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REVIEW

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Bacterial meningitis: mechanisms of disease and therapy

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Abstract Bacterial meningitis continues to be a serious infectious disease with a high morbidity and mortality in young children. Early recognition and initiation of adequate treatment are the major determinants for a good outcome. Recent advances in our understanding of the host inflammatory response by cytokines may result in the use of new therapeutic strategies. Such modulation of the inflammatory response may reduce the incidence of sequelae and death. The use of steroids as adjunctive therapy in children with bacterial meningitis probably has beneficial effects although the available data are still controversial. Additionally, studies in experimental meningitis models indicate that non-steroidal anti-inflammatory drugs and monoclonal antibodies against bacterial products, cytokines and CD18 on leucocytes reduce the extent of the meningeal inflammation. Human studies to evaluate the efficacy of these immune modulators are expected to start soon. However, prevention of bacterial meningitis by conjugate vaccines against *Streptococcus pneumoniae* and *Neisseria meningitidis* will be the most promising development in the next decade.

Key words Bacterial meningitis
Cytokines · Anti-inflammatory therapy

Abbreviations *ADH* antidiuretic hormone · *BBB* blood brain barrier *Hib Haemophilus influenzae* type b *IFN* interferon · *IL* interleukin · *LPS* lipopolysaccharide · *PAF* platelet activating factor · PGE_2 prostaglandin E_2 · *PMN* polymorphonuclear leucocyte · *SIADH* syndrome of inappropriate secretion of antidiuretic hormone · *TNF* tumour necrosis factor

Introduction

Despite continuing improvements in therapy bacterial meningitis is still associated with fatality rates of 3%–6% and the development of severe sequelae in approximately 16% of cases [6, 33, 86, 101, 115, 116]. Prevention of meningitis by the use of novel conjugate vaccines against *Streptococcus pneumoniae* and *Neisseria meningitidis* will be a point of major interest in the next decade. Recent research has contributed to our understanding of the pathophysiology of bacterial meningitis. This has resulted in new therapeutic approaches. The use of anti-inflammatory drugs in combination with antibiotics in bacterial meningitis has become a topic of major interest. This review will focus on the nature of the inflammatory response to infection in the CSF and the pathophysiological alterations induced by bacterial meningitis. Finally, recent advances in treatment will be discussed.

Epidemiology

Bacterial meningitis is mainly a disease of young children. During the neonatal period Gram-negative enteric bacilli (*Escherichia coli*, *Klebsiella* species), group B

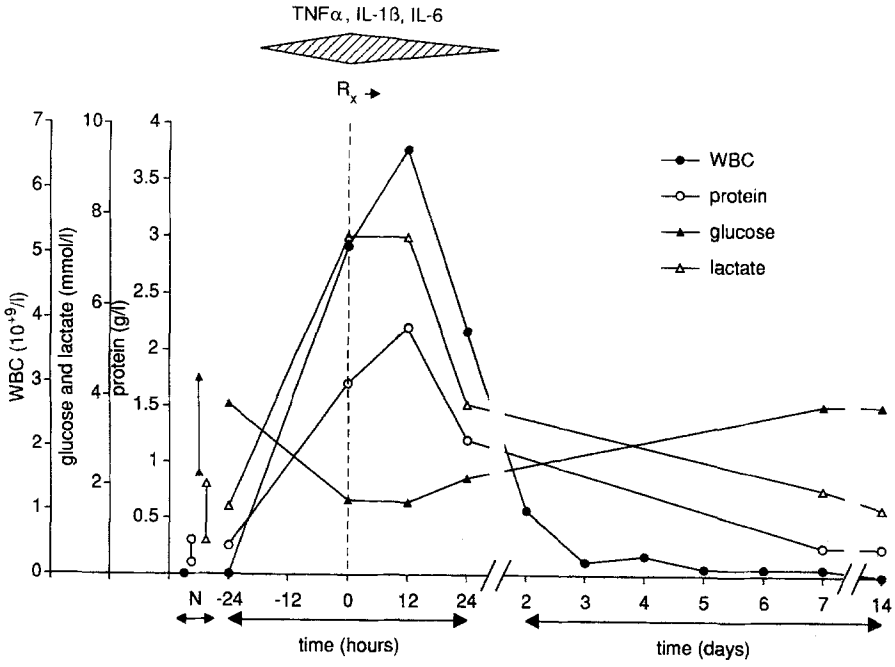

Fig. 1 Schematic view of the biochemical changes in the CSF profile and detection of elevated cytokine levels during bacterial meningitis. The normal ranges (N) for white blood cells (WBC), protein, glucose and lactate in the CSF are indicated by vertical bars. Rx marks the timepoint of initiation of antibiotic therapy

streptococci and *Listeria monocytogenes* are the most common pathogens. These organisms are mainly acquired at delivery. The three major causative organisms in infants above 3 months of age are *N. meningitidis*, *Haemophilus influenzae* and *S. pneumoniae*. They account for more than 90% of bacterial meningitis in children between 3 months and 10 years. The incidence and relative frequencies of these bacteria differ markedly depending on genetic factors, the geographic area and the recent introduction of the efficacious conjugate *H. influenzae* type b vaccine in many countries.

Epidemiological studies have identified several risk factors for bacterial meningitis. Age is the most important risk factor. Boys are affected more frequently than girls. Several studies have reported the presence of racial differences in the incidence of bacterial meningitis. Black and Hispanic populations are at 2–4 times greater risk than Caucasians [26, 31, 35, 130]. Socioeconomic rather than racially determined factors are responsible for the increased risk [31]. The native North American population also has a high incidence of bacterial meningitis. For example, rates of over 200/100 000 per year in the overall population have been described among Canadian Inuits [132]. Another host factor which increases the risk of pneumococcal sepsis and meningitis is splenectomy. Patients with deficiencies in the terminal components of complement (C5-9) also have a high risk of meningococcal meningitis. Children in day care centres have an increased risk of acquiring invasive bacterial disease in comparison with children in home care.

Diagnosis of bacterial meningitis

Nonspecific clinical findings predominate in the newborn and in young infants. These include abnormal temperature, somnolence, irritability, and poor feeding. The presence of a bulging fontanelle is a relatively characteristic sign in this age group but not present early in the disease. More characteristic findings are often seen in children and adults and include alteration of the mental status, nuchal rigidity, and the signs of Kernig and Brudzinski. A lumbar puncture has to be performed if the slightest evidence suggests the presence of bacterial meningitis. Rapid diagnosis and initiation of therapy are the major prognostic factors determining a favourable outcome. Initial management decisions are based largely on the Gram stain and CSF characteristics (leucocytes, glucose, lactate and protein). The CSF parameters reflect the metabolic and structural alterations, such as increased blood brain barrier (BBB) permeability, which characterize the inflammatory response (Fig. 1).

Leucocytes

A characteristic feature of meningitis is CSF leucocytosis. Before leucocytes reach the CSF a co-ordinated action takes place of adherence to vascular endothelium, diapedesis out of the bloodstream and subsequent migration across the endothelial monolayer into the CSF compartment. This process is mediated by adhesion-promoting receptors and ligands located on leucocytes and endothelium which are activated by exposure to cytokines (interleukin (IL)-1β, tumour necrosis factor (TNF) α and inter-

feron (IFN) γ) and lipopolysaccharide (LPS) [62, 68, 84, 85, 93]. Bacterial replication or lysis in the CSF compartment induces endothelial cells to produce IL-8. IL-8 is a potent chemoattractant [5]. The initial reversible adherence of leucocytes to endothelial cells is mediated by three lectin-like carbohydrate-binding molecules called selectins (granule membrane protein-140, endothelial cell adhesion molecule-1, leucocyte adhesion molecule-1). Each selectin recognises specific carbohydrate sequences on either leucocytes (granule membrane protein-140, endothelial cell adhesion molecule-1) or endothelial cells (leucocyte adhesion molecule-1). Strong adhesion is mediated by leucocyte integrins that bind to counter receptors on endothelium. The integrin family of adhesion receptors (CD11/CD18) consist of heterodimeric glycoproteins with an α and β subunit. They can be classified on basis of their β subunit [46]. The early selectin-adhesion decreases with continued cytokine stimulation by cleavage of the selectin of the cell surface or inhibition of its binding. At the same time β_2 integrin-mediated adherence of the neutrophils to intercellular adhesion molecule-1 (ligand) on endothelial cells is induced. Subsequently leucocytes traverse the cerebral capillary endothelium by diapedesis [103].

Glucose and lactate

The changes in glucose and lactate levels are not only induced by living bacteria and leucocytes. The anaerobic brain metabolism in bacterial meningitis contributes to the development of increased CSF lactate concentration and hypoglycorrhachia [123]. It seems likely that local changes in the brain as a result of ischaemia or mediated by humoral factors, induce an increased production of lactate. Another explanation for the development of hypoglycorrhachia was demonstrated in experimental canine meningitis. In these animals low CSF glucose reflected the inhibition of carrier-mediated transport across the BBB [21, 88]. The increased use of glucose by the brain and the abnormal glucose transport across the BBB may further contribute to hypoglycorrhachia [43].

Protein

The elevated concentration of protein in CSF during bacterial meningitis is caused by an increased permeability of the BBB. A uniform response consisting of an early and sustained increase in formation of pinocytotic vesicles and a progressive increase in the separation of tight junctions between endothelial cells is observed during the course of experimental meningitis [99]. The cytokine-endothelium-leucocyte interaction is probably responsible for the disruption of the barrier by opening intercellular junctions and permitting the passage of serum proteins into the subarachnoidal space.

Pathogenesis of infection

The three most common micro-organisms in bacterial meningitis have several properties that promote adherence, colonization and invasion of the mucous membranes of the nasopharynx. Mucosal attachment is mediated by microbial virulence factors such as pili and nonpilar adhesins. Several host defence mechanisms must be evaded before attachment may occur. The bacteria have to inactivate secretory IgA and escape from the ciliary clearance mechanisms of the nasopharyngeal mucosa. The three major pathogens all secrete a protease capable of cleaving human immunoglobulin A1. Importantly, IgA1 is the dominant immunoglobulin class in the nasopharyngeal mucosa which is the site of adherence and invasion by these bacteria [24, 83].

Invasion across the nasopharyngeal mucosa takes place by an endocytotic process (*N. meningitidis*) or through the intercellular route by separations in the apical tight junctions of columnar epithelial cells (*H. influenzae*) [106, 107]. Once the mucosal barrier is crossed, bacteria must overcome additional host defences to survive in the bloodstream and to invade the meninges. The most important virulence factor in this respect is encapsulation. The polysaccharide capsule inhibits neutrophil phagocytosis and prevents classical complement pathway bactericidal activity thus enhancing intravascular bacterial replication and survival.

Pathophysiology of the inflammatory response

Since CSF defences against infection are very limited bacteria can proliferate rapidly. Host defence (humoral factors and phagocytes) must be recruited from serum, a process that develops parallel to blood brain barrier disruption and alteration of the cerebral metabolism. These abnormalities all arise as part of an inflammatory response mediated by cytokines.

Cell-wall components

Experimental evidence has accumulated that cell-wall components are responsible for triggering the inflammatory response in the subarachnoid space. These are mainly peptidoglycan-teichoic acid in Gram-positive micro-organisms and LPS molecules (endotoxins) in Gram-negative bacteria. Both are potent inducers of inflammation. Intracisternal inoculation of any of these components into the CSF compartment of animals induces meningeal inflammation [110, 117, 118, 131]. Observations in animals with experimental pneumococcal as well as *H. influenzae* meningitis indicate that initiation of antibiotic therapy results in a more pronounced increase in inflammatory in-

dices and cytokine levels in the CSF [71, 112, 119]. Additional evidence indicates that LPS does not act alone during Gram-negative bacillary meningitis [11]. These bacteria also contain similar amounts of peptidoglycan [48]. LPS is not present in the CSF in sufficiently high concentrations to directly injure the cerebrovascular endothelium. In contrast, clinically relevant concentrations of LPS (1–10 ng/ml) are able to induce CSF leucocytosis and are potent at priming leucocytes for the production of inflammatory mediators. Peptidoglycan is only a weak inducer of inflammatory mediators. However, peptidoglycan can cause cellular separation of endothelia at concentrations 100-fold less than required for LPS and may be responsible for the induction of BBB permeability in Gram-negative meningitis [74].

Two studies in infants with Gram-negative meningitis have demonstrated increased endotoxin concentrations in CSF and ventricular fluid when intrathecal or intraventricular antibiotic therapy was given in addition to parenteral antibiotics. This increased endotoxin concentrations have been associated with an augmented meningeal inflammation and with a rise in adverse outcome in infants with coliform meningitis treated with intraventricular gentamicin [3, 65, 66, 70].

Cytokines

The host responds with the release of cytokines upon recognition of the presence of bacterial products in the subarachnoidal space. TNFα and IL-1β appear to play a pivotal role in triggering the cascade of meningeal inflammation [91]. Il-6, another cytokine found in CSF from patients with bacterial meningitis, has also been implicated in the pathogenesis of this infection. Although production of these inflammatory cytokines has been linked to the development of CNS injury, the precise mechanism has not been elucidated. It has been suggested that cytokines are produced by glial cells and brain capillary endothelial cells [67]. Experimental studies have indicated that intracisternal inoculation of endotoxin is followed by detection of TNFα and IL-1β activity. Subsequently, leucocytosis and changes in protein, glucose and lactate concentrations are observed within hours. Combined injection of TNFα and IL-1β into the CSF has a synergistic effect [119]. Administration of dexamethasone or polymyxin b before or together with *H. influenzae* type b (Hib) lipooligosaccharide, inhibits CSF TNFα and decreases the meningeal inflammatory response [51, 71, 72, 109]. TNFα and IL-1β can also be detected in initial CSF samples of children with bacterial meningitis [126]. The presence of IL-1β is associated with CSF inflammatory abnormalities, TNFα concentration and an adverse outcome [69]. Some reports describe an association between indices of inflammation or the clinical course and TNFα, IL-1β and IL-6 levels. Infants with culture-proven viral meningitis or with non-infected CSF have low or non-detectable IL-1β and TNFα levels [18, 39, 59, 61, 77, 90].

Arachidonic acid metabolites

Arachidonic acid metabolites play an important role as mediators and/or modulators of inflammation. These products may be involved in many of the pathological processes in meningitis. They are released after stimulation with bacterial and immunological antigens by a variety of cells, including neutrophils, platelets, and vascular endothelial cells. TNFα and IL-1β induce phospholipase A_2 activity thereby triggering the production of these pro-inflammatory substances [64].

Previous studies have demonstrated a significant increase in prostaglandin E_2 (PGE_2) (cyclo-ogygenase products) but not leukotriene B_4 (lipo-oxgygenase product) concentration in CSF during pneumococcal meningitis in rabbits [49]. Intracisternally administered PGE_2 did not induce detectable CSF leucocytosis, but caused a dose-related increase in protein content [50]. PGE_2 and PGI_2 are elevated in the CSF of infants and children with bacterial meningitis. The concentration of PGE_2 correlates significantly with protein, TNFα, and IL-1β concentrations in the initial CSF sample [73].

PAF

CSF platelet activating factor (PAF) concentrations are significantly higher in children with *H. influenzae* meningitis than in afebrile and febrile control subjects without meningitis. The concentrations correlate strongly with concomitant bacterial counts and with both LPS and TNFα concentrations in admission CSF samples. LPS and a variety of cytokines, such as TNFα and IL-1β, are potent inducers of PAF by polymorphonuclear leucocytes (PMN), macrophages/monocytes, endothelial cells and neuronal cells [8, 82, 125]. PAF recruits and activates PMNs and monocytes at the site of inflammation and induces the release of other inflammatory mediators. PAF in high concentrations is toxic to neuronal cells. PAF acts synergistically with LPS and TNFα in the development of microvascular tissue damage [4, 12].

Leucocytes

Several hours after meningeal infection an intense influx of leucocytes occurs. Cytokines stimulate the function of neutrophils and provoke degranulation superoxide production and increased adherence to the endothelium. It has been demonstrated that products of leucocytes, such as polyunsaturated fatty acids and oxygen-free radicals can induce brain oedema, increased lactate production,

and energy depletion in cortical brain slices of rats [16, 28]. However, not all studies demonstrate adverse effects of leucocytes. When the effects of experimental pneumococcal meningitis were compared between normal and neutropenic rabbits similar changes of brain water content (brain oedema), intracranial pressure, and CSF concentration of lactate and protein were observed [113].

Therapy

Antimicrobial therapy

The combination of ampicillin and chloramphenicol has been known for many years as an effective empirical therapy of bacterial meningitis. Ampicillin resistant β-lactamase producing *H. influenzae* has become a major problem in many European countries and the United States of America. A recent collaborative European study shows a mean rate of resistance of 10% for all participating countries [63]. In addition, sporadic cases of chloramphenicol-resistant *H. influenzae* have been documented. Combined resistance to chloramphenicol and beta-lactams is increasing [13, 14, 36, 42, 102, 124]. *N. meningitidis* resistant to β-lactam antibiotics is also increasingly encountered. Spain has been a major source for penicillin-resistant *N. meningitidis* [96]. Infections caused by resistant pathogens lead to higher rates of morbidity and mortality than infections caused by susceptible pathogens.

A consensus among experts about the choice of initial empiric therapy of childhood meningitis is still lacking. Third generation cephalosporins have become important antibiotics for the treatment of presumed bacterial meningitis in infants and children [19, 56, 75, 104]. Among these cephalosporins, cefotaxime, ceftriaxone, and ceftazidime have been studied extensively [32, 44, 92]. All three agents are extremely active against *H. influenzae* (including β-lactamase producing strains), *N. meningitidis* and *S. pneumoniae*. However, cephalosporins are inactive against *Listeria monocytogenes, Streptococcus faecalis* and methicillin-resistant staphylococci. Empiric therapy of bacterial meningitis in children up to 3 months of age should include ampicillin for activity against *L. monocytogenes* and enterococci. Once the aetiological agent has been identified and its susceptibility determined, therapy can be altered to a single drug or a combination of drugs active in vitro. The duration of therapy is dependent on the clinical response of the patients. Seven days is generally considered adequate for meningococcal infections and 10 days for *H. influenzae* and pneumococcal meningitis [89]. Despite the availability of active antibiotics against the common meningeal pathogens the outcome of meningitis has not changed over the last decades. Therefore investigators have been focusing on novel approaches to diminish neurological sequelae of meningitis.

Fluid restriction

It is generally recommended that children with bacterial meningitis receive less than maintenance fluid to treat or prevent the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [25, 52]. However, a recent study in infants with bacterial meningitis shows that elevated levels of antidiuretic hormone (ADH) may also be explained as an appropriate response to intravascular volume depletion rather than as the result of hypothalamic-pituitary axis dysfunction [87]. The loss of cerebrovascular autoregulation in bacterial meningitis may be compensated by secretion of ADH to maintain adequate cerebral blood flow. The cerebral blood flow during bacterial meningitis depends on the cerebral perfusion pressure which is the difference between the mean arterial blood pressure and the intracranial pressure. Two studies in rabbits with experimental meningitis compared fluid restriction with a normal fluid regimen. Fluid restriction resulted in reduced mean arterial blood pressure, significantly decreased cerebral blood flow and increased anaerobic glycolysis of the brain. The fluid regimen, however, did not have a major effect on the degree of brain oedema [114, 123]. Since cerebral blood flow is often reduced in bacterial meningitis, fluid restriction may even worsen the neurological outcome. Clinical trials to evaluate the effect of fluid regimen on outcome have not been performed. Current recommendation in children with bacterial meningitis may have to be revised in view of these new experimental data. Fluid restriction should possibly only be limited to those patients with meningitis who fulfil the diagnostic criteria for SIADH.

Adjunctive therapy

The improvements in our understanding of the pathophysiology of bacterial meningitis may lead to the development of novel therapeutic approaches. Modulation of the inflammatory cascade may reduce the incidence of sequelae and death in patients with bacterial meningitis. Interventions will be directed against harmful bacterial products (e.g. monoclonal antibodies, polymyxin B), cytokines (e.g. monoclonal antibodies, steroids), leucocytes (e.g. monoclonal antibodies, pentoxiphylline, radical scavengers) or some consequences of the disease, e.g. brain oedema, increased intracranial pressure or alterations of the cerebral blood flow (Table 1).

Corticosteroids

In vitro studies indicate that pretreatment of cultured cells with dexamethasone suppresses the synthesis and release of cytokines induced by bacterial products [9, 54, 58]. The inflammatory response in the CSF of rabbits after in-

Table 1 Adjunctive anti-inflammatory agents in the treatment of bacterial meningitis

- Corticosteriods
- Monoclonal antibodies
  - Anti-endotoxin
  - Anti-IL-1β; anti-TNFα
  - Anti-CD18
- Cyclo-oxygenase inhibitors
- Pentoxifylline
- Radical scavengers
  - Superoxide dismutase
  - Catalase

tracisternal inoculation of bacterial products such as endotoxin or live *H. influenzae* may be blocked by dexamethasone. However, this is only effective when dexamethasone is initiated before or at the same time as the antibiotic [51, 71, 72]. TNFα and IL-1β levels in the CSF are reduced concomitantly with concentrations of PGE_2 [73]. Dexamethasone also decreases brain water content, intracranial pressure, and CSF lactate in animals with *S. pneumoniae* or *H. influenzae* meningitis [100, 109, 111].

Clinical studies to evaluate the efficacy of dexamethasone in bacterial meningitis have yielded controversial results (Table 2). Lebel et al. [57] demonstrated that conventional antibiotic therapy (cefuroxim or ceftriaxone) plus dexamethasone resulted in improved outcome in the treatment group in comparison with a placebo-treated group. Children treated with dexamethasone had a significantly lower incidence of sensorineural deafness (15% vs 3.3%) and of other neurological sequelae 12 months later [57]. The study of Odio et al., in which dexamethasone administration was started before the initiation of cefotaxime therapy failed to find a significant reduction in hearing impairment in the steroid treated group. However, an overall reduction in the incidence of neurological complications (including hearing loss) was seen in the treatment group in comparison with a placebo group (14% vs 38%) [76]. The majority of cases of meningitis in these two studies were due to *H. influenzae* while *N. meningitidis* and *S. pneumoniae* will become more important in the coming years due to the introduction of *Haemophilus* conjugate vaccines. In a study from Egypt mortality was reduced in patients (children and adults) with pneumococcal meningitis by using dexamethasone. This corticosteroid also protected against hearing loss in this group of patients [38]. These three studies showed a significant reduction in neurological sequelae with dexamethasone, but benefits were statistically significant only when the sequelae were unusually common as result of suboptimal therapy (cefuroxim), supportive, and diagnostic management (in developing countries). The results of these studies could not be confirmed in more recent trials, which de-

Table 2 Overview of sequelae in recent placebo/dexamethasone therapy studies in children treated for bacterial meningitis (*SEQ* sequelae, *NA* not available, *NS* not significant)

Study	Antibiotic therapy	No (%) of children with audiological (A), neurological (N) or combined (C) sequelae			*P*
		SEQ	Placebo	Dexamethasone	
Lebel et al. [57]	Cefuroxim	A	16/ 38 (42)	9/ 43 (21)	< 0.05
		N	3/ 34 (9)	1/ 38 (3)	NS
		C	NA	NA	NA
Lebel et al. [57]	Ceftriaxone	A	14/ 46 (30)	7/ 49 (14)	NS
		N	6/ 41 (15)	2/ 43 (5)	NS
		C	NA	NA	NA
Odio et al. [76]	Cefotaxime	A	7/ 44 (16)	5/ 50 (6)	NS
		N	15/ 48 (31)	5/ 51 (10)	0.008
		C	18/ 48 (38)	7/ 51 (14)	0.007
King et al. [55]	Not uniform	A	4/ 51 (9)	5/ 48 (11)	NS
		N	3/ 51 (7)	3/ 48 (6)	NS
		C	NA	NA	NA
Wald et al. [127]	Ceftriaxone	A	NA	NA	NA
		N	NA	NA	NA
		C	10/ 74 (14)	6/ 68 (9)	NS
Schaad et al. [98]	Ceftriaxone	A	8/ 55 (15)	3/ 60 (5)	NS
		N	5/ 55 (9)	3/ 60 (5)	NS
		C	9/ 55 (16)	3/ 60 (5)	NS
Schaad et al. [98] (meta-analysis)	Ceftriaxone	C	28/175 (16)	12/177 (7)	0.007

tected no significant difference between steroid-treated patients and control subjects [55, 98, 127]. However, a meta-analysis of sequelae in ceftriaxone-treated bacterial meningitis in children indicated that dexamethasone as adjuvans therapy is superior to placebo [98]. The American Academy of Pediatrics advises to use dexamethasone in patients with proven or strongly suspected bacterial meningitis. However, the Canadian Pediatric Society has not yet decided to recommend routine use of dexamethasone therapy [2, 47].

Furthermore, the use of corticosteroids is associated with potential side-effects supporting the need for more information to assess the risks or benefits [45]. In the report by Lebel et al. [57], 2% of the patients had gastro-intestinal bleeding. None of the patients receiving placebo had this complication. At present, the frequency and severity of this complication of dexamethasone are unknown. Other studies indicate that glucocorticoids potentiate ischaemic injury to neurons. Since decreased cerebral blood flow appears to be one of the pathophysiological features of bacterial meningitis, it is important to know whether dexamethasone has beneficial effects on hearing but worsens cerebral cortical function [97]. These important questions concerning the place of corticosteroids should be addressed further in carefully conducted clinical trials in homogeneous populations.

Monoclonal antibodies against endotoxin

Inhibition of the effects of endotoxin may have beneficial effects on Gram-negative bacterial meningitis since the toxic moiety of endotoxins, lipid A, can be neutralized by polymyxin B or by a monoclonal antibody to lipid A [7, 128, 133, 134]. Indeed, cures of bacterial meningitis were achieved in the pre-antibiotic era by direct installation of immune serum supplemented with complement [1, 27, 29, 30]. Direct CSF inoculation was needed for this therapy. Experimental studies in rats demonstrate that intravenous administration of an IgG monoclonal antibody results in low CSF levels ($\leq$ 5.5%) [37]. Intracisternal inoculation of an IgM monoclonal antibody or polymyxin b directed against the lipid A moiety of *E. coli* LPS reduced the cefotaxim-induced increase in CSF LPS concentration and brain water content. The monoclonal antibody was clearly more effective in reducing brain water content although no differences were observed in the capacity to neutralize endotoxin [112].

Monoclonal antibodies against cytokines

Intracisternal administration of TNFα and IL-1β in rabbits induces a brisk inflammatory response which may be blocked by antibodies against the cytokines. Moreover, simultaneous intracisternal administration of anti-TNFα polyclonal antibody with Hib lipooligosaccharides neutralizes CSF TNFα activity and is associated with substantial attenuation of the meningeal inflammatory changes [72].

Monoclonal antibodies against CD18

Agents that attenuate the augmented granulocyte-endothelial interaction followed by leucocyte influx into CSF could be beneficial in preventing brain damage. Monoclonal antibodies against the CD18 family of adhesion-promoting receptors on leucocytes have been studied. Animals receiving intravenous mAb IB4 (anti-CD18) before intracisternal inoculation with living bacteria *(S. pneumoniae, H. influenzae, N. meningitidis),* endotoxin or cell-wall demonstrate a dramatic reduction in CSF leucocyte density and protein concentration. Cerebral oedema was absent in mAb-treated animals [95, 120].

Inhibition of prostaglandins

Non-steroidal anti-inflammatory agents inhibit the cyclo-oxygenase pathway and reduce meningeal inflammation in bacterial meningitis. Cyclo-oxygenase inhibitors (indomethacin, diclofenac, oxindanac) block the development of brain oedema and decrease the number of leucocytes in comparison with non-treated animals. In addition, the influx of protein in the CSF compartment is prevented by these inhibitors. Oxindanac has a stronger activity than other cyclo-oxygenase inhibitors (indomethacin, diclofenac). A study in rabbits with experimental meningitis demonstrated a dramatically decreased mortality by the use of a combination of ampicillin plus oxindanac in comparison with treatment with ampicillin alone or ampicillin plus dexamethasone or indomethacin. Trials of selected non-steroidal anti-inflammatory agents hold much promise [49, 50, 119, 121, 122].

Pentoxifylline

Recent studies suggest that pentoxifylline, a xanthine-derived phosphodiesterase inhibitor, can inhibit the inflammatory process. Pentoxifylline can reverse or counteract many of the effects of endotoxin and endotoxin-induced cytokines on leucocyte function [108]. Studies in rabbits with experimental meningitis indicate that continuous intravenous infusion of pentoxifylline compared with saline significantly reduces CSF concentrations of leucocytes, protein, and lactate [94]. Pentoxifylline also reduces the release of cytokines from primary murine microglial cell cultures. When added concomitantly with LPS, pentoxifylline blocked the release of TNFα and IL-1β but not IL-6, while dexamethasone inhibited the release of TNFα and IL-6. Pentoxifylline, but not dexamethasone, inhibited TNFα release from microglia previously stimulated with LPS [17].

Radical scavengers: superoxide dismutase and catalase

Reactive oxygen species in experimental meningitis are capable of inducing vasodilation of cerebral arterioles, increased BBB permeability, increased lactate production and brain oedema. Pfister et al. studied the effects of two radical scavengers in experimental meningitis. Superoxide dismutase completely blocked the increase of regional blood flow, intracranial pressure, and brain water content during the early phase of experimental pneumococcal meningitis. Catalase, another radical scavenger, only partly attenuated the increase of regional cerebral blood flow, intracranial pressure and brain water content. These results suggest that the increase of regional cerebral blood flow, brain water content, and intracranial pressure is mainly caused by superoxide or its products [80, 81].

Vaccination

Recently, conjugate vaccines against Hib have been developed. These vaccines, but not the previous non-conjugated ones, are immunogenic and effective during the age of the highest incidence of meningitis caused by Hib. A very low rate of side-effects was noted [20, 22, 23, 40, 41, 53, 78, 129]. Hence, Hib vaccination has been introduced in childhood vaccination programmes in an increasing number of countries. Subsequently a 90% reduction in *H. influenzae* meningitis has been observed [23, 79]. However, a substantial number of children have bacterial meningitis caused by *N. meningitidis* and *S. pneumoniae*. Meningococcal disease is caused by several serogroups *N. meningitidis*; serogroup B is the most common cause in Europe, North-America and several countries in Latin America. A meningococcal non-conjugate tetravalent A, C, Y, and W135 polysaccharide vaccine is available and has been shown to be safe and immunogenic in adults, but not in young infants. The serogroup B polysaccharide, however, is poorly immunogenic in humans and has not been useful for development of a vaccine. Therefore, vaccines based on outer membrane proteins are currently being evaluated for their efficacy [34, 60]. Recent field trials with such vaccines have demonstrated only partial protection against group B infection [10, 15]. Several pneumococcal conjugate vaccines combining the most relevant serotypes coupled to different protein antigens are already available [105].

The final aim would be a combined conjugate vaccine, including adequate immunogenic structures of Hib, meningococci and pneumococci to provide a protective antibody response at an early age.

Conclusions

Brain damage in patients with bacterial meningitis results from the combined deleterious effects of the micro-organisms and its products and of the host inflammatory response. A number of pathophysiological alterations have been demonstrated in animal models. These include brain oedema, elevation of intracranial pressure, changes in CSF outflow resistance, morphological changes of the BBB, and changes in cerebral blood flow. In addition, mediators of pathophysiological changes have been identified, including cytokines, cyclo-oxygenase metabolites, and PAF. Several adjunctive therapeutic interventions have been developed to modulate the damaging host response to invading micro-organisms. The new treatment strategies are directed against bacterial products, cytokines and white blood cells. Most of these adjunctive therapies have only shown advantageous effects when administered before or simultaneously with the induction of experimental meningitis. However, pentoxifylline has been shown to attenuate the inflammatory process by reducing the release of cytokines in a model previously exposed to endotoxin. The use of corticosteroids as adjunctive treatment in human studies shows the presence of a possible beneficial effect. Nevertheless, routine use of steroids in children with bacterial meningitis is still a subject of intense debate because recent studies did not demonstrate a significant difference in the percentage of neurological or audiological sequelae. Although improvement of treatment strategies has given encouraging results, prevention of bacterial meningitis by development and introduction of a combined conjugate vaccine against the three common causative pathogens will be the major challenge of the next decade.

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