**Bacterial meningitis in adults**

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CHAPTER 1

INTRODUCTION
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The association of headache and tinnitus with lethal inflammation of the brain was described by Hippocrates. It was not before the nineteenth century that lumbar puncture was introduced as diagnostic procedure. Soon thereafter, the use of cerebrospinal fluid drainage was advised in patients with bacterial meningitis; however, it did not have clinical efficacy. Most important in the treatment of bacterial meningitis was the introduction of penicillin in 1940, which reduced the mortality rates of bacterial meningitis to an overall fatality rate of approximately 20 percent. Worldwide 1.2 million cases of bacterial meningitis are estimated to occur each year; bacterial meningitis is a top-ten infectious cause of death worldwide.

The epidemiology of community-acquired acute bacterial meningitis has changed during the last two decades. Meningitis due to Haemophilus influenzae type b has nearly been eliminated in the Western world since routine vaccination with the conjugate H. influenzae type b vaccine started. In addition, the prevalence of penicillin resistant pneumococci increased worldwide and the introduction of conjugate vaccines against seven of the most common and resistant strains of Streptococcus pneumoniae is expected to reduce the burden of childhood pneumococcal meningitis also significantly. As a consequence, the age distribution of meningitis shifted to older age groups.

The most common etiologic agents of community-acquired bacterial meningitis in adulthood are S. pneumoniae and Neisseria meningitidis, which cause 80 to 85 percent of all cases. S. pneumoniae primarily causes respiratory infections, including otitis media, sinusitis, and pneumonia. Groups at increased risk of pneumococcal infection include the very young, the elderly, the immunocompromised, smokers, and certain other demographic groups. As individuals advance in age, pneumococci cause increasing attack rates, including meningitis. N. meningitidis most commonly causes meningitis in children and young adults. Nasopharyngeal carriage of meningococci is an important factor that leads to the development of invasive disease. The estimated prevalence of meningococcal carriage is 5 to 10 percent under nonepidemic conditions. In a small percentage of colonized people, N. meningitidis gains entry to the bloodstream, where it can cause meningococcemia and/or progress to the cerebrospinal fluid to cause meningitis.

Early diagnosis is vital to success in the treatment of patients with bacterial meningitis. Therefore, clinical recognition of meningitis is imperative to allow clinicians to efficiently complete further investigations and initiate appropriate therapy as soon as possible with a goal of minimizing adverse outcome. The classic presentation of a patient with bacterial meningitis presents few difficulties. A combination of systemic features such as fever, malaise, and vomiting, together with signs of central nervous system involvement, headache, photophobia, disturbance of consciousness, and meningism leaves little doubt of the primary diagnosis. However, not all patients present with the classic clinical triad of fever, neck stiffness, and a change in mental status. The assessment of the accuracy of clinical features in the diagnosis bacterial meningitis is limited by lack of prospective studies. Optimal use of the clinical examination aids physicians in identifying patients at sufficient risk for meningitis to require further definitive diagnostic testing with lumbar puncture. Patients in whom meningitis is suspected require this invasive
procedure to effectively establish or refute the diagnosis.

The clinical outcome of acute bacterial meningitis varies according to socioeconomic aspects, age, and the causative pathogen. In developed countries, meningitis caused by *S. pneumoniae* has the highest case fatality rate, reported from 20 to 37 percent. Of survivors, it has been estimated that up to 30 percent develop neurologic sequelae, including hearing loss and other focal neurologic deficits. The mortality and morbidity rates for meningococcal meningitis are lower with 7 and 10 percent, respectively. Identification of prognostic factors for adverse outcome can help clinicians to identify patients with high risk on adverse outcome, and thereby will be helpful in improving care. Several prognostic factors for adverse outcome in patients with bacterial meningitis have been identified so far; however, this was mainly done in retrospective cohort studies.

Bacterial meningitis is a complex disorder in which neurologic injury is caused in part by the causative organism and in part by the host's own inflammatory response. Experimental animal models are important to learn more about the pathogenetic and pathophysiologic mechanisms in bacterial meningitis. Bacterial lysis, induced by treatment with antibiotics, leads to inflammation in the subarachnoid space, which may contribute to an unfavorable outcome. Animal studies have also shown that adjuvant treatment with corticosteroids reduces cerebrospinal fluid inflammation and thereby improves neurologic outcome. In children with acute bacterial meningitis, many controlled trials have been performed to determine whether adjuvant corticosteroid therapy is beneficial. The results did not point unequivocally to a beneficial effect. A meta-analysis of randomized trials showed a beneficial effect of adjunctive dexamethasone therapy on severe hearing loss in children with *H. influenzae* meningitis; however, meningitis due to *H. influenzae* type b has nowadays nearly been eliminated. The paucity of data precludes a recommendation that corticosteroids should be administered routinely in adults with bacterial meningitis.

The outline of this thesis is twofold. First, we describe data from patients with acute bacterial meningitis (Chapter 2 to 6). Secondly, we investigate whether the use of adjuvant dexamethasone is beneficial in patients with bacterial meningitis (Chapter 7 to 10). Chapter 2 describes clinical features and prognostic factors of 696 episodes with bacterial meningitis. In Chapter 3, results of a chart review of adult patients with group A streptococcal meningitis are presented. In Chapter 4, the compliance with the Dutch national guidelines for antibiotic treatment of patients with bacterial meningitis is evaluated, and the *in vitro* susceptibility of *N. meningitidis* and *S. pneumoniae* strains from meningitis patients to a novel antibiotic agent in Chapter 5. In Chapter 6, neuropsychological outcome is assessed in patients with good recovery after meningitis. Results of a systematic review on the effect of corticosteroid therapy in children and adults with bacterial meningitis are presented in Chapter 7. In Chapter 8 and 10, the effect of dexamethasone in adults with bacterial meningitis is evaluated in a clinical trial. To further evaluate this effect an additional analysis is performed with data derived from Chapter 7 and 8 (Chapter 9). Finally, results of this thesis are discussed in Chapter 11, in which an algorithm on treatment approaches for adults with bacterial meningitis is proposed.
Chapter 1

22. Scheld WM, Dacey RG, Winn HR, Welsh JE, Jane JA, Sande MA. Cerebrospinal fluid outflow resistance in rabbits


