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Treatment strategies for central nervous system infections: an update

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Introduction: Central nervous system infection continues to be an important cause of mortality and morbidity worldwide. Our incomplete knowledge on the pathogenesis of how meningitis-causing pathogens cause CNS infection and emergence of antimicrobial resistance has contributed to the mortality and morbidity. An early empiric antibiotic treatment is critical for the management of patients with bacterial meningitis, but early recognition of bacterial meningitis continues to be a challenge.

Areas covered: This review gives an overview on current therapeutic strategies for CNS infection with a focus on recent literature since 2010 on bacterial meningitis. Bacterial meningitis is a medical emergency, requiring early recognition and treatment. The selection of appropriate empiric antimicrobial regimen, after incorporating the epidemiology of bacterial meningitis, impact of vaccination, emergence of antimicrobial-resistant bacteria, role of adjunctive therapy and the current knowledge on the pathogenesis of meningitis and associated neuronal injury are covered.

Expert opinion: Prompt treatment of bacterial meningitis with an appropriate antibiotic is essential. Optimal antimicrobial treatment of bacterial meningitis requires bactericidal agents able to penetrate the blood–brain barrier, with efficacy in cerebrospinal fluid. Emergence of CNS-infecting pathogens with resistance to conventional antibiotics has been increasingly recognized, but development of new antibiotics has been limited. More complete understanding of the microbial and host factors that are involved in the pathogenesis of bacterial meningitis and associated neurologic sequelae is likely to help in developing new strategies for the prevention and therapy of bacterial meningitis.

Keywords: antimicrobial resistance, antimicrobial therapy, bacterial meningitis, blood–brain barrier, cerebrospinal fluid, dexamethasone, *Escherichia coli*, group B streptococcus, *Haemophilus influenzae* type b, *Listeria monocytogenes*, *Neisseria meningitidis*, neurologic sequelae, *Streptococcus pneumoniae*

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1. Introduction

Bacterial meningitis continues to be a significant source of morbidity and mortality worldwide [1]. A medical emergency, suspected bacterial meningitis requires early appropriate medical interventions.

The incidence, mortality and morbidity rates of bacterial meningitis vary and are dependent on several factors, including the age and geographical location of the patient, and the causative organism [1]. The incidence of acute bacterial meningitis is significantly higher in low-income countries than in high-income countries [2]. For example, the estimated incidence of bacterial meningitis in Malawi was 20 per 100,000 in 2012 [3], while a mean annual incidence of 1.44 cases of bacterial

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Article highlights.

- The impact of *Haemophilus influenzae* type b (Hib) vaccination in preventing Hib meningitis has been documented and Hib vaccination should be promoted throughout the world.
- The implementation of protein conjugate vaccines for *Streptococcus pneumoniae* and *Neisseria meningitidis* has been efficacious in reducing bacterial meningitis and has changed the epidemiology of bacterial meningitis, and continuous surveillance of *S. pneumoniae* and *N. meningitidis* meningitis is needed.
- Bacterial meningitis is a medical emergency, requiring early recognition and treatment, but early recognition remains a challenge and requires validated biomarkers.
- Early empiric antibiotic treatment of bacterial meningitis is essential in decreasing mortality and morbidity, and should not be delayed if lumbar puncture cannot be performed.
- Antibiotic resistance has been increasingly recognized among CNS-infecting pathogens, and continued monitoring of resistant bacteria as well as development of new antibiotics should be encouraged.
- Studies are needed to identify novel targets for prevention and therapy of bacterial meningitis in the era of increasing resistance to conventional antibiotics.

This box summarizes key points contained in the article.

meningitis per 100,000 people was record in the UK between 2004 and 2011 [4]. In this review, we summarize current therapeutic strategies for bacterial meningitis, after incorporating the epidemiology of bacterial meningitis, introduction of vaccines, emergence of antimicrobial-resistant bacteria, role of adjunctive therapy and the current knowledge on the pathogenesis of meningitis and associated neuronal injury.

2. Epidemiological consideration for treatment strategies for CNS infection

The incidence and the case fatality rate of bacterial meningitis vary with the pathogen, region and age group. **Table 1** summarizes the likely pathogens based on age and immunization status. The big epidemic in recent years was in 2009 with 79,296 cases and 4288 deaths [5]. In a retrospective analysis, 295,706 cases of bacterial meningitis were identified between 1993 and 2011 in the USA with a significant reduction of meningitis in children and the elderly [6]. The highest incidence of meningitis was in the age group < 1 years with an increase of incidence in the age group 45 – 64 years. This reflects the introduction of vaccination against *Haemophilus influenzae* type b, *Neisseria meningitidis* and *Streptococcus pneumoniae*, which made up 41% of the cases in 1993 and 24% of the cases in 2011 in contrast to an increase in *Staphylococcus* and Gram-negative bacterial cases. Meningitis caused by *Staphylococcus aureus* differs from other bacterial meningitis in its pathogenesis, usually occurring following post-neurosurgical procedure or head trauma. From 1997 to 2011, the incidence of pneumococcal and meningococcal meningitis declined by 8 and 6%, respectively [6]. In a report from 1998 to 2007 in the USA, *S. pneumoniae* accounted for 58% of the cases, followed by group B *Streptococcus* (GBS) (18.1%), *N. meningitidis* (13.9%) and *H. influenzae* (6.7%) [7]. The introduction of protein conjugate vaccines has shifted the burden of meningitis to adults rather than children, with the median age shifting upwards.

2.1 Neisseria meningitidis

The incidence of meningococcal meningitis is highest in the meningitis belt extending from Senegal to Ethiopia. B and C serogroups are common in America, Europe and Australia, serogroup A in Africa and Asia [8], serogroup C in China [9] and serogroup Y in North America [8,10]. Overlaps may occur in the serogroups responsible for the outbreaks, hence it needs to be closely monitored [8]. There have been bivalent (A, C), trivalent (A, C, Y) and quadrivalent (A, C, Y, W135) polysaccharide vaccines. However, they were less effective in children, had a shorter effective period, less effect on nasopharyngeal carriage and did not provide herd immunity. Meningococcal conjugate vaccines were subsequently introduced. There is one formulation of serogroup C meningococcal conjugated to tetanus toxoid (MenC-TT) and two formulations conjugated to CRM197, a mutated diphtheria toxin (MenC-CRM197). In the USA, there are three licensed meningococcal conjugate vaccines: quadrivalent meningococcal conjugate vaccine (MenACWY) conjugated to diphtheria toxoid (MenACWY-D), MenACWY conjugated to CRM197 (MenACWY-CRM) and bivalent meningococcal conjugate vaccine against serogroups Y and C combined with *H. influenzae* type b (Hib) vaccine, conjugated to tetanus toxoid (Hib-MenCY-TT). A serogroup A tetanus toxoid conjugate vaccine called MenAfriVac (PsA-TT) was developed for the meningitis belt and was introduced in December 2010 in Burkina Faso, Mali and Niger. The incidence of meningitis during the 2012 meningitis season in these three regions was 2.48 per 100,000 (57 cases within the 2.3 million population), whereas in regions without mass vaccination the incidence was 43.8 per 100,000 (3809 cases within the 8.7 million population), a 94% difference in crude incidence ($p < 0{\cdot}0001$) and an incidence rate ratio of 0.096 (95% CI: 0.046 – 0.198). No serogroup A meningococcal meningitis cases were reported in the three vaccinated regions [11]. Herd immunity has been observed in the UK. The meningococcal C conjugate vaccine was introduced in the UK in 1999 and the incidence of serogroup C disease in the UK in persons aged > 25 years decreased from 0.55 per 100,000 persons in 1998 to 0.02 per 100,000 persons in 2009 while the total number of cases in infants aged < 3 months decreased from 13 in 1998 to 1 in 2009 [12]. However, waning antibody titers have been observed in children and serogroup replacement has been observed with an increase in serogroup Y [4]. In January 2013, the first protein-based vaccine against meningococcal serogroup B was licensed in Europe and has also

Table 1. Likely pathogens based on age and immunization status of individuals.

Age	Immunization status	Likely pathogens
< 1 month	Not applicable	Group B *Streptococcus*, *Escherichia coli*, *Listeria monocytogenes* (neonatal pathogens)
1 – 3 months	Not applicable or one dose of primary immunization	Neonatal pathogens plus *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* type b
3 – 6 months	None	*S. pneumoniae, N. meningitidis*, *H. influenzae* type b
	More than two doses of primary immunization (with *H. influenzae* type b-outer membrane protein vaccine)	*S. pneumoniae*,*N. meningitidis*
> 7 months – 5 years	None	*S. pneumoniae*, *N. meningitidis*, *H. influenzae* type b
	Primary immunization completed	*S. pneumonia* (non-pneumococcal conjugate vaccine serotypes), *N. meningitidis*
> 6 – 50 years	Primary immunization completed	*S. pneumoniae*, *N. meningitidis*
> 50 years	Primary immunization completed	*S. pneumoniae*, *N. meningitidis*, *Listeria monocytogenes*

been approved for use in Canada and Australia, but is awaiting approval in the USA.

2.2 Streptococcus pneumoniae

S. pneumoniae meningitis is most common in the very young and the very old. Since the introduction of the heptavalent pneumococcal conjugate vaccine (PCV7, containing serotypes 4, 6B, 9V, 14, 18C, 19F and 23F), the incidence of invasive pneumococcal disease (IPD) has substantially reduced [7]. IPD including meningitis among unvaccinated populations were also reduced through herd immunity. The recent meta-analysis revealed vaccine efficacy of 80% for vaccine types, and 58% for all serotypes [13]. In a retrospective population-based cohort study from 2004 to 2012 in Norway, it was found that the overall IPD incidence declined from 23/100,000 in 2005 before vaccine introduction to 15/100,000 in 2010 after PCV7 introduction. The overall incidence declined further to 13/100,000 in 2012 after PCV13 introduction. Non-PCV7 serotypes increased after its introduction (mainly serotype 7F, 19A and 22F). The incidence of PCV13 serotypes 7F and 19A have decreased with the implementation of PCV13, although the incidence of the non-PCV13 serotype 22F remained high [14].

2.3 Haemophilus influenzae

H. influenzae type b was most prevalent in the age group < 5 years. In the UK, Hib incidence was lowest in 1998 (0.26/100,000), rising to 1.8/100,000 in 2002 before falling to 0.27/100,000 in 2008 [15]. After the WHO recommendation in November 2006, Hib vaccine was included routinely in the immunization schedule, and the impact of Hib vaccination in prevention of Hib meningitis has been demonstrated throughout the world. For example, in a prospective population-based surveillance from 2002 to 2010, it was found that the proportion of suspected cases confirmed as Hib meningitis decreased from 25% (50/201) in the pre-vaccination era to 2% (4/193) in the post-vaccination era in Mongolia. The annual incidence of Hib decreased from 28 cases per 100,000 children in 2002 – 2005 to 2 per 100,000 in 2008 – 2010 ($p < 0.0001$) [16]. Hib meningitis now occurs predominantly in adults. A resurgence of invasive Hib disease was seen in the absence of a booster dose. Subsequently, a booster campaign with Hib vaccine was introduced that offered one dose to all children aged 6 months to 4 years of age and it resulted in decreased invasive Hib disease among older children and adults in the UK [17]. Serotype replacement has been seen with an increase in incidence of non-type b cases. In a statewide surveillance done in Alaska from 1983 to 2011, no *H. influenzae* type a disease was identified before 2002 but between 2002 and 11, 32 cases were identified while from December 2009 to December 2011, 15 cases were identified [18].

3. Consideration of clinical and laboratory findings for treatment strategies for CNS infection

Bacterial meningitis needs prompt diagnosis and treatment. The identification of the causative organism will determine the antibiotics to be given and the serogroup identification will decide the vaccines to be administered in the setting of meningococcal outbreaks.

The clinical features associated with meningitis include the classic triad of fever, headache and altered mental status [1]. However, the clinical presentation differs in the different age groups. Infants normally present with fever, poor feeding, irritability and vomiting while older children present with signs of meningeal irritation such as vomiting, photophobia, headache and neck stiffness. A minority of adults present with the classic triad. In a Spanish prospective observational study (n = 635), patients were divided into two age groups (15 – 64 years and > 64 years) and elderly patients had comorbid conditions more frequently ($p < 0.0001$), neck stiffness ($p < 0.0001$), skin rash ($p < 0.0001$) and more often altered mental status ($p < 0.0001$) [19]. Similar findings with regards to a more frequent altered mental status were reported by other studies [20]. In a cross-sectional study done from 2009 to 12 (n = 623), fever (87.5%), headache (80.5%) and neck rigidity (69.8%)

Table 2. Cerebrospinal fluid biomarkers proposed for predicting bacterial on meningitis.

Biomarker	Sensitivity (%)	Specificity (%)	Ref.
TNF-α	50 – 100	81 – 100	[29-33]
IL-1β	60 – 97	92 – 100	[31,33]
IL-6	80 – 96	51 – 98	[32,34-37]
IL-8	81 – 100	76 – 92	[32,38]
IL-12	96	75	[34]
Procalcitonin	88 – 100	84 – 96	[39,40]
Lactate	88 – 96	98 – 100	[41,42]
Lipocalin 2	81	93	[43]
Neutrophil gelatinase-associated lipocalin	74	100	[44]
S100B	91	82	[48]
Heparin-binding protein	100	99	[47]
Soluble triggering receptor expression on myeloid cells	73	77	[45,46]

failed to distinguish between bacterial and aseptic meningitis. However, an altered mental status (44.9 vs 27.7%), skin rash (4.4 vs 1.8%), Kernig's sign (40.9 vs 31.3%) and localizing neurological signs (5.5 vs 1.8%) occur more frequently in bacterial meningitis than in aseptic meningitis. Vomiting, irritability, photophobia, anterior fontanel bulge, excessive crying and weak suckling occur in both bacterial and aseptic meningitis [21].

Rapid diagnosis is often delayed by atypical presentation and poor sensitivity of microbiological tests [1,21,22]. A definitive diagnosis of meningitis is dependent on examination and culture of cerebrospinal fluid (CSF). Thus, whenever the physician suspects meningitis, a lumbar puncture should be undertaken. Physicians need to establish whether cranial imaging is needed before doing a lumbar puncture to minimize the potential risks of this procedure. Patients with space occupying intracranial lesions can present with symptoms identical to acute community-acquired bacterial meningitis or these lesions can complicate acute bacterial meningitis early in the disease course (e.g., subdural empyema, epidural abscess, brain abscess, cerebral infarctions or obstructive hydrocephalus). Clinical examination should thus be used to decide if head imaging is to be done. New-onset seizures, signs of raised intracranial pressure, shock, purpura, respiratory insufficiency, immunosuppression, history of CNS lesion and signs of space-occupying lesions should be followed by brain imaging [1,22,23]. CSF culture is the gold standard for diagnosis. CSF examination is essential to establish the diagnosis of bacterial meningitis, identify the causative organism and undertake *in vitro* antibiotic susceptibility testing. Antibiotic administration decreases the yield of CSF culture [1,22,23]. Gram stain is a rapid, inexpensive and easy method for diagnosis. Its positivity rates depend on CSF concentration of bacteria. Characteristic CSF findings for acute community-acquired bacterial meningitis are polymorphonuclear pleocytosis, hypoglycorrhachia and raised CSF protein concentrations [1,22,23]. There is CSF leukocytosis with a predominance of neutrophils (69% in bacterial vs 23.5% in aseptic meningitis), increased protein (> 50 mg/dl) (87.5% in bacterial vs 47.7% in non-bacterial), decreased CSF glucose < 45 mg/dl in 46.8% of the cases of bacterial meningitis. Latex agglutination test is a rapid test but has limited sensitivity. It takes < 15 min but its sensitivity varies for different organisms [1].

Polymerase chain reaction (PCR) testing has been proven to have high sensitivity and specificity for diagnosis of meningococcal meningitis and for predicting the serogroup [1,23]. In a study of 139 bacterial meningitis patients, sensitivities of multiplex PCR were 88% for *H. influenzae*, 92.3% for *S. pneumoniae* and 93.9% for *N. meningitidis* with a specificity of 100% for all three microorganisms [24]. Real-time PCR assays with improved performance have been increasingly used to monitor bacterial meningitis, particularly when antibiotics were previously administered. Different target genes have been used. For example, a study from Brazil using the *lytA* gene of *S. pneumoniae*, capsule transport gene of *N. meningitidis* and *bexA* gene from *H. influenzae* has been shown to lead to a higher confirmation rate than culture when the two methods were applied concurrently on fresh CSF specimens. The sensitivity and specificity estimates of CSF were: culture, 81.3 and 99.7%; and real-time PCR, 95.7 and 94.3%, respectively [25]. A superoxide dismutase gene (*sodC*) real-time PCR assay was shown to be a highly sensitive and specific method for detection of *N. meningitidis*, especially in carrier studies where many meningococcal isolates lack capsule genes [26].

A Rapid dipstick (RDT) was developed in early 2000s that detects *N. meningitidis* serogroups A, C, W135 and Y. The RDT is composed of two dipsticks using a one-step, vertical flow immunochromatographic principle and colloidal gold particles-conjugated antibodies for the detection of bound antigens [27]. The response could be obtained after 10 min by testing 150 – 200 µl of untreated CSF in health facilities or even at bedside. The detection limits for RDT were 10^5 CFU/ml with sensitivity and specificity for detecting serogroup A in CSF samples of 88 and 99%, respectively [28].

A number of CSF biomarkers have been examined for differentiating bacterial meningitis from viral meningitis and non-infectious etiology, and the results have been encouraging (**Table 2**). The utilization of these biomarkers in clinical practice, however, has been limited because of the relatively small

Table 3. Likely pathogens based on risk factors.

Organism	Risk factors
Streptococcus pneumoniae	Cerebrospinal fluid leak Asplenia Sickle cell disease Cochlear implant HIV infection Immunodeficiency Nephrotic syndrome Diabetes mellitus Otitis, sinusitis Fracture of cribriform plate
Neisseria meningitidis	Complement deficiencies Asplenia Freshmen living in dormitories Outbreaks
Haemophilus influenzae type b	Asplenia Sickle cell disease HIV infection Otitis, sinusitis
Listeria monocytogenes	Immunodeficiency or suppression HIV infection Neonates > 50 years of age Diabetes mellitus Pregnancy Liver disease Malignancy

number of patients included for individual studies and use of different assays, and the results of these assays should be interpreted with caution. For example, CSF TNF-α, IL-1β, IL-6 and IL-8 have shown a wide range of sensitivities and specificities, using different cut-off values (**Table 2**) [29-38]. CSF procalcitonin measurement on admission was shown to be useful [39,40], and serum C-reactive protein (CRP) level (> 20 mg/dl) can be informative, given that a normal CRP has a high negative predictive value for bacterial meningitis [40]. An elevated CSF lactate concentration (> 35 mg/dl) can be useful for acute bacterial meningitis, but its clinical utility is limited since it can be elevated in other conditions, such as cerebral hypoxia/ischemia, anaerobic glycolysis, vascular compromise and metabolism of CSF leukocytes [41,42]. Lipocalin 2 is a protein of acute innate immunity response that is involved in iron homeostasis. Lipocalin 2 levels in CSF were significantly higher ($p < 0.0001$) in patients with confirmed acute bacterial meningitis (mean 125 pg/ml, range 106 – 145 pg/ml) than in patients with acute viral meningitis (mean 2 pg/ml, range 0 – 6 pg/ml) [43]. Another biomarker that has been suggested is neutrophil gelatinase-associated lipocalin (NGAL). A significant correlation was found between CSF concentration of NGAL and CSF values of PMNs, WBC, RBC and total proteins, but not with that of glucose and mononuclear leukocytes [44]. The concentration of NGAL in CSF showed an AUC of 0.94 for identifying positive CSFs, at a diagnostic threshold of 13 ng/ml [44]. The expression of soluble triggering receptor expression on myeloid cells can be used as a biomarker at a cut-off value of 20 pg/ml [45,46]. An increase in heparin-binding protein [47], s100b [48] and brain-derived neurotrophic factor [49] have also been suggested as indicators of bacterial meningitis.

Brain imaging such as MRI has also shown to be useful. In a retrospective study of 111 infants with isolation of a pathogen from CSF, 68% (75/111) had a brain MRI performed during hospitalization; abnormalities included leptomeningeal enhancement (57%), cerebral infarct (43%), subdural empyema (52%), cerebritis (26%), hydrocephalus (20%) and abscess (11%). MRI results led to neurosurgical intervention in 23% of infants [50], and can be considered for a patient with a repeat positive bacterial culture of CSF obtained > 48 h after initiation of appropriate antibiotic therapy.

Bacterial meningitis requires early diagnosis and empirical antibiotic treatment, but the symptoms and signs depend on the age of the patients, the duration of illness and the host response to infection. CSF examination is most important in the diagnosis of bacterial meningitis, and detection of bacterial nucleic acid is most promising if Gram stains and culture of CSF is negative, and development of validated biomarkers (most likely combination of biomarkers) is preferred.

4. Consideration for chemoprophylaxis against bacterial meningitis

The aim of chemoprophylaxis is to reduce the risk of invasive disease in high-risk close contacts of invasive meningococcal and Hib disease. Risk factors for invasive meningococcal disease include: age, crowding, lower socioeconomic status, smoking and exposure to smokers, recent illness, sharing a bedroom, travelling to endemic areas, immunosuppression and asplenia (**Table 3**). Close contacts include household, sexual, travel, childcare and healthcare contacts. The public health management of close contacts includes giving appropriate information, antibiotics and vaccination. Among healthcare workers, chemoprophylaxis is recommended only for those whose mouth or nose is directly exposed to large particle droplets/secretions from the respiratory tract of a probable or confirmed case of meningococcal disease during acute illness until completed 24 h of systemic antibiotics. Post-exposure antibiotic prophylaxis should be for close contacts within 24 h of identification of index case and up to 14 days from last exposure. If vaccine-preventable serogroups are implicated in the outbreak of meningococcal disease, vaccination should be given to all unvaccinated household or close contacts. Routine vaccination of healthcare workers with meningococcal conjugate vaccines is not recommended.

Antimicrobial chemoprophylaxis consisting of penicillin is recommended daily for children < 5 years age and with functional/anatomic asplenia. Secondary cases of pneumococcal meningitis are not known, hence post-exposure chemoprophylaxis is not suggested [23]. Chemoprophylaxis is indicated for Hib but not for other types. Recommended guidelines for chemoprophylaxis are summarized in **Tables 4** and **5**.

Table 4. Chemoprophylaxis for contacts of index cases of invasive *Haemophilus influenzae* type b and *Neisseria meningitids* infections.

Organisms	Recommendation
H. influenzae type b (Hib)	For all household contacts in the following category: Household with at least 1 contact younger than 4 years of age who is unimmunized or incompletely immunized Household with a child younger than 12 months of age who has not completed the primary Hib series. Household with a contact who is an immunocompromised child, regardless of that child's immunization status For nursery school and child care centers when 2 or more cases of invasive *H. influenza* disease have occurred within 60 days For index case, if younger than 2 years of age or members of a household with a susceptible contact and treated with a regimen other than cefotaxime or ceftriaxone, chemoprophylaxis is provided just before discharge from hospital
Neisseria meningitidis	People directly exposed to a patient's oral secretions through close social contact, such as kissing or sharing of toothbrushes or eating utensils Childcare or nursery school contact during 7 days before onset of illness Direct exposure to index patient's secretions during 7 days before onset of illness Mouth-to-mouth resuscitation, unprotected contact during endotracheal intubation during 7 days before onset of illness Frequently slept or ate in the same dwelling as index patient during 7 days before onset of illness Passengers seated directly next to the index case during airline flights lasting > 8 h

Data taken from [23].

Table 5. Recommended chemoprophylaxis regimens against *Haemophilus influenzae* type b and *Neisseria meningitidis.*

Organism	Regimen	Dose	Duration
H. influenzae type b	Rifampin*	20 mg/kg once daily (max 600 mg) The dose for infants younger than 1 month is not established	4 days
N. meningitidis	Rifampin*	< 1 month, 5 mg/kg orally every 12 h ≥ 1 month, 10 mg/kg (max 600 mg), orally every 12 h	2 days
	Ceftriaxone	< 15 years 125 mg i.v. or i.m. ≥ 15 years 250 mg i.v. or i.m.	Single dose
	Ciprofloxacin	≥ 1 months, 20 mg/kg (max 500 mg) orally	Single dose
	Azithromycin	10 mg/kg (max 500 mg)	Single dose

*Not recommended for pregnant women.
i.m.: Intramuscular; i.v.: Intravenous.

5. Consideration of vaccinations

Four vaccines are licensed for use in the USA against *N. meningitidis*. These are quadrivalent polysaccharide vaccine ($MPSV_4$) and three conjugate polysaccharide protein vaccines-quadrivalent meningococcal conjugate vaccines (MCV_4), MenACWY-D, MenACWY-CRM, and HibMenCY-TT. $MPSV_4$ was licensed for persons aged > 55 years and MCV_4 for individuals of age group 2 – 55 years who are at risk [51]. The burden of meningococcal disease in infants and children is low in the USA and the majority of cases that do occur are caused by serogroup B, which is not included in any vaccine licensed in the USA. Routine vaccination against meningococcal disease is, therefore, not recommended for children aged 2 months through 10 years. Vaccination with an age- and formulation-appropriate meningococcal conjugate vaccine is, however, recommended for infants aged 2 through 23 months at increased risk for meningococcal disease. Infants at increased

risk for meningococcal disease are: i) those with persistent complement component deficiencies (C3, C5 – C9, properdin, factor D, and factor H); ii) those with functional or anatomic asplenia (including sickle cell disease); iii) healthy infants in communities with a meningococcal disease outbreak for which vaccination is recommended; and iv) those traveling to or residing in areas where meningococcal disease is hyperendemic or epidemic. MenACWY-CRM is licensed for use in infants and children aged 2 through 23 months at increased risk for meningococcal disease. MenACWY-D is recommended for use in children aged 9 through 23 months who are at increased risk for meningococcal disease, and Hib-MenCY-TT is recommended for use in children aged 6 weeks through 18 months at increased risk [52]. For children at prolonged increased risk for meningococcal disease, booster doses of conjugate meningococcal vaccine are recommended after completion of the primary series. If the most recent dose was received before age 7 years, a booster dose should be administered 3 years later. Additional boosters should be administered every 5 years thereafter.

The vaccines that have been available for pneumococcal meningitis are polysaccharide 23 valent (PPSV23), conjugate vaccines PCV7 and PCV13, but PCV13 now replaces PCV7. PPSV23 was licensed for persons > 2 years age and recommended for all adults > 65 years. PCV13 was recommended to be used as 4 dose series at 2, 4, 6 and 12 – 15 months in infants; in children > 59 months at dose same as of PCV7; single supplemental dose was recommended for children 14 – 59 months who completed PCV7 schedule and in children with underlying medical conditions through age 71 months. Infants and children who have received ≥ 1 dose of PCV7 should complete the immunization series with PCV13. PCV13 was recommended for children 6 – 18 years with immunocompromising conditions such as asplenia, cochlear implants and immunodeficiency and also for all adults > 50 years age [53].

The vaccines against Hib are protein conjugate vaccines. Routine vaccination is recommended starting at age 2 months as a 3 dose series with conjugate Hib vaccines (or a 2 dose series with polyribosylribitol phosphate [PRP]-outer membrane protein) or Hib vaccine in combination with HepB. Another option is 3 dose series with Hib PRP-T conjugated to tetanus toxoid) or in combination with diphtheria, tetanus, pertussis and polio (DTaP/IPV). MenCY/PRP-T (MenHibRix) was licensed against invasive Hib disease and *N. meningitidis* serogroups C and Y disease as a 4 dose series in infants at increased risk for meningococcal disease [54].

6. Initial treatment of suspected bacterial meningitis

6.1 Empiric treatment of suspected bacterial meningitis

Bacterial meningitis needs prompt antibiotics administration. Empirical antibiotics should not be delayed either by lumbar puncture or by CT (**Table 6**). Empirical antibiotics should be chosen based on patient history, review of patient's known illnesses and risk factors, results of CSF Gram stain and local community antibiotic resistance patterns [1,22,23]. Third-generation cephalosporins are the established empiric agents of choice. However, when penicillin- or cephalosporin-resistant pneumococcal isolates are prevalent, vancomycin should be added. Decision to add vancomycin depends on the rate of resistance to third-generation cephalosporin. In areas where the prevalence of cephalosporin-resistant *S. pneumoniae* is low (< 1% resistance), a third-generation cephalosporin (either cefotaxime or ceftriaxone) usually suffices as empirical treatment [55,56]. Treatment should always be with intravenous antimicrobials to achieve high CSF levels. It is also essential directed antibiotic therapy be used once the causative organism and antibiotic susceptibilities are identified.

6.2 Timing of antibiotic therapy of bacterial meningitis

In a prospective study, antibiotic administration beyond 3 h after hospital admission was a major independent risk factor associated with adverse outcome in adults with pneumococcal meningitis [57]. The prognostic model based on the clinical features such as hypotension, altered mental status and seizures revealed that adverse clinical outcome was predicted based on three prognostic stages (9% for Stage I, 33% for Stage II and 56% for Stage III), and delay in antibiotic therapy was associated with adverse clinical outcome when the patient's condition advanced to Stage III before the initial antibiotic dose was given. Main factors for delayed treatment include failure to administer antibiotics prior to transfer from another institution, the diagnostic-treatment sequence: head CT before lumbar puncture, followed by antibiotics and the absence of suspected meningitis symptoms and signs.

6.3 Duration of treatment

Antibiotics need enough time to kill all the bacteria in the CNS and prevent disease recurrence, but the timescale of this process varies widely and depends on the causative bacteria, disease severity and antimicrobial agent used. It is usually for non-complicated cases, 10 – 14 days for *S. pneumoniae,* 7 – 10 days for *H. influenzae*, 5 – 7 days for *N. meningitidis* and 14 – 21 days for GBS and Gram-negative bacilli [1,56]. It is, however, important to document the CSF sterility and absence of intracranial complications such as brain abscess for cases with positive Gram stain from initial CSF specimen, meningitis caused by resistant organisms and/or positive brain imaging studies.

6.4 Pre-hospital treatment of bacterial meningitis

Early empiric antibiotic treatment should not be delayed if lumbar puncture cannot be performed. Pre-hospital antibiotic treatment should be initiated for patients with strong

Table 6. Empiric antimicrobial regimen for bacterial meningitis.

Age	Antimicrobial treatment (dosage)
< 1 month	Ampicillin (50 – 75 mg/kg every 6 – 8 h) plus gentamicin (2.5 mg/kg every 12 h) (or cefotaxime, 50 mg/kg every 6 – 8 h, can be used in the setting of suspected Gram-negative bacilli)
1 – 3 months	Ampicillin (75 mg/kg every 6 h) plus cefotaxime (50 mg/kg every 6 – 8 h) or ceftriaxone (50 mg/kg every 12 h) (or vancomycin, 20 mg/kg every 6 h, can be added in the setting of suspected pneumococcal meningitis, e.g., positive Gram stain)
3 months – 5 years	Cefotaxime (50 – 75 mg/kg every 6 – 8 h, max. dose 12 g/day) or ceftriaxone (50 mg/kg every 12 h, max. dose 4 g/day) plus vancomycin (20 mg/kg every 6 – 8 h, max. dose 2 g/day) (or rifampin, 10 mg/kg every 12 h, max. dose 600 mg/day, can be added in the setting of administration of dexamethasone)
6 – 50 years	Cefotaxime (50 – 75 mg/kg every 6 – 8 h, max. dose 12 g/day) or ceftriaxone (50 mg/kg every 12 h, max. dose 4 g/day, 2 g every 12 h, max dose 4 g/day for adults) plus vancomycin (20 mg/kg every 8 – 12 h, max. dose 2 g/day) (or rifampin, 10 mg/kg every 12 h, max. dose 600 mg/day, can be added in the setting of administration of dexamethasone)
> 50 years or immunocompromised	Cefotaxime (50 mg/kg every 6 – 8 h, max. dose 12 g/day) or ceftriaxone (50 mg/kg every 12 h, max. dose 4 g/day, 2 g every 12 h, max dose 4 g/day for adults) plus vancomycin (20 mg/kg every 8, max. dose 2 g/day) plus ampicillin (50 – 100 mg/kg every 6 h, max. dose 12 g/day)

suspicion of disseminated meningococcal infection (meningococcemia) and if a delay in excess of 90 min in hospital transfer is anticipated [1,23].

7. Consideration of pharmacokinetic and pharmacodynamic properties of antimicrobial agents for treatment of CNS infection

The ability of a drug to reach and maintain effective concentrations at the site of infection is an important determinant of the efficacy of antimicrobial agents to treat bacterial meningitis. Because pharmacokinetic and pharmacodynamic profiles differ among antibiotics, an understanding of these characteristics for each agent is important in determining effective antibiotic dosing regimens. Since antibiotics are not known to be metabolized in CSF, their concentration and half-life in CSF depends on the penetration and elimination through the blood–brain barrier (BBB) and CSF dynamics [23,58].

Lipid solubility, molecular weight, ionization, protein binding ability of the drugs, efflux transporters and the infecting organism are the important factors that determine BBB and CSF penetration [23]. Lipophilic agents, such as the fluoroquinolones, chloramphenicol, rifampin and sulfonamides enter the CSF more readily, regardless of the presence or absence of meningeal inflammation. In contrast, hydrophilic agents, such as β-lactams and vancomycin have decreased CSF penetration if the meninges are not inflamed.

In bacterial meningitis, the pH of CSF is lower than that of plasma, and antibiotics with high ionization like penicillin have poor CSF penetration [59]. Only unbound fractions of antimicrobials enter the BBB and CSF, and a high degree of protein binding in the serum (e.g., ceftriaxone) limits the degree of BBB and CSF penetration. Antibiotics that are transported out of CSF by organic acid transporter-3 (oat-3, e.g., penicillin G and cephalothin) or by peptide transporter-2 (pept-2, e.g., cefadroxil) do not achieve consistent high CSF concentrations even in meningitis, hence the antibiotics that have minimal affinity for oat-3 or pept-2 are useful in patients with meningitis [60].

An additional important factor in determining the killing activity of antimicrobial agents in CSF is pharmacodynamics. β-Lactam agents and vancomycin are time-dependent, whereas the quinolones and aminoglycosides are concentration-dependent [58]. A systematic review concluded that continuous infusion of β-lactam antibiotics leads to the same clinical results as higher dosed bolus administration in hospitalized patients [61]. Effective bacterial killing activity in the CSF by and large requires a high ratio between CSF peak concentrations and the minimal bactericidal concentration (MBC) of the infecting organism and/or the time above the MBC of the infecting organism during the entire dosing interval. Experimental studies revealed that peak CSF concentrations exceeding eight times MBC are required for efficient killing activity [23].

For the treatment of CNS infections, the intravenous administration of prodrugs (which enjoy better penetration into the CNS than the active compounds) of drugs included in surface-modified liposomes or of adjuvant drugs inhibiting efflux pumps at the blood–CSF and/or BBB appears to be promising [58]. A prospective, double-blind, single-center study showed that cefotaxime infusion plus paracetamol lowered mortality at least during the first 3 days, irrespective of cause [62].

8. Consideration of antimicrobial resistance and the use of new antimicrobial drugs in the treatment of CNS infection

The emergence of antimicrobial-resistant organisms has greatly affected the choice of empiric antimicrobials. Extrapolation of current epidemiological data to the future suggests that the incidence of antibiotic-resistant pathogens is a growing problem in many countries [63].

Many strains of *S. pneumoniae* are now resistant to penicillin, and penicillin-resistant pneumococci often have reduced susceptibility to other antimicrobials such as third-generation cephalosporin, erythromycin and trimethoprim-sulfamethoxazole. Such multi-drug-resistant bacteria have been associated with treatment failure. Empiric treatment for patients living in areas with a high prevalence of penicillin- and cephalosporin-resistant *S. pneumonia* should thus include vancomycin. However, it is important to note that vancomycin penetration through the BBB and into the CSF may be reduced in the absence of meningeal inflammation or in patients receiving dexamethasone, and consideration should be given to add rifampin.

Recent reports of *Escherichia coli* strains producing CTX-M-type or TEM-type extended-spectrum β-lactamases (ESBL) are of a particular concern [64-66]. *E. coli* sequence type 131 (ST131) is a recently emerged, extensively antimicrobial-resistant *E. coli* clonal group that has spread throughout the world [67]. ST131 strains are also progressively gaining new resistance phenotypes, including those that express KPC-2 carbapenemase and NDM-1 metallo-β-lactamase [68].

Central nervous system infections caused by MRSA are uncommon, but have become a challenge because of limited alternative treatment regimens [23,63].

In recent years, few new antibiotics have gained access to clinical medicine. Several of them are of potential interest for the treatment of CNS infections [23]. These include: β-lactam antibiotics (cefepime and meropenem), lipopeptide antibiotics (daptomycin), oxazolidinone (linezolid), lipoglycopolypeptide (telavancin), fluoroquinolone (moxifloxacin) and glycylcycline (tigecycline).

8.1 Newer antibiotics

8.1.1 Cefepime

Cefepime is a fourth-generation, broad-spectrum cephalosporin antibiotic with enhanced coverage against Gram-positive and Gram-negative bacteria and stability to AmpC β-lactamases. Although cefepime is not licensed for use in meningitis, CNS penetration rates are similar to other cephalosporins used for meningitis treatment and concentrations attained in patients were generally active against many common nosocomial pathogens [69]. In a randomized controlled trial in children with bacterial meningitis, cefepime was found to be safe and therapeutically equivalent to cefotaxime for management of bacterial meningitis in infants and children [69]. However, higher doses of cefepime have been shown to induce non-convulsive status epilepticus in both normal patients and patients with reduced glomerular filtration rate [70,71]. Newer cephalosporins such as ceftobiprole and ceftaroline fosamil have shown great promise in the treatment of meningitis. In experimental rabbit meningitis models, the efficacy of ceftobiprole was significantly superior to cefepime in β-lactamase-positive *H. influenzae* [72], while ceftaroline fosamil was significantly superior to cefepime against *Klebsiella pneumoniae* and *E. coli* [73].

8.1.2 Meropenem

Meropenem is a broad-spectrum carbapenem antibiotic that has bactericidal activity against almost all clinically significant pathogens, including ESBL, AmpC-producing Enterobacteriaceae and *Pseudomonas* spp. strains [23,63]. It is the most widely studied carbapenem for the treatment of bacterial meningitis and has less seizure tendency compared with imipenem. Meropenem has similar microbiological and clinical outcomes to cefotaxime or ceftriaxone against common meningitis pathogens including *H. influenzae, N. meningitidis* and *S. pneumoniae*, and has been used successfully in the treatment of meningitis caused by multi-drug-resistant (including penicillin and cephalosporin) strains of pneumococcus. Therefore, meropenem can be used for empirical therapy of nosocomial meningitis in conjunction with vancomycin or as a monotherapeutic agent in the case of penicillin allergy for the initial treatment of community-acquired bacterial meningitis [23,63].

8.1.3 Daptomycin

Daptomycin, a cyclic lipopeptide antibiotic, has strong antibacterial activity against resistant Gram-positive bacteria and is a potential alternative to vancomycin for the treatment of pneumococcal meningitis. It is a relatively large compound and thus has a relatively low CSF penetration rate. In experimental animal models, daptomycin has been shown to be equally effective to vancomycin in the treatment of pneumococcal meningitis [74], more effective than vancomycin in the treatment of *S. aureus* meningitis [75], and superior to a combination of vancomycin and ceftriaxone in the treatment of highly resistant penicillin and/or cephalosporin and/or quinolone-resistant pneumococcal meningitis [76,77]. However, daptomycin cannot be used in the treatment of *Listeria monocytogenes* meningitis due to its relatively high MIC values, for example, MIC_{90} of 4.0 μg/ml [78].

The non-lytic mechanism of action of daptomycin has been shown to reduce host inflammatory reaction and cortical damage in rat models of experimental *S. pneumoniae* meningitis in comparison to treatment with ceftriaxone [79]. Daptomycin was more effective than ceftriaxone at reducing neuropsychological deficits in adult rat models of *S. pneumoniae* meningitis [80]. Additional studies are needed to determine whether non-lytic agents are efficacious for the downregulation of neuronal injury and improved clinical outcomes.

8.1.4 Linezolid

Linezolid, an oxazolidinone antibiotic, is active against Gram-positive bacteria and atypical organisms. Linezolid readily enters the CSF with or without meningeal inflammation [81]. In patients, it has been used successfully in the treatment of vancomycin-resistant CNS infections [82] and may be superior to vancomycin in the treatment of MRSA infection [83,84]. Linezolid resistance to enterococcus [85] and *S. aureus* [86], however, has developed and linezolid should not be used for empirical therapy of CNS infections without susceptibility testing. In addition, side effects are reported, which include optic neuropathy, peripheral neuropathy and bone marrow suppression [87].

8.1.5 Telavancin

Telavancin, a lipoglycopeptide, is a derivative of vancomycin with bactericidal activity against Gram-positive bacteria including MRSA, vancomycin-intermediate *S. aureus*, linezolid-resistant *S. aureus* and daptomycin non-susceptible strains [88]. In a rabbit model of meningitis caused by penicillin-resistant pneumococcus, telavancin penetration into the CSF was 2% and telavancin was shown to be more effective at eradicating bacteria from the CSF than the combination of ceftriaxone and vancomycin [89]. Clinical experience of telavancin has been limited to complicated skin-structure infections and hospital-acquired pneumonia [88].

8.1.6 Moxifloxacin

Moxifloxacin is a newer fluoroquinolone with excellent CNS penetration and high activity against Gram-positive bacteria [59,90]. In the absence of meningeal inflammation, fluoroquinolones have better CSF penetration rates than β-lactam antibiotics [59]. In experimental animal models of meningitis, moxifloxacin showed good activity against *E. coli* [91] and *L. monocytogenes* [92]. In penicillin-resistant *S. pneumonia* mouse models of meningitis, moxifloxacin was equally effective to the combination of ceftriaxone and vancomycin [93]. Clinical data on the use of moxifloxacin are limited, but moxifloxacin, in combination with rifampin, has been used successfully in the treatment of drug-resistant tuberculous meningitis [90]. Although moxifloxacin is generally well tolerated in clinical practice, there are concerns regarding the hepatotoxicity and dermatological side effects of moxifloxacin.

8.1.7 Tigecycline

Tigecycline is a semisynthetic derivative of tetracycline and belongs to the new class of glycylcycline antibiotic. It has a broad spectrum of activity and is active against many Gram-positive and Gram-negative bacteria. However, it does not enter the CSF readily [59]. Clinical data regarding the use of tigecycline in bacterial meningitis are limited to case reports and have been used in combination with other antimicrobials for the successful treatment of multi-drug-resistant *Acinetobacter baumannii* and multi-drug-resistant *Enterococcus faecium* [94,95]. However, subtherapeutic CSF concentrations produced by standard intravenous tigecycline doses have been observed [94].

9. Consideration of adjunctive therapy in the treatment of CNS infection

9.1 Adjunctive corticosteroid treatment

The use of corticosteroids as an adjunctive treatment remains controversial. Dexamethasone is the most commonly studied corticosteroid with regards to the treatment of bacterial meningitis. However, subsequent clinical trials have yielded mixed results. In adults, trials have shown that early treatment with dexamethasone may improve outcomes and provide an extended survival benefit of up to 20 years in patients treated for bacterial meningitis [96].

Current consensus regarding the use of dexamethasone is largely based on the results of meta-analyses. In the 2013 Cochrane review of the use of corticosteroids in acute bacterial meningitis, corticosteroids were associated with a nonsignificant reduction in mortality (17.8 vs 19.9%; risk ratio [RR]: 0.90; 95% CI: 0.80 – 1.01; p = 0.07) [97]. However, corticosteroids were associated with improved long-term outcomes including lower rates of severe hearing loss (RR: 0.67; 95% CI: 0.51 – 0.88), any hearing loss (RR: 0.74; 95% CI: 0.63 – 0.87) and neurological sequelae (RR: 0.83; 95% CI: 0.69 – 1.00). In children, corticosteroids reduced severe hearing loss in children with Hib meningitis (RR: 0.34; 95% CI: 0.20 – 0.59) if they are administered just before or with the initial antimicrobial therapy [97]. The same benefits did not extend to children with meningitis due to non-*Haemophilus* species [23].

The use of dexamethasone in children and adults with bacterial meningitis requires careful monitoring of clinical and bacteriological response to antimicrobial therapy as dexamethasone can often complicate the monitoring of clinical changes (e.g., fever curve) in a patient. In addition, animal studies have shown that the use of dexamethasone as adjuvant therapy increased hippocampal cell injury and reduced learning capacity in animals infected with pneumococcal and *E. coli* meningitis [98,99]. Data regarding long-term cognitive and neuropsychological outcomes after the use of dexamethasone therapy are limited.

9.2 Adjunctive glycerol treatment

Glycerol is a hyperosmolar agent which has been used to decrease intracranial pressure in several neurologic disorders. Its benefit in reducing neurological sequelae is, however, disputed. A Malawian study involving adults with bacterial meningitis has suggested that glycerol may be associated with increased mortality [100]. The 2013 Cochrane review has concluded that it has not demonstrated benefit on death, but may reduce deafness [101]. Thus, the use of glycerol as adjuvant therapy in the treatment of bacterial meningitis is not established.

9.3 Other potential adjunctive treatments

A number of adjunctive treatments are under investigation. These include melatonin, hypothermia and vitamin B6. Melatonin, an antioxidant, had anti-inflammatory effects but did not reduce neuronal injury in experimental rabbit models of *S. pneumoniae* or *E. coli* meningitis [102]. However, melatonin has been shown to inhibit microglial activation, attenuate pro-inflammatory cytokine levels and rescue hippocampal neurons in adult rats with acute *K. pneumoniae* meningitis [103]. Hypothermia has also been suggested as a potential adjuvant treatment. However, a randomized controlled trial was terminated early due to safety concerns over excessive mortality in patients who had been subject to hypothermia, suggesting that moderate hypothermia did not improve outcomes in patients with severe bacterial meningitis and may be harmful [104]. Experimental animal studies in adult rats subjected to pneumococcal meningitis have shown that adjuvant treatment with vitamin B6 may attenuate memory impairment by increasing brain-derived neurotrophic factor expression [105]. None of these treatments has proven effective in humans.

10. Consideration of neuronal injury and hearing loss for treatment of CNS infection

Neurologic sequelae are common in survivors across all ages recovering from bacterial meningitis despite adequate treatment. Neuronal damage is caused by the combined effects of an overwhelming inflammatory reaction and the direct effect of bacterial toxins such as pneumolysin [106,107]. Neuronal cell death in bacterial meningitis mostly occurs within the dentate gyrus of the hippocampal formation or as necrosis in the neocortex and the CA1 – 4 region of the hippocampus [106,107]. Although the hippocampus is not directly exposed to pathogens or infiltrating leukocytes, animal models have shown that it is surrounded by interstitial fluid which is contiguous with the CSF, thus allowing secreted bacterial toxins and immune system mediators to diffuse into the parenchyma [108].

A global systematic review of 132 studies revealed that the median overall risk of long-term disabling sequelae in meningitis survivors after discharge from hospital was 20% [2]. This is dependent on the organism, severity of disease and the patient's underlying health condition, and includes hearing loss, cognitive impairment and development delay [98]. The risk of developing long-term sequelae after meningitis was twice as much in the low-income regions of Africa (pooled risk estimate 25.1% [95% CI: 18.9 – 32.0%]) and Southeast Asia (21.6% [95% CI: 13.1 – 31.5%]) than in Europe (9.4% [95% CI: 7.0 – 12.3%]; $p < 0.0001$) [2]. This suggests that quality medical care and access to medical care could aid in reducing long-term sequelae.

10.1 Hearing loss

Hearing loss could be a sign of irreversible neurological sequelae and has been thought to be due to serous or suppurative labyrinthitis occurring during the acute period of meningitis, which could evolve into a labyrinthitis ossificans [109]. Studies have reported rates of major or minor hearing loss of 2 – 33% [2,110]. The frequency of hearing loss appears to differ by pathogen. Globally, the median (interquartile range) risk of major hearing loss was 9.9% (8.1 – 12.3%) for pneumococcal meningitis, which was higher than hearing loss due to Hib (4.5% [2.2 – 6.1%]) and meningococcus (4.1% [2.3 – 7.2%]) [2]. Similar results were reported with rates of hearing loss being higher in patients with pneumococcal meningitis (22%) than patients with meningococcal meningitis (14%) [1,23].

10.2 Cognitive impairment

Cognitive impairment is another major cause of concern after acute bacterial meningitis and places a social and economic burden as patients often need long-term follow-up and rehabilitation. Cognitive impairment includes a range of conditions such as developmental delay, cognitive slowness, short-term memory problems and poor academic abilities. This is of particular concern in children where up to 43% experience developmental delay after recovery from acute bacterial meningitis [111].

11. Consideration of pathogenesis of CNS infection

Central nervous system-infecting pathogens are shown to breach the BBB through transcellular mechanisms, paracellular mechanisms and/or infected phagocytes (the so-called Trojan horse mechanism) [112]. Transcellular traversal occurs when microbes penetrate cells without any evidence in the cellular injury or intracellular tight-junction disruption, paracellular traversal occurs when microbes penetrate between barrier cell with and/or without evidence of tight junction disruption and the Trojan-horse mechanism involves microbial penetration of barrier cells using transmigration within infected phagocytes [112]. These methods of infection differ based on the type of organism, but some pathogens use more than one method of infection, for example, *N. meningitidis* exploits transcellular and paracellular traversal.

A crucial event in the pathogenesis of *N. meningitidis* meningitis is the adhesion of meningococci to brain endothelium, leading to transcellular and/or paracellular penetration of the BBB [106]. The invasion through the BBB is mediated by the binding of Opc, an outer membrane protein, to fibronectin, thus anchoring it to the integrin $\alpha5\beta1$ receptor on the cell surface [112]. It also relies on bacterial type IV pili, a filamentous structure. CD147, a member of the immunoglobulin superfamily, is shown to be a host receptor for PilE and PilV [113]. *N. meningitidis* has also been shown to activate a G protein-coupled $\beta2$-adrenergic receptor signaling pathway in endothelial cells which traps β-arrestin-interacting partners, such as the Src tyrosine kinase and junctional proteins, under bacterial colonies [114]. β-Arrestin-activated Src mediates

cytoskeletal reorganization and stabilizes bacterial adhesion to endothelial cells while β-arrestin-dependent delocalization of junctional proteins results in the opening of intercellular junctions, allowing paracellular traversal of the BBB.

S. pneumoniae has been shown to breach the BBB through transcellular mechanisms [106] and transmigrates through endothelial cells by adhering to the vascular endothelial platelet activating factor receptor (PAFR). The transmigration is mediated by the binding of bacterial phosphorylcholine to the PAFR. Subsequent animal models showed that pneumococcal translocation rates were relatively low, particularly from blood to brain, in PAFR-deficient mice in comparison to wild-type mice [115]. It preferentially adheres to the subarachnoid vessels and was found to interact with the more internal cerebral areas including the cerebral cortex, septum and choroid plexus only at the later stages of infection [116].

A number of virulence factors including invasion of brain endothelial cell (Ibe) proteins, and cytotoxic necrotizing factor 1 (CNF1) have been known to facilitate and contribute to *E. coli* penetration of the BBB by interacting with BBB receptors and exploiting microbe- and host-specific signaling molecules [112]. These *E. coli*–BBB interactions contribute to transcellular penetration of *E. coli* across the BBB. IbeA protein interacts with contactin-associated protein 1, while CNF1 interacts with 37 laminin-receptor precursor, leading to activation of protein tyrosine kinases (e.g., focal adhesion kinase) and Rho GTPases (e.g., RhoA and Rac1). Rac1 activation in response to *E. coli* factors (IbeA and OmpA) and subsequent Rac1-mediated penetration of the BBB has been shown to be under the control of STAT3 [117].

The exact mechanism of how GBS (*Streptococcus agalactiae*) penetrates the BBB is still incompletely understood [112]. Studies have shown that several microbial factors of *S. agalactiae* interact with brain endothelium and exploit specific host cell signaling molecules for transcellular penetration of the BBB [112]. Srr1 has recently been shown to contribute to GBS attachment to brain endothelium via the direct interaction of its binding region with human fibrinogen [118] while the capture of host plasmin(ogen) by the GBS surface protein promotes the crossing of the BBB and contributes to the establishment of meningitis [119].

Delineation of microbial and hot factors contributing to penetration of the BBB is likely to help in identification of new targets for prevention and therapy of bacterial meningitis. A proof-of-concept study has shown that down-modulation of the human brain microvascular endothelial cells (HBMEC) receptor for a microbial factor and blockade of host cell signaling molecules involved in microbial penetration of the BBB were efficient in preventing microbial penetration into the brain [23,112]. These findings suggest that pharmacological inhibition of the HBMEC receptors and host cell signaling molecules contributing to microbial invasion of HBMEC might be a novel strategy for prevention and therapy of bacterial meningitis.

12. Expert opinion

Bacterial meningitis is a medical emergency, requiring early recognition as well as early therapeutic intervention. Early recognition is based on clinical features, but it is important to recognize that clinical symptoms and signs associated with bacterial meningitis can vary in the different age groups and hosts. Several CSF biomarkers have been introduced to predict bacterial meningitis, but they have not been validated, requiring continued investigation of biomarkers useful for predicting bacterial meningitis.

If a patient suspected of having bacterial meningitis need to be transferred to another hospital for proper medical care including lumbar puncture and/or brain imaging studies, blood cultures should be obtained and empiric antibiotics should be given before transfer. The selection of appropriate empiric antibiotic regimen requires the knowledge on epidemiology and local community antibiotic resistance patterns as well as assessment of risk factors for particular pathogens.

Successful implementations of infant vaccination programs with protein-conjugated vaccines almost eliminated Hib meningitis and considerably reduced *S. pneumoniae* meningitis caused by PCV13 vaccine types. However, the non-PCV13 types appeared, requiring continued surveillance of pneumococcal serotypes involved with IPD cases. Outbreaks of meningococcemia and *N. meningitidis* meningitis still occur throughout the world, and it is important to be familiar with risk factors and the epidemiology of meningococcal diseases. It is likely to change our landscape of endemic cases of meningococcal meningitis with the introduction of effective serogroup B meningococcal vaccine.

An emergence of antimicrobial-resistant bacteria, particularly vancomycin-resistant Gram-positive organisms and multi-drug-resistant Gram-negative bacilli illustrates our limitation of current antimicrobial armamentarium. Antimicrobial therapy should be modified according to the bacterial susceptibility results, and meningitis caused by antimicrobial-resistant bacteria need to be closely monitored, which include repeat lumbar puncture for documentation of CSF sterility and brain imaging studies with any neurologic symptoms and signs. Dexamethasone is used as an adjunctive therapy for selective cases of bacterial meningitis, and studies are needed to determine new targets and molecules for decreasing neurologic sequelae.

Microbial traversal of the BBB is essential for the development of meningitis, but our knowledge on microbial penetration of the BBB is incomplete. The continued investigation on elucidation of microbial traversal of the BBB and associated neuronal injury is likely to bring a new approach for prevention and therapy of bacterial meningitis.

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

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