Acute bacterial meningitis

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Purpose of review
Community-acquired bacterial meningitis is a continually changing disease. This review summarises both dynamic epidemiology and emerging data on pathogenesis. Updated clinical guidelines are discussed, new agents undergoing clinical trials intended to reduce secondary brain damage are presented.

Recent findings
Conjugate vaccines are effective against serotype/serogroup-specific meningitis but vaccine escape variants are rising in prevalence. Meningitis occurs when bacteria evade mucosal and circulating immune responses and invade the brain: directly, or across the blood–brain barrier. Tissue damage is caused when host genetic susceptibility is exploited by bacterial virulence. The classical clinical triad of fever, neck stiffness and headache has poor diagnostic sensitivity, all guidelines reflect the necessity for a low index of suspicion and early Lumbar puncture. Unnecessary cranial imaging causes diagnostic delays. cerebrospinal fluid (CSF) culture and PCR are diagnostic, direct next-generation sequencing of CSF may revolutionise diagnostics. Administration of early antibiotics is essential to improve survival. Dexamethasone partially mitigates central nervous system inflammation in high-income settings. New agents in clinical trials include C5 inhibitors and daptomycin, data are expected in 2025.

Summary
Clinicians must remain vigilant for bacterial meningitis. Constantly changing epidemiology and emerging pathogenesis data are increasing the understanding of meningitis. Prospects for better treatments are forthcoming.

Keywords
antibiotics, dexamethasone, meningitis, pathogenesis, vaccines

INTRODUCTION

Acute bacterial meningitis (ABM) is a disease with rapid onset, outbreak and epidemic potential, and high rates of mortality and morbidity [1,2]. Considerable advances have been made in the last 30 years towards epidemic management and disease control through vaccination, and understanding the contributions of both host and pathogen to clinical outcomes. In this review, we will summarise the rapidly changing epidemiology of ABM in the context of new vaccines. We will show how new unbiased genomics technologies are revealing specific host–pathogen interactions that cause inflammation and brain damage. Additionally, we will summarise which new adjunctive treatments are in development and describe how the current Severe Acute Respiratory Syndrome CoronaVirus2 (SARS-CoV2) pandemic may impact on the WHO's efforts to defeat meningitis by 2030.

EPIDEMIOLOGY AND IMPACT OF VACCINATION

Community-acquired bacterial meningitis is predominately caused by three pathogens, *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* type B. Additionally, *Streptococcus suis* in Southeast Asia, *Listeria monocytogenes,* Group B Streptococci, and Gram-negative bacteria such as *Escherichia coli* and *Klebsiella pneumoniae,* cause meningitis in specific groups, including neonates, pregnant women, transplant recipients and older adults [3]. Worldwide, the number of reported cases of bacterial meningitis to global surveillance sites rose between 2006 and 2016, with incidence strongly

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Curr Opin Neurol 2021, 34:386–395

DOI:10.1097/WCO.0000000000000934

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KEY POINTS

- The epidemiology of bacterial meningitis is regional and highly dynamic, influenced by vaccines, climate, latitude, population movement, viral infections and poverty.
- Serotype/serogroup specific conjugate vaccines are highly effective in preventing meningitis, but serotype replacement is increasing, effectively limiting the impact of conjugate vaccines on disease incidence
- Host and pathogen factors influence clinical outcomes, host genetic susceptibility to poor outcome from pneumococcal meningitis is linked to genes involved in NF-κB signalling and endothelial integrity.
- Dexamethasone improves outcome in pneumococcal meningitis in high-income settings only, new agents targeted on the host response are currently in clinical trials.

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related to poverty (SDI) [3]. However, the geographical incidence varies significantly. In well-resourced settings, ABM incidence has fallen to below 0.5–1.5/100 000 population [4,5,6▪▪]. Contrastingly, in countries in the African Sahel region, where epidemic meningitis due to *N. meningitidis* and *S. pneumoniae* persists, incidence reaches 1000/100 000 cases [3,7–9]. Beyond the meningitis belt, the incidence in Africa approaches 2.5–25/100 000 per population [10,11].

Bacterial meningitis is globally associated with cooler, drier seasons [9]. It is likely that climate change will impact on meningitis incidence but modelling data are lacking [11]. Social distancing measures introduced to mitigate the spread of SARS-CoV2 during the CoronaVirus Infectious Diseases 2019 pandemic are also predicted to lead to a 20–30% decrease in meningitis incidence [12▪,13].

Global meningitis epidemiology is highly dynamic; changes in the last 25 years amongst adults and children have been influenced by the widespread use of conjugate vaccines [14–16], the HIV-1 epidemic [17–19], the roll-out of antiretroviral and antibacterial treatment including prevention of mother-to-child transmission [20,21], and significant progress on development and poverty reduction strategies (SDG), including improved maternal and neonatal care [22].

Vaccination remains the most important pillar of the WHO-led roadmap towards defeating meningitis by 2030 [23]. A summary of all available vaccines against the three common pathogens is given in Table 1.

Streptococcus pneumoniae

S. pneumoniae is the commonest cause of ABM world-wide. Reports of reduction in paediatric invasive pneumococcal disease (IPD), following pneumococcal conjugate vaccine introduction in higher-income countries, were rapidly followed by evidence of herd immunity in the wider adult population, particularly the elderly [24–26]. Incidence of *S. pneumoniae* meningitis is estimated to have fallen by 48% in children [14,16,27]. However, parallel reports have emerged of IPD, including meningitis, caused by nonvaccine serotypes [14,28–30]. To mitigate against serotype replacement and better prevent meningitis, new approaches to pneumococcal vaccine design are under development, including whole capsule and protein vaccines [31–34,35▪].

Neisseria meningitidis

Conjugate meningococcal vaccines are highly effective in preventing meningitis caused by individual serogroups. Serogroup C Incidence has declined dramatically following the introduction of Men-C vaccine in children in many high-income countries [36–38]. Epidemic meningitis caused by serogroup A in the Sahel region of Africa has been dramatically reduced by low-cost MenAfriVac serogroup A conjugate vaccine by 92% [39,40]. However, virulent clones of other serogroups have subsequently emerged (C, W, X) and epidemics of meningococcal meningitis continue to occur in the Sahel [41,42].

As serogroup C disease declined, serogroup B emerged as the leading cause of meningococcal meningitis in high SDI countries [15]. In 2015, the UK government introduced protein-based serogroup B vaccine 4CMenB (Bexsero) to all children under 2 years. UK cases of invasive serogroup B in children have declined 75% with an estimated overall vaccine efficacy of 54% [43]. However, disease due to other serogroups including W and Y remains problematic. MenC conjugate vaccine has now been replaced with quadrivalent MenACWY vaccine for all teenagers and young adults in the UK [38].

Haemophilus influenzae

Hib vaccination in 1989 led to dramatic reductions in paediatric meningitis between 75 and 95% [44,45]. Subsequently, Hib meningitis has virtually been eliminated globally in countries with effective Expanded Programme of Immunisations (EPI), but persists where vaccination coverage is poor including India, Nigeria, Pakistan and the Democratic Republic of Congo [16,44,46,47]. Hib conjugate vaccines are estimated to have reduced Hib meningitis by 49% globally 2000–2016 [3], and paediatric

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Table 1. Currently available vaccinations against meningitis-pathogens

Vaccine formulation	Vaccine name	Serotypes 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, 33F	NA	Pneumovax
Conjugate	PCV-7	4, 6B, 9V, 14, 18C, 19F, 23F	CRM197[a]	Prevenar
Conjugate	PCV-10	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19A, 19F	Protein D, diphtheria toxoid, tetanus toxoid	Synflorex
Conjugate	PCV-10	1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F	CRM197	Pneumosil
Conjugate	PCV-13	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F	CRM197	Prevenar 13
Neisseria meningitidis				
Conjugate	MenACWY	ACWY	CRM197, diphtheria toxoid	Menactra, Menveo Serum Institute of India (in development)
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	Trumemba
Protein	4CMenB	B	Not used	Bexsero
Haemophilus influenzae				
Conjugate	Monovalent	Type b	CRM197	Menitorix, Pediacel

[a]CRM197 = nontoxic variant of diphtheria toxin.
NA, Not available; PCV, Pneumococcal Conjugate Vaccine; PPV, Pneumococcal Polysaccharide Vaccine.

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deaths by 90% over the same time period [16]. However, it is concerning that non-type b stains such as Hia are emerging [42].

Group B *Streptococcus*

Streptococcus agalactiae (Group B *Streptococcus*, GBS) primarily causes meningitis in neonates but also causes sepsis in older adults with co-morbidities and young adults who have consumed contaminated fish [48]. Serotypes Ia, Ib, II, III and V account for 98% of human carriage serotypes isolated globally [49]. Clonal complex 17 (CC17) strains have been shown to be hypervirulent, accounting for more than 80% of the disease [50,51]. GBS disease-causing lineages have distinct niche adaptation and virulence characteristics [52,53]. The most promising strategy to eliminate neonatal meningitis caused by GBS is vaccination in pregnancy, trials are ongoing [54–57].

PATHOGENESIS

The pathogenesis of most ABM follows a sequential pattern: nasopharyngeal colonization, bloodstream invasion across the mucosa, circulation of bacteria to the central nervous system (CNS), and subsequent CNS entry [58▪,59]. In ABM caused by *L. monocytogenes*, GBS and *S. suis*, bacteraemia has a gastrointestinal or genitourinary tract source [52,60,61]. Occasionally, ABM is acquired through direct CNS invasion through the cribriform plate [62,63]. In the majority of immunocompetent individuals, colonisation of the nasopharynx by *S. pneumoniae* and *N. meningitidis* is cleared by mucosal immunity, despite epithelial invasion [58▪]. Co-infection with *S. pneumoniae* and respiratory viruses such as influenza causes a heightened inflammatory state associated with both pneumococcal and meningococcal invasion [64–66], indeed preceding influenza is associated with seasonal ABM [11,67▪].

Bacteraemia usually precedes translocation across the blood–brain barrier (BBB) and/or blood–cerebrospinal fluid barrier into the CNS. Under basal conditions, the CNS environment is under continuous immunological surveillance [68]. This is achieved through the complexity of the BBB, where pericytes, astrocytes, microglia and specialised endothelial cells work in synergy

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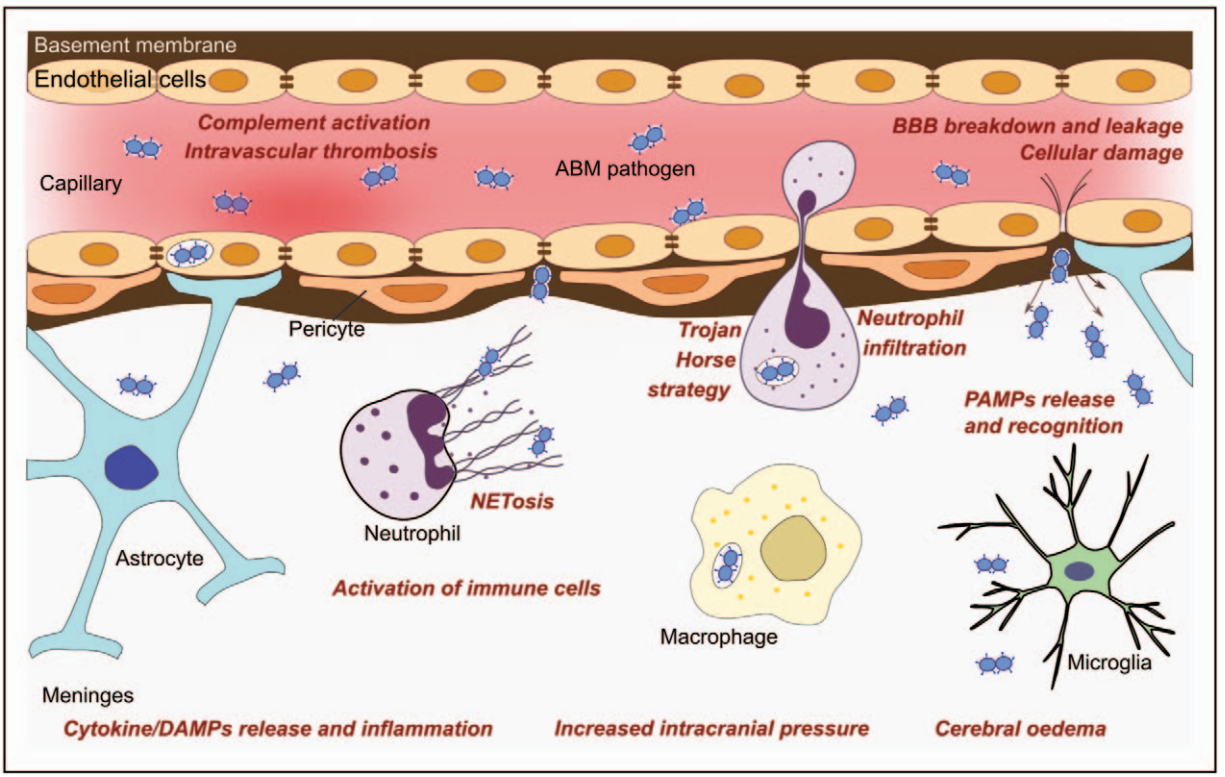

FIGURE 1. Model of BBB environment during bacterial meningitis. ABM pathogen (depicted here as blue diplococci) in the bloodstream cross the capillary endothelium using both transcellular and paracellular routes. Bacteria may also be carried across the BBB by infiltrating phagocytes (Trojan Horse strategy). Recognition of the pathogen via sensing of PAMPs leads to the activation of resident immune cells such as microglia, macrophages, astrocytes and pericytes and production of DAMPs. These cells produce a coordinated inflammatory response to contain bacteria and recruit more neutrophils to the CSF compartment. This host response, while important for killing bacteria, activates a fibrinolytic and coagulation cascade. When advanced, these processes lead to sustained tissue damage, BBB breakdown and leakage, causing death or lifelong neurological sequalae in survivors. ABM, acute bacterial meningitis; BBB, blood–brain barrier.

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to both resist pathogen invasion and kill bacteria on entry [68] (Fig. 1). Bacteria breach the BBB by interacting with laminin receptors and exploiting endocytic pathways, for example via Platelet Activating Factor Receptor signalling [69–72] (Fig. 1). However, mechanisms by which ABM-causing bacteria subvert CNS barriers to cause meningitis are not fully described.

In the 10–30% of ABM cases without concurrent bacteraemia [73], bacteria may interact with gangliosides, adhere to the olfactory bulb, invade the olfactory epithelium and directly translocate to the brain [63,74–77]. Pneumococcal strains causing nonhematogenous meningitis tend to be less frequently studied using bacteraemia-based animal models [75–77].

Inflammation and exacerbation of tissue damage in acute bacterial meningitis

Bacteria replicate rapidly in the relatively immune-privileged CNS compartment [78], releasing Pathogen Associated Molecular Pattern (PAMP)s that bind to toll-like receptors including 2,3,4 and 9, triggering the release of Damage-Accoiated Molecular Pattern Signallings (DAMPs) via Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF-κB) activation [79–82]. The subsequent release of extracellular cytokines and chemokines including Chemokine family Ligand 8 and cerebrospinal fluid (CSF)-3 drives a rapid influx of neutrophils to the CSF compartment [83▪▪,84].

Bacterial PAMPs and virulence proteins exert direct damage on the delicate structures of the CNS. Pneumococcal virulence factors, including capsule and pneumolysin, reduce microglia motility and chemotaxis [85▪]. Pneumolysin, a cytolysin and Toll Like Receptor 4 agonist is implicated in directly toxic effects on host cells, particularly within the BBB and hippocampus [86,87]. Others stimulate CERB binding protein (CBP) and receptor for advanced glycation end products (RAGE), increasing Tumour Necrosis Factor alpha (TNF-α) levels and promoting BBB disruption [88,89▪].

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Host-detection of bacteria within the CNS triggers a highly inflammatory, and predominately ineffective host response, associated with further tissue damage. Sustained inflammation exacerbates tissue damage, leading to death or irreversible neurological damage [73,90,91]. Neutrophil infiltration is important for bacterial elimination [92]. However, neutrophils can directly damage the CNS [93]. Neutrophil extracellular traps (NETs) unexpectedly impaired CNS pneumococcal clearance and increased inflammatory damage in an experimental model [83▪▪]. Damaging DAMPs released both from neutrophil degranulation and NF-κB signalling include myeloperoxidase, matrix-metalloproteinases, TNF-α and prostaglandins [94▪,95,96,97▪]. Neutrophil-mediated inflammation is strongly associated with dysfunctional coagulation and fibrinolytic cascade in the CNS, including an excess of the anaphylatoxin complement C5 [98].

Clinical improvement with dexamethasone adjunctive therapy in both Hib and pneumococcal meningitis demonstrates the importance of host-mediated inflammation in ABM [99,100]. Dexamethasone may reduce NF-κB signalling and cytokine release [101].

Leveraging new technology to interrogate acute bacterial meningitis pathogenesis

Bacterial genome-wide association studies (GWAS) have revealed loci that are implicated in invasiveness, tissue tropism and the ability to cause CNS disease [102▪▪,103▪▪,104,105]. Single Nucleotide Polymorphisms (SNPs) in the *raf* operon determine pneumococcal tropism for ear/brain or lungs in an intranasal challenge model [106▪,107]. Additionally, SNPs in *raf* modulated neutrophil recruitment, leading to strain-dependent clearance [106▪].

Gene expression in *S. pneumoniae* is niche dependent, highlighting the importance of bacterial metabolism in pathogenesis [108,109▪▪]. In a quantitative proteomics study of ABM, the abundance of pneumococcal protein Elongation Factor Tu in CSF associated with severity in human disease [97▪]. In a murine model, proteins AliB and competence peptides were implicated in pathogenesis [110]. Joint human–pathogen GWAS studies of meningitis patients suggest that genetic differences in the host response exert greater effects on susceptibility and disease severity than bacterial genotype. This GWAS identified variants in the *CCDC3* gene associated with disease severity [102▪▪]. CCDC3 is a multifunction gene involved in the metabolism and suppression of NF-κB–TNFα activation in endothelial cells [111].

NEW DIRECTIONS IN DIAGNOSTICS AND CLINICAL MANAGEMENT

Early recognition and initiation of appropriate antimicrobials are essential to minimise death and complications from ABM. The differential diagnosis in patients presenting with headache, fever, neck stiffness or altered mental state is broad: the classical meningitis triad has limited diagnostic sensitivity [112]. A high index of clinical suspicion is thus required to diagnose ABM [113]. Lumbar puncture is essential, and should be undertaken promptly before CSF is rendered sterile by broad-spectrum antibiotics [114].

Many patients with ABM present with an altered level of consciousness, leading clinicians to frequently request cranial imaging prior to diagnostic lumbar puncture. Early Lumbar puncture (LP) is strongly associated with higher diagnostic yield from the CSF; delays in LP for cranial imaging lead to substantial reductions in yield from either CSF bacterial culture or PCR [114]. Delays to diagnosis are linked to worse clinical outcomes [114–116]. Cranial imaging (either CT or MRI) in patients with clear clinical signs and symptoms of meningitis without focal neurology is thus not recommended in the majority of patients with suspected ABM [117,118]. CT has poor inter-reporting reliability to predict the risk of cerebral herniation in ABM [119]. The American, British and European infection societies meningitis guidelines all recommend immediate LP in cases of suspected ABM without delay for CT/MRI in immunocompetent adults with suspected ABM who have a stable GCS of $\geq$12/15 without seizures [119–123]. Important contraindications to LP include shock, respiratory compromise, or coagulopathy.

The diagnosis of ABM is dependent on the analysis of CSF. The leukocyte count remains the strongest predictive value of ABM. Diagnostic models including clinical, CSF and blood data show little additional benefit beyond clinical judgement [111]. Antibiotic administration prior to LP commonly renders the CSF sterile, thus clinicians are increasingly dependent on diagnostic PCR. Recent data suggest that while small multiplex panels targeting Hib, meningococci and pneumococci are highly sensitive and specific [123], larger panels that include viral, nosocomial and rarer community-acquired pathogens have varying sensitivity and specificity and are not currently recommended [124]. More recently, direct next-generation sequencing (NGS) and metagenomics of CSF have been proposed to detect pathogens in cases with a high index of clinical suspicion of ABM but negative PCR tests [125▪▪]. While this approach is promising,

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constraints around cost, bioinformatics expertise and clinically relevant turnaround times have limited clinical use of NGS to date [124].

All guidelines recommend patients with suspected ABM should receive parenteral antibiotics within 1 h. However, only 46% of patients in a clinical research study were reported to meet this target, limited by delays in the emergency department [126,127]. Antibiotic choice should be determined by patient risk group, patient allergies, and local guidelines informed by epidemiology, including antimicrobial resistance. Penicillin resistance in *S. pneumoniae* is 15–20% in some settings, but remains <5% in *N. meningitidis* [128,129]. However, quinolone resistance in *N. meningitidis* reaches 70% in Southeast Asia [15,130]. Diagnostic uncertainty in culture-negative meningitis often leads to prolonged dual antibiotic and antiviral therapies, which may be associated with nosocomial complications [114,131▪].

Adjunctive therapies

Adjunctive treatments are designed to reduce secondary inflammation in ABM and decrease the morbidity associated with CNS tissue damage. Inflammation is associated with secondary complications of ABM, including death, deafness, stroke, epilepsy and learning difficulties [91,131▪,132–134]. Delayed cerebral thrombosis is a rare complication of ABM that can occur up to 2 weeks post-admission [135,136].

In hospitals in high-income settings, patients presenting with suspected pneumococcal meningitis should receive adjunctive dexamethasone to reduce mortality [90,137]. In low-income settings, dexamethasone is only indicated in cases of suspected *S. suis* meningitis in Southeast Asia to reduce deafness [137,138]. In other settings, particularly in Low and Middle Income Countries in Africa, dexamethasone is ineffective and should not be given [139].

Other previously tested adjuncts, including hypothermia and glycerol, have been shown to be potentially harmful and should not be administered [140,141].

Emerging therapeutic targets

Empirical antibiotic treatment in most centres for suspected ABM is the third-generation cephalosporin, ceftriaxone [92]. However, bacterial lysis by ceftriaxone releases DAMPs that may prolong damaging inflammation even as bacteria killed [88]. Research in animal models has strongly suggested bacteriostatic antibiotics are associated with less CNS inflammation and improve outcomes [142]. In clinical practice, there are little data to suggest different clinical outcomes occur between bacteriostatic vs. bactericidal antibiotics [143]. As such, there are continued efforts to develop alternatives that reduce sequalae in survivors. A phase 2 clinical trial evaluating the adjunctive use of a nonlytic antibiotic, daptomycin, for pneumococcal meningitis is currently underway (ClinicalTrials.gov identifier NCT03480191). Adjunctive administration of daptomycin may dampen the inflammatory effects of ceftriaxone through currently unknown mechanisms [144].

The damaging coagulation and fibrinolytic cascade in CSF are triggered partly by excess complement C5 [98]. Inhibition of C5 improved outcomes in a murine model, clinical trials of C5 antagonists are currently underway [145].

Newer therapeutic agents with intriguing survival data in animal models are not yet in clinical trials. These include DNAse-1, targeted at disrupting ineffective NETosis, the possible neuroprotective effects of metformin, and matrix-metalloproteinase inhibitors targeted on preventing enzymatic tissue breakdown [83▪▪,146–148]. Proposed adjunctive antipneumococcal therapy includes targeting pneumolysin and P4, a pneumococcal peptide that may inhibit replication [149,150].

CONCLUSION

Community-acquired bacterial meningitis presents ongoing formidable epidemiological and clinical challenges. The ability of meningitis-causing pathogens to evolve in the ecological niche of the nasopharynx during carriage, and escape serotype-specific vaccines has led to new strategies to eliminate disease carriage through serotype-independent vaccination. The outcome of CNS host-pathogen interactions determines clinical sequelae, influenced by host genetic susceptibility.

CSF analysis is essential to make a diagnosis of ABM, leukocyte count remains the most effective predictor of ABM over newer models. Nonindicated cranial imaging introduces significant diagnostic delays. Multiplex PCR panels have increasing utility in ABM diagnostics, however NGS remains a research tool.

Patients with ABM continue to experience significant complications, including death, stroke and deafness. Adjunctive dexamethasone improves survival in high-income countries only, the results of clinical trials of more targeted approaches are awaited. Effective and affordable, pan-serogroup vaccination remains a crucial goal if we are to eliminate this devastating disease.

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Acknowledgements

Financial support and sponsorship

E.W. is supported by a postdoctoral clinical research fellowship from the Francis Crick Institute, and the National Institute for Health Research University College London Hospitals Department of Health's NIHR Biomedical Research Centre. E.C. and R.H. are funded by the National Institute for Health Research (NIHR) (project reference 16/136/46) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK government.

E.C and R.H are funded by the Medical Research Council grant number MR/T016329/1 and the National Institute for Health Research (NIHR) (project reference 16/136/46) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK government.

Conflicts of interest

There are no conflicts of interest.

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