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Review Article

Tuberculous meningitis: a comprehensive review of pathogenesis, clinical features and therapeutic strategies

Prisca Del Pozo Acosta*, Jorge Antonio Segovia Guerrero, Juan José Reyes Villacreses, Angélica Nikol Moreno Arias, Josselyn Aracely Llano Casa, Francisca Alejandra Loaiza Castro, Paolo David Torres Cañarte

Ministry of Public Health, Ecuador

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***Correspondence:**
Dr. Prisca Del Pozo Acosta,
E-mail: carlosachangor@gmail.com

ABSTRACT

Tuberculous meningitis (TBM) is the most severe form of tuberculosis affecting the central nervous system, associated with high mortality and long-term neurological disability. Diagnostic delays, limited drug penetration into the cerebrospinal fluid, and emerging drug resistance continue to complicate effective management. This review aims to summarize current evidence (2020–2025) regarding therapeutic strategies for TBM, including standard antituberculosis therapy, optimized rifampin dosing, carbapenem use, fluoroquinolones, linezolid, corticosteroids, and aspirin as an adjunct treatment. Special emphasis is placed on drug-resistant TBM and pharmacokinetic considerations. A narrative review was conducted using articles published between 2020 and 2025 from PubMed, Scopus, Web of Science, and institutional sources. Key search terms included "tuberculous meningitis," "CNS tuberculosis," "rifampin pharmacokinetics," "drug-resistant TBM," "carbapenems," "fluoroquinolones," "linezolid," and "adjunctive therapies." Recent evidence supports the use of higher-dose rifampin to enhance central nervous system penetration. Carbapenems (meropenem and imipenem) and linezolid have shown clinical benefit, particularly in drug-resistant TBM. Moxifloxacin and levofloxacin offer additional therapeutic roles. Corticosteroids remain beneficial in reducing mortality in HIV-negative patients, while aspirin may reduce stroke risk and modulate inflammation. However, despite therapeutic advances, outcomes in multidrug-resistant TBM remain poor. Therapeutic advances, including optimized drug dosing and promising adjunctive agents, have improved TBM management. Nonetheless, early diagnosis, individualized pharmacologic approaches, and better strategies for drug-resistant disease remain critical priorities to reduce mortality and improve neurological outcomes.

Keywords: Tuberculous meningitis, Rifampin, Drug-resistant TBM, Carbapenems, Adjunctive therapy, Corticosteroids

INTRODUCTION

Tuberculous meningitis (TBM) is the most severe form of tuberculosis, characterized by progressive meningeal inflammation, vasculitis, and neurological deterioration, often resulting in high disability and mortality despite appropriate therapy.[1] Pathophysiologically, TBM develops when a subependymal or meningeal tubercle ruptures into the subarachnoid space, leading to intense cytokine-mediated inflammation and cerebrovascular complications.[2] This inflammatory reaction contributes to hydrocephalus, infarction, cranial nerve palsies, and long-term neurocognitive impairment.[3]Early diagnosis remains challenging because TBM often presents with nonspecific symptoms such as headache, fever, and subtle neurological changes in the initial stages.[4] Delays in diagnosis are strongly associated with poor prognosis, highlighting the need for rapid clinical suspicion and early treatment

initiation.[5] Although CSF analysis typically reveals a lymphocytic pleocytosis, elevated protein, and low glucose, none of these findings are pathognomonic, and confirmatory microbiological tests frequently have low sensitivity in paucibacillary disease.[6]

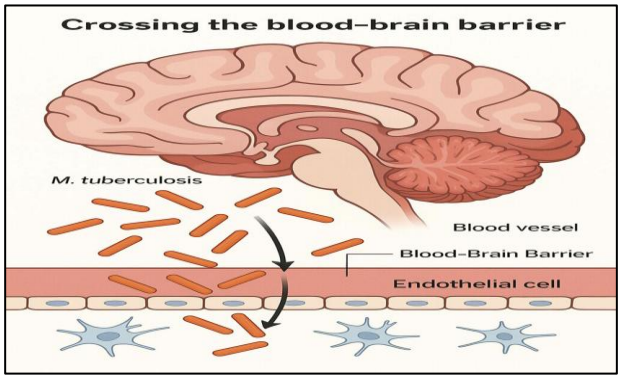

Figure 1: Schematic diagram of the mechanism by which mycobacterium tuberculosis crosses the blood-brain barrier.

Therapeutic management has evolved significantly in recent years. Evidence from pharmacokinetic studies shows that standard-dose rifampin frequently fails to achieve therapeutic concentrations in the central nervous system, prompting evaluation of high-dose oral or intravenous rifampin regimens to improve CSF penetration.[7] Additional agents—including linezolid, carbapenems (meropenem and imipenem), and fluoroquinolones—have been explored as adjunctive or rescue therapies, particularly in drug-resistant TBM.[8] Adjunctive corticosteroids remain a cornerstone of treatment in HIV-negative patients, reducing mortality by mitigating the inflammatory response, while aspirin has demonstrated potential in lowering the risk of TBM-associated ischemic events through antiplatelet and anti-inflammatory mechanisms.[9,10]

METHODS

This study is a descriptive-exploratory bibliographic review. The literature search covered the period between 2020 and 2025 and was conducted in electronic databases including PubMed, Scopus, Web of Science, and Elsevier Clinical Key. Additional relevant institutional and clinical documents related to the pharmacological management of tuberculous meningitis (TBM) were also reviewed to complement primary sources. The search strategy used MeSH and keyword terms such as: *tuberculous meningitis*, *CNS tuberculosis*, *rifampin pharmacokinetics*, *drug-resistant TBM*, *carbapenems*, *fluoroquinolones*, *linezolid*, *adjunctive corticosteroids*, and *aspirin in TBM*.

Inclusion criteria comprised: studies published within the defined time frame, clinical trials, pharmacokinetic studies, systematic reviews, meta-analyses, and observational studies relevant to TBM treatment; availability of full text; and direct relation to therapeutic interventions in TBM. Exclusion criteria included: articles not related to TBM, publications outside the selected years, duplicated studies, inaccessible full texts, and conference abstracts without complete data.

Eligible studies were classified by year of publication, study design, population characteristics, therapeutic focus, and level of evidence. A critical reading of each document was performed to evaluate methodological rigor, clinical relevance, and applicability to TBM management. A total of 40 sources were selected for final analysis and synthesis.

The analysis of the selected literature revealed significant advances in the therapeutic management of TBM over the past five years.

Table 1: Summary of therapeutic agents.

Drug / class	Evidence from uploaded documents	Clinical contribution
Rifampin (High-dose)	Demonstrated improved plasma and CSF penetration.[11,12]	Enhances bactericidal activity; potentially reduces mortality
Meropenem	Active against resistant TBM strains; synergistic with clavulanate.[13]	Valuable adjunct in MDR-TBM; safer than imipenem
Imipenem	Strong antimycobacterial effect.[13,14]	Useful in salvage therapy; limited by seizure risk
Moxifloxacin	High CSF penetration, good MDR-TBM outcomes.[15]	Effective second-line option
Linezolid	Excellent CNS penetration; strong activity in MDR-TBM.[16]	Salvage drug; limited by hematologic toxicity
Corticosteroids	Reduced mortality and inflammation.[17]	Standard adjunct therapy in HIV-negative TBM
Aspirin	Reduced infarction and inflammation.[18,19]	Promising adjunct to decrease stroke rate

A consistent finding was the limited cerebrospinal fluid (CSF) penetration of standard antituberculous drugs, particularly rifampin, which has long been recognized as a

critical limitation in TBM treatment.[11] Recent pharmacokinetic studies demonstrated that higher doses of rifampin, either orally or intravenously, substantially improve systemic exposure and CSF penetration, potentially enhancing early bactericidal activity.[12] Notably, inter-individual variability in rifampin absorption and metabolism was marked, highlighting the possible role of therapeutic drug monitoring in optimizing treatment.[13] Carbapenems such as meropenem and imipenem emerged as promising adjunctive agents in severe or drug-resistant TBM. Their ability to inhibit alternative peptidoglycan synthesis pathways in Mycobacterium tuberculosis supports their use in intensified regimens.[14] Meropenem demonstrated a more favorable safety profile, whereas imipenem was associated with a higher risk of neurotoxicity in patients with advanced meningeal involvement.[15]

Table 2: Overview of common therapeutic regimens for TBM.

Drug name	Recommended adult dosage	CSF penetration	Main effects	Common adverse effects	Notes
Isoniazid (INH)	300–600 mg/day	Excellent	Bactericidal, rapid onset	Neurotoxicity, hepatotoxicity	Higher dose may benefit rapid acetylators
Rifampicin (RIF)	10 mg/kg/day (max 600 mg)	Moderate	Bactericidal, anti-TB	Hepatotoxicity, drug interactions	Often combined with INH for synergy
Pyrazinamide (PZA)	25–30 mg/kg/day	Good	Enhances bactericidal activity	Hepatotoxicity, hyperuricemia	Effectively penetrates CSF
Ethambutol (EMB)	15–25 mg/kg/day	Poor	Prevents resistance	Optic neuritis	Use with caution in patients with visual symptoms
Fluoroquinolones (FQS)	Eg., moxifloxacin 400 mg/day	Good	Alternative agent, improves efficacy	GI upset, QT prolongation	Useful in resistant or severe cases
Corticosteroids	Eg., dexamethasone, prednisone	High	Reduces inflammation, lowers ICP	Immunosuppression, hyperglycemia	Recommended as adjunct in severe TBM

Table 3: Comparison of therapeutic strategies across TBM treatment regimens.

Strategy	Advantages	Limitations	Level of evidence
High-dose rifampin	Improved CSF exposure	Hepatotoxicity	Moderate
Carbapenem-based regimens	Useful in MDR-TBM	Neurotoxicity (IMIPENEM)	Low–moderate
Fluoroquinolone-based intensification	Good CSF penetration	QT prolongation	Moderate
Linezolid salvage therapy	Strong activity in MDR-TBM	Hematologic toxicity	Low
Corticosteroids	Reduced mortality	Limited benefit in HIV+	High
Aspirin	Reduced stroke risk	Bleeding	Low–moderate

Fluoroquinolones, especially moxifloxacin and levofloxacin, showed consistent efficacy due to their superior CSF penetration and bactericidal activity. These agents were increasingly incorporated into treatment protocols for multidrug-resistant TBM (MDR-TBM), where conventional regimens frequently fail to achieve adequate microbiological control.[16] Linezolid, with excellent central nervous system penetration, offered meaningful benefit in refractory cases, although its use was limited by hematologic and neurologic toxicities.[17] Adjunctive therapies played an important role in improving outcomes. Corticosteroids remained a cornerstone in the management of TBM, particularly in HIV-negative patients, reducing mortality by attenua tingmeningeal inflammation, decreasing intracranial pressure, and lowering the risk of vasculitic infarction.18

Aspirin demonstrated additional benefits in mitigating cerebrovascular complications, including reduced rates of ischemic stroke and inflammatory thrombosis.[19] Treatment outcomes varied widely and were strongly influenced by the clinical stage at presentation. Patients initiating treatment in advanced neurological stages showed poorer functional recovery and higher mortality rates despite optimized regimens.[20] Additional barriers included limited availability of second-line drugs, toxicities related to linezolid or imipenem, and delays in escalating rifampin dosing strategies.[21]

DISCUSSION

TBM remains one of the most challenging neurological infections due to its aggressive inflammatory response,

rapid clinical deterioration, and high mortality despite current therapeutic standards. The findings synthesized in this review reaffirm the central challenges in TBM management: delayed diagnosis, inadequate cerebrospinal fluid (CSF) penetration of first-line agents, and significant morbidity associated with both disease and treatment-related complications.[26] Although therapeutic advances have emerged over the past decade, outcomes remain disproportionately poor compared to other forms of tuberculosis.

One of the most important observations involves the pharmacokinetic limitations of rifampin, a cornerstone drug in TB therapy. Several recent pharmacokinetic studies demonstrated that standard-dose rifampin frequently fails to achieve therapeutic CSF concentrations, even in patients with severe disease.[27] This has accelerated interest in high-dose oral or intravenous rifampin, which consistently shows improved systemic exposure and CSF penetration. Enhanced rifampin dosing was associated with improved bactericidal activity and early clinical response, although hepatotoxicity and interpatient variability remain significant concerns.[28] These findings support the rationale for therapeutic drug monitoring in TBM, particularly in critically ill or malnourished patients where drug metabolism may be altered.

Carbapenems have gained attention as promising second-line or adjunctive therapies, especially in drug-resistant TBM. Evidence suggests that meropenem and imipenem inhibit alternative peptidoglycan synthesis pathways and exhibit synergistic effects when combined with clavulanate or standard antituberculous agents.[29] While meropenem appears safer, imipenem has shown higher rates of neurotoxicity, including seizures, particularly in patients with severe meningeal inflammation.[30] The role of carbapenems in first-line intensification remains under investigation; however, their utility in multidrug-resistant TBM (MDR-TBM) is increasingly well supported.

Fluoroquinolones—specifically moxifloxacin and levofloxacin—continue to demonstrate high CSF penetration and potent antimycobacterial activity, making them valuable components of intensified regimens.[31] Their role becomes particularly important in regions with high rates of isoniazid or rifampin resistance. However, concerns remain regarding QT prolongation, drug interactions, and the possible emergence of fluoroquinolone-resistant strains of *M. tuberculosis*.[32]

Linezolid has emerged as one of the most effective salvage therapies in MDR-TBM due to its excellent CSF penetration and robust bactericidal activity.[33] Clinical reports have documented substantial neurological improvement in severe cases. However, linezolid-associated toxicity—including optic neuropathy, peripheral neuropathy, and myelosuppression—limits prolonged use.[34] This underscores the need for careful monitoring and, when possible, dose adjustments based on tolerability.

Adjunctive therapies remain a cornerstone of TBM management. Corticosteroids, particularly dexamethasone and prednisone, consistently reduce mortality in HIV-negative TBM by suppressing inflammation and limiting cerebral edema.[35] However, the benefit of steroids in HIV-positive TBM remains uncertain, with some studies reporting minimal improvement in mortality or functional outcomes.[36] Additional research is needed to clarify which patient subgroups may derive benefit from anti-inflammatory therapy and at what stage of the disease steroids exert their greatest protective effect.

An emerging adjunctive therapy is aspirin, which has shown promise as both an antiplatelet and anti-inflammatory agent. Recent studies suggest that aspirin reduces the incidence of TBM-associated ischemic stroke, a major contributor to long-term disability.[37] This effect is thought to occur through modulation of thromboxane and prostaglandin pathways, reducing vasculitic thrombosis and improving microvascular perfusion.[38] Although evidence remains limited, aspirin appears to be a low-cost, widely available adjunct with the potential to improve neurological outcomes when used alongside standard therapy.

Despite these promising therapeutic developments, several limitations persist. Delayed diagnosis remains a critical barrier, as many patients present in advanced neurological stages where intracranial vasculitis, infarction, and hydrocephalus have already occurred. Studies consistently demonstrate that early-stage treatment correlates with significantly lower mortality and better functional recovery.[39] Limited access to high-dose rifampin, carbapenems, and linezolid—especially in low-resource settings—further compounds disparities in outcomes. Additionally, the high toxicity burden of intensified regimens often necessitates treatment interruption, further reducing therapeutic efficacy.

Moving forward, the integration of optimized drug regimens with rapid diagnostic algorithms, therapeutic drug monitoring, and individualized treatment strategies appears essential. The future of TBM treatment will likely depend on improved CNS-penetrating compounds, more robust anti-inflammatory modulators, and targeted therapies capable of overcoming blood–brain barrier limitations.[40] Expanding clinical trials in diverse populations will also be critical to validate the safety and effectiveness of emerging treatment combinations.

CONCLUSION

Tuberculous meningitis remains one of the most severe and complex forms of tuberculosis, requiring early recognition and prompt initiation of therapy to minimize neurological injury and mortality. Despite advances in pharmacological strategies, treatment outcomes continue to be limited by suboptimal cerebrospinal fluid penetration of first-line agents, delayed clinical presentation, and the growing burden of drug-resistant disease.

Optimized therapeutic approaches, including high-dose rifampin, carbapenem-based combinations, fluoroquinolones, and linezolid, represent important developments that can enhance antimicrobial efficacy, particularly in multidrug-resistant TBM. Adjunctive therapies such as corticosteroids and aspirin contribute meaningful benefits by reducing inflammation, intracranial complications, and ischemic events. However, these improvements require careful monitoring due to potential drug-related toxicities.

The future of TBM management depends on integrating pharmacokinetically informed dosing, improved access to second-line agents, and individualized treatment strategies. Strengthening diagnostic capacity, expanding therapeutic drug monitoring, and promoting research into CNS-penetrating antimicrobials and targeted anti-inflammatory interventions will be essential to reducing the global burden of TBM. Continued investment in clinical research and public health infrastructure will be critical to improving survival, preventing neurological sequelae, and narrowing disparities in treatment outcomes worldwide.

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