Strategies to prevent neuronal damage in pediatric bacterial meningitis

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Purpose of review

The mortality of bacterial meningitis can reach 30%, and up to 50% of survivors suffer from persisting neurological deficits as a consequence of the disease. The incidence of neurological sequelae of bacterial meningitis has not improved over the last decade. Adjunctive therapeutic options are limited, and ongoing research into the pathophysiology of brain damage in bacterial meningitis aims at providing the scientific basis for future development of more efficient adjunctive options.

Recent findings

In a population with good access to health care, dexamethasone given before or at the time of initiation of antibiotic therapy acts beneficially in pediatric pneumococcal meningitis, but not in meningococcal meningitis. In experimental animal models, brain-derived neurotrophic factor protected against brain injury and improved hearing while melatonin, which has antioxidant properties among other effects, reduced neuronal death. Transgene technology can be used to provide new insights into the pathophysiology of the disease and to identify potential therapeutic targets.

Summary

Although dexamethasone improves outcome of bacterial meningitis under defined circumstances, the morbidity of bacterial meningitis still remains unacceptably high. Experimental models may help to identify new therapeutic strategies to further improve the neurological outcome in young children suffering from bacterial meningitis.

Keywords

adjunctive therapy, bacterial meningitis in children, neuronal damage

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Abbreviations

BDNF	brain-derived neurotrophic factor
CSF	cerebrospinal fluid
GBS	Group B streptococcus
MMP	matrix-metalloproteinases
TACE	TNF-α converting enzyme
TLR	Toll-like receptor
WBC	white blood cell

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Introduction

Bacterial meningitis, and in particular meningitis of children, is associated with devastating mortality rates of up to 30%. Moreover, 20–50 % of pediatric patients who survive the infection have serious and permanent neurological sequelae, which include deafness, mental retardation and learning impairment, sensory-motor deficits, seizure disorders and cerebral palsy. The incidence of neurologic sequelae of bacterial meningitis in children has not significantly improved over the last decade [1]. For example, comparison of two timely distinct national prospective studies performed in England and Wales showed a decrease in the acute phase mortality from 22% in the time period from 1985 to 1987 to 6.6% in the time period from 1996 to 1997. In contrast, the corresponding follow-up studies on the incidence of serious disabilities in the surviving patients showed an incidence of 25.5% in the time period from 1985 to 1987 and an incidence of 23.5% in the time period from 1996 to 1997. Compared with general practice or hospital control patients, children that survived bacterial meningitis had a fourfold to 16-fold increase in the risk of developing severe disabilities [2•]. Even 12 years after the disease, survivors of meningitis are at greater risk of deficits in intellectual, academic and executive ability than grade-matched and gender-matched controls. As a consequence, children after meningitis are more than twice as likely as controls to require special educational assistance (27.0% compared with 12.5%). A younger age at illness is associated with a poorer efficiency in performing linguistic and executive functions, and may suggest that cerebral insult may have a greater impact on a developing brain [3•]. Group B streptococcus (GBS) is the most common etiological agent in neonates and *Streptococcus pneumoniae* and *Neisseria meningitidis* are the most common causes of bacterial meningitis in infants and young children worldwide [4••]. Pneumococcal meningitis is consistently associated with a particularly high incidence of neurological sequelae, with up to half of the survivors presenting some form of neurological deficits [5,6]. A retrospective study of 49 patients admitted in a single pediatric intensive care unit between 1990 and 2002 in France and diagnosed with pneumococcal meningitis recorded a mortality rate of 49% and neurological impairment in 48% of patients discharged from the hospital with a mean follow-up of 5 years (range 1–12 years) [7•].

Brain injury caused by bacterial meningitis prominently affects three brain structures, namely the cortex, the hippocampus and the inner ear. As shown in pathologic studies in patients dying from bacterial meningitis and in corresponding animal models, the cortical regions of the brain display areas of acute neuronal injury associated with areas of focal ischemic necrosis [8]. In the hippocampus, apoptotic damage occurs in the inner blade of the dentate gyrus and this damage has been associated with impairment of learning and memory in experimental models of pneumococcal meningitis [9,10]. The vulnerable cells in the dentate gyrus have been identified to include immature neurons recently generated from stem cells [11]. Necrotic cell death is also observed in the CA1–CA4 sectors of the hippocampus, and in the dentate gyrus, particularly in adult mice, when the damage is severe [12]. A different form of hippocampal damage characterized by clusters of shrunken and pyknotic nuclei affects cells spanning the entire blade of the dentate gyrus in newborn rats infected with GBS [11].

Hearing impairment is the most common neurological sequel following meningitis and is observed in up to 30% of patients, depending on the infecting pathogen [13–15]. In an adult rat model of pneumococcal meningitis the severity of permanent hearing impairment assessed two weeks after the infection correlated significantly with the loss of type I spiral ganglion neurons [16]. Thus neuronal loss in the spinal ganglion represents a histomorphological correlate of hearing impairment.

In the time period covered in this review (11/2004 to 9/2005), a number of pathogenetic factors have been evaluated for their contribution to the development of brain damage in bacterial meningitis. Matrix-metalloproteinases (MMP) have been shown to facilitate the extravasation of white blood cells (WBCs) and to participate in blood–brain barrier disruption by degrading components of the basal lamina of the cerebral vasculature [17•]. The presence of reactive oxygen species and reactive nitrogen species leads to the production of peroxinitrite and the occurrence of lipid peroxidation, as observed in inflammatory cells and penetrating cortical blood vessels in brain specimens from patients [18]. In addition, oxidants have been shown to induce DNA strand breakage and subsequent poly(ADP ribose) polymerase activation, initiating an energy-consuming intracellular cycle that ultimately leads to cellular energy depletion and death, specifically in endothelial cells of the cerebral vasculature [19]. Finally, sustained cytokine production, especially IL-1β, has been shown to correlate with adverse disease outcome and/or severity of disease [20].

Factors found to contribute to ischemic injury include the production of vasoconstrictive endothelins, the activation of platelets and the induction of a procoagulant state [21].

Different bacterial toxins have been shown to directly trigger the host apoptotic machinery: *S. pneumoniae*-produced pneumolysin and hydrogen peroxide have been shown to exert neurotoxicity *in vitro* and in an experimental model of pneumococcal meningitis [22]. Hemolysin may play a role during GBS meningitis, since it has been shown to induce apoptosis [23].

Strategies for preventing neuronal damage during bacterial meningitis: current concepts

In the time period covered by this review (11/2004 to 9/2005) the pathogenetic mechanisms identified as targets for adjuvant therapy include the following:

(1) bacterial killing and the prevention of associated release of bacterial components [24••,25,26•,27•];
(2) the host mechanisms for recognition of bacteria or bacterial components and the initiation of the inflammatory reaction [28•,29•,30,31•,32•,33•,34•,35];
(3) the modulation of the inflammatory reaction by adjuvant therapy with dexamethasone [4••,7•,36••,37,38•,39•,40•];
(4) the inhibition of inflammatory and/or neurotoxic mediators [41,42•,43•,44,45•,46••];
(5) the modulation of apoptotic pathways [47,48•,49•,50•].

Bacterial killing and the prevention of associated release of bacterial components

Bacteria and their components engage the innate immune response through activation of the members of Toll-like receptors (TLRs), including TLR2 and TLR4. Antibiotic therapy reduces the overall release of these components, when compared to unhindered replication and subsequent autolysis. Bacteriolytic antibiotics, however, have been shown to induce an initial brisk release of bacterial components that may accentuate inflammation. The use of antibiotics that inhibit RNA/protein synthesis or DNA replication (rifamycins, macrolides, clindamycin, ketolides and quinolones) reduces bacterial lysis [24••]. For example, the production of inflammatory mediators by murine macrophages is decreased when stimulated by GBS exposed to rifampin or clindamycin compared with ampicillin or cefotaxime [25]. Rifampicin, given 6 hours prior to ceftriaxone, reduced the release of bacterial components into the cerebrospinal fluid (CSF) and attenuated neuronal injury in the hippocampus [51]. Similarly, clindamycin lowered extracellular concentration of hydroxyl radicals

and glutamate, and decreased neuronal apoptosis in the dentate gyrus in a rabbit model of pneumococcal meningitis [26•]. The cyclic lipopeptide daptomycin kills bacteria by inducing a rapid depolarization of the bacterial membrane without subsequent disruption and has been suggested as a candidate for the treatment of gram-positive bacterial meningitis [27•].

Recognition of bacterial components and the initiation of the inflammatory reaction

The brain's inflammatory response to bacterial infection determines the outcome of bacterial meningitis, that is, the extent of brain injury as a consequence of the disease. Thus, adjuvant therapeutic strategies include targeting the inflammatory reaction as early and as upstream as possible. Early events in the inflammatory cascade are the recognition of the pathogens, the resulting immune activation, the recruitment of WBCs in the CSF and the release of inflammatory mediators into the subarachnoid space. Therapeutic strategies developed with this aim strive to leave the beneficial components of inflammation in place, but to attenuate the harmful ones (reviewed in [23]).

Recent data generated in experimental models concern the recognition of the pathogen and the initiation of the immune reaction. CD14 myeloid receptor, TLRs and MyD88 have all been implicated in immune activation. $CD14^{-/-}$ mice showed a higher mortality from infection by *S. pneumoniae* whereas the systemic host defence and the CSF bacterial clearance were not affected. The authors suggested, however, that CD14 deficiency leads to a stronger neutrophil recruitment into the CSF and an excessive meningeal inflammation [29•].

TLR2 is involved in the recognition of gram-positive pathogens. TLR2 deficiency leads to an increased severity of the disease and earlier mortality in murine models of pneumococcal meningitis. A stronger accumulation of bacteria in the ventricules and the meninges has also been observed. A delay in granulocyte recruitment and a weakened antimicrobial capacity are believed to contribute to the failing host response in TLR2 deficient mice [52]. TLR2 has also been recently suggested to play a role in the regulation of TNF-alpha gene expression in the brain during pneumococcal meningitis; TLR2 deficiency is associated with enhanced TNF gene expression in the brain [30].

MyD88, which acts downstream of TLR2, is necessary to mount a robust immune response to *S. pneumoniae* in the central nervous system. In transgenic animals lacking MyD88, a marked reduction of CSF pleocytosis and a decreased expression of cytokines and chemokines were observed. MyD88 deficiency, however, was associated with a worsening of the clinical disease, owing to a more severe bacteremia and an enhanced expression of TNF-alpha in the lungs [34•].

The hypothesis that avoiding leukocyte recruitment in the CSF in order to decrease the local inflammatory reaction, which would then be beneficial, has recently been challenged by Brandt *et al.* [31•]. For example, treatment with Fucoidin initiated at the time of infection in experimental pneumococcal meningitis led to a higher mortality, but had no measurable effect on brain damage or bacterial numbers in the CSF compartment. The highest mortality was associated with an increase in the numbers of bacteria in the blood, suggesting that leukocyte blockade affected the host's ability to control systemic but not central nervous system infection. This hypothesis was supported by the observation that the boosting of the peripheral neutrophil count by pretreatment with granulocyte-colony-stimulating factor (G-CSF) reduced mortality and prevented brain damage, and led to reduced numbers of bacteria in the blood and the CSF [33•]. Thus, the degree of systemic infection and the severity of brain damage are likely to contribute independently to mortality. This hypothesis may be supported by the apparent discrepancies between the previously mentioned study of Brandt and a recent study that reported the reduction of leukocyte influx by treatment with a tyrosine kinase inhibitor (tyrphostin AG126). This study [32•] in pneumococcal-cell-wall-induced meningitis showed that the attenuation of CSF-pleocytosis reduced the increases in blood flow and intracranial pressure.

Fas (CD95) and Fas ligand (FasL, CD95L) have been shown to be involved in the acute inflammatory response by attracting neutrophils and regulating their survival [53,54]. Increased levels of soluble Fas and FasL have been found in CSF of patients with bacterial meningitis. Recent data generated in experimental models using transgenic animals that lack Fas and FasL, however, could not find a contribution of Fas/FasL in the regulation of inflammatory response during pneumococcal meningitis [35].

From the data generated in the reviewed period one might conclude that a higher neutrophil count before the initiation of antibiotic therapy is beneficial to limit the spread of infection and the development of severe bacteremia. Once antibiotic therapy has been initiated, however, the contribution of neutrophils to bacterial clearance in the CSF seems small and pales in comparison to the detrimental effect of high CSF pleocytosis on brain tissue.

Modulation of the inflammatory reaction by adjuvant therapy with dexamethasone

Given the contribution of excessive inflammation to the development of brain damage in bacterial meningitis, anti-inflammatory adjuvant treatment with dexamethasone has been tested in several controlled clinical trials. Addressing a complete and critical overview on this topic goes beyond the scope of this review, but has been recently done by others [36••,55••,56••]. For meningococcal meningitis, dexamethasone was not proven to be effective in decreasing sequelae among pediatric patients in a recent study performed in Brazil [40•]. Another recent retrospective population-based study performed in Sydney (1994–1999) in childhood pneumococcal meningitis demonstrated that, in a population with good access to health care, early recognition of pneumococcal meningitis and treatment with adjunctive dexamethasone significantly improved mortality and severe disabilities in survivors [39•]. In another study performed in a pediatric intensive care unit in France [7•], dexamethasone treatment did not influence in-hospital death in a multivariate analysis; however, the beneficial effect may have been reduced by the delay between antibiotic and steroid administration and the selection of a high-severity population (49% mortality).

Experimental studies on the use of adjunctive dexamethasone have generated conflicting data. Whereas dexamethasone treatment was shown to increase both acute hippocampal injury and long-term learning deficits in an infant rat model [57], it decreased neurological sequelae and caspase activity in an adult rat model [37]. The measured outcomes, however, were different in these two studies (hippocampal injury in the first, caspase activity in the cerebellum in the second study), as well as the protocol for assessment of learning capacity; a direct comparison is therefore not possible.

Inhibition of inflammatory and/or neurotoxic mediators

Gene knockout technology combined with experimental meningitis in mice has been used to investigate the role of inflammation in the development of brain injury. This has been recently reviewed by Paul *et al.* [46••]. In TNF-α knockout mice, mortality and spatial memory deficits were increased in ceftriaxone-treated experimental pneumococcal meningitis [41]. TNF-α has been shown, however, to participate in postmeningitic hearing loss, which was reduced by blockade with neutralizing antibodies in a Mongolian gerbil model [44]. Few other selective intervention strategies have been directed against specific cytokines so far, and ongoing research focuses on the pattern and kinetic of cytokine expression during bacterial meningitis [45•]. Thus a deeper understanding of the role of the various mediators in the inflammatory network is a prerequisite for the development of individual targets for adjuvant therapy.

A number of strategies have been evaluated in infant models of bacterial meningitis, which, until now, have not been translated into clinical use (see Table 1). One main challenge seems to be the difficulty in finding therapies that are able to attenuate both hippocampal and cortical damage in bacterial meningitis. For example, experimental therapies using metalloproteinase inhibitors are generally protective against cortical damage. Furthermore, MMP-inhibition combined with inhibition of TNF-α converting enzyme (TACE) inhibitory activity has been shown in one study to also protect from hippocampal dentate gyrus injury. The beneficial effect on both forms of injury by an MMP/TACE inhibitor, however, was restricted to one compound and could not be shown for other similar MMP/TACE inhibitors. Thus the beneficial effect of MMP/TACE inhibition may not directly depend on the TACE inhibitory activity [42•,58,59]. Antioxidant therapy has been shown to protect the neocortex from damage, but not from hippocampal apoptosis. The beneficial effect on cortical injury may be attributed to a protective effect on the cerebral microvasculature leading to an amelioration of cerebral perfusion [60]. Recently, the continuous administration of melatonin in a model of ceftriaxone-treated pneumococcal meningitis in rabbit has been shown to decrease hippocampal apoptosis. Whether the observed effect was due to the radical scavenging properties of melatonin or to its influence on neurotrophic factors' expression remains to be clarified [43•].

Modulation of apoptotic pathways

Caspase inhibitors have been previously shown to attenuate hippocampal apoptosis in the dentate gyrus. While the beneficial effect of the pan-caspase inhibitor z-VAD-fmk could be attributed to the down-modulation of the inflammatory response and associated reduction of caspase inhibition [61], the specific inhibition of caspase-3 with Ac-DEVD-CHO relied solely on the interference with the apoptotic pathway [62]. Recently, it has been suggested that two phases of apoptosis were discernible. Neuronal injury at 18 h after infection was independent of the caspase-3 pathway, and neuronal cell death at 24 h after infection was attenuated in the absence of the caspase-3 pathway [47]. Pharmacological interventions aimed at increasing the survival rate of neurons in pediatric patients with meningitis will therefore need to take the kinetic aspects of the development of brain damage into account. Administration of exogenous brain-derived neurotrophic factor (BDNF) has been shown to attenuate all forms of brain damage associated with pneumococcal and GBS meningitis [48•]. The therapeutic strategy of exogenous BDNF administration has

Table 1 Therapeutic interventions in the infant rat models and their effect on cortical and hippocampal injury, as well as survival (partially adapted from [21,64]). Only new findings covering the period of the review are referenced

			Neuronal injury			
Intervention	Compound	Pathogen	Cortex	Hippocampus	Mortality	Recent references
iNOS inhibition	Aminoguanidine	GBS	increase	ND	ND	
Endothelin agonist	Bosentan	SP	decrease	no change	no change	
Antioxidants	PBN	SP	decrease	increase	no change	
		GBS	decrease	decrease[a]	ND	
	NAC	SP	decrease	no change	no change	
	DFO	SP	decrease	no change	no change	
	TLM	SP	decrease	no change	decrease	
MMP inhibition	GM-6001	SP	decrease	ND	ND	
MMP + TACE inhibition	BB-1101	SP	decrease	decrease	decrease	
	TNF484	SP	decrease	non change	no change [42•]	
TNF-α neutralization	Neutralizing Ab	GBS	no change	decrease[a]	decrease[b]	
Attenuation of inflammation	Dexamethasone	SP	ND	increase	no change	
		GBS	decrease	ND	no change	
Caspase inhibition	Ac-DEVD-CHO	SP	ND	decrease	ND	
Neurotrophin	BDNF	SP	ND	decrease	no change	[48•]
		GBS	decrease	decrease[a]	no change	
Glutamate antagonist	Kynurenic acid	GBS	decrease	decrease[a]	ND	

iNOS: inducible nitric oxide synthase; PBN: α-phenyl-butyl nitrone; NAC: N-acetylcysteine; DFO: deferoxamine; TLM: trylizad-mesylate; SP: S*treptococcus pneumoniae*; ND: not determined.
[a]Damage in the dentate gyrus of the hippocampus consisting of pyknotic cells, distinct from caspase-dependent apoptosis.
[b]Only when neutralizing antibodies were given systemically, and not intracisternally.

been further supported by the finding that expression of endogenous BDNF was found to be decreased by antibiotic treatment in experimental pneumococcal meningitis [63]. Furthermore, BDNF exerted a protective effect on hearing capacity in experimental pneumococcal meningitis [49•]. Thus, BDNF has been shown to modulate caspase-dependent and independent pathways of neuronal damage, but its mechanism of action is still poorly understood.

A new mechanism to trigger apoptosis has recently been proposed [50•]. *S. pneumoniae* was shown to inhibit phosphatidylcholine biosynthesis, presumably by the pneumococcal toxins pneumolysin and/or H_2O_2. The inhibition of this pathway causes apoptosis in a variety of brain cells *in vitro*. In a mouse model of pneumococcal meningitis, hippocampal damage was prevented by treatment with cytidine diphosphocholine.

Summary

To date, there is no ideal adjunctive therapy for the treatment of bacterial meningitis in all patient populations. The available evidence thus far supports the use of dexamethasone, when given before or together with the first dose of antibiotics, in children and adults with pneumococcal or haemophilus meningitis. Dexamethasone is not recommended for the treatment of meningococcal, gram-negative bacillary meningitis or for bacterial meningitis in neonates [36••]. Future research into antibiotic therapy for bacterial meningitis may focus on limiting the release of bacterial components, provided that a sufficiently rapid CSF sterilization can be achieved. Modulation of individual components of the inflammation cascade may be evaluated while cautiously keeping an eye on the systemic effects. This was exemplified by studies on leukocyte recruitment, where a decrease in CSF inflammatory parameters and brain damage did not contribute to a better outcome owing to an increase in severity of the systemic disease. Such 'double-edged swords' are probably hidden in a number of targets currently investigated as adjunctive strategies. The complex network of cytokines, chemokines, their receptors and other inflammatory mediators that participate in CSF inflammation will require more studies before a rational neuroprotection strategy can be developed. Finding a uniform target for adjunctive therapy is further hampered by the different pathophysiologic pathways that lead to the distinct forms of brain damage in bacterial meningitis, that is, necrosis in the cortex, hippocampal apoptosis and damage to the inner ear. Finally, meningitis in neonates, children and adults may need to be considered separately. Future research may therefore include the differences in the pathophysiology of brain damage that arises from meningitis caused by different pathogens and in defined patient populations.

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