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Review

CNS inflammatory disorders: Infectious Diseases

Acute Bacterial Meningitis

Emma C Wall[1,2], Jia Mun Chan[2], Eliza Gil[2], Robert S Heyderman[2]

1. Francis Crick Institute, London, UK
2. NIHR Mucosal Pathogens Research Unit, Department of Infection, Division of Infection and Immunity, University College London, UK

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Correspondence to:

Dr Emma Wall NE424 Francis Crick Institute, 1 Midland road, London NW1 1AT.

emma.wall@crick.ac.uk

+44203 7960000

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Structured abstract

***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 LP. Unnecessary cranial imaging causes diagnostic delays. CSF culture and PCR are diagnostic, direct next-generation sequencing of CSF may revolutionise diagnostics. Administration of early antibiotics are essential to improve survival. Dexamethasone partially mitigates CNS 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.

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 SARS CoV2 pandemic may impact on the WHO's efforts to defeat meningitis by 2030.

Main text

Epidemiology & 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]. World-wide, the number of reported cases of bacterial meningitis to global surveillance sites rose between 2006-2016, with incidence strongly related to poverty (SDI)[3]. However, geographical incidence varies significantly. In well-resourced settings, ABM incidence has fallen to below 0.5-1.5/100,000 population[4-6]. Contrastingly, in countries in the African Sahel region, where epidemic meningitis due to *Neisseria meningitidis* and *Streptococcus pneumoniae* persists, incidence reaches 1000/100,000 cases[7, 8],[3, 9]. Beyond the meningitis belt, 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 spread of SARS CoV2 during the COVID-19 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 widespread use of conjugate vaccines[14-16], the HIV-1 epidemic[17-19], 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 PCV 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 non-vaccine 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[31-35].

N. 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 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].

H. influenzae

Hib vaccination in 1989 led to dramatic reductions in paediatric meningitis between 75-95%[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 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 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[54-56] [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 GI or GU 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 and/or blood-cerebrospinal fluid barriers 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 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 PAFR 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 non-hematogenous meningitis tend to be less frequently studied using bacteraemia-based animal models[75-77].

Inflammation and exacerbation of tissue damage in ABM

Bacteria replicate rapidly in the relatively immune-privileged CNS compartment[78], releasing PAMPs that bind to toll-like receptors including 2,3,4 and 9, triggering the release of DAMPS via NFkB activation[79-82]. The subsequent release of extracellular cytokines and chemokines including CXCL8 and 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 TLR4 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 TNF-a levels and promoting BBB disruption[88, 89].

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 extra-cellular traps (NETs) unexpectedly impaired

CNS pneumococcal clearance and increased inflammatory damage in an experimental model[83]. Damaging DAMPS released both from neutrophil degranulation and NFkB signalling include myeloperoxidase, matrix-metalloproteinases, TNF-α and prostaglandins[94-97]. Neutrophil-mediated inflammation is strongly associated with dysfunctional coagulation and fibrinolytic cascade in the CNS, including 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 NFkB signalling and cytokine release[101].

Leveraging new technology to interrogate ABM pathogenesis

Bacterial genome wide association studies (GWAS) have revealed loci that are implicated in invasiveness, tissue tropism and the ability to cause CNS disease[102-104]*[105]*. 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 studies of ABM, the abundance of pneumococcal protein EF-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 exerts 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 multi-function gene involved in metabolism and suppression of NFkB- 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 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 >= 12/15 without seizures[120-123]. Important contraindications to LP include shock, respiratory compromise, or coagulopathy.

The diagnosis of ABM is dependent on 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[112]. Antibiotic administration prior to LP commonly renders the CSF sterile, thus clinicians are increasingly dependent on diagnostic polymerase chain reaction (PCR). Recent data suggest that while small multiplex panels targeting Hib, meningococci and pneumococci are highly sensitive and specific[124], larger panels that include viral, nosocomial and rarer community acquired pathogens have

varying sensitivity and specificity and are not currently recommended[125]. More recently, direct next generation sequencing (NGS) and metagenomics of CSF have been proposed to detect pathogens in cases with high index of clinical suspicion of ABM but negative PCR tests[126]. While this approach is promising, constraints around cost, bioinformatic expertise and clinically-relevant turnaround times have limited clinical use of NGS to date[125].

All guidelines recommend patients with suspected ABM should receive parenteral antibiotics within 1 hour. However, only 46% of patients in a clinical research study were reported to meet this target, limited by delays in the emergency department[127, 128]. 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* [129, 130]. However, quinolone resistance in *N. meningitidis* reaches 70% in SE Asia[15, 131]. Diagnostic uncertainty in culture negative meningitis often leads to prolonged dual antibiotic and anti-viral therapies, which may be associated with nosocomial complications[114, 132].

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, 132-135]. Delayed cerebral thrombosis is a rare complication of ABM that can occur up to 2 weeks post admission[136, 137].

In hospitals in high-income settings, patients presenting with suspected pneumococcal meningitis should receive adjunctive dexamethasone to reduce mortality[90, 138]. In low-income settings, dexamethasone is only indicated in cases of suspected *S. suis* meningitis in SE Asia to reduce deafness[138, 139]. In other settings, particularly in LMICs in Africa, dexamethasone is ineffective and should not be given[140].

Other previously tested adjuncts, including hypothermia and glycerol, have been shown to be potentially harmful and should not be administered[141, 142].

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 have strongly suggested bacteriostatic antibiotics are associated with less CNS inflammation and improve outcomes[143]. In clinical practice, there are little data to suggest different clinical outcomes occur between bacteriostatic vs bactericidal antibiotics[144]. 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[145].

The damaging coagulation and fibrinolytic cascade in CSF is triggered partly by excess complement C5[98]. Inhibition of C5 improved outcomes in a murine model, clinical trials of C5 antagonists are currently underway[146].

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 neuro-protective effects of metformin, and matrix-metalloproteinase inhibitors targeted on preventing enzymatic tissue breakdown[83, 147-149]. Proposed adjunctive anti-pneumococcal therapy includes targeting pneumolysin and P4, a pneumococcal peptide that may inhibit replication [150, 151].

Conclusions

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. Non-indicated 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.

Summary bullet 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 NFkB 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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Figure titles & legends

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.

Tables

Table 1: Currently available vaccinations against meningitis-pathogens

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