PATHOGENESIS OF BACTERIAL MENINGITIS

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SUMMARY

Bacterial meningitis is the most common serious infection of the central nervous system (CNS) and leads to significant morbidity and mortality. An improved understanding of the pathogenesis of this condition might lead to advances in management and ultimately improve outcome in patients. This article aims to describe currently held concepts about the pathogenesis of bacterial meningitis from nasopharyngeal acquisition, mucosal invasion and entry into the circulation through to the sequelae of subarachnoid space invasion and inflammation, alterations in cerebral blood flow, the blood-brain barrier and intracranial pressure. Finally, the implications of advances in the understanding of the disease process for adjunctive therapy are discussed.

INTRODUCTION

The specific pathogenetic processes that lead to the development of acute bacterial meningitis depend to a certain degree on the infecting organism. However fundamental features of the basic stages of mucosal colonisation, bloodstream invasion, subarachnoid space inflammation and the resultant effects on blood-brain barrier permeability, intracranial pressure and cerebral blood flow are common to the most frequently isolated pathogens. It is no surprise that the pathogenesis of meningeal infection has been most clearly elucidated for the commonest aetiological agent, *Neisseria meningitidis*, and whilst this article will aim to describe bacterial meningitis in general, many of the illustrative examples will draw on work with the meningococcus. Although cerebrospinal fluid (CSF) infection can occur by contiguous spread of local infection, this article will focus on the more common setting of bacterial meningitis following the acquisition of pathogens in the respiratory tract.

MUCOSAL COLONISATION

Successful colonisation of the nasopharyngeal mucosa depends on the ability of bacteria to evade host defences including secretory IgA and ciliary clearance mechanisms, and to adhere to mucosal epithelium.[1] Microbial virulence factors include the IgA proteases secreted by *N. meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* that cleave IgA to an inactive form.[2] *N. meningitidis* and *H. influenzae* infection of nasopharyngeal cell culture is injurious to ciliated epithelial cells and results in loss of ciliary activity. Adherence to epithelial cells has been studied in particular for the meningococcus, which depends on the binding of fimbriae (or *pili*) on the bacterial cell surface to microvilli on non-ciliated epithelial cells. Fimbriae have also been described in *H. influenzae* but are not essential for adherence. Interestingly, although the surface capsule is an important virulence determinant for all the major meningeal pathogens, nonencapsulated strains of meningococci adhere better than capsulated strains.

INVASION – MUCOSAL

Asymptomatic nasopharyngeal carriage of *N. meningitidis* can be detected in 5-20% of adults in nonepidemic settings, thus clearly only a fraction of colonised individuals develop disease. Recent acquisition of carriage (within two to ten days) is associated with a significantly higher rate of progression to invasive disease than carriage beyond ten to fourteen days, which is regarded as an immunising process. Meningococcal invasion occurs when the organism enters nonciliated nasopharyngeal epithelial cells by a process of endocytosis, and is then transferred across the cell in membrane-bound phagocytic vacuoles. In contrast, mucosal invasion by *H. influenzae* progresses primarily via an intercellular route, achieved by the creation of separations in the apical tight junctions between columnar epithelial cells.

INVASION – CIRCULATION

Once the mucosa has been breached and the intravascular space has been entered, the pathogen must survive in the circulation long enough to penetrate the blood-brain barrier. Survival depends on both pathogen-specific and host-specific factors.

The principal host defence mechanism is complement, although neutrophil phagocytosis and antibodies (the goal of vaccination) are also important. Individuals with inherited deficiencies of the terminal complement components (C6-C9) have a greatly increased risk of invasive meningococcal disease. Intriguingly, in these subjects infection is acquired at a later age and the case fatality rate is significantly lower than in individuals with normal levels of complement.

The principal meningeal pathogens are all capsulated and it is this virulence factor which enables evasion of phagocytosis and complement-mediated bactericidal activity, although each organism achieves this in a different way.

In *S. pneumoniae* infection the alternative complement pathway (which does not require specific antibody for activation and is thus an 'early warning system') is activated by pneumococcal capsular polysaccharides. Direct cleavage of C3 generates C3b which opsonises the organism, enhancing phagocytic clearance from the circulation. However, C3b binds inefficiently to factor B on the pneumococcal capsular surface, offering some resistance to opsonisation. Individuals with impairment of the alternative complement pathway (especially asplenic patients, either post-splenectomy or functionally asplenic as in sickle-cell disease) are at increased risk of all manifestations of invasive pneumococcal disease.

For *N. meningitidis*, capsular sialic acid facilitates binding of C3b to the complement regulatory protein factor H, thus blocking activation of the alternative pathway by preventing the binding of C3b to factor B.

INVASION – BLOOD-BRAIN BARRIER

This is the least well understood step in the pathogenesis of bacterial meningitis, but probably varies between

pathogens. In the infant rat model of *H. influenzae* meningitis, intensity of bacteraemia appears to be one factor that augments meningeal invasion. However, the rarity of meningitis in some infections characterised by prolonged bacteraemia, such as that due to viridans-type streptococci in patients with infective endocarditis, indicates that other factors must be relevant. For example S fimbriae appear to be important for the penetration of the blood-brain barrier by strains of *E. coli* responsible for meningitis in neonates. These organisms bind to sialyl galactoside units of cell-surface glycoproteins and *in vitro* bind specifically and competitively to the endothelial cells of meningeal vessels and choroid plexus epithelium of neonatal rats. Phase variation of these organisms to the non-fimbriated form may then be necessary for CNS invasion to progress.

The precise site of invasion is not established but infant rat and primate studies suggest that the choroid plexus, which has an exceptionally high (200ml/g/min) rate of blood flow, and thus large delivery of organisms per unit time, is a likely candidate. The presence of pathogen-specific receptors in this location, as described above for *E. coli*, supports this suggestion.

It is clear that an organism which has crossed the blood-brain barrier is likely to survive as CSF is a relatively immunologically incompetent medium, with virtually undetectable immunoglobulin and complement and negligible opsonic activity.[3] The average blood:CSF ratio of IgG is 800:1 in health, and though immunoglobulin levels and thus opsonic activity do increase as meningitis develops, the rise is usually late in the course of the illness.

INFLAMMATION – SUBARACHNOID SPACE

The lack of host defences in the CSF allows rapid multiplication of bacterial pathogens resulting in the release of microbial products such as lipopolysaccharide (LPS). Animal experiments demonstrate that direct intra-cisternal introduction of live organisms, bacterial cell wall fragments or LPS will all elicit a broadly similar pattern of blood-brain barrier injury, which characteristically begins two to three hours post-inoculation. This observation suggests that specific endogenous host inflammatory mediators, in particular the pro-inflammatory cytokines interleukin-1 (IL-1) and tumour necrosis factor-α (TNF-α), may be common to most episodes of bacterial meningitis regardless of the causative organism. Indeed, in intra-cisternal inoculation of IL-1α (in rats), IL-1β (rats and rabbits) and TNF-α (rats and rabbits), particularly the latter two together, the resultant inflammation induced is virtually indistinguishable from that produced by LPS.[4, 5] In patients, meningitis is associated with raised levels of CSF IL-1β, IL-6, IL-8 and TNF-α,[6-8] as well as other pro-inflammatory molecules such as PGE_2, platelet-activating-factor (PAF),[9] matrix metalloproteinases (MMPs)[10] and soluble CD14 (sCD14).[11] The outcome of patients with gram-negative meningitis correlates with CSF endotoxin (LPS) concentrations.[12] Treatment of *H. influenzae* meningitis with ceftriaxone induced a marked rise in CSF concentrations of free LPS within two to six hours, raising the possibility that the subarachnoid space inflammatory response is augmented following antimicrobial therapy in meningitis due to this organism.[13] However, in *E. coli* meningitis the two- to ten-fold rises in LPS concentration which were observed following therapy with cefotaxime or meropenem were dwarfed by increases of up to 100-fold in untreated animals.[14]

The hallmark of bacterial meningitis is recruitment of neutrophils into the CSF. Neutrophil extravasation to any site of inflammation depends on the coordinated sequential expression at the cell surface of specific adhesion molecules.

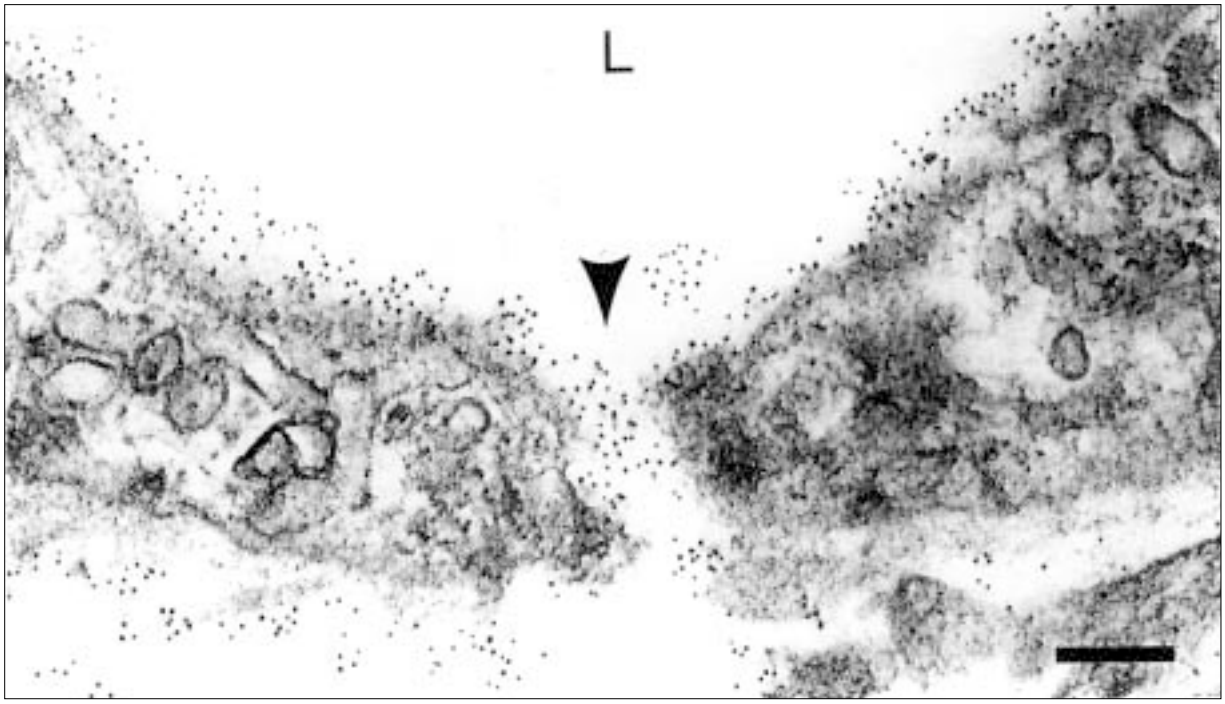

FIGURE 1

Electron micrograph of a venule within experimentally inflamed meninges of a rat – colloidal gold-albumin complexes can be seen exiting through an open intercellular junction of a pial venule. L = Lumen. (Reproduced from reference 15 with permission of Quagliarello VJ *et al*. and the *Journal of Experimental Medicine* 1991; 174(3):657-72).

L-selectin (CD62L) is constitutively expressed at the cell surface and allows the neutrophil to 'roll' along the endothelium. For extravasation to proceed L-selectin must be shed from the surface of the neutrophil and expression of the β2-integrin CD11b/CD18 must be upregulated. Neutrophil adherence to endothelium then occurs through the interaction of neutrophil CD11b/CD18 with endothelial intercellular adhesion molecule-1 (ICAM-1), and diapedesis and migration of the neutrophil along a chemotactic gradient to the focus of inflammation then follows. The shedding of L-selectin and integrin upregulation are achieved by neutrophil activation which occurs when the cell encounters 'activated endothelium' (IL-8 and PAF are typical activators of endothelium).

ALTERATIONS IN BLOOD-BRAIN BARRIER

The blood-brain barrier is responsible for maintaining homeostasis within the CNS. The cerebral microvascular endothelium has unique ultrastructural properties that account for its effectiveness, continuous intercellular tight junctions and rare plasmalemmal vesicles. Studies in rats with experimental meningitis have demonstrated an increase in cytoplasmic plasmalemmal vesicles and complete separation of the intercellular tight junctions. The same findings were observed in meningitis due to *S. pneumoniae*, *H. influenzae* and *E. coli*. Moreover, studies of *in situ* perfusion of colloidal gold-albumin complexes showed that the main site of albumin leakage (which facilitates the development of cerebral oedema) is in the venular segments of the pia-arachnoid vasculature (Figure 1).[15]

In the rat, elevated levels of gelatinase B (MMP-9) in CSF correlate with the degree of blood-brain barrier disruption, and inhibition of MMPs significantly reduces both disruption and subsequent increases in intracranial pressure.[10] Other MMPs including collagenase-3 and stromelysin-1 are also selectively increased in bacterial meningitis. MMP-targeted therapies might in the future offer the opportunity to reduce morbidity and/or mortality from meningitis.

RAISED INTRACRANIAL PRESSURE

Intracranial pressure (ICP) often rises in meningitis and can lead to life-threatening cerebral herniation. Three pathophysiologic mechanisms contribute to the development of cerebral oedema (the major cause of raised ICP) – vasogenic, cytotoxic and interstitial. Vasogenic oedema occurs directly as a result of the increased permeability of the blood-brain barrier, as discussed above. Cytotoxic oedema refers to the rise in intracellular water due to loss of cellular homeostatic mechanisms and cell membrane function, attributed to the release of undefined cellular 'toxins' from neutrophils or organisms. Antidiuretic hormone (ADH) release leads to hypotonicity of cerebral extracellular fluid and increases the permeability of the brain to water. Interstitial oedema is the result of an imbalance between CSF production and resorption, and occurs when CSF production increases (via increased choroid plexus blood flow, for example) or CSF resorption is impaired. The latter mechanism has been clearly demonstrated in the arachnoid granulations of rabbits with experimental *S. pneumoniae* meningitis.

ALTERED CEREBRAL BLOOD FLOW

Bacterial meningitis exerts profound effects on cerebral blood flow, which have been shown to correlate with adverse outcomes in both adults and children. In experimental meningitis, overall cerebral blood flow increases initially then falls to sub-normal levels in more advanced disease. There is considerable evidence of regional disturbance of cerebral blood flow, for example with relative cortical hypoperfusion demonstrated in experimental *H. influenzae* meningitis. An association between elevated blood flow velocities in basal cerebral vessels and high CSF concentrations of IL-1β and IL-6 has been reported.[16] Autoregulation is impaired during bacterial meningitis, thus a rise in systemic blood pressure is paralleled by an increase in cerebral perfusion and subsequently ICP. Equally, systemic hypotension will result in cerebral hypoperfusion. Whilst this would usually be global hypoperfusion there is also a propensity for bacterial meningitis to cause focal or regional hypoperfusion by means of a vasculitis affecting vessels in the subarachnoid space. This vasculitis is the main cause of the ischaemic damage that accounts for permanent neurological sequelae. The sequelae are most devastating when large vessels at the base of the brain are affected with luminal narrowing and a propensity for thrombus formation resulting in hemi- or quadri-paresis. Finally, changes in ICP directly correlate with changes in cerebral blood flow.

Thus, maintaining an adequate circulating volume, a non-labile blood pressure and satisfactory arterial oxygenation will minimise the potential deleterious effects of altered global and regional cerebral blood flow. (Figure 2).

Table 1
Potential therapeutic interventions for specific pathophysiological events in the development of meningitis (modified from reference 1).

Pathophysiologic event	Potential therapeutic intervention
• Nasopharyngeal colonisation	Vaccination (esp. conjugate vaccines)
• Release of pro-inflammatory bacterial cell products within CSF	Bactericidal antibiotics with less lytic activity, $rBPI_{21}$
• Generation of pro-inflammatory cytokines within CSF	Steroids, pentoxifylline
• Neutrophil entry into CSF	Steroids, anti-adhesion molecule monoclonal antibodies, cytokine antagonists
• CSF neutrophil activation	Steroids, pentoxifylline, PAF-antagonists, cyclo-oxygenase inhibitors

IMPLICATIONS FOR ADJUNCTIVE THERAPY (SEE TABLE 1)

Bactericidal antimicrobial therapy is clearly the cornerstone of the management of bacterial meningitis, and has recently been reviewed.[17] It is clear that the immunopathology of bacterial meningitis is responsible for much of the morbidity and mortality, and that improvements in antimicrobials are unlikely to dramatically alter outcome. A better understanding of the pathophysiological mechanism of disease has provided several opportunities to intervene with adjunctive agents that might modify these host responses.[18]

Steroids have been the most widely studied anti-inflammatory agents in meningitis. In experimental

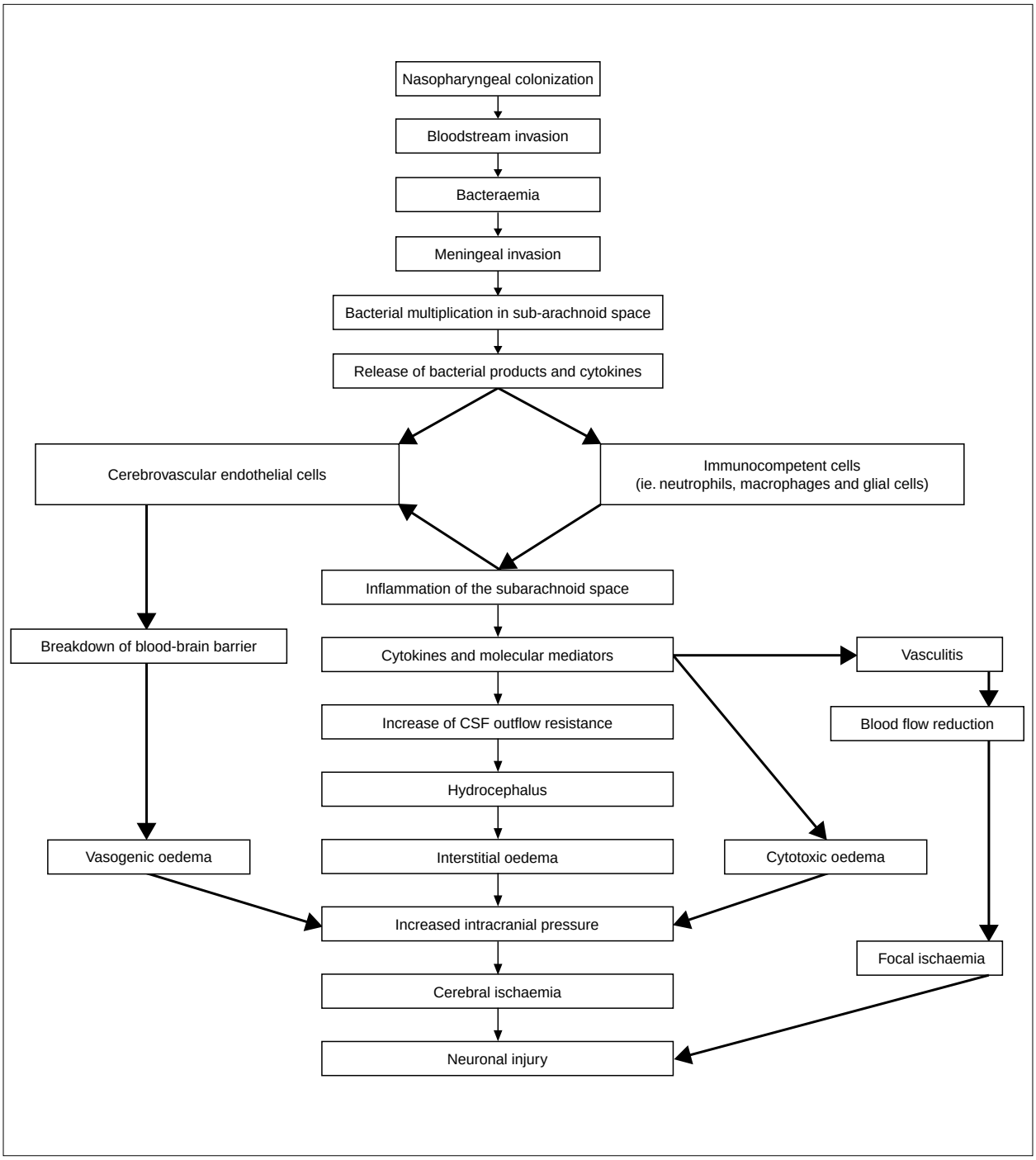

FIGURE 2
Pathogenesis of bacterial meningitis. (Reproduced from reference 23 [Section 2, Figure 15.5] with permission of Leib S, Tauber M and Churchill Livingstone and Mosby).

meningitis in animal models steroids reduce meningeal inflammation, CSF outflow resistance and cerebral oedema and are associated with a more rapid normalisation of CSF protein concentration. These effects are mediated by several means – steroids inhibit transcription of mRNA for TNF-α and IL-1β, inhibit production of prostaglandins and PAF and reduce production of inducible nitric oxide synthase (iNOS). Published controlled trial data indicate that adjunctive steroids are of proven benefit only in paediatric *H. influenzae* meningitis, significantly reducing mortality and neurological sequelae (particularly deafness).[19] Animal models indicate that steroids are effective in pneumococcal meningitis only when given before or with antibiotics. Intuitively one might expect those patients with high CSF bacterial load (a positive gram stain for example) to be at the greatest risk of bacteriolysis-induced inflammation, and for this reason some authorities recommend adjunctive steroids for such cases.

Non-steroidal anti-inflammatory drugs (NSAIDs) block the cyclooxygenase-mediated conversion of arachidonic acid to prostaglandins. CSF levels of PGE_2 are elevated in bacterial meningitis and correlate with subarachnoid space inflammation. In experimental meningitis a variety of NSAIDs have been investigated and found to have varying effects on PGE_2 levels. However, although some agents reduced CSF pleocytosis and protein concentration, none led to a reduction in ICP or improved survival.

Pentoxifylline is a substance with fibrinolytic activity and an inhibitory effect on platelet aggregation and for this reason has been used in the medical management of intermittent claudication. However, the anti-inflammatory potential of this phosphodiesterase inhibitor is mediated through an effect on neutrophils and a reduction in LPS-induced TNF-α production by macrophages. Exposure of activated neutrophils to pentoxifylline reduces adherence to endothelium, production of superoxide and release of granules. In experimental rabbit *H. influenzae* meningitis, pentoxifylline reduced CSF inflammation due to direct intracisternal inoculation with *H. influenzae* LPS, but had little effect in infection with live organisms.[20]

A monoclonal antibody directed against a human β_2 integrin, an essential adhesion molecule for neutrophil adherence to endothelium and diapedesis, has been tested experimentally. IB4 significantly reduced CSF inflammation, cerebral oedema and blood-brain barrier disruption caused by live bacteria, LPS or pneumococcal cell wall.

An alternative strategy is to target microbial rather than host factors. An obvious candidate is LPS, and much interest has focused on $rBPI_{21}$, a recombinant protein derived from bactericidal/permeability-increasing protein (BPI). BPI is a naturally occurring protein found in the azurophilic granules of neutrophils. It has the ability both to bind and neutralise LPS, and is also bactericidal for gram-negative bacteria.[21] In an open clinical trial in children with meningococcal meningitis, $rBPI_{21}$ was safe and was associated with a better outcome than a group of matched historical controls.[22] A phase III placebo-controlled trial of $rBPI_{21}$ in meningococcal meningitis has been completed but the results were not yet known at the time of writing (April 2000).

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