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REVIEW

Advances in the Treatment and Clinical Management Strategies of Tuberculous Meningitis

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Abstract: Tuberculous meningitis (TBM), a central nervous system infection caused by Mycobacterium tuberculosis, is a rapidly progressing, insidious disease with an exceptionally high disability and mortality rate. Its significant global burden has become a critical focus in public health. The clinical diagnosis of TBM faces challenges due to the lack of specific symptoms and imaging characteristics, making early detection difficult. Combined with the shielding effect of the blood-brain barrier against anti-tuberculosis drugs and the issue of drug resistance, treatment outcomes are often suboptimal. Furthermore, current early sensitive diagnostic tools are inadequate, leading to delayed treatment for many patients and adversely affecting their prognosis. This paper reviews the pathophysiological mechanisms of TBM, the types and mechanisms of action of therapeutic drugs, and the common drug selection issues and safety challenges encountered in clinical practice. The aim is to provide comprehensive guidance and references for clinical diagnosis and treatment to improve the therapeutic outcomes and quality of life for TBM patients.

Keywords: tuberculous meningitis, treatment strategies, drug selection, host-directed therapy, multidrug resistance

Introduction

Tuberculous meningitis (TBM) is a severe central nervous system infection caused by Mycobacterium tuberculosis (MTB), representing a lethal form of extrapulmonary tuberculosis with a significant risk of disability.[1] As the most common and challenging type of tuberculous meningitis, its prevention and treatment have garnered widespread global attention. Statistics[2] show that TBM accounts for approximately 1–5% of all tuberculosis cases and 5–10% of extrapulmonary tuberculosis cases, with around 30–60% of TBM patients also presenting with pulmonary tuberculosis. Age distribution exhibits certain patterns, with children, especially those under five years old, and the elderly being the primary susceptible groups. Individuals with compromised immune function, such as patients with diabetes, cancer, or organ transplants, also face a higher risk of infection.[3,4] Additionally, while most cases occur in individuals with weakened immune systems, TBM can also be observed in immunocompetent individuals, highlighting its diversity and complexity.

If TBM is not diagnosed and treated promptly, it can result in significant mortality and neurological disabilities.[5] Although advancements in anti-tuberculosis drugs have improved early diagnosis and treatment of TBM in recent years, the disease still lacks specific clinical symptoms and imaging features, especially in elderly patients, leading to frequent diagnostic delays that severely impact prognosis. This is particularly true in cases where TBM is complicated by pulmonary tuberculosis, miliary tuberculosis, or other conditions, where the disease is often more complex and prone to missed optimal treatment Windows. Delayed treatment not only increases mortality but may also result in severe sequelae such as epilepsy and persistent neurological dysfunction, further burdening the patient.[6,7] Despite the World Health Organization (WHO) recommending a series of treatment regimens, many TBM patients still fail to benefit from current therapies. This is primarily due to the emergence of drug-resistant MTB and the limitations posed by the blood-brain barrier on anti-tuberculosis drugs.[8] For clinicians, selecting an appropriate drug treatment regimen is crucial, requiring not only precise combination strategies of anti-tuberculosis drugs but also the rational use of drugs with strong blood-brain barrier penetration and those that regulate host immune responses. Recent studies[9] suggest that high-dose rifampin combined with other anti-tuberculosis drugs and

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immunomodulatory agents targeting the host response may be effective in improving treatment outcomes and prognosis. In conclusion, early diagnosis and treatment of TBM remain key challenges in current medical research, particularly in optimizing drug therapy regimens and assessing drug safety. With the deepening understanding of this disease and innovations in treatment approaches, the therapeutic outlook for TBM is expected to improve significantly. This paper aims to review the progress in TBM drug therapy, analyze the advantages and challenges of existing treatment strategies, and provide new perspectives and references for clinical practitioners (Figure 1).

This diagram illustrates the process by which Mycobacterium tuberculosis (MTB) invades the central nervous system through the blood-brain barrier (BBB). First, MTB reaches the brain capillaries via the bloodstream and can cross the BBB to enter the brain parenchyma and cerebrospinal fluid through the following three main pathways:

"Trojan horse" mechanism: MTB can be engulfed by peripheral blood monocytes, which then cross the blood-brain barrier, transporting the pathogen into brain tissue.

Transcellular traversal: The bacteria can directly cross the endothelial cells of the blood-brain barrier, entering brain tissue via endocytosis and exocytosis.

Paracellular traversal: MTB crosses the barrier by disrupting the intercellular junctions of the endothelial cells, such as tight junctions, thus entering the central nervous system.

This process involves the interaction between bacterial surface molecules and host cell receptors, while also triggering the host immune response, leading to meningitis. The diagram also shows the release of inflammatory cytokines (such as TNF-α, IL-1β, etc)., which cause further damage to the structural integrity of the blood-brain barrier, exacerbating the pathological process (Table 1).

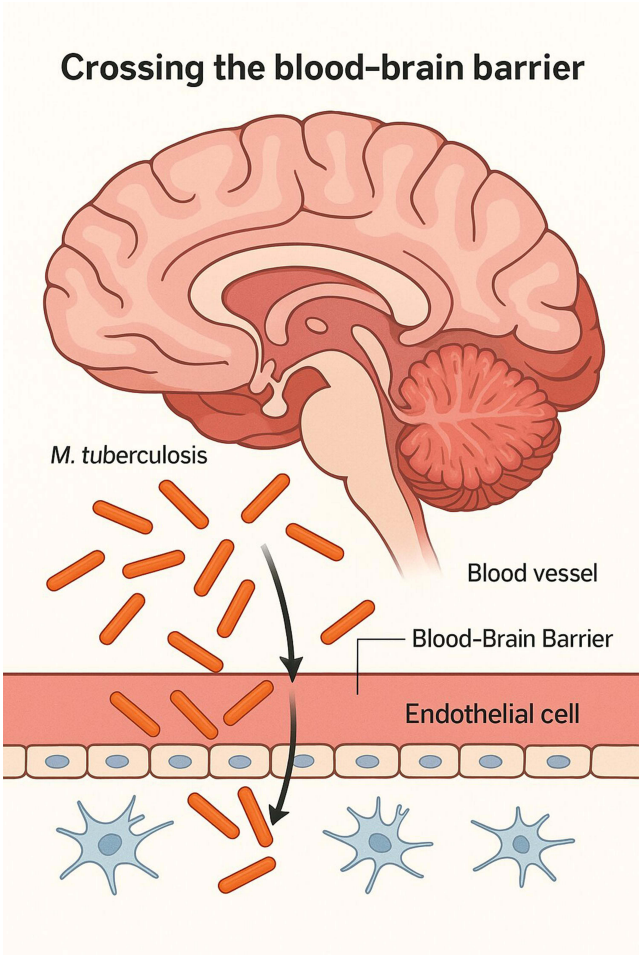

Figure 1 Schematic Diagram of the Mechanism by Which Mycobacterium tuberculosis Crosses the Blood-Brain Barrier.

Table 1 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

Chemotherapy Treatment

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Lanzhou University Second Hospital. Informed consent was obtained from all study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

Currently, for patients with drug-sensitive tuberculous meningitis (TBM), the standard treatment regimen primarily includes a combination of rifampin (R), isoniazid (H), ethambutol (E), and pyrazinamide (Z). In some cases, fluoroquinolones (FQs) are also added, and the total duration of treatment generally exceeds nine months. This chemotherapy regimen is one of the standard strategies for managing drug-sensitive TBM. In addition, to improve therapeutic outcomes, clinicians often incorporate immunotherapy, interventional treatments, and other comprehensive measures. "Immunotherapy" mainly refers to the adjunctive use of corticosteroids such as dexamethasone or prednisone, which help reduce the inflammatory response and elevated intracranial pressure caused by meningitis and may improve neurological prognosis. Some studies have also explored the use of immunomodulatory agents like interferon-gamma and interleukins to regulate host immune responses. "Comprehensive measures" include management of intracranial hypertension (eg, with mannitol, glycerol, or ventricular drainage), symptomatic and supportive care (such as maintaining fluid-electrolyte balance, nutritional support, and anticonvulsant therapy), prevention and treatment of complications (eg, antithrombotic therapy and prevention of secondary infections), and regular imaging and cerebrospinal fluid monitoring to assess disease progression. These interventions, when combined with standard anti-tuberculosis chemotherapy, can help improve clinical outcomes in TBM patients. The core treatment goals include selecting drugs with good blood-brain barrier penetration, appropriately increasing the dosage of certain medications, and combining fluoroquinolones to enhance antimicrobial efficacy and overall therapeutic effectiveness. Among these, pyrazinamide is generally recommended at a standard dose (approximately 25–30 mg/kg/day) for the treatment of TBM due to its favorable central nervous system penetration. However, Its potential hepatotoxicity must be considered, and any dose escalation should be guided by individual patient tolerance and personalized clinical assessment.

Despite the effectiveness of existing regimens, many challenges remain due to the resistance of MTB (Mycobacterium tuberculosis) to certain drugs. In particular, variability in the ability of drugs to penetrate the blood-brain barrier directly impacts therapeutic outcomes. To address these challenges, current strategies focus on optimizing drug doses and selection, as well as combining different types of anti-tuberculosis drugs. For drug-resistant TBM, treatment becomes even more complex and precise. Regimens must consider not only the penetration of drugs through

the blood-brain barrier but also their effectiveness, requiring at least four active first-line and second-line anti-tuberculosis drugs for prolonged treatment,[10] to ensure thorough eradication of the disease.

Treatment Strategies for Drug-Sensitive TBM

Currently, the WHO-recommended standard regimen for drug-sensitive TBM consists of an intensive phase of two months (2HREZ) followed by a continuation phase of 9–12 months (HR) (2HREZ/9–12HR).[11] This regimen is derived from pulmonary tuberculosis treatment protocols but does not consider the varying abilities of anti-tuberculosis drugs to penetrate the blood-brain barrier. Therefore, while this treatment regimen is effective in many cases, there is currently no universally optimal "best treatment plan" for all TBM patients.

In treating drug-sensitive TBM, it is crucial to consider factors related to patient survival, such as early diagnosis, timely treatment, and adjunctive use of corticosteroids. Additionally, the ability of drugs to effectively penetrate the blood-brain barrier and cerebrospinal fluid barrier must be emphasized. Given the limitations of existing standard anti-tuberculosis regimens in terms of drug penetration, optimizing TBM treatment—particularly in terms of drug selection and dosage—remains essential. Early and targeted treatment is especially critical.

The Role of Pyrazinamide in TBM Treatment

Pyrazinamide is a key drug in the treatment of TBM, recognized for its strong ability to penetrate cerebrospinal fluid, making it crucial for shortening treatment duration. Studies[12] have shown that pyrazinamide effectively enters cerebrospinal fluid, enhancing its bactericidal effects against MTB. For patients unable to tolerate pyrazinamide, the treatment course typically needs to be extended to 18 months to maintain sufficient drug concentrations. High doses of pyrazinamide (greater than the standard dose of 25–30 mg/kg) are considered potentially more effective, particularly in increasing drug concentrations in cerebrospinal fluid.[13] Thus, high-dose pyrazinamide may represent a potential approach to optimize TBM treatment.

Limitations of Ethambutol in TBM Treatment

Ethambutol is one of the recommended drugs for TBM treatment, but its ability to penetrate cerebrospinal fluid is relatively poor.[14] Although ethambutol is commonly used in combination therapy as a first-line anti-tuberculosis drug, its cerebrospinal fluid concentrations are often insufficient to achieve effective anti-tuberculosis action. Recent studies[15,16] have questioned the necessity of ethambutol in TBM treatment and suggested replacing it with drugs that have better blood-brain barrier penetration.

Pharmacokinetics and Clinical Application of Rifampin

Rifampin is a critical drug in TBM treatment. Despite its relatively poor penetration into cerebrospinal fluid, it remains widely used due to its potent anti-tuberculosis effects. Rifampin is a highly protein-bound drug, and its cerebrospinal fluid concentration is significantly lower than its plasma concentration, limiting its efficacy in TBM treatment. Standard doses of rifampin (10 mg/kg) typically yield cerebrospinal fluid concentrations at only 12% of plasma levels, which is much lower than the minimum inhibitory concentration (MIC) of MTB.[17] Therefore, increasing plasma rifampin concentrations is considered necessary to improve its efficacy.

Research by Svensson et al[18] indicated that higher doses of rifampin (35 mg/kg or more) may have positive clinical effects on TBM patients. Their findings showed that using 35 mg/kg rifampin significantly increased drug concentrations in plasma and cerebrospinal fluid, with drug exposure approximately 10 times higher than the standard dose (10 mg/kg). Higher rifampin exposure may improve clinical responses and survival rates in TBM patients, but further clinical trials are required to verify this conclusion. Dian et al[19] evaluated adult TBM patients treated with rifampin at doses of 450, 900, or 1350 mg (10, 20, and 30 $mg \cdot kg^{-1} \cdot d^{-1}$) combined with other drugs for 30 days. Results showed that 1350 mg rifampin significantly increased plasma and cerebrospinal fluid rifampin concentrations and was safe. However, although higher rifampin doses increased drug concentrations, studies have not definitively demonstrated a direct correlation between these changes and improved survival rates or clinical outcomes in TBM patients. Therefore, whether to universally adopt high-dose rifampin remains an unresolved question.

Improvements to Traditional Treatment Regimens

Traditional TBM treatment regimens typically follow the 2RHZE/10RH protocol, where isoniazid serves as a cornerstone drug due to its excellent blood-brain barrier penetration and strong bactericidal activity.[20] Isoniazid rapidly enters the cerebrospinal fluid, significantly enhancing anti-tuberculosis efficacy and helping to shorten treatment duration. The standard adult dose of isoniazid is 300–600 mg per day, while the pediatric dose is 10–20 mg/kg, with a maximum of 600 mg. Some studies[21] have shown that isoniazid exposure levels are closely related to patient survival rates—especially in rapid acetylators, where high-dose isoniazid may improve treatment outcomes. However, the efficacy and safety of high-dose isoniazid have not been fully validated in clinical settings, and whether dosage adjustments are needed remains an unresolved issue.[22]

It is important to note that despite its efficacy, isoniazid is associated with potential adverse effects that warrant careful attention. The most common toxicities include hepatotoxicity, peripheral neuropathy, and hypersensitivity reactions. The risk of liver toxicity increases significantly with higher doses, particularly in elderly patients, those with pre-existing liver disease, or individuals who consume alcohol regularly. Therefore, the use of high-dose isoniazid should be based on close monitoring of liver function and a comprehensive assessment of patient tolerance and acetylator status, aiming to balance potential benefits against associated risks when formulating individualized treatment plans.

Treatment Strategies for Drug-Resistant TBM

For the treatment of patients with multidrug-resistant or rifampicin-resistant tuberculous meningitis (MDR/RR-TBM), although the World Health Organization has not issued standardized guidelines for multidrug therapy (MDT), the Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis (2014) emphasizes that treatment should be guided by drug susceptibility testing results and the ability of anti-tuberculosis drugs to penetrate the central nervous system (CNS). Drugs with good CNS penetration are recommended, including fluoroquinolones (such as moxifloxacin and levofloxacin), ethionamide or prothionamide, cycloserine or terizidone, and linezolid.[23] Among them, linezolid has demonstrated rapid and significant therapeutic effects in clinical studies.[21] Although pyrazinamide also exhibits good CNS penetration, caution is advised due to the high resistance rates among MDR-TB strains. Isoniazid penetrates the cerebrospinal fluid well, and high doses can achieve effective bactericidal concentrations. Therefore, unless high-level resistance is confirmed, high-dose isoniazid is recommended as part of the treatment regimen.

Application of Fluoroquinolones (FQs)

FQs, particularly levofloxacin and moxifloxacin, play a vital role in the treatment of drug-resistant Mycobacterium tuberculosis (MTB). These drugs not only exhibit strong bactericidal effects against MTB but also have excellent penetration into the central nervous system, including CSF.[24] Thus, FQs are widely used to treat drug-resistant tuberculosis, including TBM. A randomized controlled trial[25] demonstrated that using levofloxacin alone could enhance the anti-tuberculosis effect and improve the success rate of TBM treatment. Therefore, levofloxacin and moxifloxacin are promising first-line drugs for treating drug-resistant tuberculous meningitis.

Application of Linezolid in Drug-Resistant TBM

Linezolid, a drug with significant bactericidal activity against drug-resistant MTB, has excellent CSF penetration, making it a crucial choice for treating drug-resistant TBM. Compared to other drugs, linezolid achieves CSF concentrations similar to plasma levels, ensuring effective penetration into the central nervous system and exerting its anti-tuberculosis effects.[26] Clinical studies have shown that patients treated with linezolid for tuberculous meningitis exhibit significant improvements in temperature recovery, coma index, and reductions in CSF white blood cell counts. For example, a study by Li et al[27] indicated that adding linezolid to the treatment regimen increased the success rate of TBM treatment, particularly in pediatric patients, where the effects were more pronounced.

Roles of Ethionamide and Cycloserine

Ethionamide and cycloserine are drugs targeting drug-resistant MTB, demonstrating strong CSF penetration, which adds value to their use in treating drug-resistant TBM. Ethionamide, in particular, has been proven effective against pediatric

tuberculous meningitis.[28] However, the use of these drugs is limited due to dose-related side effects, especially their impact on the nervous and gastrointestinal systems.[29] Despite these limitations, ethionamide remains a recommended part of the treatment regimen for drug-resistant TBM according to many experts.

Potential of Delamanid

Delamanid, a novel anti-tuberculosis drug, has shown promising results in recent years for treating drug-resistant TBM. Its advantages include not only its anti-tuberculosis efficacy but also its ability to penetrate brain tissue and damaged tissues.[30] This makes delamanid effective in improving clinical symptoms and increasing patient survival rates. Relevant studies[31] have shown that delamanid effectively enhances treatment response rates, alleviates the disease, and significantly reduces adverse prognoses in clinical applications.

Choices Between Meropenem and Imipenem

Imipenem and meropenem, as broad-spectrum antibiotics, also hold potential for treating drug-resistant TBM. However, due to the risk of neurological adverse reactions such as seizures in pediatric patients caused by imipenem, some studies recommend prioritizing meropenem.[32] Meropenem not only has better CSF penetration but also exhibits superior efficacy in treating drug-resistant tuberculosis compared to imipenem, making it more suitable for treating pediatric TBM.

Application of Other Therapeutic Drugs

In the treatment of drug-resistant TBM, some drugs exhibit low CSF penetration and cannot be considered primary therapeutic agents. For instance, drugs like streptomycin and amikacin, although capable of crossing the blood-brain barrier in cases of meningitis, have poor penetration capacity and should only be considered in cases of severe meningitis. Similarly, para-aminosalicylic acid (PAS) and ethambutol also have weak blood-brain barrier penetration and are therefore not recommended as first-line drugs for treating drug-resistant tuberculous meningitis.

Anti-Inflammatory Agents

Glucocorticoids

Glucocorticoids, as a classic anti-inflammatory drug, are widely used in the treatment of TBM, especially during the acute phase. Their mechanism of action is not limited to reducing inflammatory responses but also includes repairing and improving the function of the blood-brain barrier. Dexamethasone, a potent glucocorticoid with strong anti-inflammatory properties and a long half-life, is extensively used in the treatment of TBM patients.[33] Although adjunctive glucocorticoid therapy can significantly reduce inflammation, alleviate cerebral edema, and improve survival rates, its use is still accompanied by many challenges, particularly the potential neurological damage and immunosuppressive effects associated with long-term use.[34]

Anti-Inflammatory Effects of Glucocorticoids and Their Application in TBM

Glucocorticoids regulate immune responses through multiple pathways, inhibiting the secretion of cytokines and reducing the synthesis of inflammatory mediators such as leukotrienes and prostaglandins, thereby alleviating meningeal and cerebrovascular inflammation.[35] In TBM patients, inflammatory responses often lead to cerebral edema, neurological damage, and brain dysfunction. Thus, the use of glucocorticoids can effectively mitigate these symptoms and promote patient recovery. According to multiple clinical studies, the combination of glucocorticoids and anti-tuberculosis drugs can effectively reduce mortality in TBM patients, especially in those whose immune systems are not severely compromised. For example, dexamethasone, a potent glucocorticoid, enhances the intracerebral distribution of drugs by increasing blood-brain barrier permeability, thereby improving the concentration of anti-tuberculosis drugs in cerebrospinal fluid.[36] Its anti-inflammatory effects effectively reduce the brain inflammation caused by MTB, alleviating cerebral edema and improving clinical symptoms. Therefore, glucocorticoids have become one of the standard drugs for treating acute-phase TBM.

Immunosuppressive Effects and Risks of Long-Term Use

Although glucocorticoids demonstrate favorable clinical efficacy in the treatment of TBM—particularly in reducing inflammatory responses and lowering intracranial pressure—their long-term use is associated with considerable adverse effects. One of the most significant side effects is immunosuppression, which can increase patients' susceptibility to opportunistic infections during treatment, especially the risk of secondary tuberculosis infections. In recent years, host-directed therapy (HDT) has emerged as a novel research direction in tuberculosis treatment. Among these, phosphodiesterase-4 (PDE4) inhibitors have garnered attention due to their ability to regulate immune responses and suppress proinflammatory cytokines. Animal model studies (such as in rabbits or mice) have shown that PDE4 inhibitors can attenuate TBM-associated inflammatory responses and improve pathological changes.[37,38] However, there is currently a lack of clinical research evidence on the efficacy and safety of PDE4 inhibitors in human TBM patients. Therefore, their clinical application remains uncertain and is not yet recommended for routine use.

Furthermore, prolonged use of glucocorticoids may lead to hyperglycemia, osteoporosis, gastrointestinal bleeding, cardiovascular diseases, and other adverse reactions. More importantly, long-term use of glucocorticoids may negatively affect the nervous system. Some studies suggest that patients undergoing extended glucocorticoid therapy may experience cognitive decline, neurological damage, and other neurological complications. For instance, a study by Suárez et al[39] revealed that although patients with TBM experienced rapid alleviation of neurological symptoms during glucocorticoid treatment, some developed seizures or new neurological damage after discontinuing the drug. Therefore, the duration and dosage of glucocorticoids must be strictly controlled to minimize adverse effects.

Combined Use of Glucocorticoids with Other Immunomodulators

In recent years, researchers have begun exploring the combined use of glucocorticoids with other immunomodulators to enhance therapeutic effects and reduce side effects. For example, phosphodiesterase-4 inhibitors (PDE4 inhibitors) have shown promising results in TBM treatment. Studies[38] have demonstrated that PDE4 inhibitors not only effectively reduce the incidence of TBM but also significantly improve patient survival rates. Combined with glucocorticoids, PDE4 inhibitors can further reduce glucocorticoid dosage, thereby decreasing side effects while enhancing therapeutic efficacy.

Additionally, thalidomide, a novel immunomodulator, has shown potential in TBM treatment. A study by Liu et al[40] reported a case of a 40-year-old female patient who achieved certain therapeutic effects with standard anti-tuberculosis treatment and dexamethasone. However, the patient developed new tuberculomas during treatment, and subsequent treatment with thalidomide led to a good recovery without neurological complications. Thalidomide, as an anti-inflammatory drug, works by inhibiting the synthesis of inflammatory mediators such as tumor necrosis factor-α (TNF-α), effectively reducing inflammation associated with TBM and showing favorable clinical outcomes. However, the use of thalidomide is accompanied by risks, including teratogenicity, hematotoxicity, and gastrointestinal adverse reactions.[41] Therefore, its use requires careful assessment of the patient's condition and strict medical supervision.

Glucocorticoids and Post-TBM Neurological Damage

While glucocorticoids can significantly improve acute-phase symptoms of TBM and reduce mortality, their effects on long-term neurological damage remain unclear. Consequently, the long-term benefits of glucocorticoids lack sufficient clinical evidence, necessitating further research. Future studies should focus on evaluating the impact of glucocorticoids on long-term neurological recovery in TBM patients and determining whether they can improve the prognosis following neurological damage.

Aspirin

Application and Effects of Aspirin in TBM Treatment

Due to the excessive immune response in TBM, cerebral vessels and brain tissues are prone to damage, leading to a high incidence of secondary cerebral infarction. Aspirin, a widely used non-steroidal anti-inflammatory drug (NSAID), has multiple mechanisms of action, including antiplatelet aggregation, anti-inflammatory, and antioxidant properties.[42] By inhibiting cyclooxygenase (COX) activity, aspirin reduces prostaglandin synthesis, thereby decreasing platelet aggregation and exerting antithrombotic and anti-inflammatory effects. Particularly in cerebrovascular diseases, aspirin can

reduce thrombus formation, lowering the risk of secondary cerebral infarction. Hence, aspirin is considered to have potential preventive and therapeutic benefits in TBM, especially in mitigating secondary cerebral infarction caused by tuberculosis infection and alleviating inflammatory responses. Several clinical studies have evaluated the effectiveness of aspirin in TBM and preliminarily demonstrated its therapeutic potential. Misra et al[43] were the first to report the effects of aspirin in TBM treatment. Their study randomized 118 TBM patients into an aspirin group (150 mg/day) and a placebo group, with all patients receiving anti-tuberculosis treatment. The results showed that although the stroke incidence was reduced by 19.1% in the aspirin group compared to the placebo group, the difference did not reach statistical significance. However, the mortality rate in the aspirin group was significantly lower (21.7% vs 43.4%, $P<0.05$). Furthermore, logistic regression analysis revealed a significant association between aspirin use and improved survival rates, with no reported adverse events leading to discontinuation. This study indicated that while aspirin did not significantly reduce stroke incidence, it notably improved survival in TBM patients. Schoeman et al[44] conducted a randomized controlled trial on 146 children with suspected TBM to assess the efficacy of low-dose and high-dose aspirin. The results showed no significant association between aspirin dosage and mortality, secondary hemiplegia, or developmental disorders. However, the high-dose aspirin group exhibited better treatment outcomes, characterized by lower mortality and improved neurological recovery. Mai et al[45] further explored the efficacy of aspirin in adult HIV-negative TBM patients, comparing low-dose (81 mg), high-dose (1000 mg) aspirin, and a placebo. During the 60-day treatment period, the high-dose aspirin group demonstrated a lower incidence of new cerebral infarction (10.7% vs 34.4%) and a similar rate of gastrointestinal and cerebral hemorrhagic adverse events. Cerebrospinal fluid analysis showed that aspirin, in a dose-dependent manner, inhibited thromboxane A2 production and upregulated the expression of protective factors in the cerebrospinal fluid, thereby promoting brain tissue protection. Subsequent studies by Misra et al[46] also evaluated the effects of combining aspirin with corticosteroids. Results indicated that the combination therapy did not significantly improve survival rates in TBM patients. However, the mortality rate of patients receiving combination therapy was notably lower than that of untreated patients, with clinical symptoms and imaging findings showing improvement. This suggests that the combined use of aspirin and corticosteroids may exert a synergistic effect in some TBM patients, reducing complications and improving prognosis.

Side Effects and Safety

Although aspirin has demonstrated positive clinical effects, its use is also associated with certain risks, particularly in TBM patients, who may experience gastrointestinal adverse reactions and complications such as cerebral hemorrhage.[47] The adverse effects of aspirin vary with dosage: low-dose aspirin is generally well-tolerated, while high-dose aspirin may lead to more side effects, especially in patients with compromised immune systems. Additionally, the anticoagulant effects of aspirin may increase bleeding risks, necessitating careful monitoring of coagulation function during use.

Conclusion and Outlook

Despite advancements in the treatment of tuberculosis meningitis (TBM), challenges remain in developing a universally effective therapeutic regimen. The complexity of TBM's pathogenesis and the variability in patients' clinical conditions make individualized treatment strategies crucial. Future research should focus on optimizing current therapies, including the development of new drugs and treatment regimens, as well as the potential to shorten treatment durations to reduce patient burden. Additionally, adjunctive treatments, particularly anti-inflammatory agents like thalidomide, hold promise but require further investigation to confirm their safety and efficacy in TBM management.

Key areas for future research include: (1) Personalized Treatment Approaches: Tailoring therapy based on drug sensitivities, resistance profiles, and clinical characteristics can enhance treatment outcomes and minimize adverse effects. (2) Synergistic Treatment Strategies: Exploring the combined use of anti-inflammatory and neuroprotective agents alongside anti-tuberculosis drugs could improve clinical outcomes. (3) Drug Monitoring and Optimization: Enhancing drug concentration monitoring in blood and cerebrospinal fluid will be critical for ensuring therapeutic efficacy, especially in crossing the blood-brain barrier.

Ultimately, integrating new drug developments, advanced diagnostic techniques, and comprehensive treatment strategies will be key to improving TBM management, reducing mortality, and enhancing patient quality of life.

Disclosure

The authors report no conflicts of interest in this work.

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