



Deciphering the role of nanoparticles for management of bacterial meningitis: an update on recent studies

Neelam Sharma¹ · Ishrat Zahoor¹ · Monika Sachdeva² · Vetriselvan Subramaniyan³ · Shivkanya Fuloria⁴ · Neeraj Kumar Fuloria⁴ · Tanveer Naved⁵ · Saurabh Bhatia^{6,7} · Ahmed Al-Harrasi⁶ · Lotfi Aleya⁸ · Simona Bungau⁹ · Tapan Behl¹ · Sukhbir Singh¹

Received: 10 July 2021 / Accepted: 12 September 2021 / Published online: 20 September 2021
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2021

Abstract

Meningitis is an inflammation of the protective membranes called meninges and fluid adjacent the brain and spinal cord. The inflammatory progression expands all through subarachnoid space of the brain and spinal cord and occupies the ventricles. The pathogens like bacteria, fungi, viruses, or parasites are main sources of infection causing meningitis. Bacterial meningitis is a life-threatening health problem that which needs instantaneous apprehension and treatment. *Nisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus flu* are major widespread factors causing bacterial meningitis. The conventional drug delivery approaches encounter difficulty in crossing this blood-brain barrier (BBB) and therefore are insufficient to elicit the desired pharmacological effect as required for treatment of meningitis. Therefore, application of nanoparticle-based drug delivery systems has become imperative for successful dealing with this deadly disease. The nanoparticles have ability to across BBB via four important transport mechanisms, i.e., paracellular transport, transcellular (transcytosis), endocytosis (adsorptive transcytosis), and receptor-mediated transcytosis. In this review, we reminisce distinctive symptoms of meningitis, and provide an overview of various types of bacterial meningitis, with a focus on its epidemiology, pathogenesis, and pathophysiology. This review describes conventional therapeutic approaches for treatment of meningitis and the problems encountered by them while transmitting across tight junctions of BBB. The nanotechnology approaches like functionalized polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carrier, nanoemulsion, liposomes, transferosomes, and carbon nanotubes which have been recently evaluated for treatment or detection of bacterial meningitis have been focused. This review has also briefly summarized the recent patents and clinical status of therapeutic modalities for meningitis.

Keywords Bacterial meningitis; · Blood-brain barrier; · Nanoparticles; · Paracellular transport; · Transcytosis

Abbreviations

CSF cerebrospinal fluid
CNS central nervous system

BBB blood brain barrier
TLR toll-like receptor
NF-κB nuclear factor-κB

Responsible Editor: Philippe Garrigues

✉ Tapan Behl
tapanbehl31@gmail.com

✉ Sukhbir Singh
singh.sukhbir12@gmail.com

¹ Chitkara College of Pharmacy, Chitkara University, Punjab, India

² Fatima College of Health Sciences, Al Ain, United Arab Emirates

³ Faculty of Medicine, Bioscience and Nursing, MAHSA University, Petaling Jaya, Malaysia

⁴ Faculty of Pharmacy, AIMST University, Kedah, Malaysia

⁵ Amity Institute of Pharmacy, Amity University, Noida, India

⁶ Natural & Medical Sciences Research Centre, University of Nizwa, Nizwa, Oman

⁷ Amity Institute of Pharmacy, Amity University, Haryana, India

⁸ Chrono-Environment Laboratory, UMR CNRS 6249, Bourgogne Franche-Comté University, Besancon, France

⁹ Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania

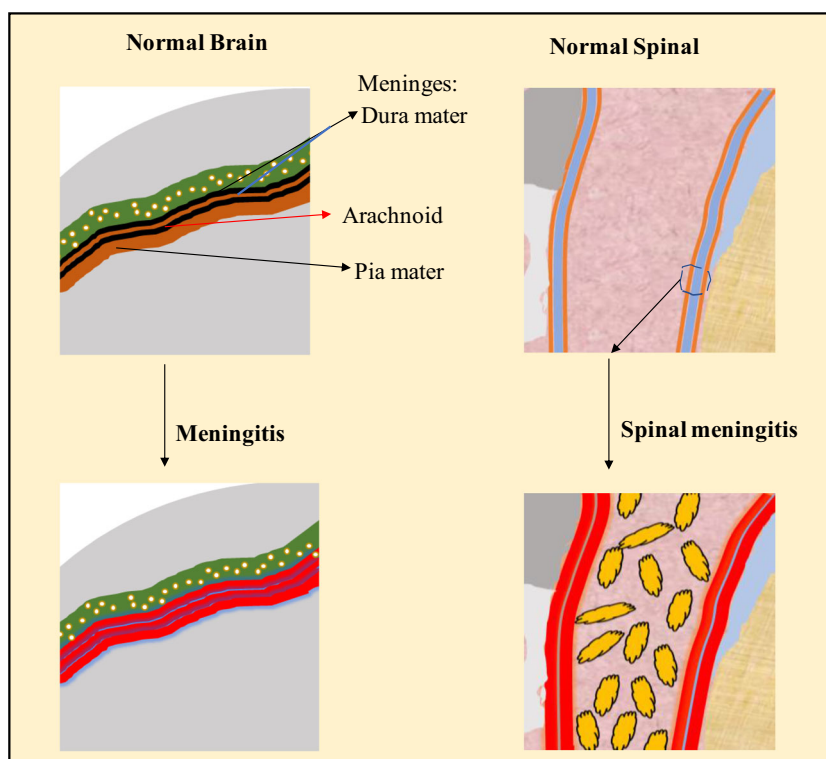
TNF- α	tumour necrosis factor- α
NPs	nanoparticles
TJs	tight junctions
SLNs	solid lipid nanoparticles
NLC	nanostructured lipid carriers
NEs	nanoemulsions
SWCNTs	single-walled nanotubes
MWCNTs	multi-walled nanotubes
BTP	brain-targeting peptide

Introduction

Inflammation of the protective membranes (meninges) and fluid contiguous the brain and spinal cord is defined as meningitis, which is caused mainly by infection with pathogens including bacteria, fungi, viruses, or parasites (Chaud et al. 2020; Rasol and Sultan 2019). The arachnoid, pia mater, and the superseding cerebrospinal fluid (CSF) are entailed in the disease. The inflammatory progression develops through the subarachnoid area of the brain, spinal cord, and ventricles (Fig. 1). Meningitis may instigate necrosis, reduced CSF and blood flow, and malfunctioning of central nervous system (CNS) (Zueter and Zaiter 2015). Meningitis might be outcome of either infectious or non-infectious sources (Barani et al. 2021). Compared with an infectious form, non-infectious cases are unusual, especially with their inability to spread from

one individual to another. Thus, as per an essence of the virulence factors, meningitis may be classified into two categories, i.e., infectious and non-infectious meningitis. Specific drugs, neoplasm, autoimmune susceptible condition, and certain chemical can elicit non-infectious meningitis. Non-infectious chemicals or else their components, for instance cancer tissues or their products could perform like inflammatory irritants which might lead to inflammatory processes in the CSF. Infectious meningitis is a severe CNS disorder which, as a result of microbial infection, causes inflammation of the meninges. Usually, this is induced through viruses and bacteria and occasionally *via* parasites and fungi (Zueter and Zaiter 2015). The viral infection in CNS produces inflammation in separate anatomical regions such as the meninges, brain parenchyma, and cranial nerves or in various areas at the same time. Although meninges inflammation leads to meningitis, brain parenchyma involvement contributes in encephalitis. An inflammatory spectrum known as meningoencephalitis can occur pathologically between these neighbouring anatomical regions (Wright et al. 2019). Viral meningitis is generally prevalent in comparison to bacterial meningitis nevertheless it is comparatively less severe (Zueter and Zaiter 2015). Most cases of community-acquired aseptic meningitis are viral meningitis which is most frequently caused by enteroviruses (e.g., coxsackievirus, type 9 echovirus) (Ranson et al. 2020) and enteroviruses (Zueter and Zaiter 2015). However, other causes include lymphocytic choriomeningitis, cytomegalovirus, herpes simplex and

Fig. 1 Pictorial representation portraying inflammation of the meninges in brain and spinal cord during meningitis disease



mumps virus (Ranson et al. 2020). Fungal meningitis, which covers a huge variety of hosts, like immunocompetent and immunosuppressed individuals, is uncommon but presents a major challenge (Zueter and Zaiter 2015). *Cryptococcus spp.* is still the most prevalent cause of fungal meningitis. *Aspergillus spp.* in highly immunocompromised individuals is still a primary cause of morbidity and mortality, although other moulds are also coming into remarkable observation for major cause of fungal meningitis (Bloch and Bailin 2019). Parasites may also develop acute meningo-encephalitis and can also invade brain tissue (Zueter and Zaiter 2015).

Bacterial meningitis is a health problem that is life-threatening and needs immediate care as well as treatment (Nair et al. 2020). In this review, we reminisce distinctive symptoms of meningitis, provides an overview of the various types of bacterial meningitis, with a focus on its epidemiology, pathogenesis, and pathophysiology. This review also describes conventional therapeutic approaches for treatment of meningitis and the difficulty encountered by the free drug while transmitting across tight junctions of blood brain barrier. The objectives of this comprehensive review are focused on nanotechnology based drug delivery systems for effective management of bacterial meningitis. For this purpose, an extensive search of the literature was conducted using the PubMed, Google Scholar, and ScienceDirect databases. Literature review was done from the papers published in peer reviewed journals from the year 2000 to year 2021. The recently published patents and clinical status of therapeutic modalities for bacterial meningitis has also been focussed in this review.

Distinguishing symptoms of meningitis

The primary symptoms which appear in the body after getting infected with meningitis are comparable to the signs of septicaemia, i.e., serious bloodstream bacterial infection. The few distinguishing characteristics symptoms between septicaemia and meningitis are given in Fig. 2 and therefore meningitis should not be confused with septicaemia.

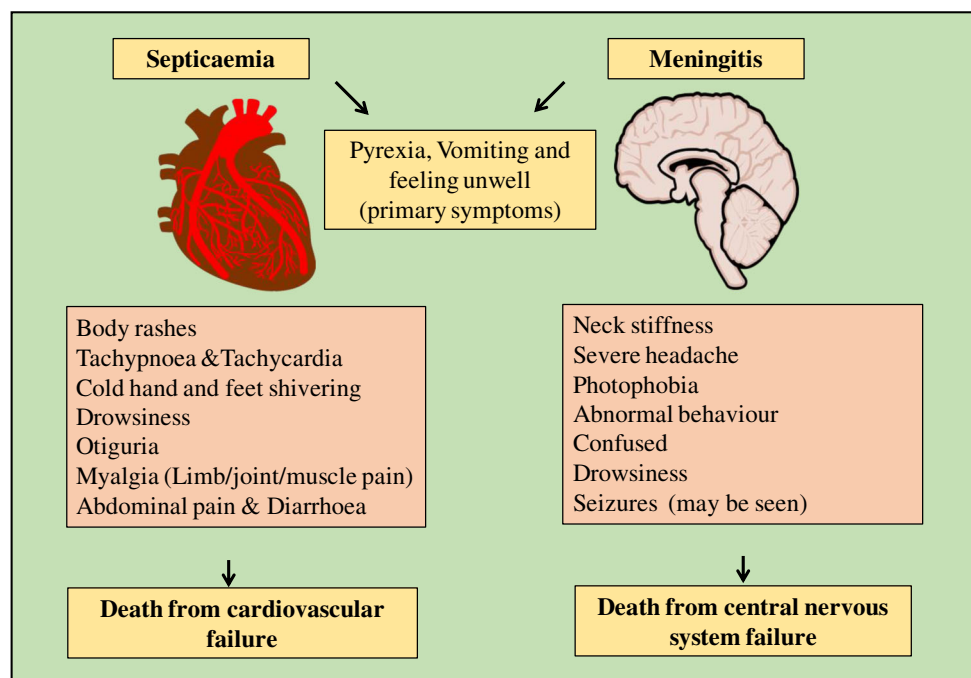
Classification of bacterial meningitis

The pathophysiologic symptoms of this disease develop and suboptimal results arise even though the infection is bacteriologically cured (Al-Obaidi and Desa 2018; Martins Gomes et al. 2019). Infections with *meningococci*, *pneumococci*, or *Hemophilus influenzae* (*H. influenza*) are the most serious cause of bacterial meningitis. *Listeria*, *Staphylococcus*, *Mycobacterium tuberculosis* (*M. tuberculosis*), and *Cryptococcus* are some of the other less common bacterial sources of meningitis.

Meningococcal meningitis

It can be transmitted by asymptomatic carriers that only have a sore throat and can be prevented by avoiding mouth-to-mouth resuscitation. Acute bacteremias either along with intermittent fever, morbilliform rash and arthritis or without these symptoms are specific characteristics of this category of meningitis. Bacteremia may be caused by a lack of the C7 or C8 complement components and the body parts like the eyes, joints,

Fig. 2 Distinguishing symptoms of meningococcal disease from septicaemia



pericardium, skin, testes, or lungs are generally involved. Seizures and comas are rare in this disease, but aggressive behaviour is normally observed. Except in chronic cases, involvement of the cranial nerves (VI, VII, VIII) is uncommon. The most common complication is disseminated intravascular coagulation; however venous thrombosis and subdural effusions are uncommon (Thakur and Wilson 2018).

Pneumococcal meningitis

In many parts of the world, *pneumococcus* is the leading cause of bacterial meningitis among adults (Beek 2009). *Pneumococcus* intercede blood brain barrier (BBB) interruption which results in fever, headache, and neck stiffness and occasionally results in serious CNS complications like hydrocephalus, brain oedema, brain haemorrhage, arterial complications and seizures, all of which can lead to death and long-term disabilities. Human death rates range from 20 to 50%, with enduring neurological effects like deafness, learning disabilities, aphasia, and recurrent seizures occurring in approximately 60% of patients (Yau et al. 2018).

H. influenzae meningitis

Before an extensive use of conjugate vaccines, *H. influenzae* type b which is a typeable strain containing polysaccharide capsule was a common trigger of meningitis, particularly in young children and infants. *H. influenzae* type b, like meningococcal disease, has virtually vanished in areas where vaccination is widespread, but still remains a concern in regions where vaccination is not widespread (Beek 2009). Their nontypeable strain causes the majority of meningitis cases. Herd immunity from childhood vaccination is most likely to be responsible for *H. influenzae's* rarity (Bahr and Boulware 2014).

Staphylococcal (staph) meningitis

Patients with incisive wounds, CSF shunt, or endocardium inflammation are all susceptible to *Staphylococcus* infection. Fever is normal, and leukocytes counts in the peripheral blood are often elevated. Murmurs, rash, splinter haemorrhage, splenomegaly, and hematuria are all possible symptoms of subacute bacterial endocarditis. The mortality rate caused by staphylococcal meningitis is approximately 40% (Thakur and Wilson 2018).

Listeria meningitis

L. monocytogenes is a gram-positive bacillus that can be present in the soil vegetation and animals and is a facultative intracellular bacterium. When neurological involvement

occurs, listeriosis is one of the most common bacterial foodborne infections, with a death rate of up to 30% (Pagliano et al. 2016). This gram-positive bacillus is generally transmitted via infected food, as revealed subsequent to listeriosis outbreaks during 1980s. *L. monocytogenes* meningitis usually influences immunocompromised or aged patients with elevated fatality rates (24 % to 62 %) (Brouwer et al. 2006).

Tuberculous meningitis

One of the most common infectious agents in the world is *M. tuberculosis*. It is disease of serious concern particularly in developing countries with an approximately 20–41% mortality rate (Hsu et al. 2010). It induces a subtle type of meningitis with headaches, low-grade fever, cranial nerve palsies and stiff neck, with an acute meningoencephalitis with coma, seizures, increased intracranial pressure, and focal neurological deficits (Tattevin et al. 2019).

Cryptococcus meningitis

In Sub-Saharan Africa, *Cryptococcus* is the leading frequent source of meningitis in HIV-positive adults. In numerous low and middle income countries, cryptococcal meningitis has been primary reason of approximately 15 to 20% of all human immunodeficiency virus-associated mortality (Pasquier et al. 2018). Despite an expansion of antiretroviral therapy, an incidence of *cryptococcal* infection in low- and middle-income countries has remained mostly unaffected unlike in high-income countries (Rajasingham et al. 2017). Fever, nausea, emesis, and a severe headache with a subacute onset are all common symptoms in 60–80% cases. Neck stiffness, sensory disturbances, and cranial nerve palsy are rare signs which are observed in 30–50% individuals. The CSF of such patients shows elevated protein intensity, reduced glucose concentration, and moderate pleocytosis at 200 cells/mm³ levels (Thakur and Wilson 2018).

Epidemiology of bacterial meningitis

Bacterial meningitis is a critical disorder that should be identified and cured promptly. *H. influenzae*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Listeria monocytogenes*, and Group B *Streptococcus* (in infants) are respiratory pathogens and are most prevalent causes of meningitis (Bahr and Boulware 2014; Nair et al. 2018). Meningitis is caused by poor living conditions and overcrowding in various centres which lead to the disease occurrence. The majority of cases of meningitis are sporadic; only meningococcal infections can be epidemic. *Meningococci* get spread from one individual to another *via* nasopharyngeal secretions which typically occurs during intimate contact. South America, Finland, Mongolia, and Sub-Saharan Africa have all experienced major epidemics

(Sáez-Llorens and McCracken Jr 2003). Meningitis caused by *N. meningitidis* is most common in an area in Sub-Saharan Africa described as the “meningitis belt” around the world. Seasonal epidemics throughout the dry season with an occurrence rate of 10 to 100 cases per 100,000 population, interrupted by catastrophic epidemics in 8–12-year cycles, characterise this hyper-endemic region that stretches from Senegal to Ethiopia with an incidence rates of greater than 1,000 cases per 100,000 population. During annual outbreaks, at least 350 million people in the meningitis belt are at risk of contracting the disease. Serogroup A is the most common source of meningitis outbreaks, however serogroups C, W135, and X have also caused outbreaks (Aguilera et al. 2002; Harrison et al. 2009). The capsular polysaccharide of *H. influenzae* is employed to divide the *H. influenzae* into six serotypes (a, b, c, d, e, and f), with *H. influenzae* type b being the most prevalent source of invasive condition known as Hib disease. Meningitis caused by *H. influenzae* is uncommon in adolescents and adults, but it is most common in children under the age of five, with an approximate occurrence frequency of 31 incidences per 100,000. Meningitis caused by *H. influenzae* has a greater case-fatality rate in young children compared meningitis caused by *N. meningitidis*. The *S. pneumoniae* meningitis is most prevalent in the very young and the very old, with an approximate occurrence frequency of 17 cases per 100,000 in children under the age of five. In some regions of the world, the case fatality rate for *S.*

pneumoniae meningitis in children under the age of five is as high as 73 percent (Leimkugel et al. 2005; Mayer et al. 2002; Antonio et al. 2008). It has been estimated that bacterial meningitis has influenced greater than 1.2 million individuals globally per year. Without treatment, the case-fatality rate for bacterial meningitis can reach 70%, and one in every five patients can suffer lifelong consequences such as deafness, neurologic dysfunction, or limb loss (Nair et al. 2018).

Pathophysiology of meningitis

The CNS is covered with proficient BBB and CSF-barrier and an outer coating of leptomeninges and the skull against blood-borne pathogen invasion. The CNS pathogens therefore require either an outer membrane defect (e.g., purulent mastoiditis, post-traumatic or post-neurosurgical dura leak) or a biological host defence gauntlet to gain entry to the CNS. Effective CNS invasion includes multiple pathogen-host interactions that simultaneously lead in mucosal colonization, invasion into, and ability to survive inside the intravascular space, and blood-brain/CSF barrier crossing (Herold et al. 2019). The sequential stepwise pathophysiology of meningitis is described below in Fig. 3 (Nudelman and Tunkel 2009; Ramakrishnan et al. 2013).

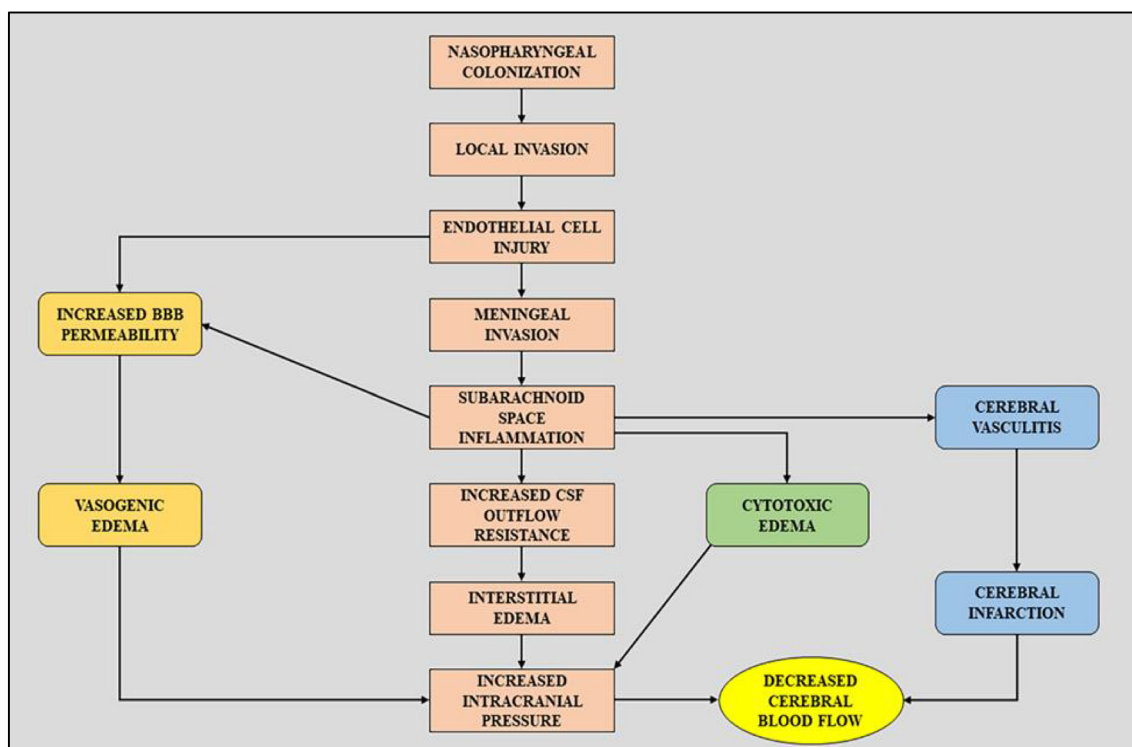


Fig. 3 Scheme depicting the pathogenesis and pathophysiology of meningitis

Nasopharyngeal epithelium transmission, colonization, and invasion

Transmission develops through direct contact or by the distribution of respiratory droplets. A crucial stage in bacterial meningitis pathogenesis is an epithelial invasion and access of pathogen into individual blood circulation. Bacterial substructures, like pili as well as certain outer membrane proteins, maintain adherence to the mucosal membrane. Mucosal epithelial primary immune response mechanisms involve entrapment of bacteria in respiratory mucus, mucosal removal and secretory immunoglobulin A (IgA) (Ramakrishnan et al. 2013). Bacteria should avoid secretory IgA, escape the ciliary clearance mechanisms of the nasopharyngeal mucosa, adhere to the apical membrane, and then move to the basolateral side of the mucosal epithelial cells to effectively connect and penetrate the host mucosal epithelium. The significant initial stage is the evasion of mucosal IgA, primarily secreted by plasma cells in the mucous blanket (Delbaz et al. 2020). Mechanisms have been established by pathogenic organisms to resolve these obstructions to maximize bacterial multiplication; for instance, *S. Pneumoniae* discharges exoglycosidases like neuraminidase-A, which decreases mucus viscosity and eliminates trapping of the mucus. Several bacterial pathogens release antibody-cleaving IgA1 proteinases which inhibits efficient opsonization. The colonization process can be enhanced *via* irritants such as cigarette smoke, damage to the mucosal epithelium, or through prior viral disease (Ramakrishnan et al. 2013).

Survival in the bloodstream

The bacteria have access to the bloodstream after the mucosal barrier is crossed and must conquer subsequent host defenses in order to live and enter the meninges. In this respect, the key significant bacterial virulence factor is encapsulation, which improves bloodstream survival and intravascular bacterial replication by efficiently preventing neutrophils phagocytosis and blocking classical complement pathway bactericidal activity (Guenneec et al. 2020). Fortunately, a variety of defensive mechanisms overcome the bacterial capsule's antiphagocytic operation. Antibodies to capsular components that allow maximum bacterial opsonization and could achieve successful phagocytosis via polymorphonuclear white blood cells and macrophages. In the deficiency of special anticapsular antibodies, the primary host defense towards encapsulated pathogens is nonspecific stimulation of the alternative complement pathway. Alternative complement pathway stimulation ends in C3 cleavage with consecutive bacterial surface deposition of C3b, promoting opsonization, phagocytosis and intravascular evacuation of the organism (Spencer et al. 2019). In non-immune hosts, the polysaccharide capsule

is considered to possess potent antiphagocytic characteristics. It appears to inhibit the interaction of phagocytic cells between C3b linked to surface proteins (Herold et al. 2019; Ramakrishnan et al. 2013; Spencer et al. 2019).

Meningeal invasion

For microbial invasion into the subarachnoid space, continuous bacteremia is considered to be major factor. The bloodborne pathogen has to navigate the physiological hurdles between the bloodstream and the CNS in order to reach the meninges. The bloodstream is segregated from the CNS by two distinct structures like the BBB and the blood-CSF barrier (Herold et al. 2019). By limiting entry to macromolecules, cells, and pathogens, the BBB preserves the CNS microenvironment's homeostasis (Spencer et al. 2019). Choroid plexus cells and cerebral capillaries may have specific bacterial adhesion receptors, allowing bacteria to be transported to CSF. Fimbriae or other cell surface components may promote the adherence of certain bacteria to epithelial or endothelial cell surfaces (Guenneec et al. 2020). Invasion by meningeal pathogens in the choroid plexus can be also promoted through elevated blood flow of 200 mL/g per minute, which supplies this structure with significantly higher numbers of pathogens. Once attachment has developed, the pathogen may employ many techniques to transport *via* BBB and get access into CSF. These involve paracellular transit through intercellular endothelial attachment disturbance or endothelial damage; transcellular transit through transcytosis; and white cell incursion during diapedesis (Spencer et al. 2019).

Inflammatory CSF activity

In the subarachnoid space, there is poor immunological defense, leading in vigorous and relatively unregulated bacterial growth in the CSF. Resident macrophages and peripheral granulocytes do not adequately phagocytose pathogens, particularly in the unavailability of opsonins such as immunoglobulins and complement components through the BBB. As a result, they can rise to very large concentrations, up to 10^9 colony-forming units per ml. In the stationary growth process, autolysis of bacteria during this greater concentration results in the release of bacterial wall components at levels enough to elicit response from immunocompetent cells like leptomeninges macrophages. The discharge of these bacterial products, through cell surface receptors, namely CD14 and toll-like receptors, triggers an intensified inflammatory response like toll-like receptor (TLR 2, 4 and 9). Intracellular signaling molecules, such as the nuclear factor kappa B, stimulate pro-inflammatory pathways like nuclear factor- κ B (NF- κ B). This results in the upregulation of the development of pro-inflammatory cytokines like tumour necrosis factor- α (TNF- α) and interleukin-1 β , produced by many CNS cells.

Interleukins, platelet-activating factor, interferon-gamma, nitric oxide, chemokines and prostaglandins are among the mediators produced by these cytokines. Within hours of infection, concentrations of TNF- α and other pro-inflammatory cytokines inside the CSF are elevated and are associated with disease severity in meningitis (Ramakrishnan et al. 2013).

Conventional therapeutic approaches for bacterial meningitis

In the previous periods, treatment of bacterial meningitis depends upon cephalosporins, i.e., penicillin G, ampicillin, ceftriaxone or cefotaxime. Currently, the newer antibiotics like Carbapenems, Daptomycin, Fluoroquinolones, Linezolid, Tigecycline, Ceftriaxone, and ceftazidime are of potential interest for treatment of community-acquired meningitis caused by multi-resistant bacteria. For patients with allergies to Penicillin, Trimethoprim, or Sulfamethoxazole should be used (Dyckhoff-Shen et al. 2021). Table 1 summarizes the various types of conventional therapeutic approaches for management of bacterial meningitis.

Blood-brain barrier (BBB): a big obstacle for meningitis treatment

BBB is a network that consists of a complicated system of endothelial cells, astroglia, pericytes, and perivascular mast cells that block most circulating cells and molecules from moving through (Gondim et al. 2019). The BBB is extremely selective and has unique transport mechanisms that permit molecules or cells to access the parenchyma of the brain to be closely regulated (Ebrahimi et al. 2020). The BBB is anticipated to guard the CNS from harmful chemicals; nevertheless this also significantly impedes the release of medications. The optimal technique for the transport of drugs *via* BBB must be regulated without causing any damage to the barrier. The conventional drug delivery approaches encounters difficulty in crossing this BBB and therefore, are insufficient to elicit the desired pharmacological effect as required for treatment of meningitis. Therefore, intranasal pathway and application of nanoparticle-based drug delivery systems has become necessitate for successful dealing with this deadly disease.

Nose-to-brain delivery

The intranasal route has emerged as a viable method of delivering drugs to the brain (Pires et al. 2009). Intranasal administration is a better solution to the oral and intravascular routes

for systemic drug delivery, as well as a suitable replacement for the invasive intraventricular, intracerebral, and lumbar puncture routes for overcoming BBB and blood-CSF barrier and delivering medications to the CNS (Miyake and Bleier 2015). The nasal epithelium is greatly vascularized, permeable, and has a wide absorption surface, allowing direct drug permeation into the systemic circulation and bypassing first-pass hepatic metabolism and gastric degradation (Chaturvedi et al. 2011; Thwala et al. 2017). The significant anatomic structure also provides a potential route for direct drug delivery in the CNS (Djupesland et al. 2014). When a medicine is given via the nasal cavity, it enters the systemic circulation via the nasal mucosa and may or may not penetrate the barriers and infiltrate the CNS. The olfactory epithelium, olfactory neurons, and trigeminal nerves, on the other hand, play a significant role in drug delivery to the brain (Pires et al. 2009). Three nose-to-brain pathways were defined which includes systemic pathway, in which the drug is directly absorbed into the systemic circulation via the nasal cavity and then can pass through the BBB; olfactory pathway, wherein the drug passes via the olfactory epithelium into the olfactory bulb and then into the brain tissue or into the CSF; and trigeminal pathway, which avoids BBB by transporting the medication via the trigeminal nerve pathway (Khan et al. 2010).

Application of nanoparticles for improved therapeutics of meningitis

Nanotechnology-based delivery methods offer the best possibility for achieving superior therapy of meningitis (Barani et al. 2021). One of the most important constituents of nanomedicines is the emerging use of nanoparticles (NPs). Nanoparticles have a broad surface-to-volume ratio, which increases the contact area between a drug and the target tissue while still allowing for controlled drug release. Nanoparticles have been introduced into everyday objects in recent years. The size, charge, and overall structure of nanoparticles decide how well they penetrate the skin or barrier (Sun et al. 2020). The vascular layers of brain capillary endothelial cells, which are linked side-by-side by tight and adherens junctions, is primarily responsible for the BBB's tightness. Tight junctions (TJs) have two functions: (i) they block small molecules and ions from moving via the space among cells, causing them to reach the cells (by diffusion or active transport). This pathway regulates the types and quantities of substances that can move through it; (ii) they stop vital membrane proteins from moving between the cells of apical and basolateral membranes, allowing each of the cells of membrane surfaces to maintain their distinct functions, such as receptor-mediated endocytosis at the apical surface and exocytosis at the basolateral surface (Gondim et al. 2019). Tight junctions that have become loose

Table 1 Conventional therapeutic approaches for bacterial meningitis

Drug	Dose/time/dosage duration period	Pathogen	References
Intravenous (I.V) route			
Ceftriaxone	2 g/12 hr/ 4–14 days	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i> , <i>Streptococcus agalactiae</i> , <i>Neisseria meningitidis</i>	(Dyckhoff-Shen et al. 2021; Principi and Esposito 2020; Hasbun 2019; Kim 2019)
Benzylpenicillin	2.4 g/4hr/ 3 days	<i>Streptococcus pneumoniae</i> , <i>Listeria monocytogenes</i>	(Dyckhoff-Shen et al. 2021; Ellis-Pegler et al. 2003; Hasbun 2019; Kim 2019)
Dexamethasone	10 mg/6 hr/ 4 days	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i>	(Dyckhoff-Shen et al. 2021; Principi and Esposito 2020; Hasbun 2019; Kim 2019; De Gans and Van de Beek 2002).
Trimethoprim	160 mg/6 hr/ 3–11 days	<i>Listeria monocytogenes</i> , <i>Staphylococcus aureus</i> , Enterobacteriaceae	(Dyckhoff-Shen et al. 2021; Jha et al. 2016; Hasbun 2019)
Sulfamethoxazole	800 mg/6 hr/ 3–11 days	<i>Listeria monocytogenes</i> , <i>Staphylococcus aureus</i> , Enterobacteriaceae	(Dyckhoff-Shen et al. 2021; Jha et al. 2016)
Moxifloxacin	400 mg/24 hr/ 5 days	<i>Streptococcus pneumoniae</i>	(Principi and Esposito 2020; Alffenaar et al. 2009; Hasbun 2019)
Vancomycin	15–20 mg/L/7–10 days	<i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i>	(Principi and Esposito 2020; Hasbun 2019)
Amoxicillin	2 g/4 hr/7–10 days	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i> , <i>Listeria monocytogenes</i> , <i>Streptococcus agalactiae</i>	(Hasbun 2019)
Meropenem	500 mg/8 hr/7–14 days	<i>Neisseria meningitidis</i> , <i>Haemophilus influenzae</i> , <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter baumannii</i>	(Hasbun 2019)
Daptomycin	5–10 mg/72 hr/14 days	<i>Staphylococcus aureus</i>	(Principi and Esposito 2020; Hasbun 2019)
Linezolid	600 mg/12 hr/10–14 days	<i>Staphylococcus epidermidis</i> , <i>Staphylococcus aureus</i>	(Hasbun 2019)
Tigecycline	100 mg/24 hr/14 days	<i>Acinetobacter baumannii</i>	(Hasbun 2019; Nau et al. 2020)
Gentamicin	5 mg/24 hr/14–21 days	<i>Streptococcus marcescens</i> , <i>Pseudomonas aeruginosa</i>	(Principi and Esposito 2020; Alamarat and Hasbun 2020; Hasbun 2019)
Tobramycin	5 mg/24 hr/4–7 days	<i>Streptococcus marcescens</i> , <i>Pseudomonas aeruginosa</i>	(Principi and Esposito 2020)
Amikacin	30 mg/24 hr/14–21 days	<i>Streptococcus marcescens</i> , <i>Pseudomonas aeruginosa</i>	(Principi and Esposito 2020; Hasbun 2019)
Streptomycin	1 mg/kg (24–48 hr)/ 10 days	<i>Haemophilus influenzae</i>	(Principi and Esposito 2020)
Colistin (polymyxin E) methane sulfonate	10 (1.6–20) mg every 24 h/10–14 days	<i>Acinetobacter baumannii</i>	(Principi and Esposito 2020)
Cefuroxime	3 g/8 hr/5–10 days	<i>Haemophilus influenzae</i>	(Hasbun 2019)
Chloramphenicol	12.5–25 mg/6 hr/8–10 days	<i>Haemophilus influenzae</i>	(Hasbun 2019)
Cefepime	500 mg/8 hr/7–10 days	<i>Pseudomonas aeruginosa</i> , <i>Haemophilus influenzae</i>	(Hasbun 2019)
Oral route			
Ciprofloxacin	500 mg as a single dose /1 day	<i>Pseudomonas aeruginosa</i>	(Dyckhoff-Shen et al. 2021; Hasbun 2019)
Rifampicin	600 mg/12 hr/2days	<i>Streptococcus pneumoniae</i> , <i>Neisseria meningitidis</i>	(Dyckhoff-Shen et al. 2021; El Bashir et al. 2003; Hasbun 2019)
Intramuscular (I.M) route			
Ceftaroline	0.25 mg/L/7–14 days	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i>	(Principi and Esposito 2020; Mermer et al. 2020; Hasbun 2019)

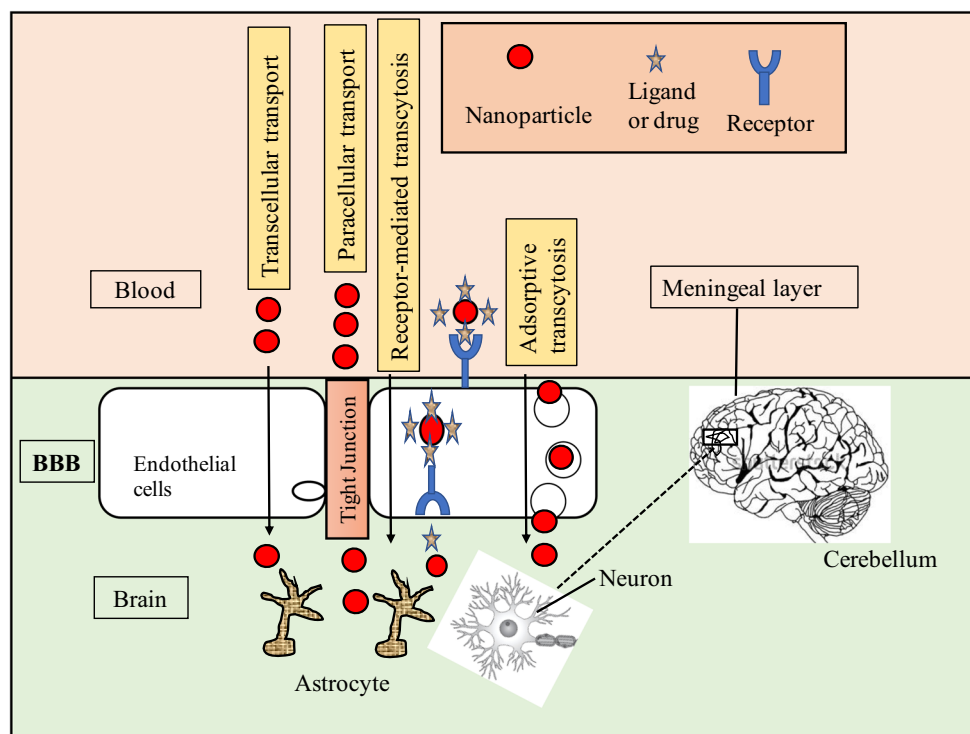
allow nanoparticles to pass across the BBB; either due to the existence of a surfactant in the NPs that can interrupt the TJs. The most popular mode of NPs entry into the brain is receptor-mediated transcytosis. The functionalized NPs may be synthesized using ligands like transferrin, antibodies or lactoferrin or surfactants, i.e., tween 80. When NPs ligands interact with their receptors on the surface of endothelial cells (luminal side), plasma membrane invaginations occur, followed by pinch-free formation of vesicles, allowing NPs to be released in the converse location of the membrane. The amount of NPs retained in the brain parenchyma could be reduced by efflux pumps. Advances in nanomedicine have resulted in the development of several platforms, including NPs, which improve drug transport across the BBB. Nanoparticles are regarded as one of the most promising and versatile drug delivery systems for inaccessible areas such as the brain, as they can protect therapeutic agents while effectively delivering them to the damaged regions (Ebrahimi et al. 2020). Pharmaceutical nanoparticles are solid colloidal particles with a size range of 1 to 1000 nm made up of macromolecular materials wherein the active principle (drug or biologically active material) is dissolved, entrapped, encapsulated, or adsorbed or attached (Hartl et al. 2021]. The passage mechanism throughout the BBB is determined by the physicochemical properties of NPs. The four important transport mechanisms for nanoparticles to across BBB have been described in Fig. 4 which includes (i) Paracellular transport in which NPs unlock TJs flanked by endothelial cells or cause confined toxic outcomes

resulting in localised permeabilization of the BBB, allowing drug penetration in free form or conjugated with the NPs; (ii) Transcellular (transcytosis) which allows the NPs to cross through endothelial cells; (iii) Endocytosis (adsorptive transcytosis) in which NPs across endothelial cells, releasing their drug into the cytoplasm, which is afterwards exocytosed in the endothelium region, or (iv) Receptor-mediated transcytosis in which NPs has been found to target several receptors, including transferrin and low-density lipoprotein receptors. The ligands like peptides, proteins, and antibodies immobilised either physically or chemically over the exterior of NPs were used to target it. Because of their ability to be modulated in terms of shape, size, hydrophobicity, coating, chemistry, and surface charge, NPs are exciting systems for brain drug delivery. Controlling these characteristics can help NPs enhance therapeutic agent stability in circulation, regulate cargo discharge to the required target location, improve BBB diffusion effectiveness, and avoid the reticuloendothelial system (Ebrahimi et al. 2020).

Ideal characteristics of NPs for drug delivery to CNS

Drugs having smaller size and high lipophilicity can undergo passive diffusion across the BBB. However, more lipophilicity has some drawbacks like development of complexes with low solubility, rapid metabolism and poor absorption

Fig. 4 Schematic overview of transport mechanisms for nanoparticle to across BBB



(Rutkowska et al. 2013; Pajouhesh and Lenz 2005). Therefore, NPs must have definite characteristics to transport across for successful drug delivery to brain. The several superlative characteristics of NPs for drug delivery to brain includes its physical stability in blood, prolonged blood circulation time, drug permeability across vessels, controlled drug delivery, non-toxic, biodegradable and biocompatible, targeted and non-invasive drug delivery to brain cells (Thassu et al. 2007; Garbayo et al. 2014).

Various types of nanoparticles explored for treatment or detection of bacterial meningitis

NPs are a broad category of materials which include particulate substances with a minimum dimension of 100 nanometers. The significance of these materials was realised when researchers discovered that size would affect a substance's physiochemical properties, such as its optical properties

(Khan et al. 2017). These can encapsulate a compound, protecting it from enzymatic and chemical degradation (Bhagwat and Vaidhya 2013; Chawla et al. 2012). The pictorial representation various types of NPs which has been researched for management of bacterial meningitis are shown in Fig. 5. The outcomes of NPs research synthesized for detection or treatment of bacterial meningitis in recent few years have been described in Table 2.

Polymeric and functionalized polymeric nanoparticles

These NPs are typically made of organic materials and are biodegradable and biocompatible. They are often in the form of nanospheres or nanocapsules. The former are matrix particles with a solid overall mass, while the other molecules are adsorbed at the outer boundary of the spherical surface. The solid mass is fully encapsulated inside the particle in the latter case. They also have a lot of potential for surface modification through chemical transformations, have good pharmacokinetic control, and can be used to entrap and deliver a variety of

Fig. 5 The outline of various types of NPs researched for bacterial meningitis

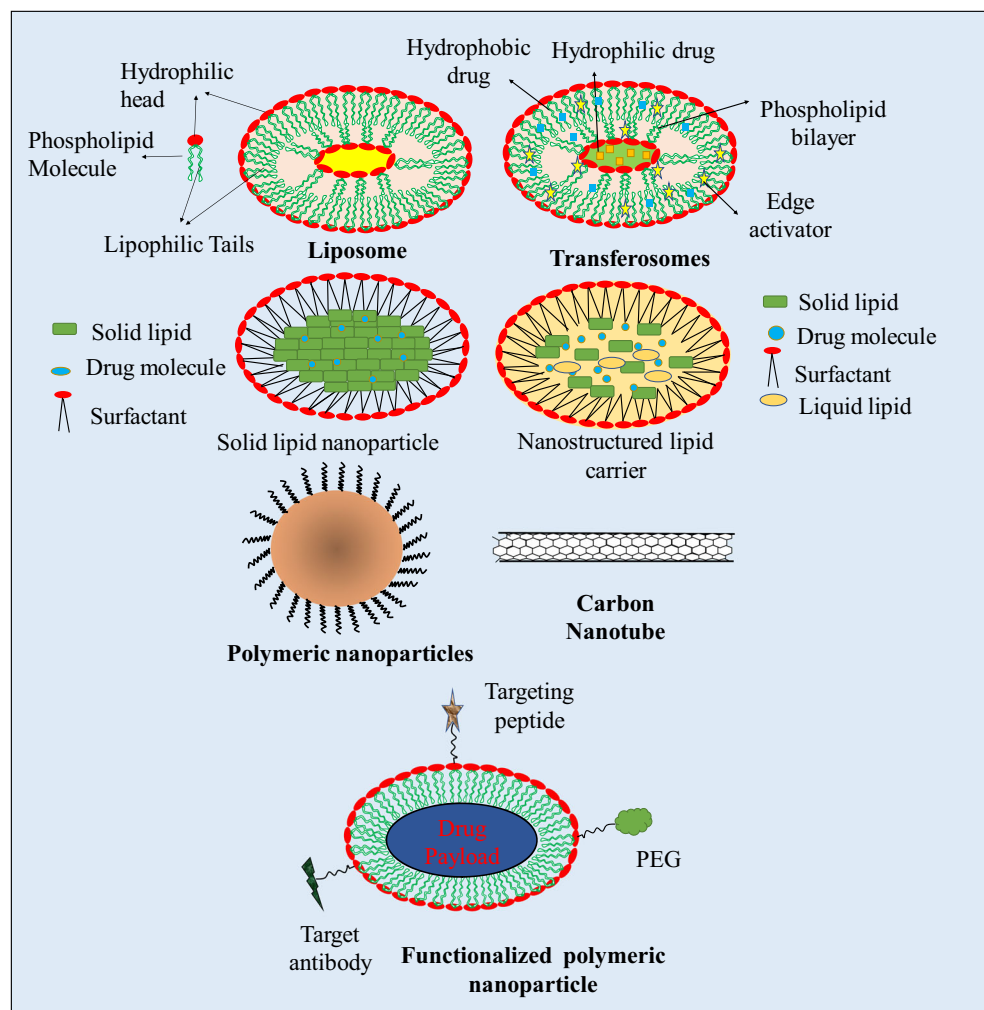


Table 2 Nanotechnology based drug therapeutics for bacterial and other meningitis

Drug (Technique)	Excipients	Dosage Form	Outcome & Significance	References
Ansamycin (Emulsification solvent diffusion)	Poly (lactic-co-glycolic acid), poloxamer	Polymeric nanoparticles	Burst drug release followed by sustained release over 36 hours for treatment of bacterial meningitis	(Nair et al. 2020)
Chloramphenicol (High pressure homogenizer)	Palm kernel oil esters, lecithin, tween 80	Nanoemulsion	Parenteral emulsion used to treat bacterial meningitis by crossing the blood-brain barrier	(Musa et al. 2013)
Gentamicin (Emulsion evaporation method)	Poly (lactide-co-glycolide), polyvinyl alcohol	Polymeric nanoparticles	Antimicrobial effects were improved <i>in-vitro</i> and <i>in-vivo</i> and controlled drug release from PLGA nanoparticles may reduce undesirable side effects and PLGA nanoparticles of Gentamicin are Effective against bacterial meningitis caused by <i>Pseudomonas aeruginosa</i>	(Abdelghany et al. 2012)
Levofloxacin (L) Doxycycline (D) (Emulsification- high-speed homogenization and ultrasonication)	Stearic acid, compritrol 888, Hydroxypropyl methyl cellulose (HPMC)	Solid lipid nanoparticle (SLN)	<i>In-vivo</i> studies explored that intranasal application of L-D-HPMC-SLN gel could achieve peak concentration of 420 and 315 ng/g while 160 and 120 ng/g for free drug solution which showed targeted brain drug delivery and combination strategy will be of a great potential in treating bacterial meningitis	(Hady et al. 2020)
Ofloxacin (Thin film hydration technique)	L- α -Phosphatidyl-choline, sodium deoxycholate, poloxamer 407, poloxamer 188, polyacrylic acid	Nano-transfersomes	Exhibited slower drug release over an 8-hour period and thus increased transnasal flux and could be a promising colloidal drug delivery system for brain targeting and bacterial meningitis treatment	(Eid et al. 2019)
Meropenem (Nano-emulsification technique)	Soya lecithin, Cholesterol, Evion 400, Tween 80, Vitamin E	Nano-liposomes	Solid-lipid Meropenem nanoliposomes could be a potential approach to cross BBB for drug delivery to intrathecal fluid and is the potential method in treatment of bacterial meningitis caused by <i>Pseudomonas aeruginosa</i>	(Ghosh et al. 2019)
Recombinant protein OmpA _{Vac} (Vo)	Chitosan, Poly (lactide-co-glycolide), sodium polyphosphate	Polymeric nanoparticles	Effective strategy to improve the stability of Vo to maintain its immunogenicity which could contribute to the future development of vaccines against <i>E. coli k1</i> in neonatal meningitis	Zhang et al. 2021)
Vancomycin, Methicillin, Ampicillin, Cell penetrating peptides (Tat ₄₇₋₅₇) (Thin lipid film rehydration)	Dioleoyl-phosphatidyl-ethanolamine, Dipalmitoylphosphatidyl-choline, Cholesteryl hemisuccinate, 1,2-distearoyl- <i>sn</i> -glycerol-3-PE- <i>N</i> -(maleimide[polyethylene glycol]-2000)	Liposome	Tat-functionalized liposomes showed total eradication of bacteria population in <i>in-vitro</i> antibacterial activity which showed its better efficacy against that antibiotic-resistant bacterial meningitis	(Garcia and Di Shi 2017)
Oleuropein (melt dispersion ultrasonication)	Precirol, lecithin	Nanostructured lipid carrier	<i>In-vivo</i> study in rats showed that neuron damage index and vascular lesion index were greatly inhibited by NLC which showed its good therapeutics against bacterial meningitis	(Reddy 2019)
Amphotericin B deoxycholate	α -butyl-cyanoacrylate, dextran T-70, Polysorbate-80	Polymeric nanoparticles	Polysorbate 80 coating over NPs provided better drug transport across the BBB and higher concentrations of drug were detected in BALB/c mice brain. Thus, provides better therapy for cryptococcal meningitis	(Xu et al. 2011)
Bacitracin A, Brain-targeting peptide (BTP) [Rabies virus glycopeptide-29 (RVG ₂₉), Pluronic® P85] (Thin film hydration method)	Poly(d,l-lactic-co-glycolic acid), Polyethylene glycol	Functionalized polymeric nanoparticles	Attachment of BTP over NPs could successfully overcome BBB and decreased the growth of drug resistant/sensitive <i>S. pneumonia</i> in the brain tissues, which revealed its prospective against <i>Pneumococcal</i> meningitis	(Hong et al. 2018)

therapeutic agents. Gelatins, chitosan, polylactic acid, polyglycolic acid, polylactide-co glycolide, polyalkylcyanoacrylate, and polymethylmethacrylate are all useful nanoparticle formulations. Polymer coatings can also be functionalized over different categories of NPs to alter and enhance their biodistribution characteristics. Polyethylene glycol, a biologically inert polymer, has been covalently connected on the surface of NPs. This polymeric coating tends to minimise immunogenicity and restrict reticuloendothelial system phagocytosis of NPs, resulting in higher drug blood levels in organs like the brain, intestines, and kidneys (Khan et al. 2017; Faraji and Wipf 2009).

Solid lipid nanoparticles (SLNs)

SLNs are sub-micron colloidal carriers with diameters varying from 50 to 1000 nm, made up of physiological lipid and distributed in water or an aqueous surfactant solution (Hnawate and Deore 2017). They were developed as a pharmaceutical substitute to liposomes and emulsions in the early 1990s. They are comparatively highly stable in biological systems than liposomes because of their rationally rigid centre of hydrophobic lipids that are solid at room and body temperatures, enclosed via a phospholipids monolayer (Faraji and Wipf 2009). The liquid lipid of the emulsion has been substituted by a solid lipid to mitigate the drawbacks associated with the liquid state of the oil droplets. They have many benefits, including better biocompatibility, minimal toxicity and improved delivery of lipophilic drugs through solid lipid nanoparticles, as well as a physically stable system solution (Hnawate and Deore 2017).

Nanostructured lipid carriers (NLCs)

To overcome problems regarding SLN, an innovative/second generation of solid lipid nanoparticle, called NLCs were created. A tiny proportion of solid lipid is replaced with liquid lipid in the formulation of NLC. It produces an intensely disordered lipid structure, allowing for further drug loading while also preventing drug leaching throughout storage. Solid lipid nanoparticle (SLN) has evolved into nanostructured lipid carriers (NLC), with some improvements in encapsulation efficiency. As solid-liquid mixing proportion is superior to single solid lipid, therefore NLC has higher encapsulation efficiency than SLN (Wu et al. 2017; Iqbal et al. 2012).

Liposomes

A liposome is a spherical vesicle made up of phospholipids with at least one lipid layer in which the drug is entrapped. A

liposome is made up of an aqueous solution core enclosed by a hydrophobic membrane in the form of a lipid bilayer, which prevents hydrophilic solutes from passing through. Liposomes are made up of phosphatidylcholine and phosphatidyl-ethanolamine, which are covered by a lipid sheet (Cagdas et al. 2014). Liposomes have remarkable ability to entrap drugs in both an aqueous and a lipid phase which makes them ideal for both hydrophilic and hydrophobic drugs (Kulkarni et al. 2011).

Transfersomes

Transfersomes are vesicular particles with at least one inner aqueous compartment and a lipid bilayer with appropriately tailored properties. As a result, transfersomes have morphology similar to lipid vesicles, or liposomes, but they are functionally deformable enough to pass through pores much smaller than their own size. They are (quasi) metastable, which means the vesicle membrane is extremely flexible, and the vesicles are extremely deformable as a result (Jain et al. 2003; Ascenso et al. 2015; Modi and Bharadia 2012).

Nanoemulsion (NEs)

NEs are colloidal dispersions comprising of two immiscible liquids (oil and water), in which one liquid is dispersed in the other liquid using suitable surfactant combination by high pressure homogenization causing generation of droplets ranging from 20–200 nm (Shaker et al. 2019; Rai et al. 2018). It has been shown that an emulsion with a very small particle size can provide greater encapsulation efficiency for delivery. NEs have particular features, i.e., nanometre size, chemically stable, biocompatible, capacity to solubilize hydrophobic and hydrophilic drugs, capability to decrease the drug toxicity, and potential to prevent enzymatic degradation and hydrolysis (Musa et al. 2013).

Carbon nanotubes

Carbon nanotubes are among the most widely known nanotechnology building blocks. Carbon nanotubes are a hexagonal network of carbon atoms with a diameter of 1 nm and a length of 100 nm that are formed by rolling a sheet of graphite into a cylinder. Single-walled nanotubes (SWCNTs) and multi-walled nanotubes (MWCNTs) are the two forms of carbon nanotubes (Pal et al. 2011). A single-walled carbon nanotube (SWCNT) is formed by wrapping a single graphene sheet around a cylinder. A multi-walled carbon nanotube (MWCNT) is a cylinder made up of concentrically nested grapheme sheets (Singh et al. 2012). CNTs have a high potential for molecular absorption and can be configured in three

Table 3 Published patent literature about bacterial meningitis therapies

Patent name	Patent number	Applicant	Publication date	References
Use of memantine (MEM) in prevention and/or treatment of diseases caused by multidrug-resistant and non-resistant bacterial infections	US20200352880	Sheng-He Huang	12.11.2020	(Huang 2020)
Target nano medicine for treating tubercular meningitis	CN111374950	Beijing Chest Hospital, Capital Medical University	07.07.2020	(Liquan et al. 2020)
Method for providing information for diagnosis of meningitis	WO2020138561	Gyeongsang National University Hospital	02.07.2020	(Cho and Chul 2020)
C band ultraviolet fiber optic device for intravenous ultraviolet light therapy (IVUFLT)	IN202021022095	Dr Sagar Arvind Jawale	26.06.2020	(Jawale 2020)
Random forest algorithm-based encephalitis and meningitis intelligent auxiliary diagnosis system	CN111292852	Shaanxi Lingchuang Precision Medical Technology Co., Ltd.	16.06.2020	(Gang et al. 2020)
Application of Hsp90ab1 Protein in Identification of Streptococcus Suis Meningitis	CN111220799	Jilin University	29.03.2020	(Liancheng et al. 2020)
Preparation Method of Porous CAB6 nanorod	CN110921675	Chengdu University of Technology	27.03.2020	(Dongge et al. 2020a, b, c)
Preparation method of CAB6 nanosheet	CN110844916	Chengdu University of Technology	28.02.2020	(Dongge et al. 2020a, b, c)
Application of micromolecule compound C29H28CL2N6O to Colibacillus Meningitis	CN110787168	China Medical University	14.02.2020	(Yuhua et al. 2020a, b, c)
Application of small-molecule compound C28H26C12N8 to Escherichia Coli induced meningitis	CN110787166	China Medical University	14.02.2020	(Yuhua et al. 2020a, b, c)
Preparation method of zirconium boride nanoparticles	CN110759350	Chengdu University of Technology	07.02.2020	(Dongge et al. 2020a, b, c)
Application of small-molecular compound C34H22FN3O5S2 in Escherichia Coli meningitis	CN110613711	China Medical University.	27.12.2019	(Yuhua et al. 2020a, b, c)
Application of small-molecular compound C29H22N2O8 in Escherichia Coli meningitis	CN110613710	China Medical University	27.12.2019	(Yuhua et al. 2019)
Use of Memantine Hydrochloride (MEM) to prevention and/or treatment of diseases caused by bacterial infection	CN110179774	Huang Shenghe	30.08.2019	(Shenghe 2019)
Vaccine	CN110179974	GlaxoSmithKline Biolog Sa	30.08.2019	(Leon et al. 2019)
Application of antibiotic substitute drug melatonin in resisting infection of meningitis Escherichia Coli pathogens on child patients	CN110151761	Yangzhou University	23.08.2019	(Hucong et al. 2019)
Medical use of HSP60 gene as target in treatment of meningitis	CN110133286	Jilin University	16.08.2019	(Liancheng et al. 2019)
Meningitis anti-inflammatory drug raw material medicine formula	CN109260372	Hubei Chengyu Pharmaceutical Co., Ltd	25.01.2019	(Hubei Chengyu Pharmaceutical Co., Ltd. 2019)
Medicine for treating meningitis	CN109125684	Yang Chao	04.01.2019	(Chao 2019)
Methods	US20180334424	Aeromics, Inc.	22.11.2018	(Pelletier et al. 2018)
Detection of bacterial infection	US20180312907	The University of Liverpool	01.11.2018	(Griffiths 2018)
Inhibition of the complement system	US20180230234	Imperial Innovations Limited	16.08.2018	(Pickering et al. 2018)
Environmental-protection fragrant antibacterial medicine cushion	CN108392015	Cheng Jinlong	14.08.2018	(Jinlong 2018)
Medicine for preventing and controlling meningitis and preparation method and application thereof	CN108210671	Zhang Mingqing	29.06.2018	(Mingqing and Wei 2018)
Traditional chinese medicine	CN108114151	Tang Hongri	05.06.2018	(Xiaoyan 2018)
Medicine for treating meningitis	CN108066726	Jiang Qianqian	25.05.2018	(Qianqian 2018)
Meningitidis vaccines comprising subtilinases	US20180125960	Sanofi Pasteur	10.05.2018	(Barbe et al. 2018)
Protein marker of bacterial meningitis	CN107817345	Beijing Normal University	20.03.2018	(Youhe et al. 2018)

Table 3 (continued)

Patent name	Patent number	Applicant	Publication date	References
Treatment device for tubercular meningitis	CN107397986	Zhou Juanjuan	28.11.2017	(Juanjuan 2017)
Diagnosing acute bacterial meningitis	WO2017178826	The University of Liverpool	19.10.2017	(Beynon et al. 2017)
Traditional chinese medicine composition capable of relieving meningitis	CN107233503	Gao Xianlin	10.10.2017	(Xianlin 2017)
Meningitidis vaccines comprising subtilinases	WO2017137085	Sanofi Pasteur	17.08.2017	(Barbe et al. 2017)
Application of eight-component medicine in preparing drug for treating meningitis	CN106668100	Xiamen Traditional Chinese Medicine Co., Ltd.	17.05.2017	(Bin et al. 2017)
Medicine for treating meningitis	CN106620557	Chen Xiaoning	10.05.2017	(Xiaoning 2017)
Pct (procalcitonin) and crp (c-reactive protein) double-label time resolution fluorescence immunoassay method for simultaneously detecting bacterial meningitis and viral meningitis	CN106404731	Wang Yan	15.02.2017	(Yan and Licheng 2017)
Applications of bacteroides fragilis in prevention and/or treatment of meningitis	CN106389475	Zhiyi Pharmaceuticals, Inc.	15.02.2017	(Fachao et al. 2017a, b)
Application of bacteroides fragilis in prevention and/or treatment of meningitis	WO2017020783	Zhiyi Pharmaceuticals, Inc.	09.02.2017	(Fachao et al. 2017a, b)
Chinese and western medicinal compound preparation for treating epidemic cerebrospinal meningitis	CN106362014	Gu Mingming	01.02.2017	(Mingming 2017)

dimensions (Pal et al. 2011). Since carbon nanotubes are hollow and much smaller than blood cells, they have the ability to transport drugs across the body (Singh et al. 2012). A group of researchers developed nanocomposite of zinc oxide CNTs immobilized with single stranded DNA probe for detection of *N. meningitidis* from CSF (Tak et al. 2016). Another group of researchers generated nanocomposite matrix of carbon mercaptooctadecane or carboxylated multiwalled CNTs immobilized with thiolated oligonucleotides probe sequence *via* physical adsorption technique. The results showed that fabricated DNA-biosensor could be successfully utilized as handheld appliance for detection of meningitis at an early phase (Dash et al. 2014).

Patents and clinical status of therapeutic modalities of bacterial meningitis

Patent and related searches were performed from official website of World Intellectual Property Organization with analytics to review and organize the recent work in the field of treatment of bacterial meningitis from the period of 2017 to 2020 (Table 3). Several new treatment modalities against bacterial meningitis are under various phases of clinical trials with basic focus on either for treatment or investigation for development of immunity among individuals against this fatal

disease and a few of them are listed in Table 4 (<https://clinicaltrials.gov>).

Conclusion and future perspectives

NPs can undergo transport to across BBB via paracellular transport by opening TJs between endothelial cells leading to localised permeabilization of the BBB which allocates drug penetration from conjugated NPs; transcellular transport by crossing through endothelial cells; endocytosis via transport across endothelial cells; or receptor-mediated transcytosis to target several receptors like transferrin and low-density lipoprotein receptors. NPs like polymeric nanoparticles, liposomes, transferosomes, solid lipid nanoparticles, nanostructured lipid carrier, functionalized polymeric nanoparticles and carbon nanotubes have capability to be remodelled in requisites of their size, shape, hydrophobicity, surface charge, coating and chemistry. The functionalized NPs surface coated with specific ligands like peptides, proteins, and antibodies either chemically or physically could be successfully used for brain targeting to achieve improved treatment of bacterial meningitis. Therefore, due to wonderful physical, chemical, and biological characteristics of NPs, they could be considered as revitalizing optimistic systems for targeted drug delivery CNS and are complementary for the diagnosis and alleviation of brain disorders like bacterial meningitis.

Table 4 Clinical status of in-progress treatment strategies for bacterial meningitis

Study Title	Sponsor	NCT No.	Phase
Single dose liposomal amphotericin for asymptomatic cryptococcal antigenemia (ACACIA)	Makerere University	NCT03945448	Phase 2 Phase 3
AmB dose for cryptococcal meningitis	Shanghai Public Health Clinical Center	NCT04140461	Phase 3
Treatment with tamoxifen in cryptococcal meningitis	Oxford University Clinical Research Unit, Vietnam	NCT03112031	Phase 2
Three induction treatments on cryptococcal meningitis (TITOC)	First Affiliated Hospital of Zhejiang University	NCT04072640	Early Phase 1
Daptomycin in pediatric patients with bacterial meningitis	University Hospital Inselspital, Berne	NCT01522105	Phase 1
Adjunctive sertraline for the treatment of HIV-associated cryptococcal meningitis (ASTRO-CM)	University of Minnesota	NCT01802385	Phase 3
Intrathecal trastuzumab administration in metastatic breast cancer patients developing carcinomatous meningitis (HIT)	Institut Curie	NCT01373710	Phase 1 Phase 2
Vietnam cryptococcal retention in care study (CRICS) federal financial report	National Hospital for Tropical Diseases, Hanoi, Vietnam	NCT02955862	Phase 1
Investigating the immune response to 4-CMENB in infants	University of Oxford	NCT02080559	Phase 4
Clinical study of meningococcal ACYWXX conjugate vaccine, in 12–16-month-olds	Serum Institute of India Pvt. Ltd.	NCT03295318	Phase 2
Immunogenicity and safety of MenACWY in infants (6 and 12 months).	Novartis Vaccines	NCT00310856	Phase 2
Immunogenicity of quadrivalent meningococcal conjugate vaccine in frequent platelets donors (PLAT)	Brigham and Women's Hospital	NCT04224311	Phase 4
Pharmacokinetic study of linezolid for TB meningitis (SIMPLE)	Universitas Padjadjaran	NCT03537495	Phase 2
Immunogenicity and safety of a booster dose of a quadrivalent meningococcal conjugate vaccine in children	Sanofi Pasteur, a Sanofi Company	NCT03476135	Phase 3
Maternal immunization with MenAfriVac™	London School of Hygiene and Tropical Medicine	NCT03746665	Phase 3
Adjunctive linezolid for the treatment of tuberculous meningitis (ALTER)	University of California, San Francisco	NCT04021121	Phase 2
Cyclophosphamide in the treatment of refractory proliferative arachnoiditis in CNS tuberculosis	All India Institute of Medical Sciences, New Delhi	NCT04620772	Phase 2 Phase 3
Confirmatory study of BK1310 in healthy infants.	Mitsubishi Tanabe Pharma Corporation	NCT03891758	Phase 3
The long-term antibody persistence of GSK biological meningococcal vaccine GSK134612 in healthy toddlers	GlaxoSmithKline	NCT00718666	Phase 2
Adolescent MenACWY booster study	Canadian Immunization Research Network	NCT03694405	Phase 4
South australian meningococcal B vaccine herd immunity study	University of Adelaide	NCT03089086	Phase 4
Hypovitaminosis D in neurocritical patients	University of Utah	NCT02881957	Phase 2 Phase 3

Acknowledgements The authors would like to thank Chitkara College of Pharmacy, Chitkara University, Punjab, India, for providing facilities for completion of this review.

Author contribution NS, TB, and SS: conceived the study and wrote the first draft of the paper; MS, VS, IZ, and SF: data compilation; NKF, TN, and SB: figure work; AAH, LA, and SBU: proof read

Data availability Not applicable

Declarations

Ethics approval Not applicable

Consent to participate Not applicable

Consent for publication All the authors have approved the manuscript for publication.

Competing interests The authors declare no competing interests.

References

- Abdelghany SM, Quinn DJ, Ingram RJ, Gilmore BF, Donnelly RF, Taggart CC, Scott CJ (2012) Gentamicin-loaded nanoparticles show improved antimicrobial effects towards *Pseudomonas aeruginosa* infection. *Int J Nanomedicine* 7:4053–4063
- Aguilera JF, Perrocheau A, Meffre C, Hahné S, W135 Working Group (2002) Outbreak of serogroup W135 meningococcal disease after the Hajj pilgrimage, Europe, 2000. *Emerg Infect Dis* 8(8):761–767
- Alamarat Z, Hasbun R (2020) Management of Acute Bacterial Meningitis in Children. *Infect Drug Resist* 13:4077–4089

- Alffenaar JW, Van Altena R, Böklerink HJ, Lijckx GJ, Van Soelingen D, Aarnoutse RE, Van Der Werf TS (2009) Pharmacokinetics of moxifloxacin in cerebrospinal fluid and plasma in patients with tuberculous meningitis. *Clin Infect Dis* 49(7):1080–1082
- Al-Obaidi MMJ, Desa MNM (2018) Mechanisms of blood brain barrier disruption by different types of bacteria, and bacterial-host interactions facilitate the bacterial pathogen invading the brain. *Cell Mol Neurobiol* 38(7):1349–1368
- Antonio M, Hakeem I, Awine T, Secka O, Sankareh K, Nsekpang D, Lahai G, Akisanya A, Egere U, Enwere G, Zaman SM (2008) Seasonality and outbreak of a predominant *Streptococcus pneumoniae* serotype 1 clone from The Gambia: expansion of ST217 hypervirulent clonal complex in West Africa. *BMC Microbiol* 8(1):1–7
- Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praça FG, Bentley MV, Simões S (2015) Development, characterization, and skin delivery studies of related ultra-deformable vesicles: transfersomes, ethosomes, and transethosomes. *Int J Nanomedicine* 10:5837–5851
- Bahr NC, Boulware DR (2014) Methods of rapid diagnosis for the etiology of meningitis in adults. *Biomark Med* 8(9):1085–1103
- Barani M, Mukhtar M, Rahdar A, Sargazi G, Thysiadou A, Kyzas GZ (2021) Progress in the Application of Nanoparticles and Graphene as Drug Carriers and on the Diagnosis of Brain Infections. *Molecules* 26(1):186
- Barbe A, Nadège, Mongenie R, Geneviève, Rokbi, Bachra (2017) Meningitis vaccines comprising subtilinases. WO2017137085.
- Barbe NA, Mongenie GR, Rokbi B (2018) Meningitis vaccines comprising subtilinases. US20180125960.
- Beek DVD (2009) Corticosteroids for acute adult bacterial meningitis. *Med Mal Infect* 39(7-8):531–538
- Beynon, Jeffrey R, Carrol, Delphine E, Baena G, Guadalupe (2017) Diagnosing acute bacterial meningitis. WO2017178826.
- Bhagwat RR, Vaidhya IS (2013) Novel drug delivery systems: an overview. *Int J Pharm Sci Res* 4(3):970
- Bin G, Hao Z, Shuhua N, Lihua Y, Shanshan Z, Zhifa Z, Xiaolin C, Erxi C, Shuyu X, Zhicheng L, Shunbiao X (2017) Application of eight-component medicine in preparing drug for treating meningitis. CN106668100.
- Bloch KC, Bailin SS (2019) Update on fungal infections of the central nervous system: emerging pathogens and emerging diagnostics. *Curr Opin Infect Dis* 32(3):277–284
- Brouwer MC, Beek DV, Heckenberg SG, Spanjaard L, Gans JD (2006) Community-acquired *Listeria monocytogenes* meningitis in adults. *Clin Infect Dis* 43(10):1233–1238
- Cagdas M, Sezer AD, Bucak S (2014) Liposomes as Potential Drug Carrier Systems for Drug Delivery. In: Sezer AD (ed) Application of nanotechnology in drug delivery, 1st edn. IntechOpen, United Kingdom, pp 1–50
- Chao Y (2019) Medicine for treating meningitis. CN109125684.
- Chaturvedi M, Kumar M, Pathak K (2011) A review on mucoadhesive polymer used in nasal drug delivery system. *J Adv Pharm Technol Res* 2(4):215–222
- Chaud MV, Rios AC, dos Santos CA, de Barros CT, de Souza JF, Alves TF (2020) Nanostructure self-assembly for direct nose-to-brain drug delivery: a novel approach for cryptococcal meningitis. In *Nanomycotoxicology* 449–80, Academic Press.
- Chawla A, Sharma P, Pawar P (2012) Eudragit S-100 coated sodium alginate microspheres of naproxen sodium: formulation, optimization and in vitro evaluation. *Acta Pharma* 62(4):529–545
- Cho, Chul M (2020) Method for providing information for diagnosis of meningitis. WO2020138561.
- Dash SK, Sharma M, Khare S, Kumar A (2014) Carbon-mercaptotetradecane/carboxylated multi-walled carbon nanotubes composite based genosensor for detection of bacterial meningitis. *Indian J Microbiol* 54(2):170–177
- De Gans J, Van de Beek D (2002) Dexamethasone in adults with bacterial meningitis. *New Eng J Med* 347(20):1549–1556
- Delbaz A, Chen M, Jen FE, Schulz BL, Gorse AD, Jennings MP, St John JA, Ekberg JA (2020) *Neisseria meningitidis* induces pathology-associated cellular and molecular changes in trigeminal Schwann cells. *Infect Immun* 88(4)
- Djupesland PG, Messina JC, Mahmoud RA (2014) The nasal approach to delivering treatment for brain diseases: an anatomic, physiologic, and delivery technology overview. *Ther Deliv* 5(6):709–733
- Dongge T, Lei C, Rui Z (2020a) Preparation method of zirconium boride nanoparticles. CN110759350.
- Dongge T, Rui Z, Ping W (2020b) Preparation method of CAB6 nanosheet. CN110844916.
- Dongge T, Rui Z, Ping W (2020c) Preparation Method of Porous CAB6 nanorod. CN110921675.
- Dyckhoff-Shen S, Koedel U, Pfister HW, Klein M (2021) SOP: emergency workup in patients with suspected acute bacterial meningitis. *Neurol Res Pract* 3(1):1–7
- Ebrahimi Z, Talaei S, Aghamiri S, Goradel NH, Jafarpour A, Negahdari B (2020) Overcoming the blood-brain barrier in neurodegenerative disorders and brain tumours. *IET Nanobiotechnol* 14(6):441–448
- Eid HM, Elkomy MH, El Menshawe SF, Salem HF (2019) Transfersomal nanovesicles for nose-to-brain delivery of ofloxacin for better management of bacterial meningitis: Formulation, optimization by Box-Behnken design, characterization and in vivo pharmacokinetic study. *J Drug Deliv Sci Technol* 54:101304
- El Bashir H, Laundry M, Booy R (2003) Diagnosis and treatment of bacterial meningitis. *Arch Dis Child* 88(7):615–620
- Ellis-Pegler R, Galler L, Roberts S, Thomas M, Woodhouse A (2003) Three days of intravenous benzyl penicillin treatment of meningococcal disease in adults. *Clin Infect Dis* 37(5):658–662
- Fachao Z, Yang B, Ye W, Yangyang L, Congfeng W (2017a) Applications of bacteroides fragilis in prevention and/or treatment of meningitis. CN106389475.
- Fachao Z, Yang B, Ye W, Yangyang L, Congfeng W (2017b) Application of bacteroides fragilis in prevention and/or treatment of meningitis. WO2017020783.
- Faraji AH, Wipf P (2009) Nanoparticles in cellular drug delivery. *Bioorg Med Chem Lett* 17(8):2950–2962
- Gang Z, Junjia Z, Tian X (2020) Random forest algorithm-based encephalitis and meningitis intelligent auxiliary diagnosis system. CN111292852.
- Garbayo E, Estella-Hermoso de Mendoza A, Blanco-Prieto JM (2014) Diagnostic and therapeutic uses of nanomaterials in the brain. *Curr Med Chem* 21(36):4100–4131
- Garcia CB, Di Shi TJ (2017) Tat-functionalized liposomes for the treatment of meningitis: an in vitro study. *Int J Nanomedicine* 12:3009–3021
- Ghosh A, Nandi S, Roy A, Singh S, Singhmura S, Basak S (2019) Fabrication of tween 80 ligand coated cholesterol-soya lecithin bilayered nanoliposomes for improved release of Meropenem against artificial blood brain barrier. *IJPSR*. 10:5471–5480
- Gondim BL, Silva CJ, Sousa MA, Silva M, Lemes MR, Carvalho-Costa TM, Lima NTR, Machado JR, Rodrigues V, Oliveira CJ, Cancado CLR (2019) Nanoparticle-mediated drug delivery: blood-brain barrier as the main obstacle to treating infectious diseases in CNS. *Curr Pharm Des* 25(37):3983–3996
- Griffiths M (2018) Detection of bacterial infection. US20180312907.
- Guenneq LL, Coureuil M, Nassif X, Bourdoulous S (2020) Strategies used by bacterial pathogens to cross the blood-brain barrier. *Cell Microbiol* 22(1):e13132
- Hady MA, Sayed OM, Akl MA (2020) Brain uptake and accumulation of new levofloxacin-doxycycline combination through the use of solid lipid nanoparticles: Formulation; Optimization and in-vivo evaluation. *Colloids Surf B* 193:111076

- Harrison LH, Trotter CL, Ramsay ME (2009) Global epidemiology of meningococcal disease. *Vaccine*. 27:B51–B63
- Hartl N, Adams F, Merkel OM (2021) From adsorption to covalent bonding: Apolipoprotein E functionalization of polymeric nanoparticles for drug delivery across the blood-brain barrier. *Adv Ther* 4(1): 2000092
- Hasbun R (2019) Update and advances in community acquired bacterial meningitis. *Curr Opin Infect Dis* 32(3):233–238
- Herold R, Schrotten H, Schwerk C (2019) Virulence Factors of Meningitis-Causing Bacteria: Enabling Brain Entry across the Blood–Brain Barrier. *Int J Mol Sci* 20(21):5393
- Hnawate RM, Deore P (2017) Nanoparticle-novel drug delivery system: A Review. *Pharma Tutor* 5(5):9–23
- Hong W, Zhang Z, Liu L, Zhao Y, Zhang D, Liu M (2018) Brain-targeted delivery of PEGylated nano-bacitracin A against Penicillin-sensitive and-resistant Pneumococcal meningitis: Formulated with RVG29 and Pluronic® P85 unimers. *Drug Deliv* 25(1):1886–1897
- Hsu PC, Yang CC, Ye JJ, Huang PY, Chiang PC, Lee MH (2010) Prognostic factors of tuberculous meningitis in adults: a 6-year retrospective study at a tertiary hospital in northern Taiwan. *J Microbiol Immunol Infect* 43(2):111–118
- Huang SH (2020) Use of memantine (MEM) in prevention and/or treatment of diseases caused by multidrug-resistant and non-resistant bacterial infections. *US20200352880*.
- Hubei Chengyu Pharmaceutical Co., Ltd. (2019) Meningitis anti-inflammatory drug raw material medicine formula. *CN109260372*.
- Hucong W, Jiaqi L, Guoqiang Z, Dong Z, Pengpeng X, Wenkai R (2019) Application of antibiotic substitute drug melatonin in resisting infection of meningitis Escherichia Coli pathogens on child patients. *CN110151761*.
- Iqbal MA, Md S, Sahni JK, Baboota S, Dang S, Ali J (2012) Nanostructured lipid carriers system: recent advances in drug delivery. *J Drug Target* 20(10):813–830
- Jain S, Jain P, Umamaheshwari RB, Jain NK (2003) Transfersomes-a novel vesicular carrier for enhanced transdermal delivery: development, characterization, and performance evaluation. *Drug Dev Ind Pharm* 29(9):1013–1026
- Jawale SA (2020) C Band ultraviolet fiber optic device for intravenous ultraviolet light therapy (IVUULT). *IN202021022095*.
- Jha P, Stromich J, Cohen M, Wainaina JN (2016) A rare complication of trimethoprim-sulfamethoxazole: drug induced aseptic meningitis. *Case Rep Infect Dis* 2016:2016–2014
- Jinlong C (2018) Environmental-protection fragrant antibacterial medicine cushion. *CN108392015*.
- Juanjuan Z (2017) Treatment device for tubercular meningitis. *CN107397986*.
- Khan I, Saeed K, Khan I (2017) Nanoparticles: properties, applications and toxicities. *Arab J Chem* 12:908–931
- Khan S, Patil K, Bobade N, Yeole P, Gaikwad R (2010) Formulation of intranasal mucoadhesive temperature-mediated in situ gel containing ropinirole and evaluation of brain targeting efficiency in rats. *J Drug Target* 18(3):223–234
- Kim KS (2019) Investigating bacterial penetration of the blood-brain barrier for the pathogenesis, Prevention, and therapy of bacterial meningitis. *ACS Infect Dis* 6(1):34–42
- Kulkarni PR, Yadav JD, Vaidya KA (2011) Liposomes: a novel drug delivery system. *Int J Curr Pharm Res* 3(2):10–18
- Leimkugel J, Adams Forgor A, Gagneux S, Pflüger V, Flierl C, Awine E, Naegeli M, Dangy JP, Smith T, Hodgson A, Pluschke G (2005) An outbreak of serotype 1 *Streptococcus pneumoniae* meningitis in northern Ghana with features that are characteristic of *Neisseria meningitidis* meningitis epidemics. *J Infect Dis* 192(2):192–199
- Leon RL, Josephe NMJ, Vincent PVHP, Jan JP, Paulette MPVMM (2019) Vaccine. *CN110179974*.
- Liancheng L Hongtao L, Tong W, Hexiang J, Li J, Yingying S, Changjiang S (2020) Application of Hsp90ab1 Protein in Identification of *Streptococcus Suis* Meningitis. *CN111220799*.
- Liancheng L, Jia L, Yang L, Hongtao L, Hexiang J, Changjiang S, Jingmin G, Xin F, Na L (2019) Medical use of HSP60 gene as target in treatment of meningitis. *CN110133286*.
- Liquan Z, Lijun BI, Xin K, Wenjing MA, Yaguo W, Linying L (2020) Target nano medicine for treating tubercular meningitis. *CN111374950*.
- Martins Gomes SF, Westermann AJ, Sauerwein T, Hertlein T, Förstner KU, Ohlsen K, Metzger M, Shusta EV, Kim BJ, Appelt-Menzel A, Schubert-Unkmeir A (2019) Induced pluripotent stem cell-derived brain endothelial cells as a cellular model to study *Neisseria meningitidis* infection. *Front Microbiol* 10:1181
- Mayer LW, Reeves MW, Al-Hamdan N, Sacchi CT, Taha MK, Ajello GW, Schmink SE, Noble CA, Tondella ML, Whitney AM, Al-Mazrou Y (2002) Outbreak of W135 meningococcal disease in 2000: not emergence of a new W135 strain but clonal expansion within the electrophoretic type-37 complex. *J Infect Dis* 185(11): 1596–1605
- Mermer S, Turhan T, Bolat E, Aydemir S, Yamazhan T, Pullukcu H, Arda B, Sipahi H, Ulusoy S, Sipahi OR (2020) Ceftaroline versus vancomycin in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) in an experimental MRSA meningitis model. *J Glob Antimicrob Resist* 22:147–151
- Mingming G (2017) Chinese and western medicinal compound preparation for treating epidemic cerebrospinal meningitis. *CN106362014*.
- Mingqing Z, Wei Y (2018) Medicine for preventing and controlling meningitis and preparation method and application thereof. *CN108210671*.
- Miyake MM, Bleier BS (2015) The blood-brain barrier and nasal drug delivery to the central nervous system. *Am J Rhinol Allergy* 29(2): 124–127
- Modi CD, Bharadia PD (2012) Transfersomes: new dominants for transdermal drug delivery. *Am J Pharmtech Res* 2(3):71–91
- Musa SH, Basri M, Masoumi HR, Karjiban RA, Abd Malek E, Basri H, Shamsuddin AF (2013) Formulation optimization of palm kernel oil esters nanoemulsion-loaded with chloramphenicol suitable for meningitis treatment. *Colloids Surf B* 112:113–119
- Nair KG, Ramaiyan V, Sukumaran SK (2018) Enhancement of drug permeability across blood brain barrier using nanoparticles in meningitis. *Inflammopharmacology* 26(3):675–684
- Nair KG, Velmurugan R, Sukumaran SK (2020) Formulation and Optimization of Ansamycin-Loaded Polymeric Nanoparticles Using Response Surface Methodology for Bacterial Meningitis. *BioNanoScience*. 1-3:279–291
- Nau R, Blei C, Eiffert H (2020) Intrathecal antibacterial and antifungal therapies. *Clin Microbiol Rev* 33(3):e00190–e00219
- Nudelman Y, Tunkel AR (2009) Bacterial meningitis. *Drugs*. 69(18): 2577–2596
- Pagliano P, Ascione T, Boccia G, De Caro F, Esposito S (2016) *Listeria monocytogenes* meningitis in the elderly: epidemiological, clinical and therapeutic findings. *Infez Med* 24(2):105–111
- Pajouhesh H, Lenz GR (2005) Medicinal chemical properties of successful central nervous system drugs. *NeuroRx* 2(4):541–553
- Pal SL, Jana U, Manna PK, Mohanta GP, Manavalan R (2011) Nanoparticle: An overview of preparation and characterization. *J Appl Pharm Sci* 1(6):228–234
- Pasquier E, Kunda J, De Beaudrap P, Loyse A, Temfack E, Molloy SF, Harrison TS, Lortholary O (2018) Long-term mortality and disability in cryptococcal meningitis: a systematic literature review. *Clin Infect Dis* 66(7):1122–1132
- Pelletier MF, Farr GW, McGuirk PR, Hall CH, Boron WF (2018) Methods. *US20180334424*.
- Pickering M, Lea S, Jorge EG (2018) Inhibition of the complement system. *US20180230234*.

- Pires A, Fortuna A, Alves G, Falcão A (2009) Intranasal drug delivery: how, why and what for? *J Pharm Pharm Sci* 12(3):288–311
- Principi N, Esposito S (2020) Bacterial meningitis: new treatment options to reduce the risk of brain damage. *Expert Opin Pharmacother* 21(1):97–105
- Qianqian J (2018) Medicine for treating meningitis. CN108066726.
- Rai VK, Mishra N, Yadav KS, Yadav NP (2018) Nanoemulsion as pharmaceutical carrier for dermal and transdermal drug delivery: formulation development, stability issues, basic considerations and applications. *J Control Release* 270:203–225
- Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, Denning DW, Loyse A, Boulware DR (2017) Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis* 17(8):873–881
- Ramakrishnan KA, Levin M, Faust SN (2013) Bacterial meningitis and brain abscess. *Medicine* 41(12):671–677
- Ranson E, Ship H, Garner O, Yang S, Bhattacharya D (2020) Unusual presentation of meningococcal meningitis in the elderly and utility of CSF PCR testing. *Access Microbiology* 2(10):acmi000158
- Rasol EA, Sultan BA (2019) Some Biochemical and Cellular laboratory Indicators in the Cerebral Spinal Fluid among Suspected Bacterial Meningitis Patients. *Kufa J Nurs Sci* 9(1):1–6
- Reddy KB (2019) In Vitro-In Vivo Characterization of Oleuropein loaded Nanostructured Lipid Carriers in the Treatment of Streptococcus pneumoniae induced Meningitis. *Asian J Pharm* 13(02)
- Rutkowska E, Pajak K, Józwiak K (2013) Lipophilicity-methods of determination and its role in medicinal chemistry. *Acta Pol Pharm* 70(1):3–18
- Sáez-Llorens X, McCracken GH Jr (2003) Bacterial meningitis in children. *Lancet* 361(9375):2139–2148
- Shaker DS, Ishak RA, Ghoneim A, Elhuoni MA (2019) Nanoemulsion: A review on mechanisms for the transdermal delivery of hydrophobic and hydrophilic drugs. *Sci Pharm* 87(3):17
- Shenghe H (2019) Use of Memantine Hydrochloride (MEM) to prevention and/or treatment of diseases caused by bacterial infection. CN110179774.
- Singh BG, Baburao C, Pispati V, Pathipati H, Muthy N, Prassana SR (2012) Carbon nanotubes. A novel drug delivery system. *Int J Res Pharm Chem* 2(2):523–532
- Spencer BL, Deng L, Patras KA, Burcham ZM, Sanches GF, Nagao PE, Doran KS (2019) Cas9 contributes to group B streptococcal colonization and disease. *Front Microbiol* 10:1930
- Sun MC, Xu XL, Lou XF, Du YZ (2020) Recent Progress and Future Directions: The Nano-Drug Delivery System for the Treatment of Vitiligo. *Int J Nanomedicine* 15:3267–3279
- Tak M, Gupta V, Tomar M (2016) A ZnO-CNT nanocomposite based electrochemical DNA biosensor for meningitis detection. *RSC Adv* 6(80):76214–76222
- Tattevin P, Tchamgoué S, Belem A, Bénézit F, Pronier C, Revest M (2019) Aseptic meningitis. *Rev Neurol* 175(7-8):475–480
- Thakur KT, Wilson MR (2018) Chronic meningitis. *Continuum (Minneapolis, Minn)* 24(5):1298
- Thassu D, Pathak Y, Deleers M (2007) Nanoparticulate drug-delivery systems: an overview. *Drugs Pharm Sci* 166:1
- Thwala LN, Préat V, Csaba NS (2017) Emerging delivery platforms for mucosal administration of biopharmaceuticals: a critical update on nasal, pulmonary and oral routes. *Expert Opin Drug Deliv* 14(1):23–36
- Wright WF, Pinto CN, Palisoc K, Baghli S (2019) Viral (aseptic) meningitis: A review. *J Neurol Sci* 398:176–183
- Wu PS, Lin CH, Kuo YC, Lin CC (2017) Formulation and characterization of hydroquinone nanostructured lipid carriers by homogenization emulsification method. *J Nanomater.* 2017.
- Xianlin G (2017) Traditional Chinese medicine composition capable of relieving meningitis. CN107233503.
- Xiaoning C (2017) Medicine for treating meningitis. CN106620557.
- Xiaoyan Z (2018) Traditional Chinese medicine. CN108114151.
- Xu N, Gu J, Zhu Y, Wen H, Ren Q, Chen J (2011) Efficacy of intravenous amphotericin B-polybutylcyanoacrylate nanoparticles against cryptococcal meningitis in mice. *Int J Nanomedicine* 6:905
- Yan W, Licheng Z (2017) Pct (procalcitonin) and crp (c-reactive protein) double-label time resolution fluorescence immunoassay method for simultaneously detecting bacterial meningitis and viral meningitis. CN106404731.
- Yau B, Hunt NH, Mitchell AJ, Too LK (2018) Blood–Brain Barrier Pathology and CNS Outcomes in Streptococcus pneumoniae Meningitis. *Int J Mol Sci* 19(11):3555
- Youhe G, Yanying N, Fanshuang Z (2018) Protein marker of bacterial meningitis. CN107817345.
- Yuhua C, Xiaoqian X, Weidong Z (2019) Application of small-molecular compound C29H22N2O8 in Escherichia Coli meningitis. CN110613710.
- Yuhua C, Xiaoqian X, Weidong Z (2020a) Application of micromolecule compound C29H28CL2N6O to Coli bacillus meningitis. CN110787168.
- Yuhua C, Xiaoqian X, Weidong Z (2020b) Application of Small-Molecule Compound C28H26C12N8 to Escherichia Coli induced meningitis. CN110787166.
- Yuhua C, Xiaoqian X, Weidong Z (2020c) Application of small-molecular compound C34H22FN3O5S2 in Escherichia Coli meningitis. CN110613711.
- Zhang J, Sun H, Gao C, Wang Y, Cheng X, Yang Y, Gou Q, Lei L, Chen Y, Wang X, Zou Q (2021) Development of a chitosan-modified PLGA nanoparticle vaccine for protection against Escherichia coli K1 caused meningitis in mice. *J Nanobiotechnology* 19(1):1–5
- Zueter AM, Zaiter A (2015) Infectious meningitis. *Clin Microbiol News* 37:43–51

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.