cranial nerve palsies—VI, III, IV Focal neurological signs, e.g. monoplegia, hemiplegia, Paraplegia Urinary retention	High opening pressure >25 cm H20 in 50% of cases, usually clear and colourless Raised white cell count ($0.05–1 \times 10^9$/l) with neutrophils and lymphocytes Raised protein (0.5–2.5 g/l) CSF to plasma glucose ratio <0.5 in 95% of cases

HIV and cancer[9,10]. The use of antitumor necrosis factor-alpha (TNFα) neutralizing antibody has also been associated with increased risk of extrapulmonary TB including TBM[11]. Most have no known history of TB, but evidence of extrameningeal disease (e.g., pulmonary) can be found in about half of patients[3,4]. The tuberculin skin test is positive in only about 50% of patients with TBM. In low TB prev-alence areas, TBM is most commonly seen with reactivation TB.

MATERIAL AND METHOD

The goal of this overview is to describe evidence-based diagnostic and treatment approaches of TBM. This paper was written for clinicians seeking a practical summary of this topic. While this paper focuses on these aspects of TBM, a brief overview of the clinical manifestations of TBM as well as past and current animal models of TBM treatment will be discussed. Literature in this field was systematically identified on PubMed using the key words "tuberculous meningitis," "tuberculosis cerebrospinal fluid," and "tuberculosis nervous system," as well as combing through the bibliography of relevant papers. More recent articles describing new findings in the field were given particular attention.

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.[12] 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 peri-tonitis. The microbiological cause of tuberculosis was not identified until 1882 when Robert Koch stained and cultured the bacterium that caused tuberculosis[13] 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 menin-geal space from focal sub-pial or sub-ependymal lesions, which were most commonly located in the Sylvian fissure.[14] Three pathological processes account for the com-monly 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 obliterative vasculitis can cause infarction and stroke syndromes.[15] 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.[16] Tuberculomas developed in 74% of patients during the course of TB treatment and the basal ganglia were the most common site of infarction. 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.[17,18] A low CSF cell count has also been associated with poor outcome. Neutrophils can predominate, especially early in the disease,[31] and a high proportion of neu-trophils in the CSF has been associated with an increased likelihood of a bacteriological diagnosis and improved survival.[20,21] 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.[22] 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 M. tuberculosis into the sub-arachnoid space results in a local T lymphocyte-dependent response, characterized by caseating granulomatous inflammation.[15] In pulmonary tuberculosis, TNF-α is thought to be important in granuloma formation.[23] Studies of acute bacterial meningitis showed that CSF concentrations of TNF-α correlated with disease severity,[24] and study in a rabbit model of TBM found that high CSF concentrations were asso-ciated with a worse outcome.[25] In humans, however, TNF-α concentrations were not correlated with disease severity or outcome.[20] Treatment with antibio-tics and thalidomide (a TNF-α antagonist) improved survival and neurological outcome in rabbits.[26] Pre-liminary research in humans found that thalidomide was safe and well tolerated,[27] 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.[28] The role of other inflammatory mediators in the pathogenesis of TBM has also been explored. Thwaites and colleagues[20] 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 concentrations of lactate, low numbers of white blood cells, in particular neutrophils, and low CSF glucose levels. A second study examined the relation-ship between pre-treatment intracerebral and periph-eral immune responses and outcome in Vietnamese adults.[29] 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 corticoster-oids in TBM.[30] Prolonged inflammatory responses were detected in all TBM patients irrespective of treatment assignment (placebo or

dexamethasone). Dexamethasone significantly modulated acute cere-brospinal 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 corti-costeroids in this disease. A potential explanation for this came from studies of mycobacterial infections in a zebrafish model.[31] 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.[32] 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 sur-vival in TBM and suggest the possibility of using host-directed therapies tailored to patient LTA4H genotypes.

Clinical Manifestations

TBM is typically a subacute disease. In one seminal review, symptoms were present for a median of 10 days (range, one day to nine months) prior to diagnosis[4]. A prodromal phase of low-grade fever, malaise, headache, dizziness, vom-iting, and/or personality changes may persist for a few weeks, after which patients can then develop more severe headache, altered mental status, stroke, hydrocephalus, and cranial neu-ropathies. Seizures are uncommon manifestations of TBM in adults and when present should prompt the clinician to con-sider alternate diagnoses such as bacterial or viral meningitis or cerebral tuberculoma; in contrast, seizures are commonly seen in children with TBM, occurring in up to 50% of pediatric cases[33]. The clinical features of TBM are the result of basilar meningeal fibrosis and vascular inflammation[13]. Classic features of bacterial meningitis, such as stiff neck and fever, may be absent. When allowed to progress without treatment, coma and death almost always ensue. In survivors of TBM, neurologic sequelae may occur that include mental retardation in children, sensorineural hearing loss, hydrocephalus, cranial nerve palsies, stroke-associated lateralizing neurological deficits, seizures, and coma[35].

DIAGNOSIS

The diagnosis of TBM can be difficult and may be based only on clinical and preliminary cerebrospinal fluid (CSF) find-ings without definitive microbiologic confirmation.

Certain clinical characteristics such as longer duration of symptoms (>six days), moderate CSF pleiocytosis, and the presence of focal deficits increase the probability of TBM[36, 37]. Char-acteristic CSF findings of TBM include the following:

1. lymphocytic-predominant pleiocytosis. Total white cell counts are usually between 100 and 500 cells/μL. Very early in the disease, lower counts and neutrophil predominance may be present,
2. elevated protein levels, typically between 100 and 500 mg/dL,
3. low glucose, usually less than 45 mg/dL or CSF: plas-ma ratio <0.5.

CSF sample should be sent for acid-fast smear with the important caveat that a single sample has low sensitivity, on the order of 20%–40%[38]. Several daily large volume (10– 15 mL) lumbar punctures are often needed for a microbi-ologic diagnosis; sensitivity increases to >85% when four spinal taps are performed[39]. Early studies demonstrated that acid-fast stains can detect up to 80%[39] although results are highly dependent on CSF volume, timeliness of sample delivery to the lab and analysis, and the technical expertise of lab personnel. While culture can take several weeks and also has low sensitivity ($\square$40– 80%), it should be performed to determine drug susceptibility. Drug-resistant strains have important prognostic and treatment implications; indeed, TBM due to isoniazid- (INH-) resistant *M. tuberculosis* strains have been associated with a twofold in-crease in mortality[40]. Given the relatively low sensitivity of acid-fast smear and inherent delay in culture, newer diagnostic methods for TBM have been more recently developed[38]. Although ELISA assays have been developed to detect antibodies directed against specific mycobacterial antigens in the CSF with vary-ing sensitivities, their limited availability precludes their use as point-of-care tests in resource-poor countries[38,41]. A recent study in children aged 6–24 months suggests that a CSF adenosine deaminase level of ≥10 U/L has >90% sensitivity and specificity of diagnosing TBM[42]. However, other studies have shown poor specificity of adenosine deaminase for TBM in certain populations, particularly in HIV-infected adults with concurrent infections or cerebral lymphomas[43]. Comparison of microscopy/culture of large CSF volumes to nucleic acid amplification (NAA) has shown that sensitiv-ity of these methods for the diagnosis of TBM is similar[44]. A meta-analysis determined that commercial NAA assays utilizing polymerase chain reaction (PCR) for the diagnosis of TBM had an overall sensitivity of 56% and a specificity of 98%[45]. The surprisingly poor sensitivity is likely due to the fact that most PCR-based studies use a single target for amplification which can

result in false-negative results due to the absence of the target gene in some TB isolates[46]. Newer PCR tests amplify several target genes simultaneously and have been shown to result in much higher sensitivities in the range of 85%–95%[47]. Currently, most experts conclude that commercial NAA tests can confirm TBM but cannot rule it out[48]. Thus, it bears emphasizing that a negative CSF ex-amination for acid-fast bacilli or *M. tuberculosis* DNA neither excludes the diagnosis of TBM nor obviates the need for empiric therapy if the clinical suspicion is high. After starting treatment, the sensitivity of CSF smear and culture decreases rapidly, while mycobacterial DNA may be detectable in the CSF for up to a month after treatment initiation[49]. Diagnosis of TBM can be helped by neuroimaging. Clas-sic neuroradiologic features of TBM are basal meningeal en-hancement and hydrocephalus[38]. Hypodensities due to cerebral infarcts, cerebral edema, and nodular enhancing le-sions may also be seen. Magnetic resonance imaging (MRI) is the imaging test of choice for visualizing abnormalities asso-ciated with TBM, as it is superior to computed tomography (CT) for evaluating the brainstem and spine. The T2- weighted MRI imaging has been shown to be particularly good at demonstrating brainstem pathology; discussion-weighted imaging (DWI) is best at detection of acute cerebral infarcts due to TBM [50]. However, CT is adequate for urgent evaluation of TBM-associated hydrocephalus for possible surgical intervention.

TREATMENT

5.1. Antimicrobial Therapy. Timely treatment dramatically improves the outcome of TBM. Thus, empiric treatment is warranted when clinical features and CSF findings are suggestive of TBM even before microbiologic confirmation. The recommended treatment regimen for presumed drug susceptible TBM consists of two months of daily INH, rifampin (RIF), pyrazinamide (PZA), and either streptomycin (SM), or ethambutol (EMB), followed by 7–10 months of INH and RIF (Table 1)[38,51–55]. INH is considered the most critical of the first-line agents due to its excellent CSF penetration and high bactericidal activity (Table 2)[56–60]. While RIF penetrates the CSF less freely, the high mortality of TBM due to RIF-resistant strains has confirmed its importance[61]. PZA has excellent penetration into the CSF and is a key drug in reducing the total treatment time for drug-susceptible TB[62]. Hence, if PZA cannot be tolerated, the treatment course for TBM should be lengthened to a total of 18 months. While SM or EMB are traditionally used as the fourth anti-TB agent in TBM, neither penetrates the CSF well in the absence of inflammation and both can produce significant toxicity with long-term use[62]. It bears emphasizing that not only the choice of antimicrobials,

but also the dose used and duration of treatment are empiric in TBM and largely based on the treatment of pulmonary TB. Given that the newer generation fluoroquinolones (FQN), for example, levofloxacin and moxifloxacin, have strong activity against most strains of *M. tuberculosis* and have excel-lent CSF penetration and safety profiles, FQN would appear to have great potential as part of first-line therapy for TBM. In a randomized controlled study for TBM treatment, addi-tion of an FQN to standard regimen enhanced anti-TB performance as measured by various clinical parameters. Al-though there was no significant difference in mortality, the study was likely not adequately powered to demonstrate such an effect[59]. It is important to note that serum FQN concentrations are lowered by concurrent RIF use; furthermore, the optimal area-under-the-curve to minimum inhibitory concentration ratio for FQN as anti-TB agents has not been well described. Another randomized controlled study is cur-rently underway to evaluate treatment of TBM with high-dose RIF and levofloxacin compared to standard treatment[63]; if they have positive results, the recommended standard treatment may change in the near future. No controlled trials have been published to date for the treatment of multidrug resistant (MDR) TBM, defined as resistance to at least INH and RIF. Furthermore, very few studies have been published on the CSF penetrance of many of the second-line and newer anti-TB agents. Clinicians of patients with MDR-TBM are left to extrapolate from guide-lines for the treatment of pulmonary MDR-TB. The World Health Organization recommends for pulmonary MDR-TB the use of a minimum of four agents to which the *M. tuberculosis* strain has known or suspected susceptibility including use of any first-line oral agents to which the strain remains susceptible, an injectable agent (i.e., an aminoglycoside or capreomycin), an FQN, and then adding other second-line agents as needed for a total of at least four drugs[34]. CSF penetration of the first- and second-line anti-TB drugs are shown in Table 2[56,64–70]. Among new anti-TB agents, bedaquiline (TMC207, a di-arylquinoline) and delamanid (OPC-67683, a nitro-di-hy-droimidazo-oxazole) appear most promising, as they are both in phase III clinical trials[71]. Three additional novel agents, sudoterb (LL3858, a pyrrole derivative), PA-824 (a nitroimidazo-oxazine), and SQ109 (an analogue of EMB) are currently in phase II trials[71,72]. Their ability to penetrate the CSF has yet to be adequately studied (Table 2). *5.2. Adjunctive Corticosteroid Therapy.* Much of the neuro-logic sequelae of TBM is considered to be due to an overexu-berant host-inflammatory response that causes

tissue injury and brain edema[73]. Since the middle of the 20th century, systemic corticosteroids have been used as adjunctive treat-ment for TBM on the basis of the notion that dampening of the inflammatory response can lessen morbidity and mortal-ity, a reasonable hypothesis as the brain is confined to a fixed space. Indeed, adjunctive corticosteroid treatment of pyogenic bacterial meningitis has shown ecacy in certain groups of patients[74,75] although this is controversial[76,77]. In attempting to determine the cell type responsible for inciting the inflammatory response, Rock *et al.*[2] found that *M. tuberculosis* was much more likely to infect brain tissue macrophages (microglial cells) with marked increases in pro-duction of proinflammatory cytokines and chemokines than stromal brain cells (astrocytes). In this *in vitro* study, coincubation of TB-infected microglial cells with dexamethasone significantly inhibited production of inflammatory mediators[2]. Although there has long been concern that corticosteroids may reduce CSF penetration of anti-TB drugs[34], one small study demonstrated that corticosteroids had no effect on CSF penetrance of first-line anti-TB agents[67]. A Cochrane meta-analysis of seven randomized controlled trials comprised a total of 1140 participants concluded that corticosteroids improved outcome in HIV-negative children and adults with TBM (RR 0.78)[78]. These results were strongly influenced by a study of 545 adults with TBM in Vietnam showing that treatment with dexamethasone was associated with significantly reduced mortality at nine months of followup[79]. One possible explanation for the survival benefit in the Vietnamese study is that the anti-inflammatory effects of corticosteroids reduced the number of severe adverse events (9.5% versus 16%), particularly hepatitis, preventing the interruption of the first-line anti-TB drug regimen[79]. Since there are no controlled trials comparing cortico-steroid regimens, treatment choice should be based on those found to be effective in published trials. One recommended regimen for children is dexamethasone 12 mg/day IM (8 mg/ day for children weighing ≤25 kg) for three weeks, followed by gradual taper over the next three weeks [80]. In the large study in Vietnam, patients with mild disease received intra-venous dexamethasone 0.3 mg/kg/day × 1 week, 0.2 mg/kg/ day × 1 week, and then four weeks of tapering oral therapy [79]. For patients with more severe TBM, intravenous dex-amethasone was given for four weeks (1 week each of 0.4 mg/ kg/day, 0.3 mg/kg/day, 0.2 mg/kg/day, and 0.1 mg/kg/day),

Table 1: Recommended standard treatment regimen for drug-susceptible TBM.

Treatment phase and anti-TB agent	Recommended dose (mg/kg/day)	Maximum dose (mg/day)	Potential side effects	Duration of treatment
Isoniazid	5–10	300	hepatotoxicity peripheral neuropathy	Minimum of 9 months
Rifampin	10	450 (<50 kg)	hepatotoxicity, rash, flu-like syndrome, and multiple drug interactions.	Minimum of 9 months
		600 (≥50 kg)		
Pyrazinamide	25–30	1500 (<50 kg)	hepatotoxicity, arthralgia, gastrointestinal upset, anorexia, and photosensitization of the skin	2 months
		2000 (≥50 kg)		
Streptomycin (IM) *	15 in adults (30 in children)	1000	nephrotoxicity, ototoxicity, and vestibular toxicity	2 months
Ethambutol *	15–20	1600 in adults (1000 in HIV (−) and 2500 in HIV (+) children)	optic neuritis, peripheral neuritis, arthralgia, and gastrointestinal upset	2 months

*For empiric induction treatment for presumed drug-susceptible *M. tuberculosis*, either streptomycin or ethambutol is recommended as the fourth agent.

Table 2: Pharmacokinetic activity and CSF penetration of anti-TB drugs

	Anti-TB drug	Activity	CSF penetration
1st-line drugs	Isoniazid	Cidal	90%–95%
	Rifampin	Cidal	5%–25%
	Pyrazinamide	Cidal	95%–100%
	Streptomycin	Static	20%–25%
	Ethambutol	Static	10%–50%
	Ciprofloxacin	Cidal	15%–35%
	Levofloxacin	Cidal	60%–80%
	Moxifloxacin	Cidal	70%–80%
2nd-line drugs	Ethionamide	Cidal	80%–95%
	Cycloserine	Static	40%–70%
	Amikacin	Cidal	10%–25%
	Streptomycin	Cidal	10%–20%
	Capreomycin	Static	unknown
	Para-aminosalicylic acid	Static	unknown
	Thioacetazone	Static	unknown
	Linezolid	Cidal	80%–100%
New agents	Bedaquiline (TMC207)	Cidal	unknown
	Delamanid (OPC-67683)	Cidal	unknown

Cidal: bactericidal Static: bacteriostatic.

Followed by four weeks of tapering oral dexamethasone therapy[79]. While neutralization of TNF α predisposes individuals to TB including TBM[11], TNFα is also considered to play an important role in contributing to the pathogenesis of TBM[81–84], consistent with the aforementioned deleterious ef-fects of the CNS inflammatory response. Indeed, Tsenova *et al*. showed that the addition of thalidomide, a potent in-hibitor of TNF α, to antibiotics was superior to antibiotics alone in protecting rabbits from dying (50% reduction in mortality) in their model of TBM[83]. In addition, there was marked reduction in TNF α levels in both CSF and blood as well as a decrease in leukocytosis and brain pathology in rabbits that received thalidomide[83]. *Fluid Management*

in TBM. In patients with TBM, there may be nonosmotic stimuli for antidiuretic hormone (ADH) expression, resulting in a syndrome of inappropriate ADH (SIADH) release. While ADH itself may not aggravate cere-bral edema, acute development of significant hyposmotic hyponatremia may worsen cerebral edema due to water shift-ing from the intravascular compartment into the extravascu-lar (intracellular and extracellular) space of the brain. While restriction of water intake is a mainstay of SIADH treatment, hypovolemia should be avoided, since it may decrease cere-bral perfusion as well as serve as a stimulus for further ADH release. In a comprehensive review of this issue, it was noted that fluid restriction to prevent cerebral edema in TBM is

unjustified[85]. Instead, it was recommended that a euvolemic state should be the goal to maintain cerebral perfusion as well as to prevent hypovolemia-induced ADH release. If symptomatic, acute hyponatremia does not respond to anti-TB treatment and appropriate fluid restriction (while maintaining euvolemia), use of V2 (ADH) receptor antag-onist should be considered although, to the best of our knowledge, this has not been studied in TBM. Care must be taken, however, to prevent too rapid of correction of chronic hyponatremia due to the risk of precipitating osmotic demy-elination syndrome.

Surgical Intervention in TBM Hydrocephalus. Hydrocephalus is a common complication of TBM; prevalence has been documented in >75% of patients in several published series[86,87]. Ventriculoperitoneal shunt placement and endoscopic third ventriculostomy are surgical techniques which have been demonstrated to relieve elevated intracra-nial pressure (ICP) in TBM, leading to improved neuro-logical outcomes[88,89]. Children are at particularly high risk for hydrocephalus and elevated ICP. In a study of 217 children with TBM in South Africa, 30% required ventriculo-peritoneal shunting for either noncommunicating hydro-cephalus or failure of medical therapy with diuretics in com-municating hydrocephalus[90]. Historically, surgical inter-vention was only recommended with grade 2 or 3 TBM hydrocephalus (normal or mildly altered sensorium; easily arousable) due to increased mortality and risk of poor surgical outcome in patients with grade 4 disease (deeply comatose). However, a retrospective analysis of 95 patients with grade 4-associated hydrocephalus who underwent shunt placement demonstrated favorable outcomes in 33%–45% of patients, suggesting that there may be a role for surgical intervention even in advanced TBM hydrocephalus[91]. In this study, poor neurological outcomes after shunt placement were associated with age < three years and > three days in duration of symptoms.

Treatment Issues of TBM in Patients with Concurrent HIV Infection. TB is the most common opportunistic infection in HIV-infected persons, and HIV infection is an independent risk factor for extrapulmonary TB including meningitis [92]. For these reasons, diagnosis of TBM should automatically trigger testing for HIV infection. In general, the diagnosis and treatment of TBM in HIV-infected individuals is similar in principle to non-HIV infected subjects although there are a few notable caveats, including the potential development of immune reconstitution inflammatory syndrome (IRIS), drug interactions and toxicities with concomitant anti-TB and antiretroviral (ARV) therapy, questionable efcacy of adjunctive corticosteroids, and higher prevalence of drug-resistant TB in HIV-positive populations. Treatment of HIV with ARV therapy can result in IRIS, causing

clinical exacerbation of TBM. Indeed, in high HIV prevalent settings, CNS TB complicated by IRIS has been shown to be the most frequent cause for neurological deterioration in patients newly starting ARV therapy[92]. Risk factors for IRIS include a high pathogen load (e.g., miliary TB), very low CD4 T-cell count (<50 cells/μL) when ARV therapy is initiated[94], and concurrent initiation of ARV and anti-TB therapy[95]. Concurrent ARV and anti-TB therapy carries the risk of drug interactions and toxicities. However, delaying ARV therapy in patients coinfected with HIV and TB has been as-sociated with higher mortality[96]. Nevertheless, due to the possibility of IRIS with ARV initiation, most guidelines do not recommend simultaneous initiation of ARV and anti-TB medications. A recent randomized controlled trial comparing mortality in patients started on immediate ARV at the time of diagnosis of TBM and HIV versus patients started on ARV two months after diagnosis found significantly more serious adverse events in the immediate arm[95]. Mortality did not dier significantly, but there was a trend towards greater all-cause mortality in the immediate ARV group at nine months follow up. The World Health Organization rec-commends that anti-TB therapy be started first, followed by ARV treatment within eight weeks[55]. The Center for Disease Control and Prevention recommends that for patients with CD4 counts <100 cells/μL, ARV therapy be started after two weeks of anti-TB therapy[97]. The benefit of adjunctive corticosteroid treatment for TBM in patients coinfected with HIV has not been demonstrated[92]. In the large study of Vietnamese adults with TBM, no mortality benefit from dexamethasone was found in the subgroup of 98 patients who were coinfected with HIV[79]. Thus, at the present time, the benefit of adjunctive corticosteroid treatment in HIV-infected individuals remains uncertain[78] although the theoretical benefit of corticosteroids to decrease TB-associated IRIS has led some experts to prescribe them to this population. There is also evidence that a particularly virulent strain of TB, the W-Beijing genotype, is associated with HIV infection and high levels of resistance in TBM[77]. Multiple studies have shown MDR-TB to be more commonly found in HIV-infected patients with concurrent TBM[99–101], often lead-ing to treatment failure and very high mortality. In high HIV prevalence settings and in all HIV-infected patients, daily anti-TB treatment as directly observed therapy should be given in order to reduce relapse and treatment failure[55,102]. It is important to note that HIV coinfection alone, even without TB drug resistance, confers worse outcomes in TBM. HIV coinfection was shown to be associated with 3.5 times higher mortality in a retrospective cohort study of TBM patients in the United States from 1993–2005[40].

PROGNOSIS

Prognosis of TBM largely depends on neurologic status at the time of presentation, and time-to-treatment initiation. While the course of TBM is generally not as rapid or fulminant as meningitis due to pyogenic bacteria, empiric treatment should be initiated as soon as the diagnosis is suspected as any delay in treatment can worsen outcome. Various case se-ries indicate a mortality rate of 7%–65% in developed coun-tries, and up to 69% in underdeveloped areas[3–5]. Mor-tality risk is highest in those with comorbidities, severe neu-rologic involvement on admission, rapid progression of dis-ease, and advanced or very young age. Neurologic sequelae occur in up to 50% of survivors[5].

CONCLUSION

TBM is a serious CNS infection associated with significant mortality and high morbidity among the survivors. Most factors found to correlate with poor outcome can be directly traced to the stage of the disease at the time of diagnosis. The only way to reduce mortality and morbidity is by early diagnosis and timely recognition of complications and institution of the appropriate treatment strategies. However, still the most challenging aspect is early diagnosis with certainty, and the diagnosis is hampered by slow and insensitive diagnostic methods. The other major emerging challenge is treating MDR TBM.

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