Encephalitis and Meningitis: Indications for Intervention

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ABSTRACT

Meningitis and encephalitis are characterized by inflammation of the meninges and brain parenchyma, respectively. The blood-brain barrier normally acts as a protective barrier against inflammation in the central nervous system (CNS), but its compromise requires prompt diagnosis and treatment to prevent morbidity and mortality. Optimizing therapy for meningitis and encephalitis can expedite resolution of symptoms, mitigating the risk of neuronal injury and minimizing potential long-term neurological sequelae. This paper aims to provide a comprehensive overview of the etiology and pathophysiology of meningitis and encephalitis, discussing the diagnostic criteria, and emphasizing the clinical indications for treatments, including current treatment strategies, and emerging therapeutic approaches.

Keywords: Meningitis; Encephalitis; Meningoencephalitis; ICP; CNS inflammation; Diagnostic criteria; Meningitis treatment; Encephalitis treatment; Emerging therapies; Immunomodulatory therapies

INTRODUCTION

Meningitis and encephalitis are two conditions that share significant clinical and etiological similarities. The pathophysiology of meningitis involves inflammation of the leptomeningeal membrane surrounding the brain, while encephalitis involves inflammation of the brain parenchyma itself [1-5]. Sometimes, inflammation caused by infectious or non-infectious causes can lead to meningoencephalitis, which can cause significant edema of surrounding structures and increase intracranial pressure (ICP) [5,6]. The blood-brain barrier (BBB) normally provides protection against CNS inflammation by preventing pathogens and other pro-inflammatory molecules from entering the cerebrospinal fluid (CSF) from the blood [5,6]. However, when the BBB is compromised, it can lead to pathology that requires prompt diagnosis and treatment to prevent the associated morbidity, as discussed above [2-6]. In most patients, infectious causes are the predominant reason for meningitis and encephalitis, with the specific pathogen depending on patient-specific risk factors [5-8]. However, depending on the patient’s history and
presentation, neoplastic, toxic, and autoimmune causes may also be considered and treated accordingly.

Meningitis is clinically characterized by symptoms such as nuchal rigidity, fever, and altered mental state (AMS), although the presence of the full triad is rare, making diagnosis challenging [5,9,10]. Children may present with specific symptoms such as vomiting, headache, and neck pain or with non-specific symptoms such as hypotonia, poor feeding, and irritability, or a combination of both [9,10]. The absence of neck stiffness, AMS, and fever can exclude meningitis, but the presence of symptoms is poorly sensitive for clinical diagnosis [10]. Kernig and Brudzinski’s signs were historically used to evaluate suspected cases of meningitis, but various studies have shown that they do not have significant predictive value for diagnosis [10]. Encephalitis, on the other hand, is characterized by encephalopathy with at least three features, including seizures, fever, CSF pleocytosis, focal neurological signs, abnormal MRI findings, and electroencephalogram [5]. Differentiating between metabolic derangements causing encephalopathy and etiologies leading to encephalitis is crucial for early diagnosis and treatment.

Epidemiology

Meningitis and encephalitis, caused by infectious and non-infectious etiologies, are important causes of disability-adjusted-life years (DALY) in both children and adults globally according to the Global Burden of Disease (GBD) study in 2016 [11]. Analysis of disease burden, epidemiology and mortality from 1990-2016 was performed and reported the global age-standardized incidence rate and death rates amongst other measures for neurological disorders. It was found that during this time-period incidence of encephalitis was reported to be 6534 per 1000,000 people while it was cause of death for 103 per 100,000 people [11]. In comparison, meningitis incidence was reported as 2821 per 100,000 people, with it being the cause of death for 318 per 100,000 people [11]. Although the incidence, death and DALY show downward trajectory, some regions of the world showcase more improvement than the others mostly owing to their socioeconomic development and subsequent increase in vaccination rates which has significantly reduced the infectious etiologies (most common cause) of meningitis and encephalitis, they still significantly contribute towards global burden of morbidity and mortality due to neurologic disorders [11]. In USA, an epidemiological study utilized Premier Healthcare Database to evaluate epidemiology, management, and outcomes of adults with all types of meningitis and encephalitis in the United States from 2011 to 2014 [12]. They found that in adults with meningitis or encephalitis, with infectious and non-infectious causes, the median length of hospital stay was 4 days and there was up to 3.2% inpatient mortality associated with the diagnosis [12]. As for discharge outcomes, 77.4% patients were discharged to home with or without home health care, but there were about 17.4% patients who were discharged to rehabilitation/nursing home or to hospice care [12].

Etiology

According to a study, enterovirus was the leading cause of meningitis in hospitalized adults in the US, accounting for 50.9% of cases, followed by bacterial infections (13.9%), herpes simplex virus (8.3%), and fungal infections (2.7%) [3,12-15]. The specific bacteria responsible for meningitis can vary depending on factors such as vaccination status, recent trauma, and age [14,15]. Streptococcus pneumoniae is the main cause of bacterial meningitis globally, affecting both adults and children, while Neisseria meningitidis is more common in young adults and children, and Listeria monocytogenes is more common in the elderly [3,8,12,13]. In neonates, the most common causes of meningitis are Streptococcus agalactiae and Escherichia coli, while in older children it is usually Streptococcus pneumoniae and Neisseria meningitides [3,8,12,13]. Viral meningitis is generally less severe than bacterial meningitis and is often caused by herpes simplex virus type 2 or enteroviruses [12,15]. The most common cause of encephalitis is viral infection, with herpes simplex virus being the main culprit [12]. Other infectious agents, including fungi, parasites, and bacteria, can also cause meningitis and encephalitis [12]. In addition, surgery, trauma, and autoimmune conditions can lead to these conditions, and patients with extra-ventricular drains have an increased risk of encephalitis due to drain infections [8,14,15]. Immunocompromised patients, such as those with HIV, hematologic malignancies (especially CNS lymphoma), or those undergoing immunosuppressant therapy, may have wide range of infectious and non-infectious causes of meningitis and encephalitis [12,16-18]. These patients are at higher risk of certain pathogens than healthy individuals, regardless of age. Besides the typical bacterial, viral, and fungal causes, neurologic involvement can occur in immunocompromised patients for L. monocytogenes, CMV,
HHV-6, JC virus (leading to PML in HIV/AIDS patients), VZV, Cryptococcus neoformans, Aspergillus species, B. dermatitidis, and C. immitis [12]. Symptoms in these patients may progress quickly with increased intracranial pressure, and they may also exhibit signs of disseminated infection involving skin, soft tissue, bone, and severe pulmonary symptoms [5,18]. Transplant or transfusion recipients are particularly vulnerable to CMV, EBV, and HHV-6, which may be transmitted from tissue to host [5,12].

Diagnosis and current treatments

Treatment time for bacterial meningitis is vital, and delays of even an hour before treatment may increase odds of an unfavorable outcome by 30% [19]. As previously mentioned, classic clinical signs and symptoms for meningitis aren’t very reliable and sensitive [20]. In the diagnosis of encephalitis and meningitis, CSF analysis via a lumbar puncture (LP) is often the most important factor [21]. Cerebrospinal fluid (CSF) and blood (serum) analysis is used to definitively diagnose many types of meningitis. This analysis can look at concentrations of leukocytes, glucose, proteins, and lactate, among other variables. A recent study found that analyzing both serum procalcitonin (PCT) and CSF lactate levels together gives higher predictive power of the presence of bacterial meningitis vs aseptic meningitis than either independently [22]. Failure to administer LP urgently, often delayed by CT scan, can lead to increased mortality in patients with bacterial meningitis [23]. It has been shown that normal neurological examination can act as an effective predictor of a normal CT scan with reported 97% negative predictive value [24,25]. The primary risk in performing LP without CT data is cerebral herniation, which has been observed to occur in patients with bacterial meningitis from 0.1%-3.0% after LP [26]. The Infectious Diseases Society of America (ISDA) guidelines published in 2004 recommend that only patients with immunocompromised state, history of central nervous system disease (including brain tumor and/or stroke), history of seizure ≤ 1 week before presentation, papilledema, abnormal level of consciousness, or certain focal neurological deficits should undergo CT scan before LP [27]. Despite this, it is common for patients to undergo inappropriate CT scans, delaying treatment [28]. It should be noted that, in a recent Dutch study, an association was not found between CT scan before LP and treatment delays [29]. It should also be known that despite being the standard of care, LP is not without risk. A recent cadaver study found a 25% probability of disk penetration during lumbar puncture, which can lead to accelerated joint degeneration [30]. There is also a small risk for delayed subdural hematoma and paraplegia, although extremely low [31,32].

In addition, culture plates are used in conjunction with polymerase chain reaction (PCR) tests to determine the presence of bacteria, fungal or virus in CSF that may be causing the infections [14,15]. However, in cases with minimal suspicion of infectious etiologies, and due to clinical presentation/patient medical history, further analysis of CSF and blood for inflammatory markers, and specific autoantibodies may be performed. In CSF analysis, the presence of inflammatory markers such as elevated protein, white blood cell count, and detection of autoantibodies in the CSF or serum can be helpful in the diagnosis of autoimmune meningitis [33,34]. Autoantibodies against neuronal cell surface antigens, such as N-methyl-D-aspartate receptor (NMDAR), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), LGI1, Caspr2, and gamma-aminobutyric acid type B receptor (GABA-BR), have been associated with autoimmune meningitis [33,34]. Common observations in CSF analysis of CNS infections and the diagnostic criteria for encephalitis are summarized in table 1 and 2 respectively.
**Table 1:** Summary of CSF findings observed in Meningitis/Encephalitis.

<table>
<thead>
<tr>
<th></th>
<th>White Blood Cell (WBC) density</th>
<th>Protein levels</th>
<th>Glucose levels</th>
<th>Gram staining</th>
<th>Lactate concentration</th>
<th>Opening Pressure</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacterial Meningitis</strong></td>
<td>&gt; 300/mm³ 3 1000 cells/µL with polymorphonuclear dominance</td>
<td>High (&gt;45mg/dL)</td>
<td>Low (&lt;60% of blood glucose) &gt;200mg/dL</td>
<td>Sometimes positive</td>
<td>Low</td>
<td>Elevated</td>
<td>17,27,56,78,14,15,79,80,81,82,83,84</td>
</tr>
<tr>
<td><strong>Viral Meningitis</strong></td>
<td>&lt;1000 cells/µL Normally mononuclear</td>
<td>Normal or high</td>
<td>&lt;200mg/dL Normal</td>
<td>Negative</td>
<td>High</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td><strong>Tuberculosis Meningitis</strong></td>
<td>100-500 cells/µL Increased, usually mononuclear</td>
<td>&gt;1g/L Usually, high</td>
<td>Usually, low</td>
<td>Negative</td>
<td>High</td>
<td>Elevated</td>
<td></td>
</tr>
<tr>
<td><strong>Fungal Meningitis</strong></td>
<td>&lt;500 cells/µL Usually mononuclear, sometimes polymorphonuclear</td>
<td>Usually, high</td>
<td>&gt;200mg/dL Normally low</td>
<td>Sometimes positive</td>
<td>High</td>
<td>Normal or Elevated</td>
<td></td>
</tr>
<tr>
<td><strong>Autoimmune Meningitis/Encephalitis</strong></td>
<td>Increased (lymphocytic and premature) or normal (depending on associated antibodies)</td>
<td>Elevated with presence of oligoclonal bands (OCB). Elevated specific antibodies (e.g AMPAR, NMDAR etc.)</td>
<td>Normal or slightly elevated</td>
<td>Negative</td>
<td>Negative</td>
<td>Normal or Elevated</td>
<td>33,34</td>
</tr>
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</table>

**Table 2:** Diagnostic criteria as provided by the International Encephalitis Consortium [35].

<table>
<thead>
<tr>
<th>Major Criteria Must be true</th>
<th>Minor Criteria 2 for possible encephalitis, 3 for confirmed encephalitis</th>
<th>Required for Confirmed 1 of the following in addition to major and minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient is presenting with altered mental status (altered level of consciousness, lethargy, or personality change) lasting 24h with no alternative cause identified</td>
<td>Documented fever 38°C (100.4°F) within the 72h before or after presentation</td>
<td>Pathologic confirmation of brain inflammation consistent with encephalitis</td>
</tr>
<tr>
<td></td>
<td>Generalized or partial seizures not fully attributable to a preexisting seizure disorder</td>
<td>Defined pathologic, microbiologic, or serologic evidence of acute infection with a microorganism strongly associated with encephalitis from an appropriate clinical specimen</td>
</tr>
<tr>
<td></td>
<td>Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset</td>
<td>Laboratory evidence of an autoimmune condition strongly associated with encephalitis</td>
</tr>
<tr>
<td></td>
<td>New onset of focal neurologic findings</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CSF WBC count &gt;5/cubic mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause</td>
<td></td>
</tr>
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</table>

Most cases of meningitis and encephalitis, especially infectious, are treated with antimicrobials (Table 3) while other treatments may be utilized for non-infectious etiologies. Regardless, drug penetration into CSF is an important consideration for adequate treatments. CSF penetration depends on the status of the blood-brain barrier, lipid solubility, molecular size, and the clearance rate of the pharmacologic agents via active transport by pumps in the arachnoid villa [36-38].
When the blood-brain barrier is normal, most beta-lactam agents (e.g., penicillin) penetrate poorly [39,40]. However, in the presence of meningeal inflammation, CSF penetration is enhanced likely as a result of separation of intercellular tight junctions and inhibition of the organic pump, raising the levels of the antimicrobials in the CSF [37,38,40]. Acknowledging this dynamic has informed decisions and recommendations for preferred drugs for treatment and the dosages to achieve therapeutic effect. Moreover, intravenous (IV) administration is preferred over parenteral (oral) dosing to improve bioavailability of the antimicrobials for BBB penetration [38,41]. In some patients intrathecal dosing is usually considered to target multi-drug resistant pathogens for which the in-vitro susceptibility data suggests insufficient penetration into CSF [41]. Usually, large molecule drugs are administered intrathecaally (aminoglycosides, colistin methanesulfonate, daptomycin, tigecycline, and vancomycin) because they are found to have limited BBB penetration [41]. All these antimicrobials are used off-label except for Colistin which is approved in USA and Europe for intra-thechal administration for treatment of CNS infections. The intrathecal application of anti-microbials represents direct access to the extracellular central nervous compartments, bypassing all barriers. High CSF levels of antimicrobials can be reached with comparatively small doses, although there have been concerns raised by experimental evidence suggesting that intrathecal therapy has a higher risk of seizures than systemic application [41].

In cases of bacterial meningitis, antibiotics and supportive care are crucial, including maintaining airway, IV fluids for hydration, and fever control [3,14,15,42]. The choice of antibiotic depends on the suspected organism causing the infection. Initially, patients are given broad-spectrum antibiotics until CSF cultures and drug susceptibilities have been identified [3,14,15]. The treatment of viral meningitis and encephalitis is primarily supportive since most central nervous system viral infections have no specific medical therapy, except for HSV encephalitis, which is treated with acyclovir [15]. The use of corticosteroids as an adjunctive therapy has been suggested due to the associated inflammation which worsens clinical symptoms [7,43]. However, it has been shown that they may not improve clinical outcomes due to their effect on reducing BBB permeability and drug concentrations in the CSF [44,45]. A Cochrane meta-analysis (including 25 studies) concluded that in patients with bacterial meningitis, use of corticosteroid was associated with lower rates of severe hearing loss but not with an overall reduction in mortality [46,47]. Although in a sub-group analysis corticosteroids were found to reduce mortality in Strep pneumoniae but not in H. influenzae or Neisseria meningitidis meningitis [46]. On the other hand, autoimmune encephalitis patients respond well to antibody-directed therapy like intravenous immunoglobulin and plasmapheresis, accompanied by the administration of corticosteroids intravenously which were associated with significant reduction of faciobrachial dystonic seizures (FBDS) in patients over the course of treatment [48-50]. These studies also show moderate evidence for rituximab and cyclophosphamide immunotherapy to treat and reverse autoimmune encephalitis [51]. Management of encephalitis (infectious or non-infectious) also involves monitoring intracranial pressure, which is associated with poor prognosis, and seizure management with anti-convulsant may be needed [50].

Although uncomplicated meningitis and encephalitis does not call for surgery, it is sometimes warranted in the case of complicated cases. Bacterial meningitis with intracranial hypertension can be ameliorated with decompressive craniotomy, although this is an invasive procedure52. Meningitis can be caused by an infection via a surgical implant, such as a CSF shunt, and is relatively common, with infections due to CSF shunt ranging from 5.2%-13.6% [53-56] . Surgical intervention is an option for many other forms of healthcare-associated encephalitis and meningitis, caused by CSF drains, intrathecal infusion pumps, deep brain stimulation hardware, neurosurgery, and head trauma [57]. In the case of CSF shunts, removal of the infected shunt with establishment of external drainage and antibiotic administration has been shown to have the highest expected treatment outcomes, while antibiotic use alone has relatively low expected treatment outcomes [58,59]. The current aspects of clinical and pharmacological management of meningitis and encephalitis are summarized in Table 3.
### Table 3: Summary of treatments for Meningitis/encephalitis of various etiologies. All medications are administered intravenously unless otherwise stated. *An equivalent antibiotic, such as ceftazidime or cefepime, may be used in place of cefotaxime. **Adjunctive corticosteroids used in some immunocompromised patients. ‘Corticosteroid therapy has been shown to be an effective treatment in patients 14 years and older. IVIG has been demonstrated to be effective for autoimmune meningitis patients 12 years or older.

<table>
<thead>
<tr>
<th>Condition / Etiology</th>
<th>Neonates (up to 1 month)</th>
<th>Older than 1 month</th>
<th>Adults (18-49 years old)</th>
<th>Adults over 50 years old</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis, otherwise nominal</td>
<td>Ampicillin</td>
<td>Ampicillin</td>
<td>Ceftriaxone</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td></td>
<td>Cefotaxime* or gentamicin</td>
<td>Ceftriaxone</td>
<td>Vancomycin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Meningitis, immunocompromised</td>
<td></td>
<td>Ceftriaxone</td>
<td>Vancomycin</td>
<td>Ampicillin</td>
</tr>
<tr>
<td>Meningitis associated with a foreign body (post-procedure, penetrating trauma)</td>
<td></td>
<td>Cefepime</td>
<td>or ceftazidime Vancomycin</td>
<td>or meropenem</td>
</tr>
<tr>
<td>Meningitis with severe penicillin allergy</td>
<td></td>
<td>Moxifloxacin</td>
<td>Vancomycin</td>
<td></td>
</tr>
<tr>
<td>Fungal meningitis</td>
<td></td>
<td>Amphotericin</td>
<td>Flucytosine by mouth</td>
<td></td>
</tr>
<tr>
<td>Tuberculosis meningitis</td>
<td></td>
<td>Corticosteroid therapy</td>
<td>Corticosteroid therapy</td>
<td></td>
</tr>
<tr>
<td>Autoimmune meningitis</td>
<td></td>
<td>Corticosteroid Intravenous immunoglobulin Rituximab and</td>
<td>Corticosteroid Intravenous immunoglobulin Rituximab and</td>
<td>Corticosteroid Intravenous immunoglobulin Rituximab and</td>
</tr>
<tr>
<td>Strep-pneumo</td>
<td></td>
<td>Corticosteroid therapy</td>
<td>Corticosteroid therapy</td>
<td></td>
</tr>
<tr>
<td>HSV encephalitis</td>
<td></td>
<td>Acyclovir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella-zoster encephalitis</td>
<td></td>
<td>Acyclovir**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV encephalitis</td>
<td></td>
<td>Ganciclovir</td>
<td>Foscarnet</td>
<td></td>
</tr>
<tr>
<td>In addition, if increased intracranial pressure:</td>
<td></td>
<td>Elevate head of bed Induce mild Osmotic</td>
<td>30 degrees hyperventilation diuretics</td>
<td></td>
</tr>
<tr>
<td>References</td>
<td></td>
<td>7,14,15,41,47,50,78</td>
<td></td>
<td></td>
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**Emerging treatments**

**Immunomodulatory therapies**

**Complement**

Complement activation is a key feature of the immune response to central nervous system (CNS) infections, including meningitis and encephalitis [7]. In the presence of meningeval inflammation, complement CSF concentrations are increased significantly [7,60,61]. Treatment with neutralizing monoclonal antibodies directed against complement C5 as an adjunct to ceftriaxone strongly reduced mortality from 33 to 0%, indicating that complement C5-specific monoclonal antibodies may be a promising new anti-inflammatory adjuvant therapy for pneumococcal meningitis [61,62].

**Toll-like Receptor**

Toll-like receptors (TLRs) are essential receptors that are responsible for initiating immune responses upon exposure to bacterial antigens, and they play a crucial role in bacterial meningitis [61-63]. In a study involving murine models of Streptococcus pneumoniae meningitis, it was found that administering adjunctive treatment with antibodies targeting TLR2 and TLR4 led to a significant reduction in meningeval...
inflammation and brain tissue damage. However, this treatment did not have any impact on mortality rates [61]. This suggests that targeting TLR2 and TLR4 with anti-inflammatory agents could potentially be a useful therapeutic strategy to reduce inflammation and tissue damage in bacterial meningitis cases. However, further research is needed to determine the optimal dosage and timing of such treatments and to assess their safety and efficacy in human clinical trials.

**PNAG antibodies**

PNAG (Poly-N-acetylglucosamine) is a bacterial surface polysaccharide that has been implicated in the pathogenesis of meningitis caused by several bacterial species, including *Streptococcus pneumoniae* and *Escherichia coli* (36709579). Antibodies to Pnag have been studied in mice model for their potential role in the therapy of meningitis and encephalitis caused by these bacteria, and revealed that Pnag-specific antibodies were effective in preventing bacterial colonization of the meninges and improved survival in mice with E.coli meningitis [64]. Moreover, a phase 1 and 2 clinical trial: NCT02853617, has been conducted to assess safety and immunogenicity test on humans for an initial conjugate vaccine for PNAG. The findings of the trial and analysis of therapeutic advantage could present a potential immunotherapy for preventing neonatal meningitis, especially in high-risk infants [64] (NCT02853617).

**Matrix Metalloproteinases (MMP)**

Bacterial meningitis can lead to an increase in the activity of matrix metalloproteinases (MMP) in the cerebrospinal fluid (CSF), which play a role in increasing BBB permeability [7,65]. Elevated levels of MMP-9, in particular, have been associated with the development of neurological complications following meningitis [66,67]. To address this issue, preclinical studies have investigated the use of broad-spectrum MMP inhibitors as a potential adjunctive therapy for meningitis [68,69]. One study conducted in a murine model of meningococcal meningitis found that administering Batimastat one hour before and 24 hours after infection reduced the breakdown of the blood-brain barrier, intracerebral hemorrhage, and hippocampal injury [26]. These studies suggested that MMP inhibition could be a promising strategy to reduce brain damage and improve outcomes in meningitis. However, further clinical studies are needed to determine whether the benefits observed in preclinical studies can be translated to human subjects.

**Proteinases**

Finally, strategies to accelerate resolution of CNS inflammation using cyclin-dependent kinase antagonist and DNase are being studied in pre-clinical models with goals of improving CSF drainage to improve edema and hence improve outcomes in meningitis and encephalitis [70,71]. Neutrophil extracellular traps, or NETs, are produced by neutrophils during the process of engulfing bacteria and have been shown to make it harder for cerebrospinal fluid to flow, leading to edema in the central nervous system and a slower clearance of the bacterial burden in the cerebrospinal fluid. In a mouse model of bacterial meningitis, the use of seliciclib (roscovitine, CYC202), a medication that inhibits cyclin-dependent kinases, as an additional treatment improved the resolution of inflammation and accelerated the healing process by promoting the death of neutrophils [71,72]. Another study documented that degradation of NET-associated DNA using DNase I resulted in improved outcome of *S pneumoniae* meningitis in terms of bacterial burden in the brain, lungs, spleen, and blood [73]. These approaches show promise for reducing the long-term effects of bacterial meningitis but require studies to evaluate the efficacy and translational capacity of these modalities in reducing edema and the neurologic consequences of CNS infections.

**Vitamin Supplementation**

Vitamin B6, also known as pyridoxine, has been studied for its potential role in the treatment of meningitis. Preclinical studies revealed that Brain derived neurotrophic factor (BDNF) is downregulated during inflammatory states, but its expression increases in response to B6 [7,74,75]. Studies conducted on neonatal and adult rat models of strep pneumoniae meningitis have shown that administration of B6 as an adjuvant therapy to antimicrobials at the time of infection can increase the levels of BDNF, which can lead to a subsequent decrease in neuronal death and prevented memory impairment [74,75]. Moreover, in rat models of meningitis, adjuvant treatment with folic acid also increased BDNF expression and decreased lipid peroxidation, protein carbonylation, and myeloperoxidase activity (hence reducing oxidative damage), hence offering an approach to minimize neuronal damage to prevent neurologic impairment due to CNS infection in experimental studies [74]. Vitamin D is also known to play an important role in the immune system, and some studies have investigated the potential role of vitamin
D in the prevention and treatment of meningitis [7,67,77]. In pre-clinical studies, deficiency of Vitamin D was associated with mice being more susceptible to *E. coli* infections with observed reduction in phagocytic activity [76,77]. Subsequent studies in human subjects are needed to assess the clinical value of this intervention.

**Stem cells**

Current treatments and experimental therapies for meningitis and encephalitis have mainly focused on preventing adverse neurological outcomes, but options for those with CNS neurologic disabilities following infections have been limited. Recent preclinical and clinical studies have suggested that mesenchymal stem cells (MSCs) transplantation could be a promising novel adjuvant therapeutic modality in addition to antibiotics for various infectious disorders, including bacterial pneumonia, sepsis, and meningitis [78]. MSC transplantation not only attenuates inflammatory responses but also enhances bacterial clearance 30188499. However, the therapeutic efficacy of MSC transplantation for attenuating brain injury in neonatal bacterial meningitis has not been tested. A study using autologous stem cells to improve motor function in cerebral palsy patients showed promising initial results, providing the proof of concept for an ongoing clinical trial (NCT04080921) [78]. This trial, NCT04080921, has enrolled 22 subjects with neurological sequelae to encephalitis or meningitis in children aged 2-15 years to assess the safety and efficacy of intrathecal administration of autologous bone marrow-derived stem cells. The trial aims to evaluate the improvement in muscle tone and monitor any adverse systemic events due to therapy at baseline, 6 months, and 12 months after transplantation. The study results will provide critical information for a possible intervention in patients who suffer from neurologic disability after meningitis or encephalitis, ultimately contributing to the reduction of the burden of DALY and neurologic disease associated with these infections.

**CONCLUSION**

The goal of optimizing therapy for meningitis and encephalitis is to achieve faster infection resolution while reducing the risk of neuronal injury and hence minimizing long-term neurologic sequelae affecting patient’s quality of life. Antimicrobial therapies have been the mainstay of therapy for the infectious sources for CNS infections while immunomodulatory approach is acquired for non-infectious etiology. To augment these therapies, various past and current experimental studies are being performed testing the efficacy of other interventions. As discussed in this review, many studies stress the importance of an adequate supply of vitamin B6, folic acid and vitamin D for the resistance of the brain against infections and infection-related damage. There has also been a development towards reducing inflammation by targeting immune receptors, various proteinases, and phagocytic products (NETs) to prevent edema associated with CNS inflammation. Development of stem cell therapy for improving and ultimately reversing the neurologic dysfunction status post meningitis and encephalitis may show promise in improving quality of life long-term for patients, especially neonates/children. Finally, continuation of educational and delivery efforts of preventative vaccinations in children and adults may ultimately prevent infectious causes of meningitis and encephalitis in high-risk groups and be most effective in reducing the neurologic disease and morbidity burden secondary to meningitis/encephalitis.

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