Bacterial meningitis in adults: Host and pathogen factors, treatment and outcome
Heckenberg, S.G.B.

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

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 1

Introduction
Bacterial meningitis occurs when bacteria invade the subarachnoid space surrounding the brain and spinal cord. This infection and the ensuing inflammatory response cause severe, life-threatening disease. Until the advent of antibacterial agents effective treatment was lacking. After initial success using intrathecal meningococcal antiserum in the first decades of the twentieth century, the introduction of sulfonamides in the 1930s provided the first effective antibiotic therapy for bacterial meningitis caused by *Haemophilus influenzae* type B and *Neisseria meningitidis*. Subsequently, penicillin treatment for pneumococcal meningitis was implemented in the 1940s. In meningococcal disease, increasing resistance to sulfonamides prompted its replacement by penicillin.\(^1,2\)

### Epidemiology

To monitor the epidemiology of bacterial meningitis, the Netherlands Reference Laboratory for Bacterial Meningitis was officially established in 1975 and isolates from cerebrospinal fluid (CSF) from patients with bacterial meningitis have been stored and collected. The implementation of conjugate vaccination against type B *H. influenzae*, group C *N. meningitidis*, and most recently, the pneumococcal vaccine have reduced the incidence of bacterial meningitis in the Netherlands. Currently, approximately 85% percent of all bacterial meningitis is caused by *N. meningitidis* and *Streptococcus pneumoniae*. Other causes are *Listeria monocytogenes, H. influenzae* and *Streptococcus agalactiae*.\(^3\) *N. meningitidis* (the meningococcus) is a common inhabitant of the human nasopharynx. Carriage is found exclusively in humans. Disease occurs when meningococci invade the mucosal space and enter the bloodstream. Invasive disease can progress swiftly and fatally, mainly through sepsis and meningitis. The incidence of meningococcal meningitis in adults in the Netherlands is approximately 1 per 100,000. In the Netherlands, the most common serogroups are B and C, while serogroup A is the cause of severe epidemics in the “meningitis-belt” in sub-Saharan Africa. Since the implementation of vaccination with the MenC vaccine, the incidence of group C disease has decreased substantially in the Netherlands. In 1998, a new method of typing meningococci was described using nucleotide sequencing of meningococcal genes. Multilocus sequence typing (MLST) has provided a useful tool for the unambiguous characterisation
of meningococci and allows for rapid identification of invasive lineages of meningococci.\(^4\)

*S. pneumoniae* (the pneumococcus) is a major cause of respiratory infections, sepsis and meningitis worldwide. In pneumococcal meningitis, mortality remains high (20-30%) despite effective antibiotic treatment. Over 90 serotypes have been described. Increasing antibiotic resistance is an emerging challenge worldwide with rates of resistance exceeding 50% in parts of the United States. However, antibiotic resistance in the Netherlands remains low. In 2006, the heptavalent pneumococcal vaccine was implemented in the national vaccination program in the Netherlands.

**Treatment and outcome**

Although the prognosis of patients with bacterial meningitis has improved greatly through effective antibiotic treatment, substantial morbidity and mortality has remained, fuelling research into adjunctive treatment. Following experimental animal studies, attenuation of the severe inflammatory response emerged as an important pathway for improving clinical outcome. Since the 1960s, clinical trials with adjunctive corticosteroid treatment have been performed with conflicting results. However, meta-analyses showed a reduction in hearing loss in patients treated with adjunctive corticosteroids.\(^5\) 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%. However, 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.\(^6\)\(^-\)\(^8\)

Adequate antibiotic and adjunctive therapy in combination with supportive care have reduced the mortality of bacterial meningitis, but neurologic sequelae in patients surviving bacterial meningitis are common, particularly in pneumococcal meningitis. They include cognitive impairment, hearing loss, epilepsy and other focal neurological deficits.\(^9\)\(^-\)\(^11\)
Aims and outline of this thesis

In chapter 2 we present the results of a nationwide study in adults with meningococcal meningitis. Details of clinical characteristics, therapy and outcome are presented, as well as the correlation of bacterial genotype, acquired through MLST analysis, and clinical characteristics. Chapter 3 describes the collaborative effort of our research group with the Netherlands Vaccine Institute. The discovery of meningococci with an impaired potential to induce cytokine production is described. Furthermore, the mutations in bacterial genome are revealed and the relationship with clinical characteristics in patients from our nationwide cohort studies is investigated. In chapters 4 and 5, we present the results of nationwide studies from 2006-2009 on the implementation of dexamethasone treatment in the Netherlands. Outcome in patients was compared to a cohort of 1998-2002, before the implementation of dexamethasone. The influence of dexamethasone treatment on outcome in meningococcal meningitis is described in chapter 4. Chapter 5 describes the change in outcome in adults with pneumococcal meningitis and we compare the observed outcome with that in a prognostic model. Chapter 6 describes the incidence of hearing loss following pneumococcal meningitis, combining two nationwide studies of adults with bacterial meningitis, from 1998-2002 and from 2006-2009. The association between clinical characteristics, pneumococcal serotype and occurrence of hearing loss is described. In Chapter 7 the results of our cooperation with a research group in Munich, Germany are presented. We describe the association of unfavorable outcome with a single nucleotide polymorphism (SNP) coding for complement factor C5. Next, C5 fragment levels in CSF and the relationship with clinical characteristics were investigated. Finally, a mouse model of C5a deficient mice and adjuvant treatment with C5-specific monoclonal antibodies are described. In chapter 8, we conclude with a general discussion describing the epidemiology, pathophysiology and treatment of bacterial meningitis incorporating the results of the presented studies and suggestions for future research are proposed.
References

10. Ostergaard C, Konradsen HB, Samuelsson S. Clinical presentation and prognostic factors of Streptococcus pneumoniae meningitis according to the focus of infection. BMC Infect Dis 2005;5:93.