CHAPTER II

COMMUNITY-ACQUIRED BACTERIAL MENINGITIS IN ADULTS -
GENERAL DISCUSSION

Diederik van de Beek, Jan de Gans, Martijn Weisfelt, Allan Tunkel

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INTRODUCTION

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.\(^1\) In addition, 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 significantly as well.\(^2,3\) As a consequence, the age distribution of meningitis shifts to older age groups.\(^3,4\)

The second epidemiological trend is the emerge of antibiotic-resistant strains of *S. pneumoniae*.\(^5\) Pneumococcal resistance to penicillin, due to changes in its penicillin binding proteins, was first reported in 1965.\(^6\) The prevalence of such resistance was limited until an epidemic of highly resistant pneumococci occurred in South Africa in 1977.\(^6\) Since then, resistance has developed worldwide and in some regions it occurs in a frequency up to 70 percent.\(^6\) Reports of reduced susceptibility of pneumococci to several antibiotics, including broad-spectrum cephalosporins, have also been published.\(^7\) In response to this epidemiological trend, recommendations for suspected and confirmed bacterial meningitis have necessarily evolved.\(^8,9\)

In this paper we give an overview on the major issues and changes in the managing of adult patients with bacterial meningitis. For that we did a Medline search from 1996 through 2004 for articles with the keywords meningitis, meningitis in adults, bacterial meningitis in adults, neuro-infection, CNS infection, brain infection, and meningeval inflammation; we also studied papers cited in those articles, papers previously collected by us, and textbooks. We assessed articles in English, French, German and Dutch language. Without discarding any factual clinical observations, we selected from the large number of non-observational studies (editorials, comments, reviews, letters) those that seemed most relevant. In addition, we used data from our Dutch cohort.\(^10\) This cohort is a large consecutive, prospective and nationwide series of adults with community-acquired acute bacterial meningitis.

In this review, we will describe the clinical presentation of adults with acute bacterial meningitis and will offer recommendations about cranial computed tomography (CT) before lumbar puncture. We also provide a simple overview of cerebrospinal fluid findings in patients with bacterial meningitis. In addition, we give recommendations for initial therapy in adults with acute bacterial meningitis. Thereafter, we discuss outcome and prognostic factors. Finally, we present a management algorithm for the initial management of adults with bacterial meningitis.

**Clinical features**

Early diagnosis is vital in the treatment of bacterial meningitis.\(^11-13\) Therefore, clinical recognition is important to efficiently complete further investigations and initiate appropriate therapy as soon as possible, with the goal of minimizing adverse outcome. In many cases the diagnosis is easily made as most patients present with classic symptoms and signs.\(^12,13\) In retrospective studies in adults with acute bacterial meningitis, fever was observed in 95 to 97 percent, neck stiffness in 70 to 88 percent, and an altered consciousness was found in 66 to 78 percent of patients.\(^12-20\)
In the Dutch cohort, the prevalence of fever was 77 percent, of neck stiffness 83 percent, and of altered consciousness (defined as a score on the Glasgow Coma Scale below 14) 69 percent. Although classic symptoms and signs are present in a large proportion of patients, the prevalence of the classic triad (fever, neck stiffness and altered consciousness) is low. In a retrospective study, the prevalence of the classic triad was 46 percent. In the Dutch cohort, the classic triad was present in 44 percent of patients; only the absence of headache, fever, neck stiffness, and an altered consciousness effectively eliminated the likelihood of community-acquired acute bacterial meningitis. Thus, individual symptoms and signs may be absent in patients with acute bacterial meningitis. In the majority of patients the classic triad is absent.

Seizures before admission occur in 5 to 9 percent of all cases, and approximately 15 percent of patients develop seizures during their clinical course. Cranial nerve palsy is relatively rare; most commonly affected are cranial nerve VIII (6 percent), nerve III (4 percent), nerve IV (3 percent), and nerve VII (2 percent). Focal cerebral findings (aphasia, hemiparesis and monoparesis) on admission occur in approximately 15 to 23 percent of patients. Papilledema is uncommon in patients with acute bacterial meningitis (3 to 4 percent of patients; however, in most studies the results of fundoscopic examination were not recorded). Systemic manifestations, such as hypotension and tachycardia, occur frequently in acute bacterial meningitis. So patients with community-acquired acute bacterial meningitis present with both neurologic and systemic symptoms and signs.

Community-acquired acute bacterial meningitis is caused by *S. pneumoniae* and *Neisseria meningitidis* in approximately 85 percent of all cases. Many patients with pneumococcal meningitis have underlying and associated conditions, such as distant foci of infection or an immunocompromised state (Table 1). The most common condition is an ear or sinus infection, being present in 33 to 58 percent of all patients with pneumococcal meningitis. Pneumonia as co-existing condition has been reported in 12 to 56 percent of patients. In the Dutch cohort, 62 percent of patients with pneumococcal meningitis had distant foci of infection. In general, patients with pneumococcal meningitis present with more severe disease, reflected by lower levels of consciousness, higher frequency of seizures and focal neurologic findings. Rash occurs more frequently in patients with meningococcal meningitis, with reported sensitivities of 63 to 80 percent, and with specificities of 83 to 92 percent. In the Dutch cohort, rash was present in 26 percent of patients, and 92 percent of patients with rash had meningococcal meningitis. Of all meningococcal meningitis patients, 64 percent had a rash (Table 1). Hence,

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pneumococcal meningitis (N=352)</th>
<th>Relative frequency (%)</th>
<th>Meningococcal meningitis (N=257)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures before admission</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Otitis or sinusitis</td>
<td>44</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>18</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>22</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>64</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Coma</td>
<td>19</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Focal neurologic deficits on admission</td>
<td>43</td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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in the presentation of patients with community-acquired acute bacterial meningitis an etiologic diagnosis could be suggested by certain symptoms and signs.

In conclusion, 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.

LUMBAR PUNCTURE AND CRANIAL CT

Cerebrospinal fluid findings are essential to establish the diagnosis in bacterial meningitis. In recent years, a number of reports, especially in pediatric literature, emphasized the risk of brain herniation complicating diagnostic lumbar puncture.21-23 As a consequence, cranial CT has been recommended as a precaution before lumbar puncture to predict and avoid the likelihood of brain herniation.24,25 Rationally, lumbar puncture can produce or hasten brain herniation in all conditions in which it may occur spontaneously.26 The withdrawal of cerebrospinal fluid removes the stopper from below, thus adding to the effect of compression from above, increasing the brain shift already present. Cranial CT can be done before lumbar puncture aimed at detecting brain shift - and not raised intracranial pressure, which is present anyway in most cases of acute bacterial meningitis.26 In those patients with 'red flags' indicating space-occupying lesions (e.g. brain abscesses), or in cases with moderate or severe impairment of consciousness, lumbar puncture should be precipitated by cranial CT.26 This does not apply if the 'focal signs' consists of cranial nerve abnormalities or an isolated Babinski sign. Contra-indications for performing lumbar puncture are given in Table 2. In a prospective study among adults with suspected bacterial meningitis in the USA, 78 percent of patients underwent CT before lumbar puncture. In 76 percent of cases the results were normal.23 In the Dutch cohort, 313 of 696 patients (45 percent) presented with signs of possible brain shift and/or a score on the Glasgow Coma Scale below 10 (unpublished data, Van de Beek). Cranial CT before lumbar puncture was performed in 337 of 696 patients (48 percent); 197 of the 337 patients (59 percent) had signs of possible brain shift and/or a score on the Glasgow Coma Scale below 10. Initial therapy was started before CT in only 35 percent of patients in whom CT before lumbar puncture was performed. In conclusion, indications for performing cranial CT before lumbar puncture are often present. In patients in whom cranial CT is performed before lumbar puncture, CT should be preceded by obtaining blood cultures, starting antibiotic therapy, and corticosteroids if indicated.

Table 2. Contra-indications for performing lumbar puncture.

<table>
<thead>
<tr>
<th>Signs of brain shift</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papilledema</td>
</tr>
<tr>
<td>Focal neurologic deficits, not including cranial nerve palsy</td>
</tr>
<tr>
<td>Glasgow Coma Scale score below 10</td>
</tr>
<tr>
<td>Septic shock</td>
</tr>
<tr>
<td>Coagulopathy</td>
</tr>
<tr>
<td>Coagulant-use</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Serious skin infection at site lumbar puncture</td>
</tr>
</tbody>
</table>

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CEREBROSPINAL FLUID FINDINGS

The cerebrospinal opening pressure is found to be increased in over 90 percent of patients with acute bacterial meningitis. Very high opening pressures of more than 400 mm water are present in 16 to 20 percent of patients and are correlated with lower levels of consciousness. In patients with bacterial meningitis cerebrospinal fluid examination often reveals (marked) pleocytosis (100-10,000 white-blood cells per mm³), elevated protein (>1 g/dL), and decreased glucose (<40 percent of serum glucose). However, normal or marginal elevated cerebrospinal fluid white-blood cell counts occur in 1 to 10 percent of patients with acute bacterial meningitis. Individual cerebrospinal fluid predictors for bacterial meningitis are a glucose level <34 mg/dL [1.9 mmol/L], glucose ratio [the ratio of glucose in the cerebrospinal fluid to that in blood] <0.23, protein level >220 mg/dL, white-cell count >2000 per mm³, or a neutrophil count >1180 per mm³. In the Dutch cohort, 88 percent of patients had at least one individual cerebrospinal fluid finding that was predictive for bacterial meningitis (as defined above). In conclusion, most patients with acute bacterial meningitis have suggestive cerebrospinal fluid abnormalities; however, normal cerebrospinal fluid findings do not rule out the diagnosis.

Reported sensitivities of cerebrospinal fluid Gram stain in adults with community-acquired acute bacterial meningitis range from 48 to 80 percent, with specificities of 97 to 100 percent. The probability of detecting the organism by Gram stain may be decreased in patients who have already been treated with antibiotics. In the Dutch cohort, cerebrospinal fluid examination revealed the microorganism that subsequently was cultured in 524 of 652 cases (sensitivity, 80 percent; specificity, 97 percent). In addition, in the patients without one individual cerebrospinal fluid finding predictive for bacterial meningitis (as defined above), Gram stain showed bacteria in 55 of 78 patients (71 percent; unpublished data, Van de Beek). In conclusion, Gram stain examination of cerebrospinal fluid permits a rapid and accurate identification of the causative organism in patients with community-acquired acute bacterial meningitis. We stress the need of performing Gram stain examination of cerebrospinal fluid in the early stage of disease.

ANTIBIOTIC THERAPY

A delay in the initiation of antimicrobial therapy may lead to poor outcome. In a retrospective cohort of 269 adults with community-acquired bacterial meningitis, the median delay between the time of emergency room arrival and the administration of antibiotics was four hours. In this study, patients were stratified according to baseline prognostic factors as having low, intermediate and high risk on adverse outcome. For patients who ‘stage-shifted’ during their stay in the emergency room to a category with higher risk on adverse outcome, an association was found between antibiotic timing and outcome. So in patients with a low level of clinical severity and without apparent progress of disease, waiting for confirmatory data before starting antibiotic therapy, and corticosteroids if indicated, seems to be justifiable. The causative organism is unknown in many cases when treatment is started. In these patients, initial antibiotic therapy should be based on the most common bacterial organisms causing the disease in the different age groups or clinical settings, and on antibiotic susceptibility
patterns of the predominant microorganisms. In most patients, initial antibiotic therapy with a third-generation cephalosporin is recommended (Table 3). However, in patients >60 years or in those with risk factors (alcoholism, altered immune status, including diabetes mellitus, recent head injury, or cerebrospinal fluid leak), additional therapy with amoxicillin is warranted, because *L. monocytogenes*, rather a common cause of meningitis in these categories, is resistant to cephalosporins. Patients with a history of recent neurosurgery should be treated with vancomycin and a third-generation cephalosporin. These recommendations require modification under special circumstances. First, in areas with low resistance rates, such as The Netherlands, penicillin remains the drug of choice for the initial treatment of patients 16-60 years old, as meningitis in this group is predominantly caused by *S. pneumoniae* and *N. meningitidis*. Secondly, in areas with high resistance rates of pneumococci to broad-spectrum cephalosporins, a combination of third-generation cephalosporin and vancomycin should be the initial choice in all patients with acute bacterial meningitis.

Therapy should be modified when results of cerebrospinal fluid Gram stain, cerebrospinal fluid culture, and antibiotic susceptibility testing become available (Table 4).

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### Table 3. Initial treatment of adults (>16 years) with acute bacterial meningitis.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Recommended antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 16-60 years</td>
<td>Third-generation cephalosporin*†</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>Amoxicillin and third-generation cephalosporin†</td>
</tr>
<tr>
<td>With risk factor present‡</td>
<td>Amoxicillin and third-generation cephalosporin†</td>
</tr>
<tr>
<td>With recent neurosurgery</td>
<td>Vancomycin and third-generation cephalosporin</td>
</tr>
</tbody>
</table>

*In areas with low penicillin-resistance rates, penicillin is the first drug of choice. †In areas with ceftriaxone-resistance, combination therapy with vancomycin and third-generation cephalosporin should be used. ‡Alcoholism, altered immune status, recent head injury, cerebrospinal fluid leak.

### Table 4. Recommendations for antibiotic therapy.*

<table>
<thead>
<tr>
<th>Type of Bacteria</th>
<th>Choice of antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td>Penicillin-susceptible</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Intermediate-penicillin-susceptible</td>
<td>Third-generation cephalosporin</td>
</tr>
<tr>
<td>Penicillin-resistant</td>
<td>Vancomycin and third-generation cephalosporin</td>
</tr>
<tr>
<td><em>Neisseria meningitidis</em></td>
<td></td>
</tr>
<tr>
<td>Penicillin-susceptible</td>
<td>Penicillin</td>
</tr>
<tr>
<td>Penicillin-resistant</td>
<td>Third-generation cephalosporin</td>
</tr>
<tr>
<td><em>Listeria monocytogenes</em></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin and aminoglycoside</td>
<td></td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td></td>
</tr>
<tr>
<td>β-lactamase negative</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>β-lactamase positive</td>
<td>Third-generation cephalosporin</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td>Methicillin-sensitive</td>
<td>Flucloxacillin</td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>Vancomycin and rifampicin</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin-sensitive</td>
<td>Amoxicillin</td>
</tr>
<tr>
<td>Amoxicillin-resistant</td>
<td>Third-generation cephalosporin</td>
</tr>
</tbody>
</table>

*The preferred dose: penicillin, 2 million units every 4 hours; amoxicillin, 2 g every 4 hours; third-generation cephalosporin: ceftriaxone, 2 g every 12 hours, or cefotaxime, 2 g every 4 hours; vancomycin, 1 g every 8 hours; aminoglycoside, gentamicin 4 mg per kg bodyweight; flucloxacillin, 2 g every 4 hours; rifampicin 600 mg every 12 hours.*
ADJUNCTIVE CORTICOSTEROID THERAPY

Not only the epidemiology has changed, the role of adjunctive corticosteroids in the treatment of patients with acute bacterial meningitis has developed as well during the last decade. Studies in animals have shown that bacterial lysis, induced by treatment with antibiotics, leads to inflammation in the subarachnoid space, which may contribute to an unfavorable outcome.\textsuperscript{33,34} The studies also showed that adjuvant treatment with anti-inflammatory agents, such as dexamethasone, reduced both cerebrospinal fluid inflammation and neurologic sequela.\textsuperscript{33,34}

Since the publication of these studies, several controlled trials have been performed to determine whether adjunctive corticosteroid therapy is beneficial in patients with acute bacterial meningitis. In 1997, a meta-analysis of randomized controlled trials performed since 1988 showed a beneficial effect of adjunctive dexamethasone therapy on severe hearing loss in children with \textit{H. influenzae} type b meningitis and suggested a protective effect in those with pneumococcal meningitis if the drug was given before or with parenteral antibiotics.\textsuperscript{35} More recently, a Cochrane review, including 1853 patients of whom 1474 children, showed a beneficial effect of corticosteroids on severe hearing loss in children with bacterial meningitis caused by \textit{H. influenzae} (relative risk, 0.31; 95 percent confidence interval, 0.15 to 0.62), as well as in meningitis caused by bacteria other than \textit{H. influenzae} (relative risk, 0.42; 95 percent confidence interval, 0.20 to 0.89).\textsuperscript{36} In children, adjuvant corticosteroid treatment of 20 patients would prevent one case of severe hearing loss. No beneficial effect on mortality was found, however, mortality rates were low. In nine studies mortality rates were three percent or less,\textsuperscript{36} whereas mortality rates in childhood bacterial meningitis in previously reported studies ranged from 8 to 20 percent.\textsuperscript{37} Inclusion in the meta-analysis of patients with less severe illness, as reflected by such low case fatality rates, will probably underestimate the protective effect of corticosteroids.\textsuperscript{38} An additional large controlled trial showed no beneficial effect of adjunctive corticosteroid therapy in children.\textsuperscript{39} However, this Malawian study included mainly children in whom treatment began late, HIV-positive children, and children receiving inappropriate antibiotic therapy.\textsuperscript{39} Therefore, the results of this trial are not representative for the typical meningitis population in industrialized countries. For patients admitted in a late stage of disease, adjunctive corticosteroid therapy is less protective and might even be harmful.\textsuperscript{38} Although in the Cochrane review the clearest effect was seen on severe hearing loss, a consistent trend towards a beneficial effect of corticosteroids in reducing mortality and neurologic sequelae among children with acute bacterial meningitis was found in absence of significant adverse effects. On the basis of this review, early corticosteroid treatment in most children with suspected bacterial meningitis appears to be justified.

The Cochrane analysis also included 259 adult patients.\textsuperscript{36} Although corticosteroids gave significant protection against death (relative risk, 0.95; 95 percent confidence interval, 0.2 to 0.8), results were interpreted cautiously because of an Egyptian study that accounted for 62 percent of all adult participants.\textsuperscript{36} In this study, which was not placebo-controlled and not double-blinded, only three pathogens were cultured from the cerebrospinal fluid, suggesting selection bias.\textsuperscript{40} The use of adjunctive corticosteroid therapy in adults with acute bacterial meningitis has notably changed after publication of the results of the European dexamethasone in adulthood bacterial
meningitis study in November 2002. In this study, treatment with dexamethasone was associated with a reduction in the risk of an unfavorable outcome (relative risk, 0.6; 95 percent confidence interval, 0.3 to 0.9; P=0.03) and with a reduction in mortality (relative risk of death, 0.48; 95 percent confidence interval, 0.2 to 0.96; P=0.04). In patients with pneumococcal meningitis, an unfavorable outcome was found in 26 percent of the patients treated with dexamethasone, as compared with 52 percent in the placebo group (relative risk, 0.5; 95 percent confidence interval, 0.3 to 0.8; P=0.006). Although no significant beneficial effect was found on neurologic sequelae in patients with pneumococcal meningitis (relative risk, 0.67; 95 percent confidence interval, 0.25 to 1.69), neurologic sequelae, including hearing loss, were predominately found in the most severely ill patients, and the proportion of severely ill patients who survived to be tested was substantial larger in dexamethasone group than in the placebo group. The benefit of adjunctive dexamethasone therapy was not undermined by an increase of severe neurologic disability in patients who survived, or by any corticosteroid-induced complication.

As the European study showed no significant beneficial effect in the meningococcal subgroup, several experts advised to discontinue dexamethasone therapy if bacterial meningitis is not caused by \( S.\ pneumoniae \). Although more studies are needed to confirm the results of the European study, and to detect a possible beneficial effect in patients with meningococcal meningitis, it took 9 years to complete this study suggesting that new information on this topic will most likely not be available in the near future. Recently, a quantitative review on this topic has been published, including five clinical trials. Treatment with corticosteroids was associated with a significant reduction in mortality (relative risk, 0.6; 95 percent confidence interval, 0.4-0.8; P=0.001) and in neurologic sequelae (relative risk, 0.6; 95 percent confidence interval, 0.4-1; P=0.05). The reduction in case fatality in patients with pneumococcal meningitis was 21 percent (relative risk, 0.5; 95 percent confidence interval, 0.3-0.8; P=0.001). In meningococcal meningitis, mortality (relative risk, 0.9; 95 percent confidence interval, 0.3-2.1) and neurologic sequelae (relative risk, 0.5; 95 percent confidence interval, 0.1-1.7) were both reduced, but not significantly. However, on the basis of overall benefit without detrimental effects in subgroups, corticosteroid therapy should be started before or with the first dose of antibiotic and continued in most patients with community-acquired acute bacterial meningitis.

Factors associated with an unfavorable outcome in acute bacterial meningitis are complex with both systemic and neurologic symptoms and signs caused in part by the causative organism and in part by the host's own inflammatory response. A post hoc analysis of the European study showed that the beneficial effect of dexamethasone in pneumococcal meningitis was attributable to a reduction in systemic complications, rather than neurologic complications. The systemic complications that were potentially preventable by dexamethasone were pulmonary complications and septic shock. It is known that high doses of corticosteroids reduce mortality among patients with non-resolving acute respiratory distress syndrome. Treatment of sepsis with corticosteroids has been investigated in several clinical trials, with varying results. A recent Cochrane review concluded that high doses of corticosteroids are not effective in the treatment of severe sepsis and septic shock, although there was a significant heterogeneity across
General discussion

included trials.\textsuperscript{53} High-dose corticosteroids may be detrimental in patients with septic shock.\textsuperscript{50,51} Therefore, we do not recommend high-dose adjunctive corticosteroid therapy in meningitis patients with septic shock.

Concern has been expressed that dexamethasone reduces blood-brain permeability, thereby impeding the penetration of vancomycin into the subarachnoid space.\textsuperscript{42-45,54,55} With the worldwide increase in the prevalence of penicillin-resistant pneumococci, combination therapy that includes vancomycin has become more important.\textsuperscript{8,9} In children with bacterial meningitis, treatment with dexamethasone did not reduce vancomycin levels in cerebrospinal fluid.\textsuperscript{56} However, treatment failures have been reported in adults who received standard doses of vancomycin and adjunctive dexamethasone.\textsuperscript{57} Therefore, patients with pneumococcal meningitis who are treated with vancomycin and dexamethasone should be carefully observed throughout therapy. Additionally, rifampicin and a third-generation cephalosporin could be given instead of vancomycin and a third-generation cephalosporin in patients treated with adjunctive dexamethasone.

We do not recommend the use of adjunctive (high-dose) corticosteroid treatment in patients who have already received parenteral antimicrobial therapy. Patients with postneurosurgical meningitis were excluded in all studies in the Cochrane analysis,\textsuperscript{56} and since postneurosurgical meningitis has different pathophysiology and predominant bacteria,\textsuperscript{29} we do not recommend routine use of corticosteroids in this patient group. Neither do we recommend the use of corticosteroids in immunosuppressed patients with acute bacterial meningitis, such as those with hematological malignancy or those receiving immunosuppressive therapy.

The available studies do not address two important issues - the minimum duration of corticosteroid therapy or the maximum length of time after parenteral antibiotic therapy for commencement. Although one study showed a two-day and four-day regimen of dexamethasone to be similarly effective in childhood bacterial meningitis,\textsuperscript{58} the four-day regimen has been used in most clinical trials.\textsuperscript{36-40} Starting corticosteroids before or with the first dose of parenteral antibiotic is more effective than starting after the first dose of antibiotic.\textsuperscript{35,36,39} Although it is possible that benefit may still accrue, the maximum allowable delay after parenteral antibiotics is not clear. If corticosteroids are indicated, a four-day regimen of dexamethasone therapy (10 mg 4 times daily) should be given and this treatment should be started before or with the first dose of antibiotic.

For patients with a low suspicion of meningitis but an urgent need for antibiotics before cerebrospinal fluid can be obtained, we suggest to start treatment with dexamethasone, and to stop dexamethasone therapy as soon as the diagnosis has been ruled out.\textsuperscript{28}

In the UK, family doctors are advised to give (parenteral) antibiotics before transferring the patient to hospital if meningococcal meningitis is suspected.\textsuperscript{60} However, a first difficulty in this setting is how to identify a patient with meningococcal meningitis. A second dilemma is whether patients benefit from such pre-hospital treatment. Although retrospective data from the UK showed a favorable outcome in patients who were treated early with parenteral antibiotics,\textsuperscript{61} pre-hospital antibiotic treatment remains controversial. In a Danish study, considerably higher mortality rates were reported in patients with suspected meningococcal meningitis who were
Subsequent analysis of all available studies showed no beneficial effect of pre-hospital parenteral antibiotic treatment (odds ratio, 0.8; 95 percent confidence interval, 0.4-1.6); however, those data were presented in a rather short communication and prospective data are lacking. In our opinion, if general practitioners decide to treat patients with suspected bacterial meningitis with parenteral antibiotics, dexamethasone should be given before or with this first dose.

In conclusion, corticosteroid therapy is indicated in most patients with community-acquired acute bacterial meningitis. We recommend a four-day regimen of dexamethasone therapy (10 mg 4 times daily), which should be started before or with the first dose of antibiotic.

**Outcome**

The outcome of community-acquired bacterial meningitis varies according to the causative organism. Meningitis caused by *S. pneumoniae* has the highest case fatality rates, reported from 19 to 37 percent. Of survivors, up to 30 percent develop long-term neurologic sequelae, including hearing loss and other focal neurologic deficits. The mortality and morbidity rates for meningococcal meningitis are lower, with case fatality rates of 3 to 10 percent, and morbidity rates of 3 to 7 percent. In the Dutch cohort, outcome was unfavorable (Glasgow Outcome Scale score below 5) in 34 percent of patients: 50 percent in patients with pneumococcal meningitis and 11 percent in patients with meningococcal meningitis. The overall mortality rate was 21 percent: 30 percent in patients with pneumococcal meningitis and 7 percent in patients with meningococcal meningitis. During the Dutch cohort study, adjunctive corticosteroid therapy was no standard treatment. One out of six patients in the cohort was treated with dexamethasone, in most cases initiated after clinical deterioration.

Patients who recover well from pneumococcal meningitis are at significant risk for cognitive impairment. In a prospective study, cognitive outcome was assessed in 51 adults with good clinical recovery (a maximum score on the Glasgow Outcome Scale, 5) after meningococcal and pneumococcal meningitis. Cognitive impairment was detected in 27 percent of patients following pneumococcal meningitis, compared to only 4 percent in patients after meningococcal meningitis and age-matched controls. Thus, large numbers of survivors of pneumococcal meningitis have cognitive problems.

In retrospective cohort studies specific risk factors present on admission were found to be associated with an increased mortality. Identification of prognostic factors can help clinicians to identify patients with high risk on adverse outcome, and thereby will be helpful in improving care. In one study of 493 patients with community- or hospital-acquired meningitis, univariate analysis identified age, obtunded mental state on admission, and onset of seizures within 24 hours after admission, to be risk factors for death. The Dutch cohort study was the first large prospective study on prognostic factors in adults with community-acquired acute bacterial meningitis. Several factors were found to be prognostic for unfavorable outcome in a profound multivariate analysis. First, patients with systemic compromise, such as brady- or tachycardia, hypotension, and positive blood cultures, and those patients with parameters of
serum inflammation, such as high erythrocyte sedimentation rate and low platelet count, were at risk for unfavorable outcome. Secondly, a low level of consciousness on admission was predictive for unfavorable outcome. Thirdly, a low cerebrospinal fluid white-cell count was associated with unfavorable outcome. Finally, patients with risk factors for pneumococcal infection were at risk for unfavorable outcome; the elderly, patients with otitis or sinusitis, pneumonia, immunocompromised patients and those without rash.

In conclusion, community-acquired acute bacterial meningitis in adults has high mortality and morbidity rates. Even those patients who survive without apparent sequelae are at risk for cognitive problems. The most important independent risk factors on admission for an unfavorable outcome are a low level of consciousness, infection with *S. pneumoniae* and factors that indicate systemic compromise.

**Supportive Therapies**

Supportive care of patients with acute bacterial meningitis usually consists of fluid management, hemodynamic management, and preventive measures for deep venous thrombosis.79

Hyponatremia occurs frequently in patients with bacterial meningitis.13 High rates of hyponatremia have been described in tuberculous meningitis and in meningitis caused by *Staphylococcus aureus* and *Streptococcus pyogenes*.74-77 In the Dutch cohort, hyponatremia (sodium level below 135 mmol/L) occurred in 30 percent of patients with pneumococcal meningitis and in 21 percent of those with meningococcal meningitis (unpublished, Van de Beek). Whether hyponatremia is caused by cerebral salt wasting or inappropriate secretion of antidiuretic hormone remains to be elucidated.78 This has resulted in the clinical dilemma whether fluids should be restricted or not. Fluid restriction does not improve either brain edema or outcome in patients with acute bacterial meningitis.79,80 The British Infection Society working party recommends that adult patients with meningitis should be kept euvolemic.81 Patients with acute bacterial meningitis are almost invariably dehydrated from vomiting and fever,73 so adequate fluid replacement should be established with at least three liter of isotonic salin.73 In conclusion, hyponatremia is frequently seen in patients with community-acquired acute bacterial meningitis and should not automatically be treated with fluid restriction.

Hemodynamic management in patients with endotoxic shock is important and complex but is beyond the scope of this review.73 Because most risk factors for unfavorable outcome indicate systemic complications,10 aggressive supportive care of patients with bacterial meningitis and systemic compromise is needed, preferably in specialized care units.10

Several supportive therapies have been described in patients with signs of an advance stage of raised intracranial pressure; however, no therapy has proven clinical efficacy. Several methods are advised: elevation of the head to 30°, hyperventilation, use of hyperosmolar agents and barbiturates,13,68,82-84
Bacterial meningitis is a relatively rare disease, so the individual doctors do not see many patients.\textsuperscript{3,10} The complex management in severely ill patients with acute bacterial meningitis can be difficult and is often done by junior doctors on duty. In addition, the desirability of giving dexamethasone before or with the first parenteral dose of an antimicrobial agent complicates the recommendations for routine management of suspected acute bacterial meningitis. Therefore, hospitals require protocols to include dexamethasone with initial antibiotic therapy. An algorithm for the initial, emergency management of adult patients with suspected bacterial meningitis is shown in the Figure.

**The bottom-line**

The prevalence of the classic triad of fever, neck stiffness, and an altered mental status is low among adults with community-acquired acute bacterial meningitis. Physicians should have a low threshold in performing a lumbar puncture in a patient with suspected bacterial meningitis. Mortality and morbidity rates among patients with community-acquired acute bacterial meningitis are high, and even those patients who survive without apparent sequelae are at risk for cognitive problems. The mortality and morbidity rates can be reduced by the use of adjunctive dexamethasone therapy. On the basis of overall benefit without detrimental effects by subgroups, dexamethasone therapy should be started before or with the first dose of antibiotic and should be continued in most patients with community-acquired acute bacterial meningitis. Hospitals will require protocols to include dexamethasone with initial antibiotic therapy. Although the case fatality rate is decreased by the use of adjunctive dexamethasone, there is still need for improvement. Optimal supportive care can further reduce the mortality and morbidity rates in acute bacterial meningitis. Risk factors for unfavorable outcome are systemic complications, a low level of consciousness, or infection by \textit{S. pneumonias}. Therefore, advanced supportive care of such patients with bacterial meningitis is needed.
**General discussion**

**Figure. Algorithm for initial management of adults with acute bacterial meningitis.**

**Suspicion for bacterial meningitis**
Typical signs may be absent, prior antibiotics may mask severity of illness

- Assess severity:
  - Ventilation
  - Circulation
  - Neurologic examination

- Start Investigations:
  - Blood cultures
  - Blood gases
  - Serum laboratory
  - Rash: skin biopsy

- Shock (diastolic blood pressure < 60 mmHg) and/or coagulopathy (coagulant-use or disseminated intravascular coagulation)?
  - **YES**
  - Empiric antimicrobial therapy
    - Shock: no dexamethasone
    - Coagulopathy without shock: dexamethasone 10 mg
  - Stabilization and/or correction coagulopathy

- **YES**
  - Contra-indications lumbar puncture?
    - Papilledema
    - Focal neurologic deficits, not including cranial nerve palsy
    - Glasgow Coma Scale score < 10

- **NO**
  - Dexamethasone 10 mg and empiric antimicrobial therapy

- **YES**
  - Lumbar puncture

- **NO**
  - Cloudy CSF or apparent progress of disease?
    - **YES**
    - Dexamethasone 10 mg and empiric antimicrobial therapy
    - CT scan brain
    - Space-occupying lesion causing significant brain-shift?
      - **YES**
      - CSF consistent with bacterial meningitis?
      - **NO**
      - CSF consistent with bacterial meningitis?
    - **NO**
      - No lumbar puncture
      - Bacterial meningitis

- **NO**
  - Lumbar puncture

- **YES**
  - CSF consistent with bacterial meningitis?

- **NO**
  - Bacterial meningitis

- Reconsider diagnosis
Chapter 11


General discussion


Chapter 11

General discussion


75. Singh BS, Parwari AK, Deb M. Serum sodium and osmolar changes in tuberculous meningitis. Indian Pediatr 1994; 31: 1345-50.


