Community-acquired bacterial meningitis

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Progress has been made in the prevention and treatment of community-acquired bacterial meningitis during the past three decades but the burden of the disease remains high globally. Conjugate vaccines against the three most common causative pathogens (*Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*) have reduced the incidence of disease, but with the replacement by non-vaccine pneumococcal serotypes and the emergence of bacterial strains with reduced susceptibility to antimicrobial treatment, meningitis continues to pose a major health challenge worldwide. In patients presenting with bacterial meningitis, typical clinical characteristics (such as the classic triad of neck stiffness, fever, and an altered mental status) might be absent and cerebrospinal fluid examination for biochemistry, microscopy, culture, and PCR to identify bacterial DNA are essential for the diagnosis. Multiplex PCR point-of-care panels in cerebrospinal fluid show promise in accelerating the diagnosis, but diagnostic accuracy studies to justify routine implementation are scarce and randomised, controlled studies are absent. Early administration of antimicrobial treatment (within 1 hour of presentation) improves outcomes and needs to be adjusted according to local emergence of drug resistance. Adjunctive dexamethasone treatment has proven efficacy beyond the neonatal age but only in patients from high-income countries. Further progress can be expected from implementing preventive measures, especially the development of new vaccines, implementation of hospital protocols aimed at early treatment, and new treatments targeting checkpoints of the inflammatory cascade.

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Introduction

The epidemiology of bacterial meningitis has changed with the introduction of conjugate vaccines but globally the number of cases is rising,[1] with a strong association with poverty.[2] Diagnostic dilemmas often occur in patients with suspected meningitis, since the typical clinical characteristics such as headache, neck stiffness, fever, and an altered mental status are often absent. Rapid administration of antimicrobial therapy while controlling the host's inflammatory response is key to a good outcome, but the global emergence of multi-drug resistant bacteria threatens the effectiveness of antimicrobial drugs and the benefit of adjunctive anti-inflammatory treatment with dexamethasone remains limited to high-income settings.[3] In this Seminar, we provide an overview of progress and challenges in bacterial meningitis, focusing on the epidemiology and pathogenesis, and provide recommendations for diagnostics and treatment.

Burden of community-acquired bacterial meningitis

The incidence of bacterial meningitis varies substantially by geographical region. In well-resourced settings, particularly in high-income countries, incidences have fallen to 0·9 per 100 000 population, as reported in 2014 in the USA and the Netherlands.[4,5] However, globally, the number of reported cases has risen during the past decade, with incidence strongly related to measures of deprivation.[2] The greatest burden of disease remains in Africa, particularly within the Sahel region of west and central Africa, with incidences up to 1000 per 100 000 population.[6,7] There is notable seasonality, with increased incidence rates occurring during cooler, drier seasons in both the northern and southern hemispheres.[8] The timing of the seasonal meningitis peak correlates with the latitude of a country's most populous city. In countries above 30°N latitude, peak meningitis season is between December and February, whereas countries in the Sahel (20°N to –5°N) have a peak incidence between March and May, and in places with a latitude below –20°N the peak occurs in June and July.[8] Outside of the so-called meningitis belt in Africa (a region of sub-Saharan Africa where the incidence of meningitis is very high), estimates of incidence in Africa are scarce but vary between three and 25 cases per 100 000 population.[6,7] In other low-income and middle-income countries, especially within densely populated countries including India, Pakistan, Brazil, and China, the incidences varies between 20 and 80 cases per 100 000 population, representing a substantial disease burden.[2]

Search strategy and selection criteria

We searched the Cochrane Library (The Cochrane Library 2021, issue 1) and MEDLINE (January, 1966 to February, 2021). We used the search terms "bacterial meningitis" or "meningitis" or "meningococcal disease" or "*Neisseria meningitidis*" or "pneumococcal disease" or "*Streptococcus pneumoniae*" or "*Haemophilus influenzae*" in combination with the terms "vaccination" or "vaccines" or "prevention" or "epidemiology" or "surveillance" or "diagnosis" or "diagnostic techniques" or "spinal puncture" or "cerebrospinal fluid" or "imaging" or "therapy" or "antibiotics" or "antimicrobial" or "treatment" or "complication". We restricted our search to publications in the English language. We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles and book chapters are cited to provide readers with more details and more references than this Seminar has room for. Our reference list was modified on the basis of comments from peer reviewers.

	Vaccine name	Serotypes or serogroups covered	Protein conjugate	Commercially available vaccine
Streptococcus pneumoniae				
Polysaccharide	PPV-23	1, 2, 3, 4, 5, 6B, 7F, 8, 9V, 9N, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F	NA	Pneumovax
Conjugate	PCV-7	4, 6B, 9V, 14, 18C, 19F, and 23F	CRM197*	Prevenar
Conjugate	PCV-10	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, and 19F	Protein D, diptheria toxoid, tetanus toxoid	Synflorex
Conjugate	PCV-10	1, 5, 6A, 6B, 7F, 9V, 14, 19A, and 19F	CRM197*	Pneumosil
Conjugate	PCV-13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, and 19F	CRM197*	Prevenar 13
Neisseria meningitidis				
Conjugate	MenACWY	ACWY	CRM197*, diptheria toxoid	Menactra, Menveo
Polysaccharide	MPSV4	ACWY	NA	Menimmune
Conjugate	MenC	C	CRM197* or tetanus toxoid	Menitorix, NeisVac-C, Menjugate, Meningitec
Conjugate	Hib_MenCY-TT	CY, Hib	Tetanus toxoid	MenHibrix
Conjugate	Men A	A	Tetanus toxoid	MenAfriVac
Protein	Men B bivalent vaccine	B	Not used	Trunemba
Protein	4CMenB	B	Not used	Bexsero
Haemophilus influenzae				
Conjugate	Monovalent	Type b	CRM197*	Menitorix, Pediacel

Hib=*Haemophilus influenzae* type b. NA=not applicable. *CRM197 is a non-toxic variant of diptheria toxin.

Table 1: **Available licensed vaccines against pathogens causing community-acquired bacterial meningitis**

The epidemiology of bacterial meningitis has undergone major shifts during the past four decades. The incidence of the disease increased with the start of the HIV-1 epidemic in the 1980s, and subsequently decreased with the introduction of antiretroviral treatments in the 1990s and the introduction of conjugate vaccines for children from 1987 onwards.[9] The persistence of bacterial meningitis and burden on children and young people has thus led to WHO developing a roadmap towards defeating meningitis by 2030.

For the **WHO roadmap towards defeating meningitis** see https://www.who.int/emergencies/diseases/meningitis/meningitis-2030.pdf

As a result of the success of childhood immunisation programmes, the focus of preventive measures has somewhat shifted away from the three most common causative pathogens, *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*, towards other common causative bacteria of meningitis. *Streptococcus agalactiae* (group B streptococci) is the most common cause of bacterial meningitis in neonates and young infants.[10] In 2015, an estimated 319 000 infants suffered from invasive group B streptococcus disease worldwide, causing approximately 90 000 deaths and at least 10 000 children with disability that year.[11] Prevention of neonatal meningitis and sepsis is predominately achieved through maternal screening and improved neonatal care. In the Netherlands, the incidence of neonatal group B streptococcal sepsis increased by 60% from 0·20 per 1000 livebirths in 1987 to 0·30 per 1000 livebirths in 2011 in patients aged 3 months or younger, despite the introduction of intrapartum antibiotic prophylaxis for women in labour at risk for perinatal group B streptococcal disease.[10,12] However, in the USA, universal antenatal screening for group B streptococcus has resulted in a decrease in early-onset invasive group B streptococcal disease in the period 2002–2010 compared with 1990–2002.[13] The notable differences in efficacy of these approaches could be explained by the different methods of screening, but also by differences between the countries in baseline incidence of disease prior to implementation, adherence to guidelines, and the emergence of hypervirulent strains.[12,13] Neonatal meningitis is also associated with Gram negative bacteria, such as *Escherichia coli*.[14,15] In a prospective, observational, single-site study of meningitis in infants aged younger than 90 days in Luanda, Angola, a causative pathogen was identified in only 212 of 1287 neonates with suspected or proven bacterial meningitis, most commonly *Klebsiella* spp, *S pneumoniae*, *S agalactiae*, and *E coli*.[16]

Listeria monocytogenes causes food-borne meningitis in specific risk groups, particularly in immunocompromised individuals.[17] The incidence of listerial meningitis is low in countries with regulated food hygiene requirement and food safety criteria, accounting for less than 5% of all community-acquired meningitis cases.[18] A South African study including 937 listeriosis cases showed that *L monocytogenes* caused disproportionate illness in pregnant girls and women and HIV-infected individuals.[19] *Streptococcus suis* is the most common cause of meningitis in southeast Asia, particularly Vietnam and Thailand.[20] This zoonotic cause of meningitis is contracted through contact with pigs, and primarily observed in adults involved in pig farming or pork butchery.[20] Nontyphoidal *Salmonella* is an emerging cause of meningitis in neonates and HIV-infected adults and is associated with substantial mortality and morbidity in African countries.[15]

Effect of vaccines

Conjugate vaccines provide substantially increased serotype-specific T-cell-mediated immunity compared with polysaccharide vaccines, reducing both mucosal carriage and invasive disease.[1] However, efficacy is limited to included serotypes, and the emergence of non-vaccine and non-typeable serotypes has limited the efficacy of vaccines.[21] Currently available licensed meningitis vaccines are listed in table 1. The only protein-based meningitis vaccines so far have been licensed vaccines against *N meningitidis* serogroup B.

Streptococcus pneumoniae

S pneumoniae is the most prevalent cause of meningitis worldwide, and has therefore been an important target for prevention by vaccination for more than 40 years.[22] More than 90 pneumococcal capsular serotypes have

been described and those recognised to cause the greatest burden of disease have been included in the pneumococcal vaccines (PCVs; table 1). The first pneumococcal vaccine consisted of pneumococcal polysaccharides (PPVs), targeting 14 serotypes, and was licensed in the USA in 1977.[1] In 1983, this was replaced by a 23-valent formulation, PPV23. Few reports have studied the effect of these vaccines on meningitis, but research has shown low efficacy against pneumonia in adults and no effect on pneumococcal infection incidence in HIV-infected Ugandan adults.[23] After development of the conjugated vaccines, PPV23 was replaced in most settings by the seven-valent conjugate vaccine (PCV7), which was licensed in 2000.[1] Introduction of the PCV7 vaccine in the USA in 2000 reduced invasive pneumococcal disease in children by more than 90% by virtually eliminating disease caused by the serotypes included in the vaccine.[24] Similar reductions in serotype-specific pneumococcal bacteraemia and meningitis have been observed in children and adults in high-income countries.[25] The incidence of pneumococcal meningitis in the UK was unchanged by the introduction of PCV7, but cases fell by 48% following a change to the PCV13 vaccine in 2010.[25] PCV13, available since 2010, covered up to 80% of meningitis-causing serotypes worldwide, with variations in coverage in different geographical regions.[25,26] PCV13 was introduced to the Expanded Program on Immunization (EPI) schedule in Global Alliance for Vaccines and Immunization (GAVI)-eligible countries in 2012, and estimates of the consequent reductions in pneumococcal meningitis are emerging.[27] PCV13 might have low efficacy against epidemic serotype 1 meningitis in Ghana, but has led to reductions in meningitis prevalence in children in low-income and middle-income countries outside the Sahel.[28,29] The implementation of PCV13 globally has been limited by its high cost for non-GAVI-eligible countries.[30] In 2020, WHO licensed a low-cost PCV10 from the Serum Institute of India, containing ten serotypes that cause more than 80% of pneumococcal disease in children in low-income and middle-income countries (Pneumosil). Pneumosil was designed to contain disease-causing serotypes in high-incidence, resource-poor settings.[31] Pneumosil will thus increase accessibility for PCV in non-GAVI-eligible countries, and could substantially reduce the burden of pneumococcal meningitis in these nations.

Reports of reductions in invasive pneumococcal disease, including meningitis, in children following the introduction of PCVs in high-income countries, were rapidly followed by evidence of herd immunity in the whole population.[1] In a large, randomised study, PCV13 was effective in preventing vaccine-type invasive pneumococcal disease but not in preventing community-acquired pneumonia from any cause.[32] In parallel, reports have emerged of increasing cases of invasive pneumococcal disease (including meningitis) caused by non-vaccine serotypes.[25] In Denmark and Germany, the introduction of PCV-13 resulted in a decrease of invasive pneumococcal disease, but not in pneumococcal meningitis.[25] These differences might be related to serotype tissue tropism of some serotypes predisposing for meningitis. In France, introduction of PCV in 2003 led to a major decrease in incidence of invasive pneumococcal disease, preventing an estimated 44 667 cases between the start of the PCV programme in France in 2003 and 2017.[33] However, from 2015 onwards, the incidence of invasive pneumococcal disease, including pneumococcal meningitis, increased rapidly due to disease caused by non-PCV13 serotypes.[33]

Neisseria meningitidis

The incidence of meningococcal meningitis and the responsible serogroups vary widely, both geographically and over time.[33] Among the 12 meningococcal serogroups, the five main disease-causing serogroups have a specific geographical distribution, with A, W, and X being most prevalent in the Sahel and across Africa.[1] Serogroup B followed by Y is most prevalent in Europe,[34] and Y followed by B in the USA. In 2013, serogroup W emerged in the UK and was linked to a highly virulent South American clone St11.[35] This development led to a shift in vaccine policy in Europe from the serogroup C monovalent vaccine to the quadrivalent ACWY vaccine.[22] The St11 clone is also linked to a subtype of serogroup C with epidemic potential that was also associated with outbreaks in men who have sex with men.[36] Conjugate meningococcal vaccines are highly effective in preventing disease caused by specific meningococcal serogroups.[1] Elimination of meningococcal disease through vaccination is a major target of the WHO strategy to defeat meningitis by 2030.

Serogroup C was highly prevalent across Europe in the past, but its incidence has declined dramatically following the introduction of a serotype C conjugate vaccine in children in 1999.[22,37] A national surveillance study from the Netherlands showed that herd protection was responsible for more than a third of the impact of meningococcal serogroup C vaccine and lasted for more than 10 years.[38] Epidemic meningitis caused by serogroup A in the Sahel has been virtually eliminated in countries that have introduced the low-cost[6] MenAfriVac serogroup A conjugate vaccine, with no cases reported to sentinel sites since the vaccine was introduced in 2011.[39] However, other, virulent clones have emerged to fill the ecological niche left by the elimination of serogroup A, and epidemics of meningococcal meningitis continue to occur in the Sahel.[39]

With the decline of serogroup C in many regions, serogroup B emerged as the most frequent cause of meningococcal meningitis and septicaemia, responsible for outbreaks and severe disease with substantial morbidity and mortality.[40] In 2015, the UK government pioneered universal access to the protein-based

	Host receptors	Function
Streptococcus pneumoniae[47,116–119]		
PspC	67 kD laminin receptor	Adherence
NanA	67 kD laminin receptor	Adherence
Phosphorylcholine	CD31	Penetration
Pilus-1, RrgA	PAF receptor	Penetration
Low capsule and PLY expression	pIgR, CD31	Penetration
High PLY and H_2O_2 levels	Not applicable	Paracellular passage
Adhesion lipoprotein, pneumococcal histidine triad protein A	Unknown	Unknown interaction
Neisseria meningitidis[50,120,121]		
Type IV pili (Tfp)	CD147, β2 adrenergic receptor	Adherence
Opc	Fibronectin, $\alpha_5\beta_1$ receptor vitronectin, HSPG, ErbB2	Adherence or penetration
PilQ/PorA	67 kD laminin receptor	Penetration
Listeria monocytogenes[122–124]		
InlB	gC1q/Met	Penetration
InlF	Vimentin	Penetration
Vip	gp96	Penetration
Streptococcus agalactiae[51,125–127]		
FbsA	Fibrinogen	Adherence
PilA, PilB	Unknown	Adherence
PbsP	Plasminogen	Adherence
BspC	Vimentin	Adherence
IagA	Unknown	Adherence
Lmb	Laminin	Penetration
Escherichia coli[52,125,128,129]		
OmA	gp96	Adherence
Fim H	CD48, α_7 nAChR	Adherence
CNF1	67 kD laminin receptor	Penetration
IbeA	Caspr1	Penetration
YojI	IFNAR2	Adherence

BspC=group B streptococcal surface protein C. Caspr1=contactin-associated protein 1. CNF1=cytotoxic necrotising factor 1. FbsA=fibrinogen-binding protein A. Fim H=type I fimbrial adhesin. IagA=invasion-associated gene A. IFNAR2=interferon-alpha/beta receptor beta chain. InlB=internalin B. InlF=internalin F. Lmb=laminin-binding adhesin. nAChR=nicotinic acetylcholine receptor. NanA=neuraminidase A. OmA=outer membrane protein A. Opc=outer membrane protein. PAF=platelet-activating factor. PbsP=plasminogen-binding surface protein P. Pil=pilus biogenesis and competence protein. pIgR=polymeric immunoglobulin receptor. PLY=pneumolysin. PorA=class 1 protein. PspC=pneumococcal surface protein C. RrgA=major adhesin of the pneumococcal pilus-1. YojI=thiamine biosynthesis lipoprotein ApbE.

Table 2: **Microbial–endothelial interactions in blood–brain or blood–cerebrospinal fluid barrier penetration by major meningeal pathogens and their bacterial ligands or virulence factors**

serogroup B vaccine 4CMenB (Bexsero).[41] Protein-based meningococcal vaccines were licensed on the basis of serological response as a correlate of protection instead of disease incidence. Cases of invasive serogroup B in UK children have declined by 75% in the period from September, 2015, through August, 2018, with the introduction of the sergroup B vaccine in September 2015.[41] Reports suggest cross-protection of the MenB FHBP bivalent protein vaccine (Trumenba) against *Neisseria gonorrhoea* as well as *N meningitidis* in New Zealand.[42] However, these vaccines did not interrupt outbreak transmission or reduce nasopharyngeal carriage in university students in the USA.[43]

Haemophilus influenzae *type b*

Until the inclusion of the *H influenzae* type b conjugate vaccine in the EPI schedule in 2006, *H influenzae* type b was a leading cause of meningitis in children worldwide, in addition to causing pneumonia, epiglottitis, and otitis media.[1] The *H influenzae* type b polysaccharide vaccine was first introduced in 1985, followed by the conjugate vaccine in 1989. Dramatic reductions in the incidence of paediatric meningitis of between 75% and 95% were reported in the first year after vaccine introduction in all countries.[1] Since inclusion in the EPI schedule, *H influenzae* type b meningitis has virtually been eliminated around the world in countries where vaccination has been implemented, with estimated global reductions of 49% between 2000 and 2016, and paediatric deaths due to this pathogen estimated to have declined by 90% during the same time period. *H influenzae* type b remains a clinical problem where vaccination coverage is poor.[1,27] A substantial *H influenzae* type b disease burden, including meningitis, persists in countries including India, Nigeria, Pakistan, and the Democratic Republic of the Congo.[27] In many settings, *H influenzae* type b has been replaced by non-typeable *H influenzae* in children, with implications for early antibiotic management of paediatric meningitis because non-typeable *H influenzae* type b is associated with antibiotic resistance.

Pathogenesis and pathophysiology

Bacteria can reach the leptomeninges through bony defects, such as those caused by mastoiditis, or via the bloodstream. The latter is the most common route taken by classical meningeal pathogens. Pathogens such as *S pneumoniae*, *N meningitidis*, and group B streptococci initially colonise epithelial surfaces either in the respiratory tract (*S pneumoniae* and *N meningitidis*) or in the gastrointestinal or lower genital tract (group B streptococci).[44] Sustained bacteraemia is important for the development of bacterial meningitis in this context, as illustrated by a genome-wide association analysis of invasive *S pneumoniae* isolates that reported a pneumococcal *PBP1* gene mutation associated with delayed bacterial killing and development of meningitis.[45] Sustained bacteraemia increases the likelihood of a microbial exploitation of the blood–brain barrier or blood–cerebrospinal fluid barrier which is formed of highly specialised endothelial cells and supporting cells, including pericytes and astrocytes.[46]

Bacterial traversal of the blood–brain barrier

Meningeal pathogens express a variety of adhesins and invasins, which enable binding to and traversal of the brain endothelium (table 2). *S pneumoniae* adheres to endothelial cells through selected surface molecules and their interaction with host receptors: the pneumococcal surface protein C and the surface neuraminidase A can ligate to the 67 kDa laminin receptor, and neuraminidase A can also bind to CD31.[46] The cell wall component phosphorylcholine mimicking the host phospholipid

mediator platelet-activating factor can interact with its respective binding partner, the platelet-activating factor receptor.[47] The activation of this receptor is assumed to enhance the expression of CD31 and the polymeric immunoglobulin receptor that function as receptors for the pilus-related pneumococcal adhesin subunit RrgA.[48] These (but also other) bacterial–endothelial interactions facilitate transcellular passage of *S pneumoniae* across the endothelium. *S pneumoniae* can also release toxins such as pneumolysin and hydrogen dioxide, which can cause endothelial monolayer disruption, thus allowing bacteria to cross the blood–brain barrier or blood–cerebrospinal fluid barrier through a paracellular pathway.[46] *N meningitidis* expresses type IV pili (Tfp) mediating bacterial adhesion on CD147 on the host endothelial cells.[49,50] After binding, the meningococcal type IV pilus activates the β2-adrenoceptor, inducing structures in the cytoplasm called cortical plaques.[51] These plaques lead to stimulation of actin polymerisation, resulting in membrane protrusions protecting *N meningitidis* from the complement-mediated lysis and opsonophagocytosis by the immune system and stimulating the opening of the inter-endothelial junctions. *L monocytogenes*, group B streptococci and *E coli* similarly express many factors promoting interaction with the brain endothelium (table 2).[52,53]

Host immune response

Once bacteria have gained access to the leptomeningeal space, they can take advantage of the weaknesses of the host's immune system inside this compartment and multiply almost as efficiently as they can in vitro, resulting in high bacterial concentrations. During their nearly unrestrained proliferation, large quantities of pathogen-associated molecular patterns are released into the leptomeningeal space. Their presence is recognised by specialised host receptors (pattern recognition receptors), which include Toll-like receptors, nucleotide-binding leucine-rich repeat-containing receptors, and scavenger receptors (appendix p 1).[54] Multiple pathogen-associated molecular patterns can trigger more than one pattern recognition receptor. These activated receptors operate in an integrated manner to orchestrate distinct immune responses to invading pathogens and are characterised by the production of selected pro-inflammatory mediators such as cytokines, chemokines, and complement factors (eg, the anaphylatoxin C5a).[55] The secreted chemotactic factors attract highly activated leukocytes, mainly granulocytes, to the brain where they liberate anti-microbial substances, such as strong oxidants and proteolytic enzymes. These molecules can also damage host cells. Stressed and dying host cells can release danger-associated molecules, such as high mobility group box 1 protein or myeloid-related protein 14, that fuel further inflammation through interaction with pattern recognition receptors.[56] The main target of inflammation is the cerebral vasculature; vascular inflammation results in disruption of the blood–brain barrier with consecutive brain oedema formation, as well as in a narrowing or even occlusion of cerebral vessels (figure 1).[57] The importance of coagulation and fibrinolytic dysregulation during pneumococcal meningitis is also illustrated by the high number of cerebrovascular complications that occur in patients with meningitis caused by this bacterium.[57]

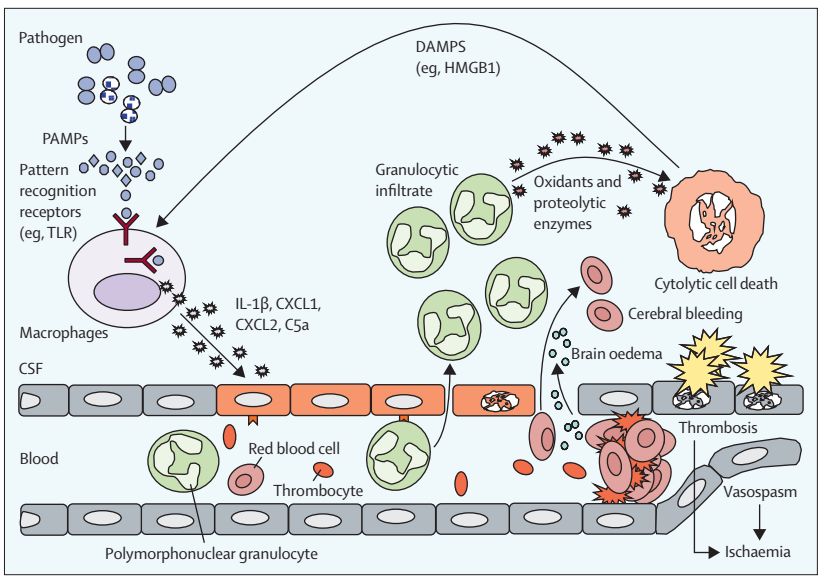

Figure 1: **Schematic diagram of the key pathogenic steps of bacterial meningitis**
Bacterial meningitis develops when pathogens reach the CSF-filled subarachnoid space, either via a haematogenous route or by direct migration from nearby infection. Autolysis or host-induced and antibiotic-induced bacterial lysis results in the liberation of diverse PAMPs. Their presence is recognised by resident immunocompetent cells (eg, macrophages) by means of pattern recognition receptors (eg, TLRs), which results in cell activation and the production of a huge variety of cytokines, chemokines, and complement factors (eg, IL-β, CXCL1, CXCL2, or C5a). Consequently, large numbers of polymorphonuclear granulocytes are recruited into the CSF, which also liberate pro-inflammatory and chemotactic agents, thereby exaggerating and perpetuating inflammation. Also among the factors released by granulocytes are cytotoxic products such as oxidants and proteolytic enzymes that can damage host tissue (eg, by inducing pyroptosis, pyronecrosis, or necrosis). Damaged cells can, in turn, liberate so-called DAMPs, like high mobility group box 1 protein (HMGB1), which can fuel inflammation by interacting with pattern recognition receptors like TLR-4. The main target of inflammation is the cerebral vasculature. Key pathological findings are arterial narrowing due to vasculitis and vasospasm, causing cerebral hypoperfusion and ischaemia. The inflammatory attack on the vessel wall can also lead to the formation of brain oedema, to cerebral bleeding, or thrombosis, thus worsening tissue perfusion and oxygenation. CSF=cerebrospinal fluid. DAMP=damage-associated molecular pattern. PAMP=pathogen-associated molecular pattern. TLR=Toll-like receptor.

In pneumococcal meningitis, neutrophil inflammation can even hinder bacterial clearance. In the cerebrospinal fluid, neutrophil extracellular traps that are released to trap and kill bacteria during infections actually shield pneumococci against the attack by antimicrobial peptides and phagocytosis.[58] The importance of the host immune response is underlined by a recent genome-wide association study on a large number of samples of patients and pathogens of pneumococcal meningitis, revealing that host genetic variation explains 50% of the variation in disease severity, whereas the bacterial genome did not affect disease severity.[59] As shown by a substantial body of experimental work and the clinical observation of the beneficial treatment of pneumococcal meningitis with dexamethasone,[60,61] blockade of check-points of the inflammatory cascade is highly promising in ameliorating the outcome of bacterial meningitis.

See Online for appendix

Clinical presentation

Early recognition of patients with bacterial meningitis is needed because of the urgent need for treatment. Children and adults with bacterial meningitis most commonly present with headache, neck stiffness, fever, and an altered mental status, with each of these symptoms occurring in 70–80% of patients.[9] However, the combination of neck stiffness, fever, and an altered mental status, known as the classic triad of meningitis, is present in only 40–50% of patients.[5,62] Moreover the differential diagnosis in a patient presenting with fever, headache, and neck stiffness is broad and includes central nervous system infection, malaria, autoimmune inflammatory diseases, drug-induced aseptic meningitis, carcinomatous or lymphomatous meningitis, and, when onset of headache is acute, subarachnoid haemorrhage.[63,64]

Neonates with bacterial meningitis often present with nonspecific signs and symptoms, such as poor feeding, irritability, hypertonia or hypotonia, and respiratory distress.[9] Fever and seizures are the most common presenting features in neonates presenting with bacterial meningitis.

Extrameningeal foci of infection like otitis, sinusitis, pneumonia, or endocarditis are present in about 43% of patients, and are more likely to occur in episodes of pneumococcal meningitis (51%) than in meningococcal (6%) or listerial meningitis (11%).[5,62] Hypervirulent meningococcal clones have been associated with a primary abdominal infection focus.[65] A large proportion (33%) of adults with bacterial meningitis have a history of immunocompromise. Patients might present with seizures or focal neurological deficits, such as aphasia and hemiparesis, or with cranial nerve palsies. Rashes occur more frequently in patients with meningococcal meningitis, with a reported incidence of 63–80% and a specificity of 83–92% for the diagnosis of meningococcal disease.[66] Rash can also be observed in patients with meningitis caused by *S pneumoniae* and *S suis* infection.[5,20]

Meningeal irritation manifests at physical examination as neck stiffness.[67] Other classic signs of meningeal irritation as described by Kernig and Brudzinski were shown to have poor sensitivity (5–30%) to diagnosis bacterial meningitis.[68] Naturally, physicians rely on several tests to diagnose meningitis, and in clinical practice, local epidemiology, multiple clinical characteristics, and test results will be used to estimate the likelihood of bacterial meningitis.[67]

Diagnosis

Cerebrospinal fluid examination is essential in the diagnostic workup of all patients with suspected meningitis. Prior to a lumbar puncture, the safety of the procedure should be assessed.[69] Lumbar puncture can be performed safely in the most patients with bacterial meningitis.[70] Nevertheless, in patients with brain shift due to a mass lesion, a lumbar puncture might be contra-indicated due to the risk of brain herniation.[64] Other contraindications for lumbar puncture include coagulopathy, either due to anticoagulant use, severe thrombocytopenia or an uncorrected bleeding diathesis, and local skin infections at the site of the puncture.[69]

We recommend considering cranial imaging prior to lumbar puncture to exclude brain shift (either from a focal space-occupying lesion or severe diffuse brain swelling)[69] in people with these clinical criteria: new-onset seizures, focal neurological deficits, an immunocompromised state (eg, HIV/AIDS infection or immunosuppressive medication after organ transplantation) or a moderate-to-severe impairment of consciousness.[64,71] A prospective study of 301 adults with suspected meningitis showed absence of characteristics such as an altered level of consciousness, epileptic seizures, focal neurological deficits but not including cranial nerve palsy or an isolated Babinski sign, and a severely immunocompromised state, and had a negative predictive value of 97% for an intracranial abnormality.[72] Since neuroimaging has been identified as risk factor for a delayed antibiotic treatment and poor disease outcome, it is imperative to start antimicrobial treatment and adjunctive dexamethasone therapy before sending the patient for a CT scan.[71]

In the majority (96%) of patients with bacterial meningitis, cerebrospinal fluid examination shows typical abnormalities (a glucose concentration <340 mg/L [1·9 mmol/L], cerebrospinal fluid glucose to blood glucose ratio of <0·23, protein concentration >2200 mg/L, white cell count >2000 cells per µL, or >1180 polymorphonuclear leukocytes per µL).[66] The cerebrospinal fluid opening pressure at the lumbar puncture is often elevated.[62] Several prognostic models have been developed and validated that combine clinical, blood and cerebrospinal fluid characteristics to predict the risk of bacterial meningitis. Although these models show a fair to good prognostic value, the incremental value of such models in addition to the physician's clinical judgement is unclear.[73] A prospective series of patients with suspected central nervous system infection showed that combining clinical characteristics, blood, and cerebrospinal fluid parameters did not provide a more accurate diagnostic test than the cerebrospinal fluid leukocyte count alone in predicting bacterial meningitis.[63] Cerebrospinal fluid lactate has been found to accurately discriminate bacterial meningitis from aseptic meningitis, except in patients who received antibiotic treatment prior to the lumbar puncture, but the incremental diagnostic value in addition to routine measurements remains unclear.[66,74]

Cerebrospinal fluid culture is the gold standard for the diagnosis of bacterial meningitis, being positive in 85% of cases, while allowing antimicrobial sensitivity testing of the identified pathogen.[9] In a multicentre cohort study of adults with suspected meningitis, cranial imaging delayed lumbar puncture, with an associated reduced diagnostic yield from cerebrospinal fluid culture,[75] emphasising the importance of early lumbar puncture if safe and consequently the need of imaging only when

indicated. Cerebrospinal fluid Gram staining can quickly identify bacteria with a high specificity.[9] Bacterial antigen testing in cerebrospinal fluid can provide a rapid diagnosis but was previously found to have little additional value compared with cerebrospinal fluid culture and Gram stain,[9] although a 2020 validation study showed high sensitivity and a high negative predictive value for the identification of meningococcal antigens.[76] Such a test could be especially useful in low-income countries in the meningitis belt with few laboratory facilities. Blood cultures are positive in up to 75% patients with community-acquired bacterial meningitis, depending on causative pathogen, time of presentation, and help-seeking behaviour, and should be included in the routine workup of those with suspected bacterial meningitis.[71] Gram staining and culture of skin lesions can identify the pathogen in patients with suspected meningococcal disease,[9] and is especially useful when a lumbar puncture is contraindicated because of coagulation disorders.

The use of PCR to identify bacterial DNA in cerebrospinal fluid or blood has become a quick and highly specific alternative to microscopy and culture. The diagnostic accuracy of PCR in cerebrospinal fluid has been primarily studied for *S pneumoniae*, *N meningitidis*, and *H influenzae*, and was found to be nearly 95–100% in case of culture-positive bacterial meningitis.[66] Multiplex PCR point-of-care panels have recently been developed to provide rapid diagnosis within hours. Included pathogens are commonly *E coli*, *H influenzae*, *L monocytogenes*, *N meningitidis*, *S pneumoniae*, and *S agalactiae*.[77] A meta-analysis of the FilmArray meningitis or encephalitis panel (BioFire Diagnostics LLC, Salt Lake City, UT, USA) showed a 90% sensitivity for detection of all pathogens (viral, bacterial, and yeast) and a 97% specificity, with the highest false-positive rate for *S pneumoniae* (2%).[78] These multiplex tests are not comprehensive for all pathogens that cause bacterial meningitis, limiting their utility as a standalone test in bacterial meningitis diagnostics; well-designed prospective studies on these tests are scarce and no randomised trials have been done, so the results are difficult to interpret without confirmatory microbiological tests. There are no good data available showing that PCR and other rapid diagnostic tests alter the management of patients with suspected or proven bacterial meningitis.

Treatment

European Society for Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend treatment for bacterial meningitis to be started as soon as possible, but at least within 1 h of presentation.[71] A prospective cohort study showed this goal was achieved in 46% of patients in the Netherlands, with risk factors for delayed treatment being cranial imaging and the absence of typical clinical features such as neck stiffness and fever.[79] The choice of initial antimicrobial therapy is based on the most common bacteria causing the disease based on age, local antimicrobial susceptibility patterns, and the need to add amoxicillin or ampicillin against *L monocytogenes* (table 3). Neonates should be treated for infection with *E coli* and *S agalactiae*. Extended-spectrum β-lactamase-positive *E coli* outbreaks have been described in neonatal intensive care.[80] Antimicrobial therapy against *L monocytogenes* should be included in the treatment for neonates, adults older than 50 years of age, and immunosuppressed individuals.[71]

Penicillin and cephalosporin resistance in *S pneumoniae* strains has been increasing worldwide during the past four decades,[21] changing the initial therapy of patients with bacterial meningitis in several regions.[3] Meningococcal strains with reduced susceptibility to penicillin have been associated with unfavourable outcomes in meningococcal meningitis.[81] The ESCMID guideline recommends vancomycin and a third-generation cephalosporin as part of the initial treatment, although in areas with very low pneumococcal cephalosporin resistance rates ceftriaxone alone is considered appropriate.[71] Once the causative pathogen and bacterial antimicrobial susceptibility patterns have been determined, therapy must be optimised. Individuals who have been in close contact with patients

	Bacterial pathogens	Empirical therapy*
Age <1 month	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes*	Amoxicillin or ampicillin plus cefotaxime; or amoxicillin or ampicillin plus an aminoglycoside
Age 1–23 months	*S agalactiae, E coli, Streptococcus pneumoniae, Neisseria meningitidis*	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)†
Age 2–50 years	*S pneumoniae, N meningitidis*	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)†
Age >50 years	*S pneumoniae, N meningitidis, L monocytogenes*, aerobic Gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)
Immunocompromised patients	*S pneumoniae, N meningitidis, L monocytogenes, Staphylococcus aureus, Salmonella* spp, aerobic Gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin plus ampicillin plus either cefepime or meropenem
Patients with recurrent meningitis	*S pneumoniae, N meningitidis, H influenzae*	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)
Patients with basilar skull fracture	*S pneumoniae, H influenzae*, group A b–haemolytic streptococci	Vancomycin plus a third-generation cephalosporin (either cefotaxime or ceftriaxone)

*The preferred total daily intravenous doses in patients with normal renal and hepatic function are as follows: neonates aged <1 week: ampicillin 150 mg/kg/day; cefotaxime 100–150 mg/kg/day; gentamicin 5 mg/kg/day. Neonates aged 1–4 weeks: ampicillin 200 mg/kg/day; gentamicin 7·5 mg/kg/day; tobramycin 7·5 mg/kg/day; amikacin 30 mg/kg/day; cefotaxime 150–200 mg/kg/day. Infants and children aged >4 weeks: vancomycin 60 mg/kg/day to achieve serum trough concentrations of 15–20 mg/mL; cefotaxime 225–300 mg/kg/day; ceftriaxone 80–100 mg/kg/day. Adults: vancomycin 30–60 mg/kg/day to achieve serum trough concentrations of 15–20 mg/mL; ceftriaxone 4 g/day; cefotaxime, 8–12 g/day; cefepime 6 g/day; ceftazidime 6 g/day; amoxicillin or ampicillin 12 g/day; penicillin 24 million units/day; meropenem 6 g/day. In patients with impaired renal function, the loading—or initial—dose of the antibiotic is based on the extracellular fluid volume and is not altered in the presence of decreased renal function; subsequent doses or dosing interval require alteration in patients with impaired renal function.
†Add amoxicillin or ampicillin if meningitis caused by *L monocytogenes* is also suspected.

Table 3: **Empirical antibiotics for presumed bacterial meningitis by age group or risk factor[3,71]**

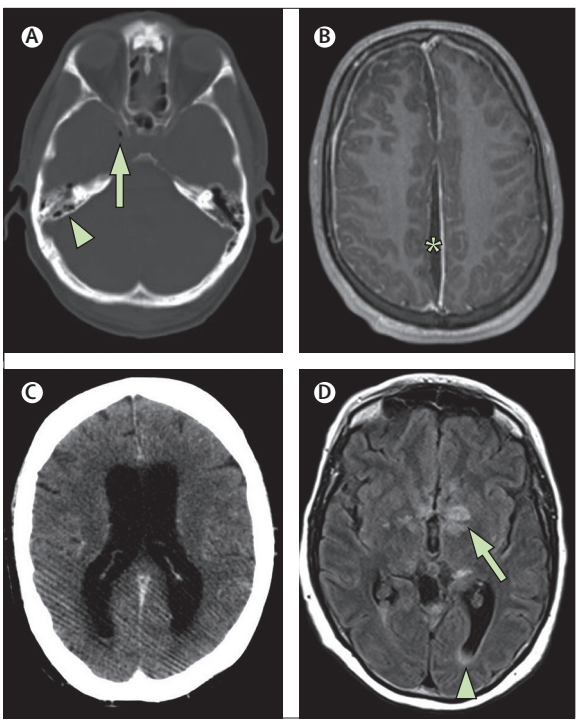

Figure 2: **Cranial imaging of complications**
(A) Opacification of the mastoid cells (arrowhead) and intracranial air (arrow) on an axial CT image. (B) T1-weighted MRI of parafalcine subdural empyema (asterisk), with mass effect on right hemisphere. (C) CT of hydrocephalus. (D) Multiple bilateral T2-weighted fluid-attenuated inversion recovery hyperintense lesions (arrow) in a patient with secondary deterioration consistent with delayed cerebral ischaemia and ventriculitis with intraventricular sediment (arrowhead).

with meningococcal meningitis should be treated with antibiotic prophylaxis.[44]

Adjunctive dexamethasone therapy is recommended in patients with bacterial meningitis beyond the neonatal age (from 6 weeks upwards) in countries with a high level of medical care.[71,82,83] Randomised controlled trials and meta-analyses have shown that dexamethasone therapy reduces hearing loss and neurologic sequelae in children and neurological sequelae and death in adults with bacterial meningitis caused by *S pneumoniae*.[60,61,84] Cohort studies have shown improved outcomes of bacterial meningitis after implementation of adjunctive dexamethasone therapy in several countries.[5,85–87] No beneficial effects of adjunctive corticosteroids have been identified in studies done in low-income countries.[60,88] Dexamethasone treatment should be started with the first dose of antibiotics (table 3) and continued for 4 days. In patients in whom antibiotic treatment has already been started, adjunctive dexamethasone treatment can still be started up to 4 h after starting antibiotics.[71]

Dexamethasone should be continued for 4 days in all patients, except in those with *L monocytogenes*. A prospective cohort study found a reduced survival in patients with neurolisteriosis treated with adjunctive dexamethasone.[17] The use of dexamethasone is also not recommended for neonates because of the paucity of randomised studies using this drug in neonates. In adults with bacterial meningitis, adjunctive therapy with moderate hypothermia and glycerol were associated with worse outcomes in randomised, controlled studies.[89,90]

Complications and outcome

Common complications of bacterial meningitis are hearing loss,[91] hydrocephalus,[92] seizures,[93] and cerebrovascular complications (figure 2).[64] The mechanisms of these complications are discussed elsewhere.[44,46,57,94] Co-existing septic shock has been identified as a predictor for poor outcome.[62] For patients with a decline in consciousness, or those whose condition fails to improve within 48 h after starting appropriate therapy, brain imaging is indicated to detect hydrocephalus,[92] brain infarction, empyema, or a developing brain abscess.[95] Seizures should prompt the initiation of anti-seizure medication. A non-convulsive status epilepticus should be ruled out with an electroencephalogram if consciousness is not regained or if it fluctuates.[93]

Cerebrovascular complications are particularly common in pneumococcal meningitis.[96] In pneumococcal meningitis, arterial stroke occurs in up to 30% of patients, cerebral venous thrombosis in up to 9%, and intracerebral hemorrhage in up to 9%.[97] Anti-coagulant treatment should generally be withheld in patients with bacterial meningitis as it is associated with high risk for intracerebral haemorrhage.[94] Delayed cerebral thrombosis is a rare complication in patients with pneumococcal meningitis, involving a hyperinflammatory syndrome and extensive cerebral infarction, days to weeks after initial good recovery.[98] Adjunctive dexamethasone therapy seems to predispose to this devastating complication, as does an initially high level of complement factor C5a.[99] In patients with delayed cerebral thrombosis, there might be a need for prolonged immunosuppression, for example with a longer duration of dexamethasone treatment.[99]

Intensive observation and early treatment of complications[92,95] might improve a patient's outcome, but nevertheless a fulminant disease course can still result in severe brain damage and death. Aggressive treatment for intracranial pressure using high doses of corticosteroids, osmotic diuretics, ventriculostomy, and even decompressive craniectomy has been advocated,[100] but is not supported by existing evidence. Nevertheless, in case of impeding brain herniation, placement of an intracranial pressure monitor can be considered. Therapy should not be withdrawn early during admission in comatose patients with preserved brainstem reflexes, since a prospective cohort study has shown that even in these severe cases a quarter of patients eventually fully recovered.[101]

Case-fatality rates from bacterial meningitis vary with age, specific risk factors, causative pathogen, and

country income status.[2] Global meningitis case-fatality rates have fallen during the past three decades in response to early disease recognition and treatment, use of highly effective broad-spectrum antimicrobials, and adjunctive treatment with dexamethasone in high-income countries, but the disease burden remains high.[2] Reported case-fatality rates for pneumococcal meningitis range from 10–37% in high-income countries and are up to 54% in low-income countries.[2,5,62] Case-fatality rates for meningococcal meningitis are 3–10% in both high-income and low-income countries.[2,5,62] Listerial meningitis has a reported case-fatality rate of 35%,[17,18] whereas the reported rate for neonates with group B streptococcal meningitis is 4–6%. Neurological sequelae are estimated to occur in a substantial number of surviving patients: about half of survivors suffer from focal cerebral deficits, including hearing loss, epilepsy, and cognitive impairment.[102,103] After a bacterial meningitis infection, adults are at high risk of long-term neurological and neuropsychological deficits that impair their daily life activities and quality of life.[102] Meningitis sequelae have a substantial economic burden on health-care systems.[2]

Secondary prevention

Recurrence of meningitis occurs in 7% of patients, with risk factors for recurrence including cerebrospinal fluid leakage and specific immunodeficiencies such as asplenia or hyposplenism.[104,105] In patients with meningitis and persistent cerebrospinal fluid leakage, surgical repair of the leakage and vaccination against *S pneumoniae*, *N meningitidis*, and *H influenzae* type B are advised.[71,106] Patients with asplenia or hyposplenism should be vaccinated against *S pneumoniae* and *H influenzae* type B.[71] The ESCMID guideline on acute bacterial meningitis advises that after pneumococcal meningitis, all patients should be vaccinated with both PPV23 and PCV13, because of the high risk for recurrence.[71] A meta-analysis of five randomised controlled trials and 18 comparative studies showed no evidence supporting antibiotic prophylaxis against meningitis in patients with skull base fractures.[107]

Challenges

The implementation of conjugate vaccines against the most common causative pathogens of bacterial meningitis has led to substantial reductions in the meningitis disease burden. For the first time, effective vaccines against all meningococcal serogroups are available or are nearing licensure.[108] Extension of vaccination programmes using available conjugate vaccines in Africa and Asia will be key to further reduce the global disease burden of meningitis. There are substantial divergences for mass vaccination strategies, even within Europe.[108] Vaccination programmes should aim for both direct prevention and also maximised herd protection, helping to protect infants who are too young to be fully immunised and elderly people (aged ≥65 years) who have a poor immunological response to vaccination. Enhanced surveillance systems, including bacterial whole-genome sequencing, are needed to monitor the effects of vaccine implementation, but also to detect emerging pathogens and guide vaccine development. Replacement of causative pathogens by non-vaccine serotypes reported in several countries shows that pneumococcal meningitis continues to pose a major challenge. We need new approaches to prevention, new vaccines, and continued efforts to improve treatment for patients with pneumococcal meningitis. Conjugate group B streptococcal polysaccharide vaccines have been shown to be safe and immunogenic in phase 1 and 2 trials in pregnant women.[109,110] This finding bodes well for maternal group B streptococcal immunisation, but vaccine efficacy, disease burden, and cost-efficacy all need to be evaluated with care prior to implementation.

Host–pathogen interactions should be studied in detail, over the different disease compartments, for example for pneumococcal meningitis in the nasopharynx, blood and cerebrospinal fluid compartments, including spatio-temporal variations in the expression of bacterial virulence factors.[59] Knowledge about the pathways by which bacteria penetrate the blood– brain barrier could be used to develop new strategies to prevent or even cure bacterial meningitis, such as the reduction of bacterial invasion by specific inhibitors of host brain endothelial receptors. Knowledge about the temporal pattern of the host's inflammatory response in the brain compartment leading to an overwhelming initial inflammatory response, secondary deterioration, and long-lasting cognitive impairment could help to guide the development of new treatments.

Controlling the host's inflammatory response has shown to be key in achieving good outcome. Promising targeted anti-inflammatory treatments, such as metalloproteinase inhibitors, or inhibitors in the complement system and the cytokine receptor signalling pathway, have been identified in experimental studies and await validation in clinical trials.[44,111–113] For example, macrophage migration inhibitory factor has been identified as a predictor of morbidity and mortality of pneumococcal meningitis.[114] Inter-individual differences in macrophage migration inhibitory production has been associated with long-term cognitive impairment 1–5 years after pneumococcal meningitis, suggesting a potential role for macrophage migration inhibitory factor as a target of immune-modulating adjunctive therapy.[115] For neonates with bacterial meningitis, randomised, controlled trials should evaluate the use of adjunctive dexamethasone treatment.

The use of multiplex PCR point-of-care panels to diagnose bacterial meningitis requires evaluation with prospective clinical cohort studies and the impact of implementation of panels in clinical practice should be investigated in randomised clinical studies before they can be introduced into practice. Existing knowledge should be implemented in improved hospital protocols

and logistics, which should aim to start treatment at least within 1 h of presentation.[71]

Contributors

All authors contributed to the design, literature search, interpretation, and writing of this Seminar.

Declaration of interests

We declare no competing interests.

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