Bacterial meningitis in adults
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Bacterial meningitis is an important and frequently devastating disease, despite optimum antibiotic therapy. Many bacterial pathogens have been reported to cause meningitis; however, approximately 80 percent of all cases are caused by *Streptococcus pneumoniae* (pneumococcus) and *Neisseria meningitidis* (meningococcus). Vaccination of children against *Haemophilus influenzae* type b and *S. pneumoniae* has led to a shift in age distribution of meningitis towards adults. In this thesis we give an overview on the major issues in the management of adults with bacterial meningitis.

In the first part of this thesis we describe data from our Dutch cohort study. This cohort is a large consecutive, prospective and nationwide series of adults with bacterial meningitis. In Chapter 2, we describe clinical features and prognostic factors in the Dutch cohort. In many cases the diagnosis is easily made as most patients present with the classic symptoms and signs of fever, neck stiffness and an altered consciousness. However, the clinical presentation of patients with bacterial meningitis may not always be classic. Therefore, in patients with a suspicion for bacterial meningitis the threshold to perform lumbar puncture should be low to rule out meningitis. In the Dutch cohort, the mortality rate was 21 percent, and was higher among patients with pneumococcal meningitis, compared with meningococcal meningitis. Overall, outcome was unfavorable in 34 percent of patients. Most risk factors for unfavorable outcome indicate infection with *S. pneumoniae* and systemic compromise.

Meningitis due to group A streptococci (*Streptococcus pyogenes*) is rare. In Chapter 3, we review the charts of 41 Dutch patients with group A streptococcal meningitis during a period of 14 years. In contrast with data from the literature, we found that group A streptococcal meningitis is a fulminant disease with high mortality and morbidity rate.

In October 1997, national consensus-based guidelines for the treatment of adult patients with bacterial meningitis were introduced in The Netherlands. In Chapter 4, we describe the results of a prospective, nationwide study in which we evaluate whether the recommended initial treatment provides adequate microbiological coverage. Although the microbiological coverage for patients who were treated in compliance with the guidelines was almost complete, only one out of three patients received treatment in compliance with the guidelines.

In Chapter 5, we investigate the *in vitro* susceptibility of strains causing meningitis in The Netherlands to the novel antibiotic meropenem and conclude that meropenem is highly active against the two most common causative organisms of bacterial meningitis, *N. meningitidis* and *S. pneumoniae*.

Adults without neurologic sequelae after bacterial meningitis are supposed to live without restrictions. In Chapter 6, we assess neuropsychological outcome in adults with apparent good recovery after bacterial meningitis from the Dutch cohort study. Patients who recovered well after pneumococcal meningitis showed cognitive slowness; a cognitive disorder was present in one out of four of these patients. Cognitive slowness is related to lower scores on general health and quality of life scales.

In the second part of this thesis we investigate whether the use of adjuvant dexamethasone is beneficial in patients with bacterial meningitis. Meningitis studies in animals have shown
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that adjuvant treatment with corticosteroids, such as dexamethasone, reduces the inflammatory response and thereby improves outcome. Several controlled trials in children have been performed to determine whether adjuvant corticosteroid therapy is beneficial. The results did not point unequivocally to a beneficial effect. In Chapter 7, we perform a systematic review on this topic. In children, adjuvant corticosteroid treatment of 20 patients would prevent one case of severe hearing loss. On basis of this review, early corticosteroid treatment in most children with suspected bacterial meningitis appears to be justified.

The use of adjunctive corticosteroid therapy in adults with acute bacterial meningitis has changed after publication of the results of the European dexamethasone in adulthood bacterial meningitis study. In Chapter 8, we present the results of this randomized, double-blind clinical trial. Treatment with dexamethasone gave a reduction in the risk of both an unfavorable outcome and mortality. The effect was most apparent in patients with pneumococcal meningitis and was not undermined by an increase of corticosteroid-induced complications.

In the European study no significant beneficial effect is found in patients with meningococcal meningitis, however, a beneficial effect cannot be ruled out since the number of patients in this subgroup was small. In Chapter 9, we perform a systematic review on this topic. In meningococcal meningitis, mortality and morbidity were both reduced, but not significantly. Since treatment with corticosteroids reduces both mortality and neurologic sequelae in patients bacterial meningitis, without detectable adverse events in subgroups, routine corticosteroid therapy is justified in most adult patients in whom bacterial meningitis is suspected.

Whether mortality is reduced by a beneficial effect of dexamethasone on neurologic or systemic complication is evaluated in a post hoc analysis. In Chapter 10, we describe that the beneficial effect of dexamethasone on death in pneumococcal meningitis is attributable to effects on systemic complications.

Finally, the results of this thesis are discussed in Chapter 11, in which an algorithm on treatment approaches for adults with bacterial meningitis is proposed.