Bacterial meningitis in adults: Host and pathogen factors, treatment and outcome
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Citation for published version (APA):
Heckenberg, S. G. B. (2013). Bacterial meningitis in adults: Host and pathogen factors, treatment and outcome

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Summary
Bacterial meningitis is a life-threatening infectious disease. Two common inhabitants of the human nasopharynx, *Streptococcus pneumoniae* and *Neisseria meningitidis*, are the most prevalent causes of bacterial meningitis. When bacteria invade the membranes lining the brain, meningitis occurs. Effective antibiotic treatment and adequate critical care have improved the prognosis greatly, but mortality remains substantial and in survivors neurologic sequelae such as hearing loss are common.

In chapter 2 of this thesis we describe 258 patients with meningococcal meningitis who were included in a nationwide prospective cohort study from 1998-2002. On presentation, the prevalence of the classical triad of fever, neck stiffness, and change in mental status was low (27%). Rash, a common presenting symptom of meningococcal disease, was found in 64% of patients. When septic shock occurs, hypotension and tachycardia are common and these were found 31% of patients. The clinical importance of identifying a rash in meningococcal disease was underlined by the presence of rash in all 5 patients with normal initial cerebrospinal fluid examination. Bacterial genotyping was performed through MLST analysis and disease caused by meningococci belonging to clonal complex 11 was associated with sepsis and poor outcome. Sepsis was the leading cause of mortality.

In chapter 3, the collaborative effort of our research group with the Netherlands Vaccine Institute is described. In Gram-negative bacteria such as *N. meningitidis*, lipopolysaccharide is a major component of the outer membrane, and lipid A is an important part of that lipopolysaccharide. The human immune system recognizes lipid A through binding with Toll-like receptor 4 (TLR4), which induces activation of the innate immune system and induction of cytokine production. A meningococcal strain with reduced TLR4 activation was investigated and found to have a changed lipid A structure, caused by mutations in the meningococcal *lpxL1* gene. We found these mutations in 7% of meningococci from the patients in our prospective cohort study and investigated if clinical characteristics in these patients were different. In these patients, we found that rash and reduced platelet counts were less common, consistent with less systemic inflammation and reduced activation of the coagulant system. These results provide the first example of a specific mutation in *N. meningitidis* that can be correlated with the clinical course of meningococcal meningitis.
In 2002, a European randomized clinical trial showed beneficial effect of adjunctive dexamethasone in adults with bacterial meningitis. The effect was most pronounced in pneumococcal meningitis and mortality in those patients was reduced by 10%. While these results were not reproduced in clinical trials from other parts of the world, an individual patient data-analysis and subsequent Cochrane review supported the continued use of dexamethasone in children and adults in high-income countries. However, the use of adjunctive dexamethasone in meningococcal meningitis remained controversial, and some international guidelines recommended discontinuing dexamethasone in suspected meningococcal meningitis. In clinical practice, Gram staining of cerebrospinal fluid is frequently negative and the results of cultures requires several days. Furthermore, lumbar puncture may be contraindicated, prohibiting CSF analysis. Therefore, the cause of bacterial meningitis may remain unknown in the first days of treatment, when dexamethasone is administered. In chapters 4 and 5, we used a historical cohort design to compare the prognosis of patients with meningococcal and pneumococcal meningitis in 2 cohorts, one from 1998-2002, before the implementation of adjunctive dexamethasone, and one from 2006-2009 after the introduction of adjunctive dexamethasone. In chapter 4, we showed that the prognosis of meningococcal meningitis has not changed since the introduction of adjunctive dexamethasone treatment. We found no reason to discontinue the use of adjunctive dexamethasone in these patients. In chapter 5, we studied the effect of adjunctive dexamethasone in pneumococcal meningitis. The prognosis of patients with pneumococcal meningitis has improved substantially since the introduction of bacterial meningitis. The absolute reduction in both mortality (from 30% to 20%) and unfavorable outcome (from 50% to 39%) could not be attributed to other factors, such as changes in epidemiology or disease severity. These studies support the continued use of adjunctive dexamethasone in adults with bacterial meningitis in the Netherlands.

In patients that survive bacterial meningitis, neurologic sequelae are common and include cognitive impairment and hearing loss. In chapter 6 we studied the incidence and severity of hearing loss in patients surviving pneumococcal meningitis. Otitis was a common presenting feature (36% of patients) and predictive of hearing loss at discharge. Hearing loss was most common in patients infected with pneumococcal serotype 3.
In patients with bacterial meningitis, the improvement in outcome with adjunctive dexamethasone is based on reduction of the inflammatory response. The complement system is an important part of the innate immune system and reducing the proinflammatory effect of complement activation may further improve prognosis. In chapter 7, we found that common genetic variants in the complement system influence outcome. Patient with pneumococcal meningitis with the GG genotype in a gene coding or complement factor 5 (rs17611) were at higher risk for unfavorable outcome. In a mouse model, treatment with C5a antibodies improved outcome in pneumococcal meningitis and further research of this new adjuvant treatment is warranted.

In chapter 8 we discuss the epidemiology, pathophysiology and treatment of bacterial meningitis and provide context for the findings of our research and recommendations for future research. Improving the prognosis of patients with bacterial meningitis remains an important challenge. We have shown that both bacterial genotype and human genetic variants influence disease course and outcome in this life-threatening disease. While treatment with dexamethasone has reduced unfavorable outcome in the Netherlands substantially, further research is warranted to continue improving the prognosis of patients with bacterial meningitis.