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Community-acquired bacterial meningitis

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Abstract | Meningitis is an inflammation of the meninges and subarachnoid space that can also involve the brain cortex and parenchyma. It can be acquired spontaneously in the community — community-acquired bacterial meningitis — or in the hospital as a complication of invasive procedures or head trauma (nosocomial bacterial meningitis). Despite advances in treatment and vaccinations, community-acquired bacterial meningitis remains one of the most important infectious diseases worldwide. *Streptococcus pneumoniae* and *Neisseria meningitidis* are the most common causative bacteria and are associated with high mortality and morbidity; vaccines targeting these organisms, which have designs similar to the successful vaccine that targets *Haemophilus influenzae* type b meningitis, are now being used in many routine vaccination programmes. Experimental and genetic association studies have increased our knowledge about the pathogenesis of bacterial meningitis. Early antibiotic treatment improves the outcome, but the growing emergence of drug resistance as well as shifts in the distribution of serotypes and groups are fuelling further development of new vaccines and treatment strategies. Corticosteroids were found to be beneficial in high-income countries depending on the bacterial species. Further improvements in the outcome are likely to come from dampening the host inflammatory response and implementing preventive measures, especially the development of new vaccines.

Meningitis is an inflammation of the meninges and subarachnoid space that can also involve the brain cortex and parenchyma owing to the close anatomical relationship between the cerebrospinal fluid (CSF) and the brain (FIG. 1). Per definition, bacterial meningitis is an infection of the CSF-filled subarachnoid space. Inflammation of the meninges and subarachnoid space leads to the classic triad of meningitis symptoms — headache, fever and neck stiffness — and to pleocytosis (an increased cell count, particularly of leukocytes) in the CSF[1]. Involvement of the brain cortex and parenchyma, because of either direct inflammation or vascular complications, might result in behavioural changes, focal neurological abnormalities and impairment of consciousness[1], which are typically considered symptoms of encephalitis. Acute meningitis can be caused by a wide variety of infectious agents, but can also be a manifestation of non-infectious diseases[2]. Bacterial meningitis is considered the most severe form of this disease; the routes of exposure are mainly respiratory, but can be enteric, as is the case in listerial infection. Meningitis can be acquired spontaneously in the community — community-acquired bacterial meningitis[2] — or in the hospital as a complication of invasive procedures or head trauma (nosocomial bacterial meningitis)[3].

Despite the existence of antibiotic therapies, acute bacterial meningitis causes substantial morbidity and mortality, both in high-income and low-income countries[4,5]. Bacterial meningitis is an emergency situation and individuals with suspected disease require immediate evaluation and treatment. In this Primer, we provide an overview of community-acquired bacterial meningitis, focusing on the epidemiology, disease mechanisms, diagnosis, screening, prevention and management.

Epidemiology

H. influenzae, S. pneumoniae *and* N. meningitidis

Bacterial meningitis is associated with high mortality and morbidity worldwide, with an estimated 16 million cases in 2013, causing 1.6 million years lived with disability each year[6]. Globally, the pathogens implicated in this disease vary somewhat and incidence varies widely between regions. Africa is the region with the highest meningitis disease burden; before the introduction of a vaccine (BOX 1), the estimated incidence of invasive disease due to *Haemophilus influenzae* type b (Hib) infection was 46 per 100,000 population per year among children <5 years of age and *Streptococcus pneumoniae* (pneumococcus) infection was 38 per 100,000 population

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per year; *Neisseria meningitidis* (meningococcus) infection was >1,000 per 100,000 per year among all ages during epidemics[4]. The overall rates of community-acquired bacterial meningitis caused by specific aetiologies in Africa remain unclear owing to a lack of diagnostic tools. Incidence rates of community-acquired bacterial meningitis in high-income areas (such as Europe, the United States and Australia) are 1–3 per 100,000 population per year[4]. In the Netherlands, the incidence of adult meningitis declined from 1.72 to 0.94 per 100,000 per year from 2007 to 2014; *S. pneumoniae* caused 72% of episodes[7]. Reported case fatality rates are high and vary with patient age, causative pathogen and country income[5,8]. Meningitis caused by *S. pneumoniae* has the highest case fatality rates: 20–37% in high-income countries and up to 51% in low-income countries[8]. Case fatality rates for meningococcal meningitis are distinctly lower, in the range of 3–10% worldwide[5,9].

The epidemiology of community-acquired bacterial meningitis is changing as prevention measures become increasingly used[4]. The most common causes of bacterial meningitis are *S. pneumoniae* and *N. meningitidis*, with varying prevalence depending on age group and region[8,10]. Pneumococcal meningitis is in general more common than meningococcal meningitis in children <5 years of age and in the elderly (≥65 years of age), whereas meningococcal meningitis is more frequent among older children, adolescents and young adults[11]. Pneumococcal conjugate vaccines, which are routinely used in most high-income countries and increasingly in developing countries, have reduced the rates of pneumococcal meningitis not only among vaccinated young children but also among age groups that are not targeted for vaccination through reduced transmission of invasive strains (herd protection)[7,12]. In the past, Hib caused the majority of bacterial meningitis in children <12 months of age and approximately 50% of all Hib meningitis cases occurred in children <5 years of age[13]. Now, most national immunization programmes for infants include a vaccine that provides coverage against Hib, rendering Hib-driven meningitis unusual in areas with high immunization coverage[4].

In Africa, epidemics of meningococcal disease occur in a well-defined region — the meningitis belt[4] (FIG. 2). This sub-Saharan area from Senegal to Ethiopia is prone to intermittent epidemics of meningococcal meningitis, with rates reaching nearly 1% of the population in the worst outbreaks[4]. Epidemics were usually caused by serogroup A *N. meningitidis*, but a vaccination programme, initiated in 2010, against this bacterium has reduced its incidence[14]. Epidemics caused by serogroup X (2006–2010), serogroup W (2010–2011) and serogroup C (2015) have also been reported[15–17].

Certain serotypes or serogroups of the leading pathogens that cause bacterial meningitis have been shown to have a higher ability to cause severe disease than others. Thirteen serogroups of meningococcus have been identified, although six account for the majority of disease (serogroups A–C and serogroups W–Y). Although at least 94 pneumococcal serotypes have been identified, the currently available 10-valent and 13-valent vaccine formulations cover the serotypes that cause ≥70% of cases in most areas of the world[18]. Serotype 2, a non-vaccine serotype, recently emerged as a common cause of pneumococcal meningitis among children in Bangladesh[19]. Pneumococcal meningitis typically does not occur in outbreaks, although periods of hyper-endemicity (that is, of high and continuous incidence) caused by serotype 1 pneumococcus have been observed in Burkina Faso and Ghana, with high case fatality rates of >40%[20].

Other pathogens

Among other aetiologies are group B streptococcus[21], a leading cause of meningitis in infants <3 months of age, and *Listeria monocytogenes*[22], which is most commonly seen in infants[8]. For group B streptococcus, serotype III is the most likely serotype to cause meningitis in infants[23]; a nationwide surveillance study in the Netherlands showed the emergence of a serotype III group B streptococcus with a genotype belonging to clonal complex 17 (REF. 21). Aerobic Gram-negative (for example, *Escherichia coli*) meningitis occurs especially in neonates, the elderly and debilitated or diabetic people[8,24].

In pig-farming countries in Asia, *Streptococcus suis* (group R haemolytic streptococcus) is the most common cause of meningitis[25]. Large case series of *S. suis* serotype 2 meningitis (and rarely infective endocarditis and septicaemia) were reported in Hong Kong, Thailand, China and Vietnam[25]. The precise epidemiology remains unclear, but *S. suis* infection is correlated with occupational contact with pigs or pork. Splenectomized patients are particularly susceptible to infection by capsulated Gram-positive organisms, such as *S. suis*[26]. Although rarely fatal, this strain is commonly associated with bilateral permanent deafness.

Risk factors

In addition to age, other factors have been linked to community-acquired bacterial meningitis risk. Immunocompromised individuals are at increased risk for meningitis caused by *S. pneumoniae* and *L. monocytogenes*[8,27]. T cell deficiencies, such as those caused by HIV infection, increase the risk of bacterial meningitis by approximately eightfold, despite the widespread use of combined antiretroviral therapy[28]. Genetic risk

factors (for example, deficiencies in complement components and asplenia)[29] and social and behavioural factors (for example, smoking)[30] have been associated with increased risk of meningococcal meningitis. Outbreaks of meningococcal meningitis have occurred among college students, participants in the annual Muslim pilgrimage of Hajj and recently in the United States among men who have sex with men[31]. Certain ethnic groups have been shown to have higher rates of bacterial meningitis; for example, American Indian and Alaska Native children have higher Hib meningitis rates than the general US population[32]. All leading aetiologies are spread by human-to-human transmission, except for *L. monocytogenes*[22,33], which is food-borne[8].

Mechanisms/pathophysiology

Bacteria can reach the subarachnoid space through the bloodstream or through the spread of infections from contiguous sites, such as the paranasal sinuses or mastoid of the inner ear. Blood-borne pathogen invasion is assumed to be the main route of subarachnoid space entry; this multistep process involves mucosal colonization followed by invasion, survival and replication of the bacteria in the bloodstream and eventual traversal of the blood–brain barrier.
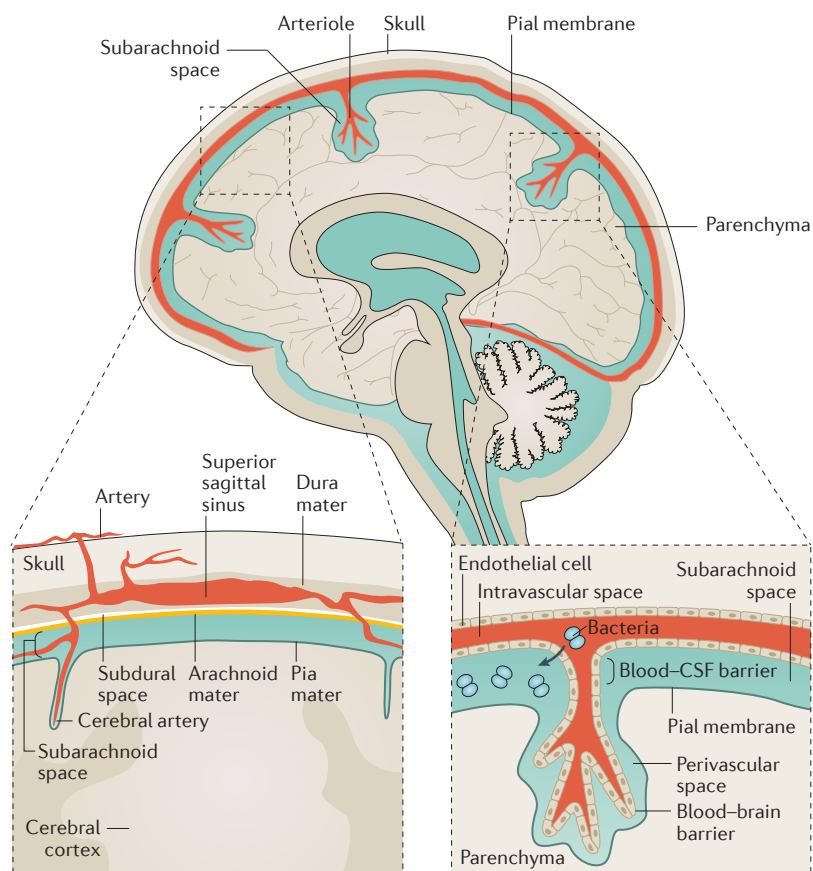
Figure 1 | **Anatomical considerations for the diagnosis of bacterial meningitis.** Mid-sagittal view of the brain showing the meninges: the dura mater, the subarachnoid mater and the pia mater. The meninges and cerebrospinal fluid (CSF) are in close anatomical relation with the cerebral cortex and brain parenchyma. Bacteria can reach the meninges through the blood–CSF barrier.

Colonization of the host by the pathogen

Pathogens such as *S. pneumoniae*, *N. meningitidis*, group B streptococci and *E. coli* initially colonize epithelial surfaces either in the respiratory tract (*S. pneumoniae* and *N. meningitidis*) or in the gastrointestinal or lower genital tract (group B streptococci and *E. coli*) before advancing to the bloodstream. The molecular and cellular events underlying colonization and epithelial invasion have been reviewed in detail elsewhere[34–37]. The exact mechanisms why bacterial bloodstream infections occur in some individuals but not in others are unclear, but seem to depend on a complex interplay between environmental factors (for example, prior influenza virus infection, smoking or alcohol abuse) and genetic factors of the host and pathogen[29,34]. Host factors that confer susceptibility to invasive infection by meningeal pathogens include congenital asplenia, complement deficiency, immunosuppressive treatment and antibody deficiency[38] (TABLE 1). Furthermore, other genetic variations have recently been linked to predisposition to pneumococcal disease (for example, single-nucleotide polymorphisms (SNPs) in *NFKBIA* (which encodes nuclear factor-κB (NF-κB) inhibitor-α (IκBα)), or deficiencies in IL-1 receptor-associated kinase 4 (IRAK4) as well as myeloid differentiation primary response protein 88 (MYD88)) and meningococcal disease (for example, SNPs in pattern recognition receptor (PRR) genes, such as Toll-like receptor 9 (*TLR9*))[29,39–41].

Regarding the pathogens, multilocus sequence typing of *N. meningitidis* has demonstrated that strains associated with asymptomatic carriage are highly genetically diverse, as the bacterial genome undergoes horizontal gene exchange and recombinant events while the bacteria colonize the nasopharynx, whereas only a limited number of genotypes, known as hyperinvasive lineages, are linked with invasive disease[11,42]. To some extent, the same is true for *S. pneumoniae*[43], group B streptococci[44] and *E. coli*[45]. The 94 capsular serotypes of *S. pneumoniae* have been shown to differ greatly in nasopharyngeal carriage rate, disease incidence and severity; serotypes 3, 6A, 6B, 9N and 19F seem to be associated with an increased risk for fatal disease[43]. Using complementary approaches comprising serotyping, multilocus sequence typing, cell culture and animal experiments, a serotype III, ST-17 group B streptococcal clone has recently been shown to be hypervirulent, accounting for the majority of neonatal group B streptococcal infections in the Netherlands[44]. Given the many *E. coli* serotypes (>80 serologically unique capsular (K) antigens), it is striking that K1 *E. coli* strains possessing K1 are predominant (approximately 80%) among isolates from neonates with *E. coli* meningitis[45].

Survival within the bloodstream

Once the bacteria reach the bloodstream, they have to withstand the bactericidal environment of the blood. The polysaccharide capsules of *N. meningitidis*, *S. pneumoniae*, *H. influenzae*, group B streptococci and *E. coli* are anti-phagocytic and act as inert shields, inhibiting surface deposition of opsonins, especially complement factors[46,47] (FIG. 3). Meningococcal capsular polysaccharides can also

attenuate surface deposition of the complement component C4-binding protein (C4bp), thereby limiting complement-mediated direct bacterial killing[48]. In addition to the capsule, an array of bacterial surface molecules target specific complement components to reduce complement-mediated bacterial clearance[49] (FIG. 3). *N. meningitidis* can directly bind to factor H (fH), which is the main regulator of alternative complement activation, through surface molecules, including fH-binding protein (fHbp), neisserial surface protein A (NspA) and porin B[38,50]. The increase in the environmental temperature that occurs as the bacteria change habitat from the nasopharynx to the bloodstream has been identified as a 'danger signal' for *N. meningitidis*, which prompts an upregulation of capsular biosynthesis and fHbp expression, thus enhancing its capacity to withstand complement attack[51]. Similarly, *S. pneumoniae* has many surface proteins that interact with and deplete complement, as well as inhibit the complement cascade (FIG. 3).

Outer membrane protein A (OmpA), a major surface protein in *E. coli*, confers resistance against the serum bactericidal activity by binding to C4bp, which is an endogenous inhibitor of the classical and lectin pathways[52]. The group B streptococcal capsular polysaccharide contains a terminal α2,3-linked *N*-acetylneuraminic acid, which is identical to the most common sialic acid of many surface glycans of human cells (an example of molecular mimicry). The presence of sialic acid on human cell surfaces is essential for complement regulator fH-mediated protection against self-attack by complement. Thus, by displaying sialic acid on its own surface, the group B streptococcus impairs surface deposition of opsonin-activated C3 and protects itself from clearance[53]. In addition, sialylated capsular polysaccharides of group B streptococci can engage inhibitory receptors, such as sialic acid-recognizing immunoglobulin superfamily lectin 9 (Siglec9) on host leukocytes, thereby downregulating their immune responsiveness[54]. Similar to *E. coli*, group B streptococci also have evolved mechanisms that facilitate survival within phagocytic cells. For instance, the same operon containing the gene (*cylE*) that encodes the β-haemolysin cytotoxin has been linked to the production of a carotenoid pigment that can detoxify reactive oxygen species, shielding the bacteria against several antimicrobial weapons of leukocytes.

Finally, besides coping with host defence mechanisms, to survive in the bloodstream, microbial invaders have to exploit the host iron pool. Iron is essential for bacterial physiological processes, such as DNA replication, transcription, metabolism and energy generation[55]. Hence, bacteria have developed diverse iron uptake mechanisms, including surface-associated haem uptake pathways and high-affinity iron-scavenging siderophores[55].

Entry into the central nervous system

Prolonged high levels of bacteraemia are shown to favour bacterial penetration into the subarachnoid space for *S. pneumoniae*, group B streptococci and *E. coli* in humans and experimental animals, presumably by directly increasing the likelihood that bacteria interact with the endothelial cells of the blood–CSF barrier[38]. Post-capillary venules and veins within the subarachnoid and perivascular spaces might be the primary bacterial entry sites. Evidence in support of this assumption includes the fact that bacteria were found post-mortem in the arachnoid mater and pia mater of patients and laboratory animals with meningococcal or pneumococcal meningitis[56,57]. In addition, post-capillary venules and veins belong to the 'leaky' part of the vascular tree of the brain and are in close proximity to the CSF[58]. Finally, the shear stress in these vessels, defined as the tangential force exerted on the vascular wall by a moving fluid, is lower than in capillaries or arterioles[59]. Low shear stress has been determined to be paramount for the intimate contact between *N. meningitidis* and the host endothelial cells[60].

S. pneumoniae and N. meningitidis. The initial adhesion step seems to be mediated by the binding of bacterial adhesins, such as the outer membrane protein porin A for *N. meningitidis* and the pneumococcal surface protein PspA for *S. pneumoniae*, to the laminin receptors expressed on brain endothelial cells[61]. The adhesion process is described in FIG. 3 and involves several factors, including the platelet-activating factor receptor (PAFR) on the endothelial cell surfaces, ultimately facilitating transcellular (involving receptor-mediated mechanisms) passage of *S. pneumoniae* and paracellular (following barrier disruption) passage of *N. meningitidis* through the blood–brain barrier. This process in *N. meningitidis* includes the pilus components PilE and PilV, which mediate bacterial adhesion by interacting with the immunoglobulin superfamily member CD147 on the host endothelial cells[62]. Following primary adhesion, the meningococcal type IV pilus mediates the recruitment and activation of the β2-adrenoceptor, triggering the organization of specific molecular complexes named cortical plaques in the corresponding underlying cytoplasm[63]. Plaque formation is accompanied by the local stimulation of actin polymerization, resulting in the formation of membrane protrusions that protect bacterial colonies from the complement-mediated lysis and opsonophagocytosis in the blood. Cortical plaques also stimulate the opening of the inter-endothelial junctions, which allows *N. meningitidis* to migrate to the CSF by slipping through adjacent cells (a paracellular route)[64].

Box 1 | The conjugate vaccine against Hib: a success story

In meningitis, prevention is crucial, as death or long-term disabling consequences are substantial in all settings, particularly in contexts in which patients have limited access to health care. The introduction of a routine *Haemophilus influenzae* type b (Hib) conjugate vaccine programme has resulted in a rapid and substantial decline in the incidence of Hib infection in the susceptible childhood population. Hib vaccination has been highly successful because one capsular serotype (Hib) is responsible for the majority of disease and the infection mainly affects children <5 years of age. Hib vaccines have been demonstrated to be very effective and devoid of severe adverse effects, and are now routinely used in childhood vaccination programmes in 192 countries[4]. Furthermore, trials introducing Hib vaccination in developing countries (for example, Chile, Uruguay and the Gambia), where meningitis rates are the highest, have yielded promising results. Thus, the widespread introduction of conjugate vaccines is having major beneficial effects on the global disease burden of bacterial meningitis.
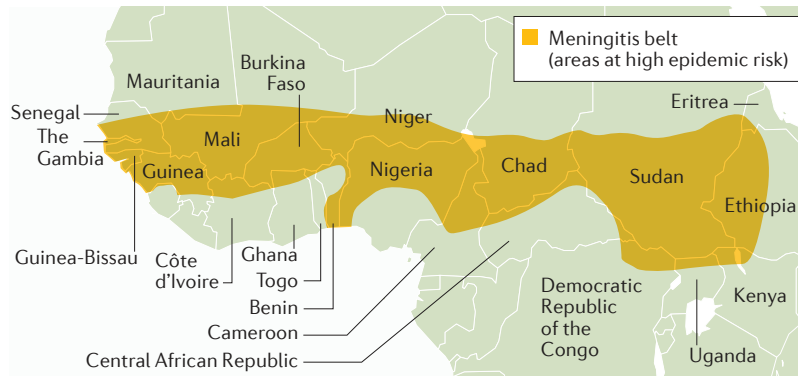
Figure 2 | The meningitis belt. The meningitis belt is a sub-Saharan African region that has experienced recurring large epidemics of meningococcal meningitis for over a century. Areas at high epidemic risk are marked in orange. The disease incidence and outbreak history in Niger, a typical meningitis belt country, have been extensively studied[180]. For example, the climate in Niger is dry, with an average yearly rainfall of 300 mm and a wintry warm, dry and dusty wind (the Harmattan). Outbreaks typically begin at the onset of the dry season in January and end abruptly at the start of the rainy season in May or June[180,200]. This distinct seasonality is striking and might be correlated with numerous factors, including the drying effect of the weather on mucous membranes and the seasonal transmission of respiratory viruses, although this has not been shown definitively[200]. Adapted from REF. 201, which was produced using data from the WHO (http://www.cdc.gov/travel-static/yellowbook/2016/map_3-11.pdf).

Other pathogens. *E. coli* K1 binding to and invasion of the brain endothelium is thought to involve several bacterial proteins, including the type 1 fimbrial adhesion protein FimH, cytotoxic necrotizing factor 1 (CNF1), invasion of brain endothelial cell proteins (Ibe) and OmpA. FimH (presumably via interacting with endothelial CD48) and CNF1 (via co-opting the 37/67 kDa laminin receptor) can induce cytoskeletal rearrangements through the activation of the GTPase RHOA, ultimately leading to bacterial invasion. In addition, binding of IbeA and OmpA to their respective putative receptors, vimentin or polypyrimidine tract-binding protein (PTB)-associated splicing factor (PSF; also known as SFPQ) and Ecgp96 (a β-form of the heat shock protein gp96 that is expressed on human brain-derived endothelial cells), can trigger the activation of RAC1, another member of the RHO GTPase family, thereby contributing to cytoskeletal rearrangements and bacterial internalization[47,65,66]. Ecgp96 also forms complexes with TLR2 and type 1 angiotensin II receptor (AT1AR)[67,68]. This interaction can activate protein kinase Cα (PKCα), which in turn can associate with vascular endothelial (VE)-cadherin at the endothelial tight junctions. This interaction promotes the dissociation of β-catenin from the endothelial tight junctions, which increases endothelial permeability. Thus, *E. coli* seems to be capable of invading the central nervous system (CNS) via the blood–brain barrier by both transcellular and paracellular pathways.

Group B streptococci possess many virulence factors that can promote bacterial interaction with the brain endothelium, including lipoteichoic acid, β-haemolysin, serine-rich repeat proteins and hypervirulent group B streptococcus adhesin laminin-binding protein (LMB), bacterial surface adhesin of group B streptococcus (BsaB), streptococcal fibronectin-binding protein A (SfbA)

and the pilus tip protein PilA. LMB, BsaB and SfbA function by associating with extracellular matrix components, such as fibronectin[44,47,69], whereas PilA can bind to collagen, which promotes its interaction with endothelial α2β1-integrins. This interaction leads to the activation of focal adhesion kinase and a subsequent intracellular signalling pathway that, among other effects, can result in phosphoinositide 3-kinase-dependent actin rearrangement and bacterial uptake[70]. Moreover, group B streptococci can induce the expression of the host transcriptional repressor Snail1, which impedes the expression of tight junction genes. This process involves bacterial cell wall components and extracellular signal-regulated kinase 1 and 2 (ERK1/2)–mitogen-activated protein kinase (MAPK)-dependent signalling and can cause disruption of the blood–brain barrier, facilitating the paracellular passage of group B streptococci into the CNS[71].

Immune activation in bacterial meningitis
Once the pathogens reach the CSF, they are likely to survive because host defences in the subarachnoid space seem to be ineffective against encapsulated bacteria[72]. This immune deficit might be owing to the virtual absence of soluble PRRs, such as complement proteins, which bind to the surface of pathogens and mark them for phagocytosis. Moreover, complement deposition can cause lysis of susceptible bacterial species, namely, *Neisseria* spp., through membrane attack complex (MAC) formation. However, in normal CSF, complement levels are too low (100–1,000-fold lower than in blood) to exert substantial antibacterial activity. Blood complement proteins are prevented from entering the CSF by the blood–brain barrier, which acts like a molecular sieve to restrict the passage of large molecules and immunocompetent cells[73]. Even in the presence of high levels of inflammation (as in bacterial meningitis), which abnormally increases the permeability of the blood–brain barrier, complement levels remain substantially below those in the blood. As a consequence, when pathogens succeed in invading the CSF, they can grow efficiently and achieve a high population density within hours[38].

PRRs. With increased bacterial density, the pathogens begin to die in response to various stress conditions, such as nutrient deprivation and antibiotic treatment[74]. As a result, bacterial fragments can accumulate within the CSF. Their interaction with surface-bound or intracellular PRRs that are expressed by immunocompetent cells can trigger the host immune response (FIG. 4). Unlike in the brain parenchyma, functionally active macrophages, dendritic cells and mast cells are present in sufficient numbers in tissues lining the CSF. Each of these cell types is a potential sentinel of bacterial invasion. However, animal studies addressing this topic are scarce. In a rat model of pneumococcal meningitis, depletion of meningeal and perivascular macrophages was associated with increased bacterial titres and decreased leukocyte counts in the CSF[75]. In a rabbit model, macrophage depletion was ineffective in dampening meningeal

Table 1 | **Genes identified from association studies on the susceptibility for invasive bacterial diseases**

Study	n (controls)	Gene (SNP)	System	Odds ratio (95% CI)
Meningococcal disease				
Owen et al.[218]	140 (–)	C5 (rs112959008, rs121909587 and rs12109588)	Complement	NA
Davila et al.[219]	1,442 (6,079)	• CFH (rs1065489) • CFHR3 (rs426736)	• Complement • Complement	• 0.64 (0.56–0.73) • 0.63 (0.55–0.71)
Biebl et al.[220]	248 (835)	• CFH (rs1065489) • CFHR3 (rs426736)	• Complement • Complement	• 0.60 (0.44–0.82) • 0.61 (0.45–0.83)
Lundbo et al.[221]	608 (673)	MBL2 (rs5030737, rs1800450 and rs1800451)	Complement	0.75 (0.56–1.01)
Bacterial meningitis				
Vardar et al.[222]	31 (50)	MBL2 (rs5030737, rs1800450 and rs1800451)	Innate immunity	9.89 (2.50–39.0)
Dunstan et al.[223]	390 (751)	LTA4H (rs17525495)	Arachidonic acid metabolism	1.27 (1.05–1.54)
Adriani et al.[224]	439 (302)	ADRB2 (rs1042714)	Adrenoreception	1.35 (1.04–1.76)
Adriani et al.[225]	439 (302)	C3 (rs1047286)	Complement	4.50 (1.62–12.50)
Sanders et al.[226]	464 (392)	TLR9 (rs352140)	Innate immunity	0.6 (0.4–0.9)
Pneumococcal meningitis				
Brouwer et al.[227]	299 (216)	MBL2 (rs5030737, rs1800450 and rs1800451)	Complement	8.21 (1.05–64.1)
Lundbo et al.[221]	370 (1,263)	MBL2 (rs5030737, rs1800450 and rs1800451)	Complement	0.87 (0.70–1.28)
Lundbo et al.[228]	372 (1,273)	NFKBIE (rs522948)	Innate immunity	1.38 (1.20–2.36)
Meningococcal and pneumococcal meningitis				
Sanders et al.[229]	473 (1,141)	• TLR4 (rs4986790) • NOD2 (rs2066844)	• Innate immunity • Innate immunity	• 9.4 (3.0–29.2) • 12.2 (2.6–57.8)

NA, not available; SNP, single-nucleotide polymorphism.

inflammation and neuronal injury, which questions the role of these cells as major initiators of inflammation in bacterial meningitis[76]. Cells of the arachnoid mater and pia mater are also capable of producing and releasing a vast variety of pro-inflammatory factors upon exposure to *N. meningitidis*, *S. pneumoniae* and *E. coli* K1 (REF. 77), and might therefore detect pathogens within the CSF.

For *N. meningitidis*, our understanding of the inflammatory process within the subarachnoid space has been largely limited by its human host specificity, hampering the ability to reproduce the infection in animals[64]. By contrast, well-characterized animal models of *S. pneumoniae*, group B streptococci and *E. coli* meningitis are available that closely recapitulate human disease[74]. With respect to *S. pneumoniae,* the seminal studies involved the injection of pneumococcal cell wall components into the CSF of laboratory animals to provoke clinical signs of meningitis[78,79]. Indeed, high pneumococcal cell wall concentrations have been associated with functional clinical outcomes, as determined by the Glasgow Outcome Scale, in patients with pneumococcal meningitis[80]. In the past 15 years, a handful of PRRs have been identified that can detect *S. pneumoniae* within the CSF[38]. These include surface-bound TLRs and cytosolic nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), which function as sensors for cytoplasmic pathogen-associated molecular patterns (PAMPs; FIG. 4). NLRs are likely to be required to achieve maximum inflammation against *S. pneumoniae*, as NOD2-deficient mice exhibited substantially lower levels of inflammatory mediators

in the brain than wild-type mice following intracerebral *S. pneumoniae* administration[38,81]. Accordingly, *S. pneumoniae*-induced inflammation activation *in vitro* depends on the presence of NOD2 (but not NOD1)[82].

Another potential sensor of pneumococcal infection of the subarachnoid space is NOD-, LRR- and pyrin domain-containing 3 (NLRP3). In cell culture experiments, NLRP3 activation was induced through pore-building bacterial toxins, such as pneumolysin (Ply)[83,84]. In a mouse meningitis model, NLRP3 deficiency was associated with a markedly diminished immune response to pneumococcal infection, and NLRP3-dependent secretion of IL-1β into the CSF was substantially lower following infection with Ply-deficient rather than with Ply-producing pneumococci[85]. Moreover, in patients with bacterial meningitis, the levels of IL-1β and IL-18 in the CSF are related to complications and unfavourable disease outcomes[86].

Activation of the complement cascade. The activation of TLRs and NLRs leads to the activation of inflammatory transcription factors, in particular, NF-κB. In turn, complement proteins are among the most crucial inflammatory mediators that are produced upon NF-κB activation, particularly in pneumococcal meningitis. The complement system consists of >30 regulators and receptors and serves two main functions: to kill bacteria, either directly via MAC formation or by labelling them for phagocytosis (for example, C1q or C3b), and to enhance the inflammatory response via

the release of anaphylatoxins (for example, C3a or C5a) or the terminal complement complex (soluble C5b-9)[87].

Analyses of CSF samples collected from patients with pneumococcal meningitis showed that C5a and C5b-9 concentrations were markedly increased during the acute stage of the disease and correlated positively with CSF leukocyte counts and disease severity[88,89].

Similarly, in a rabbit model of pneumococcal meningitis, C5-derived chemotactic activity largely accounted for the accumulation of neutrophils in the CSF[90]. In a mouse model of pneumococcal meningitis, C5a deficiency was associated with a drastic reduction in CSF pleocytosis and brain cytokine production[88]. Moreover, treatment of infected, wild-type (that is, complement
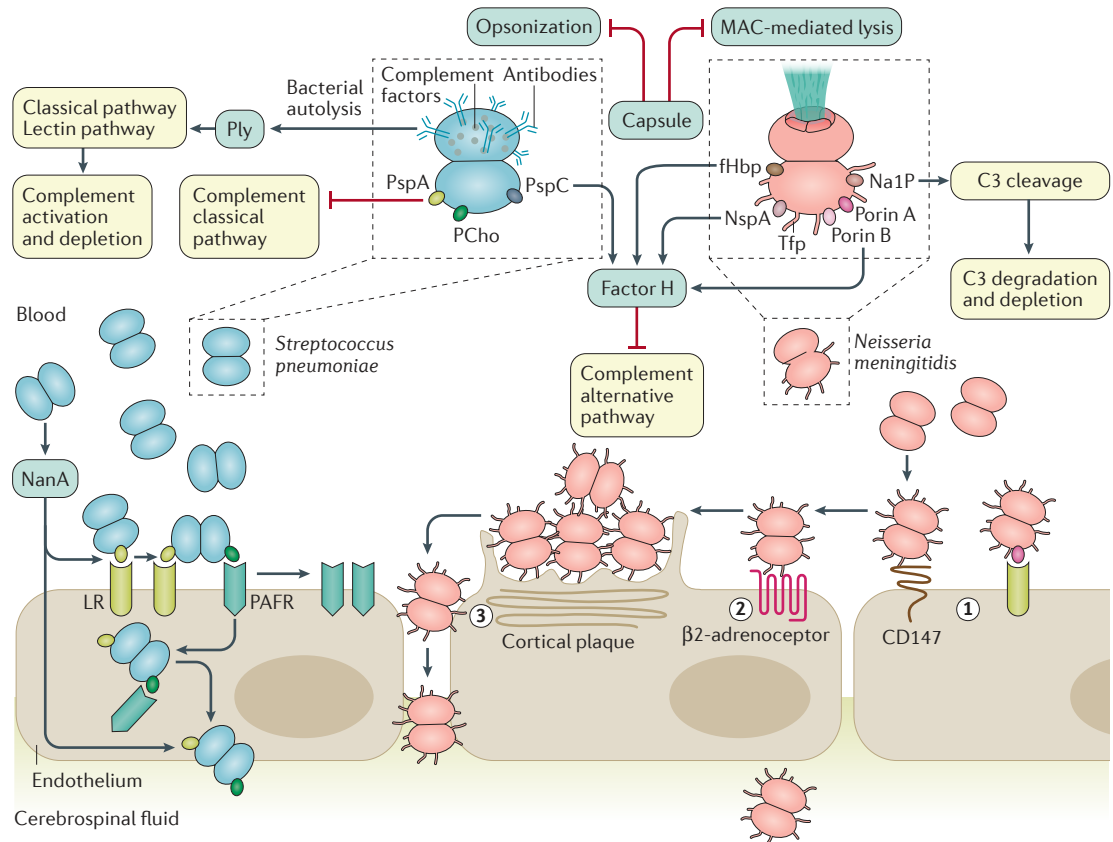

Figure 3 | **Microbial survival in the bloodstream and central nervous system invasion.** After initiation of bacteraemia, the pathogens must evade opsonophagocytosis and/or membrane attack complex (MAC)-induced lysis. Microbial factors that are involved in the inhibition of complement activation and bacterial killing include the polysaccharide capsule, the pneumococcal surface proteins PspA and PspC and the toxin pneumolysin (Ply) of *Streptococcus pneumoniae*. For *Neisseria meningitidis*, the polysaccharide capsule, the outer membrane proteins factor H-binding protein (fHbp), neisserial surface protein A (NspA) and porin B as well as the autotransporter Na1P are essential factors for host avoidance. Ply, which is released during bacterial autolysis, can activate the classical (via direct binding to nonspecific IgM or IgG3) and lectin (via interaction with L-ficolin) complement pathways, thereby diverting complement away from the bacterial surface[202] and leading to complement depletion within the pneumococcal environment. By contrast, PspA can reduce C-reactive protein-mediated, complement factor C1q-dependent classical pathway of complement activation[203]. fHbp, NspA and porin B of *N. meningitidis*[38,50] and PspC of *S. pneumoniae* can interact with factor H, interfering with the alternative pathway of complement activation. In addition, Na1P cleaves human complement C3, which facilitates C3b degradation and depletion. Bacterial invasion of the cerebrospinal fluid (CSF) requires pathogen adhesion to the endothelial surface. The initial adhesion step is mediated by the binding of bacterial adhesins (PspA for *S. pneumoniae* and type IV pili (Tfp) and porin A for *N. meningitidis*) to the laminin receptor (LR)[61]. In the case of *S. pneumoniae*, bacterial neuraminidase A (NanA) can also promote adherence and invasion through its laminin G-like lectin domain[204]. Binding of *S. pneumoniae* to the vascular wall seems to activate the underlying endothelial cells, specifically increasing the amount of platelet-activating factor receptor (PAFR) on the endothelial surface[205]. PAFR then binds to its proposed binding partner phosphorylcholine (PCho), which is displayed on the surface of *S. pneumoniae*, and internalizes the pneumococcus, enabling it to cross the endothelium intracellularly and move from the bloodstream into the CSF. PAFR activation has also been proposed to cause an upregulation of the polyimmunoglobulin receptor and CD31 on endothelial cells; the two receptors jointly facilitate the crossing of *S. pneumoniae* across the blood–CSF barrier (not shown)[206]. In addition to LR, the immunoglobulin superfamily member CD147 is a crucial host receptor for the primary attachment of *N. meningitidis*. Following primary adhesion (step 1), Tfp mediates the recruitment and activation of the β2-adrenoceptor (step 2), finally leading to the organization of the so-called cortical plaques (step 3), which ultimately results in the opening of the inter-endothelial junctions and paracellular transmigration of *N. meningitidis*.

sufficient) mice with anti-C5 antibodies and an antibiotic 24 hours after infection was protective against meningitis-induced brain damage, presumably through its anti-inflammatory action[88]. Combined treatment with anti-C5 antibodies and dexamethasone has been reported to improve survival in severe experimental pneumococcal meningitis[91].

Of note, the effect of anti-C5 antibodies in bacterial meningitis other than pneumococcal meningitis is unclear and needs to be carefully evaluated before considering their use in patients. For example, treatment of

patients with paroxysmal nocturnal haemoglobinuria or atypical haemolytic uraemic syndrome with an anti-C5 antibody (eculizumab) was associated with an increased risk for fungal and bacterial infections, primarily meningococcal infections[92]. Thus, an alternative approach might be to use anti-C5a antagonists that are more selective than eculizumab, which have been shown to inhibit the potentially harmful effects of *N. meningitidis*-induced C5a formation while preserving complement-mediated meningococcal killing via MAC[93].
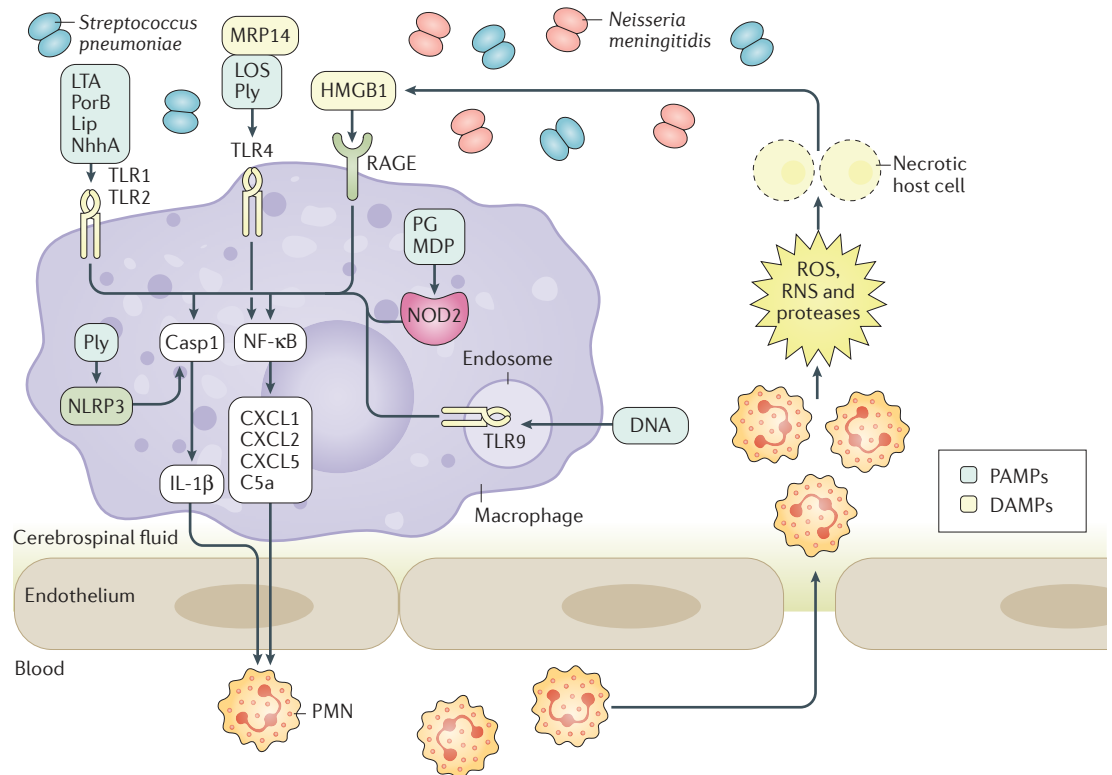
Figure 4 | **Host–pathogen interactions and immune activation in bacterial meningitis.** *Streptococcus pneumoniae* pathogen-associated molecular patterns (PAMPs) can activate immune cells within the cerebrospinal fluid (CSF) through membrane-bound Toll-like receptor 1/2 heterodimers (TLR1/2), TLR4 and TLR9, as well as cytosolic nucleotide-binding oligomerization domain (NOD)-like receptors, NOD2, NOD-, LRR and pyrin domain-containing 3 (NLRP3) and other yet unidentified pattern recognition receptors (PRRs). Pneumococcal lipoteichoid acid (LTA), pneumolysin (Ply) and DNA are recognized by TLR1/2 (REFS 207,208), TLR4 (REF. 209) and TRL9, respectively, whereas internalized peptidoglycan (PG) and muramyl dipeptide (MDP) are recognized by NOD2. PG might also be sensed by TLR1/2, although this has not been definitively shown; similarly, the detection of Ply by TLR4 is also under debate[83]. Notably, TLR9, which is localized within endosomes, has only been shown to recognize *S. pneumoniae* DNA *in vitro*[210]. However, experiments in mice carrying a single point mutation in *UNC93B1*, which encodes a multi-pass transmembrane protein required for several TLRs[211,212], have suggested that one or more of these receptors have a key role in pneumococcal sensing within the CSF (U.K., unpublished observations). Meningococcal porin B (PorB), Lip antigen and *Neisseria* hia/hsf homologue (NhhA) are recognized by TLR1/2, lipooligosaccharide (LOS) by TLR4 and DNA by TLR9. These interactions result in the activation of the enzyme caspase 1 (Casp1), which catalyses the conversion of the pro-form of IL-1 family cytokines into the active molecule, and of transcription factors, such as nuclear factor-κB (NF-κB), which in turn regulates the production of diverse pro-inflammatory factors (including neutrophil chemokines CXC-chemokine ligand 1 (CXCL1), CXCL2 and CXCL5 and the anaphylatoxin C5a). Indeed, long-lasting NF-κB activation is detectable in the brains of infected mice, especially in areas of heavy inflammation and along penetrating cortical vessels. Moreover, pharmacological blockade of NF-κB markedly attenuated pneumococci-induced inflammation in a rat model[213,214]. Consequently, large numbers of polymorphonuclear leukocytes (PMNs) are recruited. These infiltrating cells can release numerous cytotoxic products, including reactive oxygen species (ROS) or reactive nitrogen species (RNS) that can cause necrotic cell death. Damaged bacterial cells can release alarm signals (so-called damage-associated molecular patterns (DAMPs)), including myeloid-related protein 14 (MRP14) and high-mobility group box 1 (HMGB1), which can fuel inflammation by interacting with PRRs, such as TLR4 and receptor for advanced glycation end products (RAGE).

Brain injury

Histopathological studies document a wide range of brain injuries associated with bacterial meningitis in humans, including brain oedema formation, hydrocephalus, petechial haemorrhages, necrotic lesions in cortical and subcortical structures and loss of myelinated fibres in the white matter[94,95]. In addition, a recent autopsy study uncovered mild-to-moderate hippocampal apoptosis in 26 out of 37 (70%) cases[96]. By contrast, no significant differences in the number of apoptotic cells in the hippocampus were detected between patients with meningitis and control patients in a more recent study[94]. In animal models of the disease, the occurrence and degree of neuronal apoptosis depend on multiple factors, such as the age, strain and species of the animal used as well as the causative pathogen[97–99].

The mechanisms underlying hippocampal apoptosis are not fully identified; in experimental bacterial meningitis, apoptotic cell death is thought to occur through caspase-dependent or mitochondrial cytochrome c-induced, apoptosis-inducing factor-dependent signalling events, depending on the time after infection and the causative pathogen[95,100]. Thus, treatment with caspase inhibitors might rescue only a fraction of the stressed hippocampal neurons. Of note, broad-spectrum caspase inhibitors, such as z-VAD-fmk, can also dampen inflammation by blocking the production of IL-1β and IL-18. Neutrophilic inflammation is a well-established contributor to meningitis-related tissue injury[38]. Neutrophils are armed with a collection of chemical weapons, such as oxidants and proteases. Their release cannot only be harmful to the pathogen but also to the host itself[38]. Besides neutrophils, microglial cells and astrocytes are a potential source of cytotoxic factors. In mouse astrocytes, Ply can initiate the release of the excitotoxic amino acid glutamate[101]. Similarly, mouse microglial cells can release toxic nitrogen species as well as pro-inflammatory cytokines upon exposure to Ply[38]. However, there is still no direct in vivo evidence (for example, no studies using microglia depletion models) to support the involvement of these cell types in brain pathology due to meningitis.

In this context, in post-mortem studies, S. pneumoniae has been detected in the subarachnoid, perivascular and ventricular spaces, but generally not (except in the rare case of abscess formation) within the brain parenchyma[102]. Moreover, leukocyte infiltration into the brain parenchyma has only been observed during late infection and in the direct vicinity of the fluid-filled spaces[94]. This distribution pattern argues against a dominant role of direct bacterial-derived and host-derived toxin-induced cytotoxicity in meningitis-related brain damage. Instead, brain damage is likely to be mediated to a greater extent by pathological changes in the vasculature[103]. The predominant findings in patients are vasculitis (an arterial narrowing due to severe inflammation of the vessel wall) and/or vasospasm, causing cerebral hypoperfusion and ischaemia[104,105]. Cerebral infarction can also occur as a result of thrombosis, embolization or a combination of both[106,107].

Diagnosis, screening and prevention
Clinical presentation

Bacterial meningitis is a medical emergency: early recognition and immediate treatment are essential[108]. Neonates with bacterial meningitis often present with nonspecific signs and symptoms, such as poor feeding, irritability, hypertonia or hypotonia and respiratory distress[8]. Fever and seizures affect <40% and <35% of infected babies, respectively[109]. Patients with bacterial meningitis beyond the neonatal age commonly present with headache, photophobia, nausea and vomiting[110].

Patients with bacterial meningitis often show signs of coexisting systemic compromise (that is, meningococcal or pneumococcal sepsis)[1], which is associated with poor disease outcome. Furthermore, one systematic assessment of the development of early symptoms in children and adolescents with meningococcal disease (including sepsis) in the United Kingdom showed that rash, impaired consciousness and the other typical meningitis signs develop late in the pre-hospital illness, if at all, implicating that physicians should be aware that early recognition of bacterial meningitis can be difficult[111].

A prospective nationwide study of 1,268 adults with community-acquired bacterial meningitis in the Netherlands showed that classic features of meningitis, such as headache (83% of patients), neck stiffness (74%), fever (≥38 °C; 74%) and impairment of consciousness (defined as a score of <14 on the Glasgow Coma Scale; 71%), were present in a high proportion of patients[7]. However, the 'classic triad' signs (neck stiffness, fever and altered mental status) were reported in only 41% of patients[1]. Other possible symptoms include focal neurological deficits, such as aphasia and hemiparesis, seizures or cranial nerve palsies[7]. Petechial skin rash, which is usually considered the hallmark of meningococcal infection, can also be observed in pneumococcal meningitis[1].

Meningeal irritation manifests at physical examination as neck stiffness, the Kernig sign (painful knee extension after flexing the thigh with the hip and knee at 90° angles) and the Brudzinski sign (reactive hip and knee flexure when the neck is flexed)[108]. Neck stiffness is tested by passively flexing the neck, and if the manoeuver is painful and the chin cannot be brought to the chest. Notably, a prospective study of 297 adults in the United States showed that these signs do not accurately identify patients with meningitis, as they all showed poor sensitivity (5–30%) and high specificity (68–95%); meningitis was defined as >6 leukocytes per μl of CSF[112]. Doctors rely on multiple tests to diagnose meningitis, and the combination of test results and clinical characteristics indicates which further investigations will be appropriate.

Differential diagnosis

Bacterial meningitis is difficult to diagnose, as many illnesses share its symptoms. The differential diagnosis includes brain abscess[113], tuberculous meningitis, viral encephalitis or septic encephalopathy, as well as benign conditions such as aseptic (that is, non-bacterial) meningitis or sinus infection. Depending on the setting, malaria,

Table 2 | Characteristics assessed to diagnose bacterial, viral and tuberculous meningitis*

Characteristic	Normal	Bacterial meningitis	Viral meningitis	Tuberculous meningitis
C-reactive protein	<10 mg per l	40–400 mg per l	<10 mg per l	10–100 mg per l
Blood leukocytes	$4–10 \times 10^9$ per μl	$10–30 \times 10^9$ per μl	$4–10 \times 10^9$ per μl	$5–15 \times 10^9$ per μl
Opening pressure[‡]	6–20 cm H_2O	20–50 cm H_2O	6–30 cm H_2O	15–40 cm H_2O
CSF white cell count	<5 cells per μl	>1,000 cells per μl	10–1,000 cells per μl	10–1,000 cells per μl
CSF protein level	<0.60 g per l	>2 g per l	<0.60 g per l	1–4 g per l
CSF/blood glucose ratio	>0.60	<0.40	>0.60	<0.40

CSF, cerebrospinal fluid. *See REF. 230. ‡Defined as the pressure of the CSF on lumbar puncture.

arboviral infections, HIV-related and parasitic infections of the CNS and mumps should be considered. Most patients with suspected bacterial meningitis will eventually receive a different diagnosis. In the United Kingdom, in a prospective study of 388 children with suspected bacterial meningitis, only 3% were actually affected, whereas 62% had a non-CNS infection and 16% had a non-infectious condition[114]. Similar results were found in a Swiss study in patients of all ages[115].

Making the diagnosis
Several diagnostic algorithms have been developed to help predict the likelihood of bacterial meningitis[116,117]. Most of these algorithms aim to discriminate bacterial from aseptic (viral) meningitis in paediatric populations[118], and can be used in patients with suspected acute bacterial meningitis to determine whether a patient needs further diagnostic studies (for example, CSF analysis) or immediate therapy[117]. CSF examination is essential to confirm or rule out bacterial meningitis and to identify other non-bacterial CNS infections or inflammatory neurological diseases included in the differential diagnosis. Typical CSF and serum characteristics that are assessed in the diagnosis of bacterial, viral and tuberculous meningitis are provided in TABLE 2. However, the physician first needs to verify whether the lumbar puncture is safe for the patient. A space-occupying intracranial lesion or diffuse brain oedema, which both cause a substantial brain shift, results in an increased risk of cerebral herniation when a lumbar puncture is performed[108]. A history of CNS lesions, new-onset seizures, focal neurological deficits, an immunocompromised state (for example, HIV/AIDS infection or immunosuppressive medication after organ transplantation) or a moderate-to-severe impairment of consciousness have been identified as predictors of abnormalities on cranial CT[119]. Other contraindications for immediate lumbar puncture are coagulation disorders, septic shock and respiratory failure[2]. Thus, cranial imaging (by CT scan) might be indicated to rule out this possibility. However, because preliminary imaging delays treatment and can worsen outcomes, physicians must select who needs it and who can immediately and safely undergo lumbar puncture[2].

Classic abnormalities of the CSF in bacterial meningitis include pleocytosis (mainly of polymorphic leukocytes), low glucose concentration and increased protein levels[117], which are signs of a self-propelling inflammatory response in the subarachnoid space caused by the accelerating bacterial growth. These three parameters are individual predictors of bacterial meningitis[120], and at least one was present in 96% of 1,268 patients with community-acquired bacterial meningitis in a prospective cohort[7]. However, in neonates with bacterial meningitis, CSF examination often does not show an increased leukocyte count[121]. A measurement of CSF lactate concentration can be performed using a widely available, cheap and rapid diagnostic test that differentiates between bacterial and viral meningitis, although it has limited usefulness in patients who have been pre-treated with antibiotics before the lumbar puncture or with other CNS diseases in the differential diagnosis[117,121]. Thus, because CSF examination is not definitive, if bacterial meningitis is suspected, antimicrobial therapy should be started immediately and maintained until CSF culture results are negative[8].

The gold standard for the diagnosis of bacterial meningitis is CSF culture, which is positive in 50–90% of patients (although the yield is lower when CSF is collected once antibiotic treatment has started) depending on the causative pathogen[8]. The specific bacteria can be identified by blood cultures in 50–80% of cases, making blood cultures a valuable, readily available alternative diagnostic tool[8]. CSF Gram staining is also a well-validated and rapid method to detect bacteria in the CSF, with a reported yield of 70–90% and 30–90% for pneumococcal and meningococcal meningitis, respectively[8].

PCR on CSF has been increasingly used for the diagnosis of bacterial meningitis[117,122], with real-time PCR reported to have better sensitivity, through-put, speed and specificity than conventional PCR[123]. The reported sensitivity of conventional PCR was 79–100% and 91–100% for *S. pneumoniae* and *N. meningitidis*, respectively[8]. The specificity of a multiplex PCR approach simultaneously detecting *S. pneumoniae*, *N. meningitidis* and *H. influenzae* DNA was generally high (95–100% for all microorganisms)[124]. PCR was shown to have incremental value compared with CSF culture and Gram stain, as it can provide a diagnosis when conventional methods fail[125]. For example, PCR is especially useful in patients who started antibiotic treatment before the lumbar puncture, as in these individuals, CSF and blood cultures are often negative. In several countries, such as the United Kingdom and Spain, PCR has become the standard (if not the only) method for confirmation of meningococcal disease[126,127]. Furthermore, false-negative PCR results are uncommon (about 5% of cases)[8]. Disadvantages of PCR compared with CSF culture include the lack of an isolate on which traditional

antimicrobial susceptibility testing, serogrouping and serotyping can be performed. However, PCR assays are now available for both serogrouping and serotyping, and are used for surveillance and vaccine evaluation[128].

Antigen and immunochromatographic tests provide tools for rapid identification of the pathogen[8,109]. Latex agglutination testing in CSF has a widely varying reported sensitivity depending on the causative pathogen: for example, 59–100% and 22–93% for *S. pneumoniae* and *N. meningitidis*, respectively[8]. Furthermore, the sensitivity of latex agglutination tests was shown to drop considerably in patients who had started treatment before undergoing lumbar puncture[129]. The efficacy of immunochromatographic antigen testing in CSF was assessed in large studies in children with suspected acute bacterial meningitis[130]. These studies showed a 98.6–100% sensitivity and a 99.3–100% specificity for pneumococcal meningitis[8], although false-positive results have been reported in patients with meningitis due to other streptococcal species[109].

C-reactive protein and pro-calcitonin have been advocated as diagnostic serum markers, enabling differentiation between bacterial and viral meningitis[117]. Both C-reactive protein and pro-calcitonin are acute-phase inflammation proteins that are stimulated by cytokines (for example, IL-1, IL-2, IL-6 and tumour necrosis factor) that play an important part in the pathophysiology of bacterial meningitis. However, although these markers have the potential to differentiate between bacterial and viral infection in general, their values in patients with suspected bacterial meningitis have not yet been studied[117].

Severely immunocompromised patients, such as untreated HIV-positive individuals or patients who have received bone marrow or solid organ transplantation, can develop bacterial meningitis, but might present with only a minimal inflammatory response[28,131,132]. In these patients, CSF Gram stain might be especially important, showing high bacterial loads with minimal leukocytosis. Although the majority of these patients will eventually be diagnosed with pneumococcal meningitis, uncommon pathogens should also be suspected[8].

Vaccine-based prevention

Bacterial meningitis is in part a preventable disease, as vaccines are available against the most common causative pathogens[4] (TABLE 3). The first generation of meningococcal, pneumococcal and Hib vaccines were made from purified capsular polysaccharides[4]. Although the vaccines

Table 3 | Designs of vaccines for preventing bacterial meningitis and their typical recommended uses*

Vaccine design	Pathogen serotypes or serogroups covered	Indication	Where used
Haemophilus influenzae			
Protein–polysaccharide conjugate	• Type b • Most often used as a component of a combination vaccine	Infants	192 countries
Streptococcus pneumoniae			
Protein–polysaccharide conjugate	10 or 13 serotypes	• 10-valent and 13-valent vaccines are recommended for infants and children <5 years of age • 13-valent vaccine is licensed for adults	• 117 countries by the end of 2014 in infants • Routine use in the United States for adults ≥65 years of age
Polysaccharide	23 serotypes	Individuals ≥2 years of age	• Some middle-income and high-income countries • Mostly used in adults >65 years of age or in younger individuals with high-risk medical conditions
Neisseria meningitidis			
Protein–polysaccharide conjugate	Monovalent serogroup A	• 'Catch up' campaigns for individuals 1–29 years of age • Routine in infants 9–18 months of age	Meningitis belt countries
	Monovalent serogroup C (alone or in combination with *H. influenzae* type b)	Infants and adults up to 24 years of age	Routinely used in European countries
	Quadrivalent A/C/W/Y	• One dose for individuals 2–55 years of age • Two doses for children 9–23 months of age	Used routinely in the United States, Canada and Europe for specific groups, including university students, individuals with high-risk medical conditions, laboratory workers and individuals travelling to high-risk areas (for example, the Hajj), and outbreak response
Polysaccharide	Bivalent A/C, trivalent A/C/W and quadrivalent A/C/Y/W	Individuals ≥2 years of age	• Limited routine use • For outbreak control if the conjugate vaccine is not available
Protein	Serogroup B	Children and at-risk adults	• Used routinely in the United Kingdom • Used in high-risk groups, such as immunocompromised individuals and laboratory workers, and for outbreak control

*See REFS 231–233.

were useful, their effectiveness among children <2 years of age was limited. Contemporary vaccine formulations were made with capsular polysaccharides conjugated to carrier proteins; protein–polysaccharide vaccines trigger a T cell-dependent immune response, which can be elicited even in young infants. By contrast, vaccines that target *N. meningitidis* serogroup B are made with protein antigens.
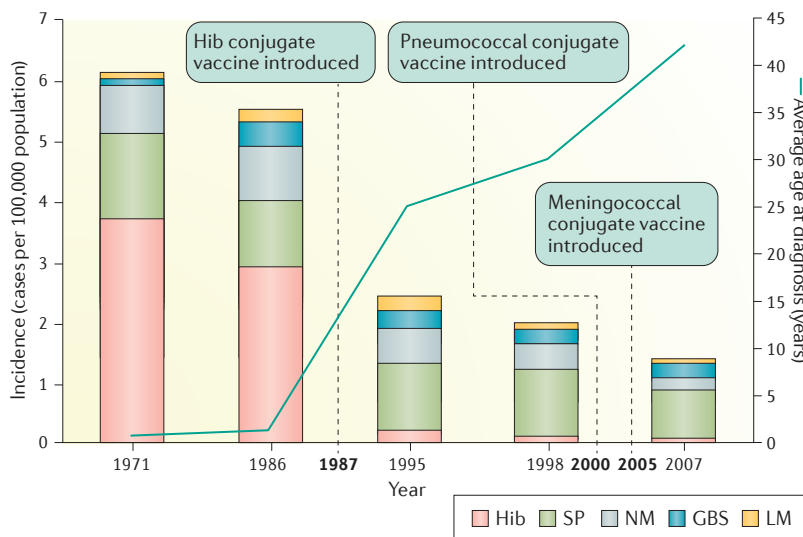
Hib conjugate vaccines. Hib conjugate vaccines, first used in 1987 in the United States, are now available from several manufacturers as either a monovalent vaccine or as part of a polyvalent vaccine that includes some combination of pertussis, diphtheria, tetanus, polio, meningococcal disease or hepatitis B antigens[4]. Hib and pneumococcal conjugate vaccines are given to infants in 3–4 dose series[4], whereas older children require fewer doses. This vaccine has been successful in reducing the incidence of Hib infection in the susceptible childhood population (BOX 1).

Pneumococcal conjugate vaccines. A pneumococcal conjugate vaccine targeting the seven serotypes that cause the most severe pneumococcal infections in high-income countries was first licensed in 2000. In late 2009 and early 2010, second-generation conjugate vaccines targeting 10 or 13 serotypes became available, with the 13-valent vaccine replacing the earlier 7-valent version[4]. The 10-valent and 13-valent formulations both include an antigen that targets serotype 1, a frequent cause of meningitis in many low-income and middle-income countries[18]. Some national immunization policies recommend pneumococcal vaccines for adults who are at higher risk of pneumococcal infection because of older age or immunocompromising or chronic medical

conditions such as sickle cell disease[133]. The 13-valent vaccine prevented invasive pneumococcal disease and pneumonia caused by the covered serotypes among the elderly population in a large clinical trial[134]. The 23-valent pneumococcal polysaccharide vaccine, available since 1983, is more often recommended for adults, although the 13-valent conjugate vaccine is now also licensed for adults and recommended routinely for adults ≥65 years of age in the United States[135].

Meningococcal vaccines. Of the 12 known meningococcal serogroups, vaccines are available for serogroups A, B, C, Y and W, either in single (A, B or C) or multiple (A/C, A/C/Y or A/C/Y/W) serogroup-targeting versions. Conjugate vaccines are used for routine disease prevention, whereas either conjugate or polysaccharide versions are used for emergency control of outbreaks or epidemics. Vaccination of high-risk individuals (for example, those with asplenia or complement deficiency) is common, but universal vaccination policies vary between countries. In the United Kingdom, serogroup C vaccination has been implemented in England and Wales since 1998 and serogroup B vaccination in 2015 (see 'Outlook' section)[136]. As part of this programme, meningococcal vaccines targeting serogroups B and C are given routinely to all infants, and teenagers receive a booster dose with an A/C/Y/W conjugate vaccine[136]. In the United States, where meningococcal disease rates are low overall in the general population but somewhat higher in adolescents and young adults, a 4-valent vaccine targeting serogroups A, C, Y and W is recommended in children between 11 and 12 years of age, with a booster dose at 16 years of age; a more permissive recommendation for serogroup B vaccine has been given by a recent policy, which states that the vaccine may be used for individuals 16–23 years of age who are at increased risk of meningococcal disease[137]. MenAfriVac (Serum Institute of India Pvt. Ltd, Pune, India), a serogroup A monovalent conjugate vaccine specifically made to be affordable for low-income settings, was first introduced in Burkina Faso in 2010 (REF. 138). The WHO recommends MenAfriVac vaccination to target all individuals 1–29 years of age in all meningitis belt countries and the establishment of routine vaccination programmes for children 9–18 months of age[138]. Early reports on serogroup A disease control in the meningitis belt (FIG. 2) are promising[14].

Effect of vaccine use on meningitis rates. Hib and pneumococcal conjugate vaccine programmes have resulted in substantial drops in the rates of meningitis caused by the covered bacterial strains[12,139] (FIG. 5). Pneumococcal conjugate vaccines reduced pneumococcal carriage, transmission and meningitis not only in vaccinated children but also in older non-vaccinated individuals via herd protection[7,12,139]. However, the widespread use of the 7-valent pneumococcal vaccine led to an increase in pneumococcal diseases caused by bacterial strains that were not covered by the vaccine, a phenomenon known as replacement disease[140]; whether a similar effect will occur with the 10-valent and 13-valent vaccines remains unclear.

Figure 5 | **Effect of conjugate vaccines on bacterial meningitis infections.** Incidence (left axis, bars) and average age at diagnosis (right axis, line) are shown for patients with bacterial meningitis in the United States from 1971 to 2007 (REFS 10,215–217). The decreasing proportion of disease caused by *Haemophilus influenzae* type b (Hib) and, later, *Streptococcus pneumoniae* (SP) and the increase in overall age of remaining cases show the effect of routine infant vaccination programmes. GSB, group B streptococcus; LM, *Listeria monocytogenes*; NM, *Neisseria meningitidis*.

Table 4 | Empirical antibiotic therapies for presumed bacterial meningitis

Patient age or risk factor	Common pathogens	Empirical therapy
<1 month	• *Streptococcus agalactiae* • *Escherichia coli* • *Listeria monocytogenes*	Amoxicillin or ampicillin plus cefotaxime, or amoxicillin or ampicillin plus an aminoglycoside
1–23 months	• *S. agalactiae* • *E. coli* • *Streptococcus pneumoniae* • *Neisseria meningitidis*	Vancomycin plus either cefotaxime or ceftriaxone*,‡
2–50 years	• *S. pneumoniae* • *N. meningitidis*	Vancomycin plus either cefotaxime or ceftriaxone*,‡
>50 years	• *S. pneumoniae* • *N. meningitidis* • *L. monocytogenes* • Aerobic Gram-negative bacilli	Vancomycin, ampicillin and either cefotaxime or ceftriaxone
Immunocompromised state§	• *S. pneumoniae* • *N. meningitidis* • *L. monocytogenes* • *Staphylococcus aureus* • *Salmonella* spp. • Aerobic Gram-negative bacilli	Vancomycin, ampicillin and either cefepime or meropenem

*Add amoxicillin or ampicillin if meningitis caused by *L. monocytogenes* is also suspected. ‡In countries where the prevalence of cephalosporin-resistant pneumococcus is <1%, cefotaxime or ceftriaxone alone is appropriate. §For example, owing to HIV infection or immunosuppressive therapies (for example, post-transplantation). Adapted from REF. 143.

Vaccination policy and advocacy. Pneumococcal and Hib conjugate vaccines are recommended by the WHO for routine use in infant immunization programmes globally and are widely used[13,141]. Meningococcal vaccines are not routinely recommended for use in countries where rates are generally low, but are increasingly used in epidemic-prone areas or risk groups with higher rates of endemic disease. Conjugate vaccines targeting group B streptococcal infections are in development[21]. Group B streptococcal vaccines in development are being designed for use in pregnant women to protect newborns through transplacental antibody transfer.

Meningococcal vaccine campaigns are used to control disease outbreaks. Updated guidelines from the WHO specify when mass vaccination campaigns should be ordered to fight epidemic meningitis in Africa[142]: when the number of suspected meningitis cases has reached five in a week or has doubled over a 3-week period in a population of <30,000 people, or when the number has reached ten in a week in populations of 30,000–100,000 people, mass vaccination should then start as soon as possible and within 4 weeks. For refugee populations or institutional outbreaks, vaccination is recommended when two cases of meningococcal meningitis are detected within a week[142].

Chemoprophylaxis
Antibiotic prophylaxis is recommended for individuals who have had close contact with patients with meningococcal meningitis or bacteraemia (for example, household members) immediately after exposure[109,143]. Although the risk of nosocomial meningitis in patients with basilar skull fracture is high[3], antibiotic prophylaxis has shown no clear benefit in these patients[3]. Several

guidelines recommend universal screening for recto-vaginal colonization by group B streptococci in pregnant women at 35–37 weeks of gestation, with intrapartum antibiotic prophylaxis for patients who test positive. This strategy has decreased neonatal early-onset group B streptococcal meningitis in the United States[144], but a similar risk-based chemoprophylaxis in the Netherlands did not prove beneficial[21].

Management
Given the high mortality of acute bacterial meningitis, treatment should be started in suspected cases even before the diagnosis can be confirmed[109]. The vital functions of the patient should be evaluated and weighted with the degree of suspicion for bacterial meningitis. Blood cultures and blood tests should be performed immediately[143]. Collection of CSF for examination and culture should be done as soon as possible. Even if a head CT scan is indicated before CSF collection, antimicrobial therapy should not be withheld, as a delay can result in a higher probability of adverse clinical outcomes[145].

Antibiotic therapy
Empirical antibiotic therapy should be bactericidal and achieve adequate CSF levels. Both these parameters depend on lipid solubility, molecular size and protein-binding capacity of the antibiotic and on the patient's degree of meningeal inflammation[143] (TABLE 4). The choice of the initial empirical antibiotics should be based on age, local epidemiological patterns of pneumococcal resistance and the need to add amoxicillin or ampicillin against *L. monocytogenes*[143]. Treatment for neonatal bacterial meningitis should cover at least *E. coli* and *Streptococcus agalactiae*[8]; indeed, outbreaks of extended-spectrum β-lactamase-positive *E. coli* meningitis in neonatal wards have been described[146]. *Listeria* spp. are resistant to cephalosporin; thus, amoxicillin or ampicillin should be given to all immunosuppressed patients with meningitis, including pregnant women or patients >60 years of age[143]. Once the causative pathogen and its specific antimicrobial susceptibility have been determined, the antibiotic therapy must be optimized for targeted treatment (FIG. 6).

Penicillin resistance among *S. pneumoniae* strains has been increasing worldwide, changing the initial therapy of patients with bacterial meningitis in several parts of the world[143]. In March 2008, the Clinical and Laboratory Standards Institute (CLSI) revised the susceptibility breakpoints of penicillin against *S. pneumoniae*. In pneumococcal meningitis, penicillin resistance occurs when the minimum inhibitory concentration (MIC) is ≥0.2 µg per ml, and third-generation cephalosporin resistance is defined as an MIC of ≥2 µg per ml[147]. According to these criteria, the prevalence of penicillin resistance was 9% in 2010 in Europe[148,149] and 35% in 2012 and 2013 in the United States, where 21% of the cases had multidrug resistance (defined as resistance to at least two other classes of antibiotics besides penicillin)[150]. Because of the variable geographical distribution of penicillin resistance, it is important to
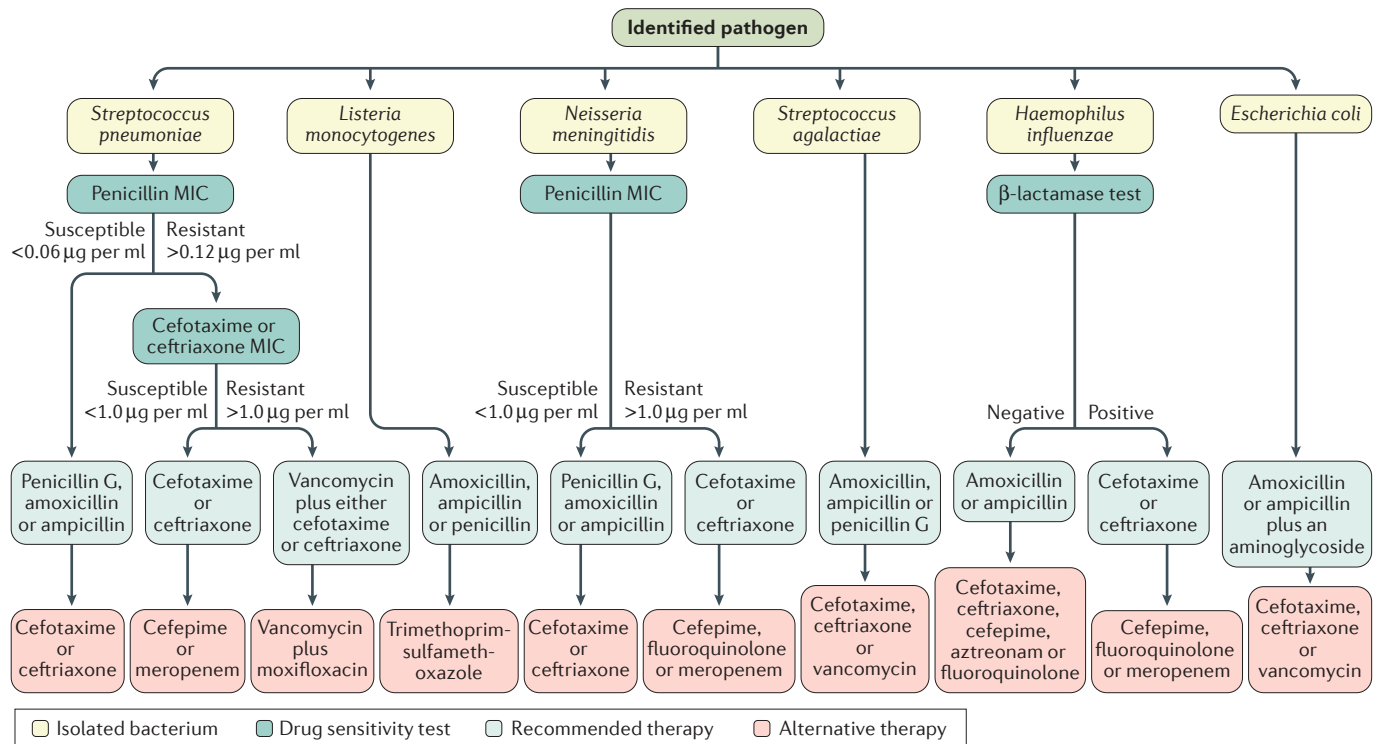
Figure 6 | Antibiotic therapies. Examples of first-line and alternative antibiotic therapies for bacterial meningitis based on the causative pathogen and its *in vitro* susceptibility test. Alternative therapies are prescribed if there are contraindications to the recommended treatment. MIC, minimum inhibitory concentration.

know the regional patterns when deciding on local empirical antibiotic therapy[143]. Penicillin resistance is also associated with decreased susceptibility to other antibiotics. Thus, guidelines from the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommend vancomycin and a third-generation cephalosporin as part of the initial treatment; however, in countries where the prevalence of cephalosporin-resistant pneumococcus is <1%, ceftriaxone alone is appropriate[109,151]. Empirical therapy should consist of vancomycin combined with either cefotaxime or ceftriaxone in areas with cephalosporin resistance[109] (FIG. 6).

N. meningitidis strains with reduced susceptibility to penicillin have been associated with increased risk of poor disease outcome in children with meningococcal meningitis[152]. Strains with reduced susceptibility to penicillin resistance accounted for nearly 12% of strains in 2011 in the United States, although <1% were fully resistant[153]; however, all isolates remain susceptible to ceftriaxone, which is, therefore, the empirical antibiotic of choice in suspected meningococcal meningitis.

L. monocytogenes should be suspected in neonates, adults >50 years of age and immunosuppressed individuals. In these groups, amoxicillin or ampicillin should be added to the empirical therapy, as cephalosporins have no activity against *Listeria* spp.[143]. Retrospective clinical data indicate that gentamicin can reduce mortality in listerial meningitis[154]. However, another study showed that adding an aminoglycoside (such as gentamicin)

to the treatment was associated with increased rates of kidney injury and mortality[155].

International guidelines on the duration of treatment[109] recommend 7–10-day treatment for *H. influenzae* or *N. meningitidis* meningitis, a 10–14-day treatment for *S. pneumoniae* meningitis[143,151] and a prolonged, 21-day treatment for *L. monocytogenes* meningitis[109]. Efficacy and safety of 5-day versus 10-day ceftriaxone regimens were compared in a multi-country randomized study involving 1,004 children with bacterial meningitis[156]. No significant difference was found between groups in bacteriological failures (none of the patients in both groups had persistent positive CSF cultures 6–40 days after starting therapy) or relapses (2 out of 496 patients (0.4%) in the 5-day group versus 0 out of 508 patients (0%) in the 10-day group (risk difference: −0.4 (95% CI: −0.15–0.96)); however, the sample sizes of aetiological subgroups were relatively small, so caution is advised when extrapolating these results.

Adjunctive therapies

Despite antibiotic therapy, the mortality for bacterial meningitis has remained at 20–25% for several decades[2]. The high morbidity and mortality prompted the investigation of several adjunctive therapies in animal models[38], which, unfortunately, have delivered poor performances in subsequent clinical trials so far, with the exception of steroids. The common goal of adjunctive therapies is to reduce inflammation-related neuronal death and brain damage. Bactericidal antibiotics lyse pathogens, causing the release of pro-inflammatory bacterial components

that trigger the host immune response, which in turn contributes to brain damage. Some of the failed adjunctive treatments include therapeutic hypothermia, which resulted in increased mortality[157], paracetamol, which did not lead to any improved outcomes[158], and glycerol, which did not reduce or sometimes even increased death or neurological morbidity[159,160].

Following several paediatric studies[161,162], a large multi-centre European randomized controlled trial in adults showed a significant reduction of unfavourable outcomes and death in patients who were treated with adjunctive dexamethasone (an anti-inflammatory corticosteroid) in addition to antibiotic therapy compared with patients who only received antibiotics, with the most striking results observed in the subgroup of patients with pneumococcal meningitis[163]. A post-hoc analysis of 25 studies using several different antibiotics showed that dexamethasone mainly reduced deaths in pneumococcal meningitis by preventing systemic complications[164]. Other meta-analyses showed that corticosteroids significantly reduced hearing loss and neurological complications but not overall mortality[161,165,166], whereas subgroup analyses showed corticosteroid-associated reduction of severe hearing loss in children with *H. influenzae* meningitis and mortality in adults with *S. pneumoniae* meningitis[161]. Notably, corticosteroids had no beneficial effects for patients in low-income countries[165], most likely because patients present late in the course of the disease, when the inflammatory process in the CNS has already started. The results from the aforementioned studies imply that the effect and efficacy of adjunctive dexamethasone depend on the type of meningeal pathogen, the age of the patient and the income level of the countries. Dexamethasone is the only adjunctive therapy that has been advocated by the IDSA and ESCMID guidelines[109,151].

Available evidence suggests that, in high-income countries, dexamethasone treatment should be started with or even before the first dose of antibiotics[2] and continued for 4 days in both children and adults (although with different dose regimens)[2,109]. Guidelines recommend suspending dexamethasone treatment if the bacterial meningitis diagnosis is not confirmed or if the causative pathogen is other than *H. influenzae* or *S. pneumoniae* (although some experts advise dexamethasone to be continued irrespective of the meningeal pathogen)[109]. In patients with bacterial meningitis and severe sepsis or septic shock, the survival benefit provided by corticosteroid treatment outweighs the potential risks of high-dose steroid administration in sepsis[143].

Intensive care

Patients with bacterial meningitis should be admitted to an intensive care unit, where the patient's consciousness and the development of complications, such as brain infarctions, hydrocephalus and seizures, can be closely watched[2]. Such heightened medical care can improve the outcome, but nevertheless a fulminant course might inevitably result in permanent damage or brain death. Furthermore, some patients seem to be refractory to treatment and their condition can escalate to a major systemic infection.

Occasionally, CT scanning can provide important direction for treatment. In patients with clinical deterioration, serial CT scanning might show cortical and sylvian fissure effacement, compression of the ventricles and eventually obliteration of the basal cisterns. Some experts would then advocate the standard treatment for intracranial pressure[167]: high doses of corticosteroids, osmotic diuretics, decompressive craniectomy and ventriculostomy in case of hydrocephalus. However, no conclusive evidence supports this treatment option and such aggressive strategies might be more harmful than beneficial[168]. Nevertheless, in case of impeding brain herniation, placement of an intracranial pressure monitor is advised, followed by continuous osmotic therapy to reduce high intracranial pressure[169]. Hypertonic saline might also control the commonly observed hyponatraemia[170]. Serial CT scanning can also show the development of hydrocephalus, which, in a prospective case series, was diagnosed in 5% of patients[171]. In case of hydrocephalus, repeated lumbar punctures or placement of an external lumbar drain can reduce intracranial pressure. Invasive procedures should be withheld in patients with mild enlargement of the ventricular system without clinical deterioration. Seizures, particularly focal, can be attributed to focal oedema, early cortical venous thrombosis and cerebral infarction from occlusion of penetrating branches that are encased by the basal purulent exudate[172].

Palliative care (supportive care only) might be necessary owing to a poor neurological prognosis. However, early withdrawal of therapy in patients with preserved brainstem reflexes is inappropriate, as these seemingly hopeless patients can actually survive and some fully recover[173]. In one prospective cohort study, 3% of patients with bacterial meningitis had a score of 3 on the Glasgow Coma Scale (that is, totally unresponsive)[174], and although such low levels of consciousness are commonly associated with high morbidity and mortality, as many as 20% of these patients will make a full recovery[174], stressing the need for continued supportive care.

Quality of life

Individuals who have had bacterial meningitis (particularly pneumococcal meningitis) are at high risk of neurological complications that affect their quality of life[175–178]. About half of survivors experience focal neurological deficits, such as hearing loss, epilepsy and cognitive impairment[179–182]. A meta-analysis showed that the risk of major sequelae was twice as high in low-income countries compared with high-income countries[181]. A systematic review (which combined data from high-income and low-income countries) of bacterial meningitis complications in 18,183 children (in which the most common pathogen was Hib) showed that the most common were hearing loss (in 34% of patients), epileptic seizures (13%), motor deficits (12%), cognitive defects (9%) and hydrocephalus (7%)[181]. Post-meningitis complications have a relevant economic burden on health care systems[179–182].

Patients with *S. pneumoniae*, *H. influenzae* and *S. suis* meningitis often develop hearing loss, probably because bacterial products and inflammatory mediators spread from the meninges directly to the cochlea[25,183–185]. Otitis media is an important risk factor for meningitis; it is found in up to 55% of patients with pneumococcal meningitis with hearing loss[184] and might require invasive treatment. In patients with meningitis and hearing loss, obliteration of the cochlear lumen might follow the meningitis episode and has been associated with decreased success rates of cochlear implant surgery[186]. Thus, early identification of hearing loss is crucial and screening is advised before discharging a patient.

Survivors of bacterial meningitis are at high risk of cognitive impairment (reduced processing speed)[175], which can be observed in approximately one-third of patients who have had pneumococcal or meningococcal meningitis[177]. In Denmark, a nationwide population-based cohort study showed that bacterial meningitis during childhood negatively affects educational level[178].

Outlook

Despite advances in prevention and treatment, bacterial meningitis remains one of the most widespread and lethal infectious diseases worldwide. Prevention of disease and early initiation of the appropriate treatment in patients with suspected or proven bacterial meningitis are the key factors to reduce morbidity and mortality. Furthermore, as drug resistance spreads and serotype and serogroup incidences shift, novel antibiotic and adjuvant treatment strategies must be developed[38], although growing evidence supports the decrease of antibiotic resistance for pneumococci since the implementation of conjugate vaccines[139]. Vaccination programmes and health education are needed to prevent the disease. Extending the use of the available conjugate vaccines in Africa and Asia, where the burden of acute bacterial meningitis is the greatest, will contribute to defeating the disease globally. Herd protection plays a major part in the effectiveness of conjugate vaccines[12,139,187], helping to protect infants who are too young to be fully immunized and the elderly who have poor immunological response to vaccination[7].

In view of the changing epidemiology, uniform surveillance systems should be implemented in many countries to monitor the effect of conjugate vaccines on serotype incidences, including emerging strains that are not covered by current vaccines. Molecular epidemiology of bacterial strains is key: whole-genome sequencing has been highly valuable in tracking the emergence, virulence and pathophysiology of these bacterial agents[188–190]. Thus, surveillance studies will also need to evaluate the effects of different bacterial genotypes on the clinical outcome[191]. Meanwhile, improved protein vaccines with broad coverage are needed[192]. In the United Kingdom, a nationwide vaccination campaign using a multicomponent meningococcal B protein vaccine[193,194] was launched in September 2015 and an assessment on disease prevention is eagerly awaited[136].

The pathophysiological mechanisms of bacterial meningitis are complex. In the 1980s, studies on twins and adopted children showed that genetic factors are major determinants in the development of infectious diseases, including meningitis[29,195]. The association between genetic factors and susceptibility and outcome of invasive meningococcal and pneumococcal disease has been confirmed by 'extreme phenotype' and case–control studies[29]. However, unbiased genome-wide association studies that take into account gene–gene interactions between host and pathogen could reveal new targets for vaccine development and treatment[191]. These types of studies require large numbers of patients, so joined efforts among research groups and countries should be sought; afterward, genetic, functional and experimental validation will be needed to distinguish real from spurious results.

Experimental animal models are essential to unravel the pathophysiology of pneumococcal meningitis and to evaluate new treatment strategies. The main goal for new therapies will be dampening the inflammatory response, and the targets with the highest therapeutic potential belong to the signalling cascades that regulate damage mediated by reactive oxygen species and reactive nitrogen species[196], caspase inhibition[197], complement system activation[88] or vascular integrity[198]. Animal studies of new treatments should adhere to current standards of comparative experimental research[191]. These studies should include a standard treatment arm that consists of antibiotics plus dexamethasone (the current standard treatment strategy) and should be designed to detect a relevant clinical outcome, which is convincing enough to justify a clinical trial. Blocking the complement cascade seems to be the most promising strategy[91]. Clinical evaluation of complement-blocking therapies should be facilitated by the pharmaceutical industry.

New and more-specific anti-inflammatory treatments are urgently needed. Randomized controlled trials are crucial to establish efficacy, safety and treatment modalities of new drugs against bacterial meningitis[199]. To maximize the results, these clinical trials should be conducted on an international scale. Thus, international networks on clinical research in neurological infectious diseases, using uniform diagnostic and enrolment criteria and research standards, need to be established. In clinical practice, early treatment (ideally within 1 hour of presentation), implementation of adjunctive dexamethasone therapy and intense supportive care might contribute to improvement in the prognosis of patients with bacterial meningitis.

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Competing interests
The authors declare no competing interests.