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KEY POINTS

- Several adjuvant therapies to attenuate the injurious proinflammatory reaction in pneumococcal meningitis have been identified in animal experiments but have not been tested in human patients yet.
- Inhibition of the complement system, reduction of the release of proinflammatory bacterial components by using nonlytic antimicrobials, and prevention of IFN-γ and MMP-mediated inflammatory processes including BBB breakdown seem to be promising candidates for adjuvant therapy.
- Protein-based pneumococcal vaccines are currently being studied in early phase clinical trials and promise to provide broader coverage than current conjugate pneumococcal vaccines.
- Emerging antimicrobial-resistant *S. pneumoniae* strains have been isolated necessitating close surveillance and the development of new antibiotics.

dexamethasone has been found to significantly reduce mortality and sequelae from pneumococcal meningitis in adults [12,13] and is currently recommended in the American and European guidelines for adults with suspected pneumococcal meningitis. For potential benefit, dexamethasone must be given before or concomitantly with the antibiotics [3▪▪,14]. Of note, the beneficial effects of dexamethasone only apply to adult patients with pneumococcal meningitis in high-income countries [13]. Although to date no differences on long-term neuropsychological sequelae were reported in meningitis patients treated with dexamethasone compared with placebo, adjunctive dexamethasone has been reported to negatively affect survival and hippocampal neuroregeneration in experimental meningitis [15▪,16]. The effect of dexamethasone indicates that immunomodulatory treatments (might) have the potential to improve the outcome of pneumococcal meningitis. Its limitations in applicability and also efficacy underline the need for novel adjunctive medications. Several interesting candidates have been identified in recent studies. The purpose of this review is to provide a brief overview of our current understanding of the pathogenesis of pneumococcal meningitis and its potential implications on the management of this life-threatening disease in humans.

PATHOGENESIS OF PNEUMOCOCCAL MENINGITIS

The principal ecological niche of *S. pneumoniae* is the human nasopharynx. To successfully invade the central nervous system (CNS), it must overcome many obstacles on its journey through the blood to the brain. The CNS is protected externally by its covering leptomeninges and internally (against blood-borne pathogen invasion) by the blood-brain barrier (BBB) and the blood-cerebrospinal (CSF) barrier (BCSFB). To get access to the CNS, the successful pathogen therefore requires a defect in the external barrier (e.g., a posttraumatic dura leak). It also uses a multistep process involving the colonization of the nasopharyngeal mucosa, followed by the invasion into the blood with successful survival and replication, and finally the traversal of the BBB [17,18].

PREVENTION OF BACTERIAL TRAVERSAL OF THE BLOOD–BRAIN BARRIER

The BBB is formed by brain endothelial cells, astrocytes, and pericytes to protect the CNS from invading pathogens [19]. It has recently been shown that *S. pneumoniae* that were able to enter the CNS expressed adhesive rlrA-regulated gene A (RrgA)-containing pili [20]. Using brain biopsies from patients who died of pneumococcal meningitis and a murine meningitis model, *S. pneumoniae* was further found to colocalize with two BBB endothelial receptors, namely polymeric immunoglobulin receptor (pIgR) and platelet endothelial cell adhesion molecule (PECAM-1). Thereby, the bacteria–receptor interaction is predominantly mediated by the above-mentioned pilus protein RrgA [21▪▪,22]. Blockade of pIgR and PECAM-1 with targeted antibodies substantially reduced bacterial invasion of the subarachnoid space in a bacteremia-derived meningitis model [21▪▪] (Fig. 1). More interestingly, these antibodies further decreased bacterial CNS load in mice cotreated with ceftriaxone, the first-line empiric antimicrobial recommended for community-acquired bacterial meningitis in humans [3▪▪,21▪▪]. Therefore, blockade of pIgR and PECAM-1 could be an interesting target for adjuvant therapy of pneumococcal meningitis, namely by shielding the brain against pneumococcal (re)entry. Not only the prevention of pneumococcal (re)entry but also the preservation of BBB integrity has been shown to be beneficial during bacterial meningitis. Matrix metalloproteinases (MMPs) participate in the disruption of the BBB by degrading the extracellular matrix, and their pharmacological inhibition reduced BBB permeability and improved the outcome (mortality and neuronal damage) in different experimental models [11,23–26].

TARGETED IMMUNOMODULATION

Excessive inflammation significantly contributes to meningitis-associated brain damage and thus an

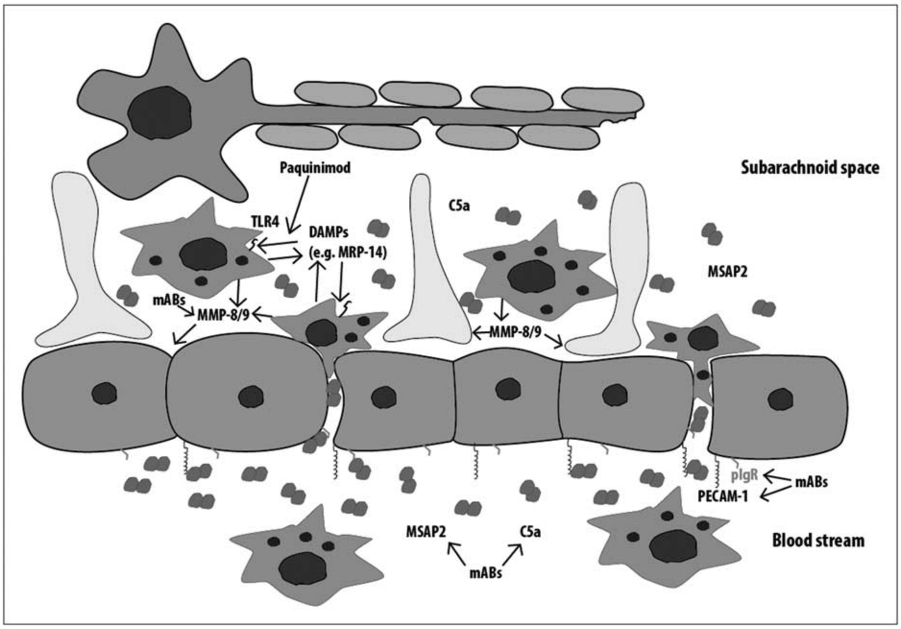

FIGURE 1. Selected pathogenetic aspects of pneumococcal meningitis and potential therapeutic targets. BBB, blood–brain barrier; CNS, central nervous system; DAMP, danger-associated molecular pattern; IFN, interferon; mAB, monoclonal antibodies; MASP, mannose-binding lectin-associated serine protease; MMP, matrix metalloproteinase; MRP, myeloid-related protein; PECAM, platelet endothelial cell adhesion molecule; pIgR, polymeric immunoglobulin receptor; TLR, toll-like receptor.

unfavorable disease outcome [27–31]. This hyperinflammatory reaction is related to the host's initial incompetence to handle pneumococcal infection in the CSF, because of a lack of innate immune agents including complement and other opsonins. Thus, *S. pneumoniae* can proliferate almost unrestrained and large quantities of immune-stimulatory pathogen-associated molecular patterns can be released into the CSF, resulting in a fulminant inflammatory reaction [30▪]. This resulting hyperinflammation causes collateral tissue damage with release of endogenous danger-associated molecular patterns (DAMPs) which in turn can propagate and aggravate inflammation. Therefore, several promising candidates for new adjuvant therapies act by modulating this detrimental hyperinflammatory reaction via various mechanisms (Fig. 1).

Fast and efficient bactericidal antimicrobial substances that do not cause bacteriolysis prevent the release of bacterial components and dampen the inflammatory burst after initiation of antimicrobial therapy. Daptomycin, which has been successfully used in individual case reports of meningitis because of Gram-positive drug-resistant bacteria, fulfills these characteristics [32–36]. In these studies, daptomycin given intravenously was found to penetrate into the CSF at approximatively 0.8–5% of the serum concentration (11.5% when corrected for protein binding) [34,36–39]. Compared with ceftriaxone it more rapidly cleared *S. pneumoniae* from the CSF, decreased the levels of proinflammatory cytokines in the CSF, and was associated with less neuronal injury and improved outcome in several experimental studies of pneumococcal meningitis [40,41]. Given the increasing prevalence of penicillin-resistant *S. pneumoniae* strains as well as the emergence of ceftriaxone and fluoroquinolone-resistant isolates, new antibiotics such as daptomycin provide an additional therapeutic option for severe or antibiotic-resistant cases [42–46]. However, daptomycin acts on Gram-positive pathogens only and, thus, needs to be combined with a broad-spectrum antibiotic for empirical therapy [41].

The complement cascade is activated via three different pathways with the classic complement path being the most important one for invasive pneumococcal infection [47]. All pathways converge not only to mediate opsonization of bacteria for phagocytosis and/or direct cell lysis via the membrane-attack complex but also to enhance inflammation through the production of anaphylatoxins like complement component 5a (C5a) [27]. Pathogenic pneumococcal strains have developed several virulence factors such as surface receptors, a polysaccharide capsule, and pneumolysin to counteract complement-mediated clearance from the blood stream [27,48,49,50▪]. Acquired or congenital defects of the complement system are associated with a higher susceptibility to and worse outcomes of bacterial meningitis [27,51–53]. On the other hand, genetic deficiency and/or pharmacologic inhibition of complement factors like complement components 1q (C1q), 3 (C3), 5 (C5) and mannose-binding lectin-associated serine protease (MASP) 2 were highly effective in suppressing the CNS inflammatory response to pneumococcal infection [54▪▪,55–57] (Fig. 1). Accordingly, an association between elevated levels of various complement factors and a more severe disease course and worse prognosis were demonstrated in CSF samples from patients with pneumococcal meningitis [58]. CSF concentrations of complement factors and their clinical correlations clearly differ between pneumococcal and meningococcal meningitis [58]. In pneumococcal meningitis, high CSF complement levels were a strong indicator of disease severity and mortality, whereas an inverse relationship between terminal complement complex-9 levels and mortality is observed in meningococcal meningitis [58]. Accordingly, complement activation by application of recombinant properdin afforded protection against meningococcal sepsis and reduced the severity of pneumococcal infection by enhancing bacterial killing [59]. These data highlight different roles of the complement system in the host defense against major meningeal pathogens. Therapeutic inhibition of the complement system needs, therefore, to be highly specific by preventing uncontrolled immune activation while preserving complement-mediated bacterial killing as demonstrated with specific C5a neutralization in a human whole blood model of meningococcal sepsis [60].

Another potential new target might be the inhibition of the proinflammatory mediator, macrophage migration inhibitory factor (MIF). MIF is a central modulator of the innate immune system and increased levels are associated with an adverse outcome in severe bacterial infections including pneumococcal pneumonia and meningitis [28▪,61–64]. Additionally, inhibition of MIF signaling has been shown to ameliorate disease outcomes in animal models of pneumococcal and *Escherichia coli* sepsis [65,66].

Recent experimental studies have also suggested involvement of the proinflammatory cytokine interferon (IFN)-γ in pneumococcal meningitis, which is released mainly by natural killer cells via an inflammasome-induced, interleukin 18-mediated mechanism [67,68]. In murine pneumococcal meningitis models, IFN-γ has been shown to be a key modulator of proinflammatory cytokine production via the induction of nitric oxide synthase 2 and to thereby mediate breakdown of the BBB and ultimately impact disease outcome [67–70]. Accordingly, antibody-mediated inhibition as well as genetic deficiency of IFN-γ or components of the interleukin 18-inflammasome pathway induced a strong protective effect in murine models of pneumococcal meningitis [67,68,71]. Importantly, these effects of IFN-γ were reproduced in different clinically pathogenic *S. pneumoniae* strains making attenuation of the IFN-γ mediated hyperinflammatory response another promising target for adjuvant therapy [68].

Several MMPs not only mediate brain damage by degrading the extracellular matrix and increasing BBB permeability but also participate in the modulation of inflammation by virtue of their sheddase activity. For example, a disintegrin and metallopeptidase (ADAM) domain 17, also known as tumor necrosis factor-α converting enzyme (TACE), processes precursor tumor necrosis factor into a soluble, more active form which contributes to the spread of inflammation. TACE, therefore, contributes to the hyperinflammatory pathophysiology of bacterial meningitis. In several experimental studies, MMP inhibitors with TACE inhibiting activity attenuated CSF inflammation in pneumococcal meningitis, reduced brain damage and improved survival rate and neurofunctional outcome rendering them highly attractive candidates for adjuvant therapy [11,24] (Fig. 1). Moreover, combining the effects of MMP inhibitors with another modulator of the inflammatory reaction, such as daptomycin may increase the beneficial effects (Muri L, Grandgirard D, Leib SL, unpublished data).

Massive inflammation is only little altered by appropriate antibiotic therapy over days even though complete CSF sterilization occurs within hours. Inflammation-induced cell injury leads to the release of DAMPs that further sustain inflammation and exacerbate damage [31,72]. Among the DAMPs involved in this process are the myeloid-related protein (MRP) 14 and high-mobility group box-1 protein. When injected intrathecally, MRP14 was sufficient to induce meningitis in mice by activating toll-like receptor 4 and both MRP14 deficiency and direct inhibition of MRP14–toll-like receptor 4 interaction with paquinimod attenuated disease outcome [31,73] (Fig. 1). Although treatment with high-mobility group box-1 protein inhibitors had no effect on the development of meningitis, it led to a better resolution of inflammation during antibiotic therapy, which was accompanied by reduced brain disease and better disease outcome [72].

In summary, several interesting candidates for immunomodulatory adjunct therapy have been identified recently. Among these, highly specific complement system inhibitors, MMP/TACE inhibitors as well as nonbacteriolytic antibiotics such as daptomycin seem to be the most promising ones in

Table 1. Mechanisms of action and stage of development of potential adjuvant therapies

	Mechanisms of action	**Stage of development**	**References**
Paquinimod	Direct and specific inhibition of MRP14–TLR4 interaction	Cell culture and rodent experiments	[31]
Anti-MIF antibody	Attenuation of excess inflammatory response of innate immune system	Cell culture and rodent experiments Antibody used in phase I clinical study for other indication	[28▪,56–62]
Anti-IFN-γ antagonists	Antibody-mediated inhibition of IFN-γ prevents BBB breakdown and reduces production of proinflammatory cytokines	Cell culture and rodent experiments	[63–68]
Specific complement inhibitors	Blockade of complement factor C5a or MASP2	Cell culture and rodent experiments	[54▪▪,55,47,50▪,51–53]
Daptomycin	Attenuation of antibiotic-mediated hyperinflammation	Rodent experiments and sporadic use in clinics	[31–33,35–41]
MMP/TACE inhibitors	Inhibition of BBB disruption and/or soluble cytokine release	Cell culture and rodent experiments	[11,24,26,36]

BBB, blood–brain barrier; IFN, interferon; MASP, mannose-binding lectin-associated serine protease; MIF, migration inhibitory factor; MMP, matrix metalloproteinase; MRP, myeloid-related protein; TACE, tumor necrosis factor-α converting enzyme; TLR, toll-like receptor.

ameliorating disease severity and reducing mortality in rodent experimental models. These findings strengthen the hypothesis that a large extent of neuronal injury in pneumococcal meningitis is not caused by toxic effects from *S. pneumoniae* itself but is rather mediated by the hyperinflammatory response of the host's immune system. No clinical studies have been performed in humans thus far and it remains to be elucidated whether these promising results can be reproduced across species. Table 1 summarizes the mechanism of action and stage of development of potential immunomodulating adjuvant therapies.

NEURODEGENERATION AND REGENERATION: ADDITIONAL THERAPEUTIC TARGETS?

Histopathological studies document a wide spectrum of brain injury associated with pneumococcal meningitis in humans, including cortical petechial hemorrhages, focal necrotic lesions in cortical and subcortical structures, and loss of myelinated fibers in the white matter [74▪▪]. Additionally, mild-to-moderate apoptosis of granular cells in the dentate gyrus was found in more than two-thirds of cases in a previous autoptic study [75]. More recently, however, no significant differences in the number of apoptotic cells were detectable between meningitis cases and control patients [74▪▪]. In animal studies, the occurrence and degree of neuronal apoptosis depend on multiple factors, such as the age, strain, and species of the animal used as well as the causative pathogen. Although previous research focused primarily on strategies to prevent neurodegeneration, recent work also investigated neuroregenerative processes following meningitis.

Neurotrophic factors are key mediators of neuronal survival and neurogenesis. Amongst them, brain-derived neurotrophic factor (BDNF) is up regulated during pneumococcal meningitis in both mice and humans via activation of the myeloid differentiation primary response 88 (MyD88)/nuclear factor kappa B (NF-kB) signaling pathway, a classical pathway of the innate immune system involved in the pathogenesis of pneumococcal meningitis [76–78]. Activation of this pathway, therefore, seems to be essential to counter *S. pneumoniae* infection but to also protect neurons from excess injury and initiate functional recovery. As dexamethasone has been shown to attenuate MyD88/NF-κB signaling [79], this link between neuroregeneration and immune response might also explain why dexamethasone increased neuronal apoptosis and impaired neuroregeneration in the hippocampus in an infant rat model of pneumococcal meningitis [14,80]. Conversely, treatment with exogenous BDNF decreased hippocampal apoptosis and stimulated neurogenesis and differentiation of neural progenitor cells in the hippocampus following pneumococcal meningitis in rodent models [81▪▪,82,83]. However, whether these new neurons can integrate into neuronal circuits and facilitate functional recovery remains to be elucidated.

FUTURE PERSPECTIVES

One of the major causes for the reduced incidence of pneumococcal meningitis has been the introduction and widespread use of pneumococcal conjugate vaccines [2]. The reduction in incidence is most prominent for pneumococcal serotypes included in pediatric conjugate vaccines but an increase in invasive pneumococcal infections caused by nonvaccine serotypes is observed [1▪,2,84–86]. This serotype replacement is of clinical importance as it has been shown that the *S. pneumoniae* capsule type has a direct effect on disease severity [50▪]. Alternative pneumococcal vaccines using highly conserved protein antigens such as pneumococcal histidine triad protein D and pneumolysin are currently in development and have been shown to have an acceptable safety and reactogenicity profile in phase I/II studies. These novel vaccines promise to provide broader coverage than the current conjugate vaccines and would thereby eliminate the problem of serotype replacement [87–89].

Although primary prophylaxis through widespread vaccination should remain the primary goal in the future, we should also remain vigilant to the emergence of multidrug-resistant *S. pneumoniae* strains [45,46,90,91]. Therefore, the development and clinical testing of novel antimicrobials is highly warranted. The ideal profile of potential agents is a good BBB penetration and a rapid bactericidal activity with limited release of bacterial structures causing the inflammatory burst associated with an adverse outcome [40]. Also clinical trials investigating the combination of nonlytic antibiotics such as daptomycin, as well as MMP/TACE and complement system inhibitors may yield promising results (Muri L, Grandgirard D, Leib SL, unpublished data).

CONCLUSION

Although the incidence and mortality from pneumococcal meningitis have declined over recent years, several challenges remain. Pneumococcal meningitis still has a mortality rate of up to 18% and a substantial proportion of surviving patients sustains debilitating neurologic sequelae. Even as new protein-based pneumococcal vaccines promise a broader coverage of pneumococcal serotypes, further systematic research on adjuvant therapy and new antimicrobials is highly warranted. Promising targets focus on modulating the excessive immune response that has been repeatedly linked to worse clinical outcomes. Potential new therapeutic options include nonlytic antimicrobials such as daptomycin, highly specific complement system inhibitors, and exogenous neurotrophic factors. Optimally, modulating the immune response should preserve its ability to eradicate the pathogen, should limit the extent and duration of the hyperinflammation causing damage, and should favor the initiation of regenerative processes.

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Conflicts of interest

There are no conflicts of interest.

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