ESCMID guideline: Diagnosis and treatment of acute bacterial meningitis

Type of Guidance
Clinical Practice Guideline

Target patient population
Adults and children with community acquired bacterial meningitis patients.

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Funding
This guideline project was funded by a grant of the European Clinical Microbiology and Infectious Disease Society (ESCMID)
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Chapter 1 General introduction

1.1. Motivation for guideline development

Bacterial meningitis is a severe infectious disease of the membranes lining the brain resulting in a high mortality and morbidity throughout the world. In the past decades the epidemiology and treatment strategies for community-acquired bacterial meningitis have significantly changed. First, the introduction of conjugate vaccines in Europe resulted in the virtual disappearance of Haemophilus influenzae type b, while conjugate pneumococcal and meningococcal vaccines have substantially reduced the burden of bacterial meningitis. As a result, community-acquired bacterial meningitis has become a disease that currently affects more adults than infants, with its specific complications and treatment options. A second important development is the increasing rate of reduced susceptibility to common antimicrobial agents amongst strains of Streptococcus pneumoniae (pneumococcus) and Neisseria meningitidis (meningococcus). Large differences in resistance rates in Europe exist and empirical antibiotic treatment needs to be adjusted according to regional epidemiology. Finally, several adjunctive treatments have been tested in randomized controlled trials, often with conflicting results. These developments leave the physician in need of a clear practical guideline, summarizing the available evidence for diagnostic methods, and antimicrobial and adjunctive treatment in bacterial meningitis. To this end the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) promotes guidelines development in the field of infectious diseases. This guideline project was initiated by the ESCMID Study Group for Infections of the Brain (ESGIB).

1.2. Aim of the guideline

The guideline is aimed at providing guidance in daily practice for diagnosis and treatment of community-acquired bacterial meningitis in hospitals. The conclusions of the guideline provide the up-to-date scientific evidence for the best medical practice. The recommendations are aimed at explicating this best medical practice and are based on available scientific evidence and the considerations of the guideline committee.

The committee formulated 9 key questions and several subquestions, which aim to address the full spectrum of current clinical dilemmas in the diagnosis and treatment of community-acquired bacterial meningitis.

Epidemiology

1. What are the causative micro-organisms of community-acquired bacterial meningitis in specific groups (neonates, children, adults, and immunocompromised patients)?

Diagnosis

2. What are the clinical characteristics of community-acquired bacterial meningitis and what is their diagnostic accuracy?

3. What is the diagnostic accuracy of algorithms in the distinction between bacterial and viral meningitis?

4. Can we use clinical characteristics to predict the absence of intracranial abnormalities associated with increased risk of lumbar puncture?

4.1. If lumbar puncture is delayed, should we start treatment?

Treatment

5. What is the optimal type, duration and method of administration of antibiotic treatment when started empirically, after the pathogen has been identified or in culture negative patients?

5.1. Does the addition of vancomycin or rifampicin to a 3rd generation cephalosporin improves outcome in pneumococcal meningitis patients in the setting of a high resistance rate of pneumococci?

6. Does dexamethasone have a beneficial effect on death, functional outcome and hearing loss in adults and children with bacterial meningitis?

6.1 Up to what point in time is treatment with dexamethasone indicated if antibiotics are already given?

6.2. Should dexamethasone be stopped if pathogens other than S. pneumoniae are identified?

7. Do glycerol, mannitol, acetaminophen/paracetamol, hypothermia, antiepileptic drugs or hypertonic saline have a beneficial effect on death, functional outcome and hearing loss in adults and children with bacterial meningitis?

8. Does the use of prophylactic treatment of household contacts decrease carriage or secondary cases?

8.1 Is vaccination indicated after community-acquired (pneumococcal) meningitis?
9. What complications occur during community-acquired bacterial meningitis, what ancillary investigations are warranted when complications occur and how should they be treated?

Follow-up
10. What follow-up of community-acquired bacterial meningitis patients should be provided (e.g. testing for hearing loss, neuropsychological evaluation)?

NB Meningococcal disease but also other bacterial infections can present with both meningitis and sepsis.
This guideline is not aimed at the urgent recognition and treatment of sepsis patients. Therefore, if e.g. meningococcal sepsis is suspected the physician should refer to other guidelines specific for recognising children/patients with developing shock who need acute sepsis management (for instance NICE guidelines, https://www.nice.org.uk/).

1.3. Professional audience
This guideline is written for all clinicians involved in diagnosis, treatment and follow-up of bacterial meningitis in adults and children with community-acquired bacterial meningitis in the context of hospital care, including: Infectious disease specialists, Neurologists, Intensive care specialists, Paediatricians, and Microbiologists.

1.4. Composition of the guideline committee
The initiation of the guideline project was announced at the ESGIB business meetings of 2011 and 2012 during the European Conference on Clinical Microbiology and Infectious Diseases (ECCMID). During this meeting ESGIB members were invited to join the guideline committee by approaching the guideline chairman. In composing the guideline committee considerations were given to establish a balance in country of origin, gender and medical specialty of the guideline members. Following the first meeting, the guideline committee was reinforced with two additional members since their specific expertise was underrepresented in the committee.

1.5. Approach of the committee to guideline development
After the guideline preparation project was granted ESCMID funding in Summer 2013, a kick-off meeting was staged in Amsterdam (Oct 2013) at which the key and sub questions were formulated and divided between guideline members. A clinical librarian and a research fellow at the chair’s institute were appointed to perform the literature searches for each question. Guideline committee members received the identified literature and formulated the answers to the questions, which were discussed during a second meeting simultaneous with the 2014 ECCMID in Barcelona. During the meeting consensus was reached for most issues and unanswered questions were identified and distributed between committee members. The research fellow and chair prepared a draft version of the guideline, which was distributed, first to other guidelines members, and subsequently to ESGIB members and ESCMID for comments.

1.6. Patient participation
For the development of a high quality guideline, patient input is essential, as the treatment has to fulfil the demands and expectations of patients and care-givers. To incorporate these factors into the guideline, the UK-based Meningitis Research Foundation was approached to participate in the guideline development and provide comments.

1.7 Methods of guideline development.

Literature search
As preparation for this guideline development project, a search was performed for existing guidelines from guideline institutes (http://www.guideline.gov/, http://www.nice.org.uk/, http://sumsearch.uthscsa.edu/ and http://www.sign.ac.uk/) and (inter)national societies for neurologists, paediatricians and infectious disease specialists. Furthermore, systematic reviews were searched in the Cochrane Library and SUMsearch. Subsequently, for all identified questions a specific search was performed in scientific publications using electronic databases Pubmed, Medline and Embase (1966-2014). Additional publications were identified by cross-reference checking of identified literature. In the search hierarchy, the initial aim was to identify systematic meta-analysis or meta-analyses of randomized controlled trials (RCTs). In the absence of RCTs a further search was performed for prospective controlled studies. Key questions were formulated in a PICO
format (Population, Intervention, Control, Outcome) when appropriate. Search strategies were developed by a clinical librarian at the chair’s institute (AMC, Amsterdam, The Netherlands) for all PICO formatted questions (Appendix 1).

Quality of evidence scoring

The literature was selected by the committee members, and graded for quality based on the ESCMID quality of evidence system (Table 1.1). The quality of used articles to substantiate the conclusions by the committee is provided with the concluding answer to each question. The scientific evidence is summarized in a conclusion, in which references to the key literature are provided.

<table>
<thead>
<tr>
<th>Class</th>
<th>Conclusions based on</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Evidence from at least one properly designed randomized controlled trial</td>
</tr>
<tr>
<td>2</td>
<td>Evidence from at least one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from &gt;1 centre); from multiple time series; or from dramatic results of uncontrolled experiments</td>
</tr>
<tr>
<td>3</td>
<td>Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies.</td>
</tr>
</tbody>
</table>

Strength of recommendation assessment

Based on the identified literature the committee reached consensus on a recommendation for or against use of diagnostic methods or treatment. The strength of the recommendation is expressed using the ESCMID Strength of recommendation system (Table 1.2.) and does not link with the quality of evidence. High quality evidence may result in marginal support for use, while low quality evidence may result in a strong recommendation for use.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>ESCMID strongly supports a recommendation for use</td>
</tr>
<tr>
<td>B</td>
<td>ESCMID moderately supports a recommendation for use</td>
</tr>
<tr>
<td>C</td>
<td>ESCMID marginally supports a recommendation for use</td>
</tr>
<tr>
<td>D</td>
<td>ESCMID supports a recommendation against use</td>
</tr>
</tbody>
</table>

1.8. Implementation and assessment of impact

We will disseminate and promote the guideline by publication in a peer-reviewed journal and active promotion of the guideline to all European national organisations of infectious disease specialists, intensive care specialists, neurologists, microbiologists and paediatricians. Members of the guideline committee will be asked to gather local, regional and/or national treatment guidelines from their home country (and if possible for other countries) to assess whether these have been updated to include evidence provided by the ESCMID guidelines. We aim to have at least half of the European national guidelines adapted to the ESCMID European guideline recommendations within two years. This will be assessed on a biannual basis and presented at the ESGIB meeting at the ECCMID.

1.9. Revision of the guideline

Two members of the guideline committee (Chair + 1 other) will give a yearly update on developments in the field of meningitis research applicable to the guideline, and will assess the need for updating the guidelines. This update will be provided during the ESGIB business meeting at the ECCMID. Significant amendments or updates to the guideline will be submitted for publication. The ultimate date of updating the protocol will be 4 years after the final version is published.

1.10. Legal status of the guideline

Guidelines do not contain legal regulations, but provide evidence based recommendations. Clinicians may strive to provide optimal care by adhering to the guideline. Since the guideline is based on general evidence of optimal care and the guideline committee’s expert opinion, physicians may choose to deviate from the
guideline based on their professional autonomy when necessary in individual patients. Deviating from the
guideline may in fact be required in specific situations. When deviating from advice provided in the guideline, it
is advisable to document the considerations for doing so.
Chapter 2 Epidemiology of community-acquired bacterial meningitis in Europe

Key question 1: What are the causative micro-organisms of community-acquired bacterial meningitis in specific groups (neonates, children, adults and immunocompromised patients)?

The epidemiology of community-acquired bacterial meningitis worldwide has changed in the past decades due to the introduction of conjugated vaccines against H. influenzae type b, N. meningitidis serogroup C and 7, 10 and 13-valent pneumococcal conjugate vaccines.\(^1\) This resulted in a dramatic reduction of the incidence of bacterial meningitis in children,\(^4\) and currently the majority of patients are adults. The causative pathogens of bacterial meningitis depend on age of the patient and predisposing factors.

2.1. Bacterial meningitis in the neonatal age.

Bacterial meningitis in the neonatal period is considered early when occurring during the first week of life and late when occurring between the second and sixth week.\(^5\) In early neonatal meningitis the primary mode of infection is by vertical transmission (mother to child) through the birth canal, whereas in late neonatal meningitis transmission is nosocomial or horizontal (person to person). The most common pathogens in neonatal meningitis are Streptococcus agalactiae (group B streptococcus, GBS) and Escherichia coli, causing two thirds of all cases (Table 2.1).

Preventive penicillin in women colonized with S. agalactiae has been implemented as a measure to decrease the incidence of GBS meningitis in neonates following positive trials and meta-analyses.\(^6\) Initially, this was reported to result in a strong decrease in GBS neonatal disease in the 1990’s,\(^7,8\) however recent studies from the UK and USA showed increased incidence rates in the 2000’s.\(^9,10\) A recent epidemiological study from the Netherlands showed similar incidence rates of GBS meningitis over the past 25 years.\(^11\)

Historically, Listeria monocytogenes is considered an important cause of neonatal meningitis,\(^2\) but recent cohort studies and surveillance data identified L. monocytogenes in only a minority of cases. Streptococcus pneumoniae, the primary causative organism of bacterial meningitis in patients beyond the neonatal age, is only incidentally found in neonates.

Table 2.1. Causative organisms of neonatal meningitis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S. agalactiae</td>
<td>69</td>
<td>258</td>
<td>69</td>
<td>88</td>
<td>447 (55%)</td>
</tr>
<tr>
<td>E. coli</td>
<td>23</td>
<td>123</td>
<td>12</td>
<td>27</td>
<td>185 (23%)</td>
</tr>
<tr>
<td>L. monocytogenes</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>1</td>
<td>15 (2%)</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>3</td>
<td>19 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>59</td>
<td>43</td>
<td>22</td>
<td>14</td>
<td>138 (17%)</td>
</tr>
<tr>
<td>Total</td>
<td>166</td>
<td>444</td>
<td>66</td>
<td>133</td>
<td>809</td>
</tr>
</tbody>
</table>

2.2. Community-acquired bacterial meningitis in children beyond the neonatal age.

Historically, the three main pathogens causing bacterial meningitis in children beyond the neonatal age, were H. influenzae type b, N. meningitidis and S. pneumoniae. Following vaccination against H. influenzae type b introduced in the 1990’s this pathogen has virtually disappeared as a major cause of bacterial meningitis in children.\(^7\) H influenzae meningitis currently occurs incidentally in unvaccinated children or may be due to serotypes other than b.\(^15\) Following a peak in incidence of serogroup C meningococcal meningitis in the early 2000’s, several countries have introduced the Men C vaccine in their vaccination programs.\(^16,17\) This resulted in a sharp decrease in Men C cases, and provided long-term herd immunity.\(^16,17\) Currently, serogroup B cause most meningococcal meningitis cases in both children and adults.\(^18\) The incidence of meningococcal meningitis due to serogroup B has decreased in some countries in the past decade, which is probably due to stochastic variation.\(^19\) Due to this decrease pneumococcal meningitis is now as common as meningococcal meningitis in children beyond the neonatal age, and reductions in incidence rates have been achieved following introduction of pneumococcal conjugated vaccines (PCVs) against 7, 11 or 13 pneumococcal serotypes.\(^19\)
Table 2.2. Causative organisms of paediatric meningitis beyond the neonatal age.

<table>
<thead>
<tr>
<th>Country</th>
<th>Observation period</th>
<th>France&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Denmark&lt;sup&gt;b&lt;/sup&gt;</th>
<th>France&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Netherlands&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. meningitidis</td>
<td>1303</td>
<td>159</td>
<td>35</td>
<td>308</td>
<td>1805 (50%)</td>
<td></td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>802</td>
<td>195</td>
<td>35</td>
<td>310</td>
<td>1342 (37%)</td>
<td></td>
</tr>
<tr>
<td>H. influenzae</td>
<td>78</td>
<td>8</td>
<td>11</td>
<td>73</td>
<td>170 (5%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>137</td>
<td>56</td>
<td>8</td>
<td>101</td>
<td>302 (8%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2320</td>
<td>418</td>
<td>89</td>
<td>792</td>
<td>3619</td>
<td></td>
</tr>
</tbody>
</table>

2.3. Community-acquired bacterial meningitis in adults.

The majority of bacterial meningitis cases in adults is caused by <i>S. pneumoniae</i> (table 2.3). Following the introduction of PCVs a reduction in cases has been observed due to a reduction of disease due to serotypes included in the vaccine. In adults serotype replacement has also been observed and continuous surveillance and vaccine development remains important. Meningococcal meningitis in adults is mostly found in adolescents, and is mostly caused by serogroup B. Similar to the paediatric population, the incidence of meningococcal meningitis has declined in the past decade. <i>L. monocytogenes</i> is the third most common cause of meningitis in adults and is commonly associated with old age and an immunocompromised state.

Table 2.3. Causative organisms of adult bacterial meningitis.

<table>
<thead>
<tr>
<th>Country</th>
<th>Denmark&lt;sup&gt;25&lt;/sup&gt;</th>
<th>Turkey&lt;sup&gt;26&lt;/sup&gt;</th>
<th>UK&lt;sup&gt;27&lt;/sup&gt;</th>
<th>Czech republic&lt;sup&gt;28&lt;/sup&gt;</th>
<th>Netherlands&lt;sup&gt;9&lt;/sup&gt;</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. meningitidis</td>
<td>42</td>
<td>251</td>
<td>550</td>
<td>75</td>
<td>171</td>
<td>1089 (27%)</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>92</td>
<td>457</td>
<td>525</td>
<td>82</td>
<td>1001</td>
<td>2157 (53%)</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>3</td>
<td>2</td>
<td>48</td>
<td>3</td>
<td>56</td>
<td>112 (3%)</td>
</tr>
<tr>
<td>L. monocytogenes</td>
<td>5</td>
<td>6</td>
<td>48</td>
<td>21</td>
<td>74</td>
<td>154 (4%)</td>
</tr>
<tr>
<td>Other</td>
<td>30</td>
<td>68</td>
<td>124</td>
<td>35</td>
<td>291</td>
<td>548 (13%)</td>
</tr>
<tr>
<td>Total</td>
<td>172</td>
<td>784</td>
<td>1295</td>
<td>216</td>
<td>1593</td>
<td>4060</td>
</tr>
</tbody>
</table>

2.4. Community-acquired bacterial meningitis in immunocompromised patients

The spectrum of causative pathogens that needs to be considered is different when the patient has certain specific medical conditions. Deficiencies of the immune system, either iatrogenic (e.g. use of immunosuppressive medication or splenectomy), due to diseases influencing the immune system (such as cancer, diabetes mellitus, alcoholism, human immunodeficiency virus [HIV] infection) or hereditary (e.g. hypogammaglobulinemia, late complement component deficiency, common variable immunodeficiency) increase the risk of bacterial meningitis. The incidence of pneumococcal meningitis is increased in patients after splenectomy or with a hyposplenemic state, chronic kidney or liver disease, HIV infection, alcoholism, hypogammaglobulinemia, diabetes mellitus and patients using immunosuppressive drugs. Patients with complement system deficiencies have been identified to have a strongly increased risk of meningococcal meningitis. Predisposing conditions associated with <i>H. influenzae</i> meningitis include diabetes mellitus, alcoholism, splenectomy or asplenic states, multiple myeloma, and immune deficiency such as hypogammaglobulinemia. <i>L. monocytogenes</i> meningitis is more often found in elderly patients (>60 years) and those with acquired immunodeficiencies, such as diabetes, cancer and use of immunosuppressive drugs.

Conclusions

<table>
<thead>
<tr>
<th>Level 2</th>
<th>Most common causative pathogens in neonatal meningitis are &lt;i&gt;Streptococcus agalactiae&lt;/i&gt; and &lt;i&gt;Escherichia coli&lt;/i&gt;.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Most common causative pathogens in children beyond the neonatal age are &lt;i&gt;Neisseria meningitidis&lt;/i&gt; and &lt;i&gt;Streptococcus pneumoniae&lt;/i&gt;.</td>
</tr>
<tr>
<td></td>
<td>Most common causative pathogens in adults are &lt;i&gt;Streptococcus pneumoniae&lt;/i&gt; and &lt;i&gt;Neisseria meningitidis&lt;/i&gt;. Another important causative microorganism in adults is &lt;i&gt;Listeria monocytogenes&lt;/i&gt;.</td>
</tr>
</tbody>
</table>
Chapter 3 Diagnosis of community-acquired bacterial meningitis

Key question 2: What are the clinical characteristics of bacterial meningitis and what is their diagnostic accuracy

3.1. Clinical characteristics in children with bacterial meningitis

3.1.1. Clinical characteristics of neonatal bacterial meningitis

Neonates with bacterial meningitis often present with non-specific symptoms, like irritability, poor feeding, respiratory distress, pale or marble skin and hyper- or hypotonia. Fever is present in a minority (6-39%) of the cases. Seizures are reported in 9%-34% of cases and are more commonly reported amongst those with group B streptococcal (GBS) compared to E.coli meningitis. Respiratory distress or failure is frequently reported as one of the initial symptoms of neonatal meningitis. In neonates with GBS meningitis within 24 hours of birth, respiratory (72%), cardiovascular (69%) and neurological (63%) symptoms were the predominant initial signs. Concomitant septic shock may be diagnosed in about 25% of the cases of neonatal meningitis. The diagnosis of neonatal meningitis cannot be ruled out by clinical examination alone, and therefore a low threshold should be kept in neonates with suspected bacterial meningitis to perform a lumbar puncture. The diagnostic accuracy of clinical characteristics in assessment of neonatal meningitis is presumed to be low, although few studies have evaluated this systematically.

3.1.2 Clinical characteristics of bacterial meningitis in children beyond the neonatal age.

Classical signs and symptoms of bacterial meningitis consisting of fever, altered mental status and neck stiffness are less frequently present in younger infants compared to older children and adults. Typically, childhood bacterial meningitis begins with fever, chills, vomiting, photophobia, and severe headache (table 3.1). In general, the younger the patient with bacterial meningitis, the more subtle and atypical are the symptoms such as headache, photophobia, vomiting and neck stiffness. Headache is reported in 2-9% of children with bacterial meningitis up to 1 year of age and in 75% of children older than 5 years. Fever is the most commonly reported symptom in childhood bacterial meningitis with an occurrence rate of 92-93%. Vomiting is reported in 55-67% of children with bacterial meningitis.

Table 3.1 Clinical characteristics of paediatric meningitis beyond the neonatal age upon presentation

<table>
<thead>
<tr>
<th>Country</th>
<th>Greece</th>
<th>USA</th>
<th>Kosovo</th>
<th>France</th>
<th>Iceland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1631</td>
<td>231</td>
<td>227</td>
<td>89</td>
<td>140</td>
</tr>
<tr>
<td>Fever</td>
<td>93%</td>
<td>93%</td>
<td>51%</td>
<td>25%</td>
<td>67%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>58%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered mental status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>78%</td>
<td>13%</td>
<td>51%</td>
<td>25%</td>
<td>60%</td>
</tr>
<tr>
<td>Neck stiffness</td>
<td>82%</td>
<td>40%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td>19%</td>
<td>10%</td>
<td>22%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>Focal neurological deficits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>39%</td>
<td>4%</td>
<td>16%</td>
<td>11%</td>
<td>51%</td>
</tr>
</tbody>
</table>

Seizures have been reported on hospital admission in 10 to 56% of children. Altered mental status was reported in 13 up to 56% of the cases of childhood bacterial meningitis. Some signs or symptoms are associated with specific pathogens of childhood meningitis. Petechial and purpuric rash are usually signs of meningococcal disease, although a rash has also been described in pneumococcal meningitis. In a large study performed in Greece, 511 of 838 (61%) patients with confirmed meningococcal meningitis presented with haemorrhagic rash, compared to 17 of 186 (9%) patients with meningitis due to S. pneumoniae. Diagnostic accuracy of clinical characteristics in children with bacterial meningitis has been assessed in several studies, recently summarized in a meta-analysis. Seven of 10 included studies were performed in African countries and therefore the applicability of these data to the European situation may be limited. The meta-
Conclusions

Level 2 Neonates with bacterial meningitis often present with non-specific symptoms.

Level 2 In children beyond the neonatal age the most common clinical characteristics of bacterial meningitis are fever, headache, neck stiffness and vomiting. There is no clinical sign of bacterial meningitis that is present in all patients.

Recommendation

Grade A Bacterial meningitis in children can present solely with non-specific symptoms. Characteristic clinical signs may be absent. In all children with suspected bacterial meningitis ESCMID strongly recommends cerebrospinal fluid examination, unless contra-indications for lumbar puncture are present (see 3.5).

3.2. Clinical characteristics in adults with bacterial meningitis

Multiple studies have been performed on the clinical characteristics of adults with bacterial meningitis.25,41-44 These studies have shown that headache, fever, neck stiffness and altered mental status are common signs and symptoms on admission. The classic triad of fever, neck stiffness and altered mental status however, is reported in only 41-51% of patients (table 3.2). A petechial rash is identified in 20-52% of patients, and indicative of meningococcal infection in over 90% of patients.41

Studies assessing the usefulness of neck stiffness, Kernig’s sign, and Brudzinski’s sign in the differential diagnosis of bacterial meningitis in adults have recently been summarized.40 These clinical findings have low diagnostic accuracy for prediction of CSF pleocytosis (sensitivity neck stiffness 31%, Brudzinski 9%, Kernig 11%) suggesting that absence of these findings cannot be used to exclude the possibility of bacterial meningitis.

Table 3.2 Presenting clinical characteristics of adults with bacterial meningitis

<table>
<thead>
<tr>
<th>Country</th>
<th>Observation period</th>
<th>Number of patients</th>
<th>Headache</th>
<th>Nausea/vomiting</th>
<th>Neck stiffness</th>
<th>Rash</th>
<th>Fever (&gt;38.0°C)</th>
<th>Altered mental status</th>
<th>Coma</th>
<th>Focal neurologic deficits</th>
<th>Triad of fever, neck stiffness and altered mental status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td>Observation period</td>
<td>Number of patients</td>
<td>Headache</td>
<td>Nausea/vomiting</td>
<td>Neck stiffness</td>
<td>Rash</td>
<td>Fever (&gt;38.0°C)</td>
<td>Altered mental status</td>
<td>Coma</td>
<td>Focal neurologic deficits</td>
<td>Triad of fever, neck stiffness and altered mental status</td>
</tr>
<tr>
<td>Netherlands</td>
<td>98-02</td>
<td>696</td>
<td>87%</td>
<td>-</td>
<td>83%</td>
<td>26%</td>
<td>77%</td>
<td>69%</td>
<td>14%</td>
<td>34%</td>
<td>44%</td>
</tr>
<tr>
<td>France</td>
<td>01-04</td>
<td>60</td>
<td>87%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>93%</td>
<td>30%</td>
<td>-</td>
<td>23%</td>
<td>-</td>
</tr>
<tr>
<td>Spain</td>
<td>96-10</td>
<td>295</td>
<td>-</td>
<td>45%</td>
<td>69%</td>
<td>-</td>
<td>95%</td>
<td>54%</td>
<td>-</td>
<td>15%</td>
<td>-</td>
</tr>
<tr>
<td>Iceland</td>
<td>75-94</td>
<td>119</td>
<td>-</td>
<td>-</td>
<td>82%</td>
<td>52%</td>
<td>97%</td>
<td>66%</td>
<td>13%</td>
<td>15%</td>
<td>-</td>
</tr>
<tr>
<td>Denmark</td>
<td>89-10</td>
<td>172</td>
<td>-</td>
<td>-</td>
<td>85%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

These data indicate that clinical characteristics cannot be used to rule out bacterial meningitis.40
### Conclusions

| Level 2 | In adults the most common clinical characteristics of bacterial meningitis are fever, headache, neck stiffness and altered mental status. Characteristic clinical signs and symptoms such as fever, neck stiffness, headache and altered mental status can be absent. |

| Level 2 | The sensitivity and negative predictive value of Kernig and Brudzinski’s sign is low in the diagnosis of meningitis and therefore do not contribute to the diagnosis of bacterial meningitis. |

### Recommendation

| Grade A | In adults with bacterial meningitis classic clinical characteristics may be absent and therefore bacterial meningitis should not be ruled out solely on the absence of classic symptoms. |
### 3.3 Diagnostic algorithms

Most patients with suspected bacterial meningitis eventually receive an alternative diagnosis, which consists of viral (or aseptic) meningitis in the majority of cases with CSF pleocytosis. Several diagnostic algorithms have been developed to help the clinician differentiate between bacterial meningitis and viral meningitis. This could especially be helpful in patients without a positive CSF Gram stain or culture, as the diagnosis of acute bacterial meningitis can be difficult to establish or reject in these patients.

In our literature search 311 articles were identified, of which 29 were selected based on the abstract for full reading. We analysed eight algorithms that were validated in an independent cohort (table 3.3). Studies were mostly performed in paediatric populations beyond the neonatal age. No diagnostic algorithm to differentiate neonatal meningitis from other conditions was identified.

#### Table 3.3. Overview of diagnostic algorithms identified in this survey

<table>
<thead>
<tr>
<th>Score</th>
<th>Population Items</th>
<th>Studies / level of evidence</th>
<th>Lowest reported sensitivity</th>
<th>Lowest reported specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyer</td>
<td>Children</td>
<td>Score including temperature, rash, neurologic impairment/ seizures or altered mental status, CSF protein, glucose and CSF WBC count, PMN count. If &gt;5 points=bacterial meningitis, 3-4=unclear, &lt;3=no bacterial meningitis</td>
<td>5 / 2</td>
<td>89%</td>
</tr>
<tr>
<td>Oostenbrink</td>
<td>Children</td>
<td>Score including duration of complaints, vomiting, meningeal irritation, cyanosis, petechiae or ecchymosis, disturbed consciousness, CRP, CSF PMN count, CSF to blood glucose ratio. If score is &lt;8.5: low risk of bacterial meningitis</td>
<td>5 / 2</td>
<td>79%</td>
</tr>
<tr>
<td>Bacterial Meningitis Score</td>
<td>Children</td>
<td>Item list including CSF Gram stain, CSF protein, peripheral absolute neutrophil count, seizures before or on admission, CSF absolute neutrophil count. If all items are absent low risk of meningitis</td>
<td>8 / 2</td>
<td>96%</td>
</tr>
<tr>
<td>Bonsu</td>
<td>Children</td>
<td>Formula including CSF WBC count, CSF protein concentration and age. If score is &lt;0.1: low risk of bacterial meningitis</td>
<td>4 / 2</td>
<td>92%</td>
</tr>
<tr>
<td>Hoen</td>
<td>All ages, except neonates</td>
<td>Formula including CSF PMN count, CSF protein, blood glucose and blood white blood cell count. If score is &lt;0.1: low risk of bacterial meningitis</td>
<td>6 / 2</td>
<td>77%</td>
</tr>
<tr>
<td>Score</td>
<td>Population Items</td>
<td>Studies / level of evidence</td>
<td>Lowest reported sensitivity</td>
<td>Lowest reported specificity</td>
</tr>
<tr>
<td>-------</td>
<td>------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Freedman</td>
<td>Children</td>
<td>Item list including patient’s age, blood WBC count, peripheral band count, CSF glucose concentration, CSF/serum glucose ratio, CSF protein concentration, and positive CSF Gram staining. <em>If all items are absent low risk of meningitis</em></td>
<td>3 / 2</td>
<td>98.7%</td>
</tr>
<tr>
<td>Meningitese</td>
<td>All ages, except neonates</td>
<td>Item list including WBC, CSF WBC, CSF PMN, CSF protein, and glucose CSF/blood ratio. <em>If all items are absent low risk of meningitis</em></td>
<td>2 / 2</td>
<td>79%</td>
</tr>
<tr>
<td>Spanos51</td>
<td>All ages, except neonates</td>
<td>Formula including age, time of year, glucose ratio, and total CSF PMN count. <em>The probability of meningitis is calculated by use of a nomogram</em></td>
<td>6 / 2</td>
<td>89%</td>
</tr>
<tr>
<td>Tokuda</td>
<td>Adults</td>
<td>Item list including disturbed consciousness, CSF gram stain, neutrophil count and percentage. <em>If all items are absent low risk of meningitis</em></td>
<td>2 / 2</td>
<td>88%</td>
</tr>
<tr>
<td>De Cauwer</td>
<td>Children</td>
<td>Item list including CRP, CSF neutrophil count, CSF protein and CSF glucose concentration. <em>If all items are absent low risk of meningitis</em></td>
<td>2 / 2</td>
<td>99%</td>
</tr>
<tr>
<td>Schmidt</td>
<td>All ages, except neonates</td>
<td>Item list including CSF WBC, CSF protein and CSF lactate. <em>If all items are absent low risk of meningitis</em></td>
<td>2 / 2</td>
<td>59%</td>
</tr>
</tbody>
</table>

*CSF=cerebrospinal fluid, WBC=white blood cells, PMN=polymorphonuclear cells, CRP=C-reactive protein.*

None of the published diagnostic algorithms were 100% sensitive upon validation in independent cohorts, showing that every algorithm will fail to recognize a proportion of bacterial meningitis patients. An important limitation of the prediction models described is that they all differentiate between viral and acute bacterial meningitis, but in clinical practice many other causes might need to be considered. Furthermore, they only apply to the population they were tested in and cannot be used in other groups, for example neonates. This further limits the use of the algorithms in clinical practice.

In individual patients with suspected acute bacterial meningitis, a prediction model could have value, but clinicians’ judgment should continue to be used to estimate the risk of bacterial meningitis and whether empirical antibiotic and adjunctive therapy needs to be initiated.40

**Conclusion**

None of the published diagnostic algorithms were 100% sensitive upon validation in an independent cohort, indicating that bacterial meningitis patients will potentially be missed when any of the algorithms are used.

**Recommendation**

**Grade C** Use of diagnostic algorithms may be helpful to guide management in individual patients with suspected acute bacterial meningitis but clinical judgement is key when considering whether to start empirical antibiotic and adjunctive therapy.
3.4. Diagnostic accuracy of laboratory techniques in bacterial meningitis

The diagnosis of bacterial meningitis cannot be proven without CSF examination. A positive CSF culture is diagnostic for bacterial meningitis and enables in vitro testing of the antimicrobial susceptibility patterns, after which antibiotic treatment can be optimized. Gram staining, latex-agglutination, immunochromatographic antigen testing and polymerase chain reaction could provide additional information, especially when the CSF culture is negative. If CSF examination is not possible serum markers of inflammation may provide a supportive role in the diagnosis of bacterial meningitis.5

3.4.1. CSF leukocyte count, glucose, total protein and lactate levels

Classic abnormalities of CSF composition in bacterial meningitis are a pleocytosis of mainly polymorphic leukocytes, low glucose concentration and elevated protein levels. In neonates however, these abnormalities are regularly absent. A study in 146 neonates with S. agalactiae meningitis showed completely normal CSF in 6% of cases.52 In a large cohort of 9111 neonates in whom a lumbar puncture was performed 98% had culture-proven meningitis, of which 10% had fewer than 3 white blood cells (WBC)/mm³ in the CSF. The median CSF WBC count was low (6 cells/mm³, range 0-90,000/mm³), interquartile range 2-15/mm³). For culture-proven meningitis, CSF WBC counts of more than 21 cells per mm³ had a sensitivity of 79% and a specificity of 81%. CSF glucose concentrations varied from 0 to 11 mmol/liter (median, 1.1 mmol/liter or 20 mg/dl), and protein concentrations varied from 0.4 to 19.6 g/liter (median, 2.7 g/liter); culture-proven meningitis was not diagnosed accurately by CSF glucose or by protein.53

A retrospective study assessed the value of CSF parameters for differentiating between viral and bacterial meningitis in children beyond the neonatal age and adults.54 It was shown that glucose levels lower than 1.9 mmol/L, protein levels over 2.2 g/L and leukocyte count over 2000 cells/mm³ are individual predictors of bacterial meningitis.51 Prospective studies showed that at least one of these predictors was present in 82.94% of patients with community-acquired bacterial meningitis.51,53 A study of 198 children of whom 98 had bacterial meningitis revealed that lower thresholds for CSF protein level (>0.5 g/L) and a leukocyte count over 100 cells/mm³ were also strongly associated with bacterial meningitis (odds ratio 12 and 14).54 A mildly elevated or normal number of leukocytes in the CSF can be found in patients with bacterial meningitis, especially in patients with concomitant septic shock.55 In a prospective study of 258 patients with CSF culture-proven meningococcal meningitis 19% of patients had less than 1000 cells/mm³ and 5 patients (1.7%) had a completely normal composition of CSF.55 In three of these five patients bacteria could be identified in the CSF Gram stain, which enabled the diagnosis of bacterial meningitis. The extent of CSF abnormalities depends on the causative micro-organism.5 In culture proven pneumococcal meningitis, 5% of 153 patients have CSF white cell counts less than 10 cells/mm³, and 17% less than 100 cells/mm³.56 In a prospective cohort study of 62 patients with L. monocytogenes meningitis, CSF abnormalities were not typical for bacterial meningitis in 26% of cases.57 It is commonly assumed that antibiotic treatment prior to hospital admission modifies CSF pleocytosis, but one retrospective study in 245 children with bacterial meningitis suggested that the CSF white cell count is not greatly different between patients who have received, or have not received lengthy courses of antibiotics prior to lumbar puncture.57

The CSF lactate concentration is a widely available, cheap, and rapid diagnostic test.58 Two meta-analyses were performed on the diagnostic use of CSF lactate in the differentiation of bacterial meningitis vs. other types of meningitis. One included 25 studies with 1692 patients (adults and children)59 and the other 31 studies with 1885 patients (adults and children).60 These meta-analyses concluded that the diagnostic accuracy of CSF lactate is better than that of CSF white blood cell count. In patients who received antibiotic treatment prior to the lumbar puncture, CSF lactate concentration had a lower sensitivity (49%) compared with those not receiving antibiotic pretreatment (98%).60 CSF lactate concentration is less accurate for differentiating patients with other CNS diseases from meningitis, such as herpes encephalitis or seizures, as the concentrations may also be raised.51,62 Therefore, the usefulness of CSF lactate concentrations in patients pretreated with antibiotics, or those with other CNS diseases in the differential diagnosis, is probably limited.

3.4.2. CSF culture, PCR, antigen and latex agglutination tests

A retrospective study in 875 patients in whom the diagnosis of bacterial meningitis was based on a CSF leukocyte count of >1000 WBC/mm³ or over 80% polymorphonuclear cells, CSF culture was positive in 85% of patients, if not pre-treated with antibiotics.63 CSF culture positivity differed per causative micro-organism: CSF culture was positive in 96% of H. influenzae meningitis cases, compared to 87% in pneumococcal and 82% in
meningococcal meningitis cases. In another retrospective study in 231 children, 82% of CSF cultures were positive. A retrospective study from Brazil including 3973 patients showed a lower yield of CSF cultures: CSF culture was positive in 67% of patients. The yield of CSF culture decreases when a patient is treated with antibiotics prior to the lumbar puncture. Two large cohort studies showed a decrease in culture positivity from 66 to 62% and from 88 to 70% when the patients received antibiotics prior to lumbar puncture.

The CSF Gram stain is a quick method to identify the cause of bacterial meningitis. Furthermore, the test is cheap and validated. CSF Gram stains have been shown to have incremental value when the CSF culture is negative, for instance when a patient is treated with antibiotics prior to the lumbar puncture. In a retrospective study of 875 patients, the Gram stain was the only positive microbiological finding in 4% of patients. The sensitivity of the Gram stain depends on the causative micro-organism. The aggregate diagnostic yield of CSF Gram stain is 25-35% in *L. monocytogenes* meningitis, 50% in *H. influenzae* meningitis, 70-90% in meningococcal meningitis and 90% in pneumococcal meningitis. Quality and speed of performing a Gram stain depends on the hospital’s infrastructure and the experience of the assessor. If these are optimal, the specificity of the Gram stain is almost 100%. The yield of the Gram stain may decrease slightly if antibiotic treatment has been commenced prior to lumbar puncture. A Danish study in 481 children showed that the yield decreased from 56 to 52%. In an American study of 245 children there was a similar yield whether or not antibiotic treatment had been started (63% positive with antibiotic pretreatment, 62% without pretreatment).

Latex-agglutination is a diagnostic method that can be used to determine rapidly the causative micro-organism. The reported sensitivity of latex agglutination testing in CSF differs per causative micro-organism: for *H. influenzae* the reported sensitivity varies between 78% and 100%, for *S. pneumoniae* between 59% and 100%, and for *N. meningitidis* between 22 and 93%. In clinical practice latex agglutination testing has offered little incremental value over other tests. In a retrospective study in 176 children with negative CSF cultures, who were treated with antibiotic before the lumbar puncture, no latex agglutination test was positive. A study of 28 patients with negative CSF cultures, but clinical and CSF characteristics of bacterial meningitis, showed a sensitivity of 7% of latex agglutination tests. A third study showed 7 positive latex agglutination tests in 478 CSF samples: in all 7 the pathogen had been identified by Gram stain as well. The sensitivity of latex agglutination tests decreased from 60% to 9% in patients in whom treatment was started before the lumbar puncture was performed. Because of the limited value of latex agglutination these tests are not advised in the diagnosis of bacterial meningitis when other methods are available such as Gram staining.

An immunochromatographic antigen test for the detection of *S. pneumoniae* in CSF has been evaluated in a study including 450 children with suspected acute bacterial meningitis. The test was shown to be 100% sensitive and specific for the diagnosis of pneumococcal meningitis; the overall sensitivity of this test ranged from 95% to 100%. Another study including 1179 CSF samples from children in Bangladesh with suspected bacterial meningitis also revealed high sensitivity (98.6%) and specificity (99.3%). CSF immunochromatography was superior to CSF culture and latex agglutination testing in this study, but a comparison to CSF Gram staining was not done. False-positive results have been reported in patients with meningitis due to other streptococcal species. Further studies in patients with negative CSF culture and Gram stain should be performed to determine whether this method has any value in addition to standard diagnostic methods.

Several studies have assessed the test characteristics of polymerase chain reaction (PCR) on CSF in the diagnosis of bacterial meningitis and reported sensitivities of 79-100% for *S. pneumoniae*, 91-100% for *N. meningitidis* and 67-100% for *H. influenzae*. Reported specificity was between 95 and 100% for all micro-organisms. PCR was shown to have incremental value compared to CSF culture and Gram stain. A study in 409 patients from Burkina Faso showed 33% of patients were diagnosed with PCR only, and could not be diagnosed with conventional methods. The availability of rapid CSF PCRs is variable per country. PCR is particularly useful in patients who received intravenous antibiotic treatment prior to the lumbar puncture, as CSF and blood cultures in these patients are often negative. PCR can be performed on both CSF and EDTA blood. A disadvantage of PCR compared to CSF culture is the lack of antimicrobial susceptibility data and subtyping of the micro-organism: when detecting meningococci, only the serogroup can be determined by PCR. In children, PCR for pneumococcal DNA within blood may be positive even when the child is merely colonised
and has no bacteraemia, but this varies according to the test that is used. Therefore, as yet PCR will not completely usurp CSF culture in the diagnosis of bacterial meningitis, but is a very useful additional test, especially if the Gram stain is found negative.

### 3.4.3. Serum markers of inflammation – C-reactive protein, procalcitonin

When differentiating between viral and bacterial meningitis, serum inflammatory markers may contribute to the diagnosis. Several retrospective studies have suggested that serum concentrations of C-reactive protein and pro-calcitonin are highly discriminatory between paediatric bacterial and viral meningitis.⁵⁶,⁷⁷ The reported sensitivity in a study of 507 children of a C-reactive protein level >40mg/L was 93% with a specificity of 100%.⁷⁷ A meta-analysis of several small studies including 198 children showed increased serum pro-calcitonin and C-reactive protein concentrations were associated with acute bacterial meningitis.⁵⁴ No studies in adults were identified. In clinical practice other bacterial infections such as sepsis and pneumonia may be included in the differential diagnosis of bacterial meningitis, and in these situations C-reactive protein and pro-calcitonin may be of little value for the diagnosis of bacterial meningitis.

### 3.4.4. Blood cultures

Blood cultures are valuable for detection of the causative organism and establish susceptibility patterns if CSF cultures are negative or unavailable, for instance when a lumbar puncture is contra-indicated.⁷ The rate of blood culture positivity is different for each causative organism and is 75% of pneumococcal meningitis patients, between 50 and 90% for H. influenzae meningitis patients, and between 40% and 60% of patients with meningococcal meningitis.⁷ The yield of blood cultures was shown to decrease by 20% if patients are treated with antibiotic prior to the blood culture.⁵⁷

### 3.4.5. Other diagnostic methods studied in bacterial meningitis

A plethora of studies have assessed whether individual CSF chemokine, cytokine, complement factors and metabolite levels, quantitative EEG, cranial MRI or a thermogram can be useful in the diagnosis of bacterial meningitis. Few markers were replicated in independent cohorts or compared the test characteristics of the marker to standard diagnostics tests. These studies may be valuable for pathophysiological research but so far have not reached implementation in a clinical setting.

### Conclusions

<table>
<thead>
<tr>
<th>Level 2</th>
<th>In neonatal meningitis, CSF leukocyte count, glucose and total protein levels are frequently within normal range or only slightly elevated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 2</td>
<td>It has been shown that in both children and adults, classic characteristics (elevated protein levels, lowered glucose levels, CSF pleocytosis) of bacterial meningitis are present in ≥90% of patients. A completely normal CSF occurs but is very rare.</td>
</tr>
<tr>
<td>Level 2</td>
<td>CSF lactate concentration has a good sensitivity and specificity for differentiating bacterial from aseptic meningitis. The value of CSF lactate is limited in patients who received antibiotic pre-treatment or those with other CNS disease in the differential diagnosis.</td>
</tr>
<tr>
<td>Level 2</td>
<td>CSF culture is positive in 60-90% of bacterial meningitis patients depending on the definition of bacterial meningitis. Pre-treatment with antibiotics decreases the yield of CSF culture by 10-20%.</td>
</tr>
<tr>
<td>Level 2</td>
<td>CSF Gram stain has an excellent specificity and varying sensitivity, depending on the microorganism. The yield decreases slightly if the patient has been treated with antibiotics before the lumbar puncture is performed.</td>
</tr>
</tbody>
</table>
In patients with a negative CSF culture and CSF Gram stain, PCR has additive value in the identification of the pathogen.

Latex-agglutination testing has little incremental value in the diagnosis of bacterial meningitis.

It is unclear whether immunochromatographic antigen testing has incremental value in the diagnosis of bacterial meningitis.

In children with meningitis elevated CRP and pro-calcitonin levels in blood are associated with bacterial infections. The diagnosis of bacterial meningitis can however not be made with these tests.

In adults and children with bacterial meningitis blood cultures are useful to isolate the causative micro-organism. The yield of blood cultures decreases if the patient is pretreated with antibiotics.

**Recommendation**

In patients suspected of bacterial meningitis it is strongly recommended to determine CSF leukocyte count, protein and glucose concentration, and to perform CSF culture and Gram stain.

In patients with negative CSF cultures, the causative micro-organisms can be identified by PCR, and potentially immunochromatographic antigen testing.

In patients suspected of bacterial meningitis it is strongly recommended to perform blood cultures before the first dose of antibiotics is administered.
Key question 4: Can we use clinical characteristics to predict the absence of intracranial abnormalities associated with increased risk of lumbar puncture?

3.5. Imaging before lumbar puncture

3.5.1. When is cranial imaging indicated before lumbar puncture

A lumbar puncture is crucial in the diagnosis of bacterial meningitis to confirm the diagnosis, identify the pathogen and determine the resistance pattern to rationalize antibiotic treatment. Before the lumbar puncture is performed, the physician needs to establish whether contra-indications exist. A lumbar puncture can be hazardous if brain shift is present due to space-occupying lesions. The withdrawal of CSF at the lumbar level can increase brain shift that may lead to cerebral herniation. The literature search identified 19 studies, describing 74 bacterial meningitis patients in whom cerebral herniation occurred in timely association to the lumbar puncture. However, a causal relationship is difficult to establish as brain herniation also occurs during bacterial meningitis disease course irrespective of lumbar puncture. The risk of cerebral herniation due to lumbar puncture may be reduced by detecting conditions associated with brain shift by cranial imaging (usually computed tomography – CT), such as brain abscess, subdural empyema, or large cerebral infarction. Cranial imaging, however, was shown to lead to a substantial delay in initiation of antibiotic treatment, which is associated with poor outcome. A study in 235 adults with suspected bacterial meningitis showed that intracranial space occupying lesions are associated with clinical characteristics. Therefore, clinical examination can be used to select patients at risk for lesions causing brain shift in whom CT before lumbar puncture is warranted. Based on the abovementioned study a set of criteria have been proposed to select patients for cranial imaging:

- focal neurologic deficits (excluding cranial nerve palsies),
- new-onset seizures
- severely altered mental status (defined as a score on the Glasgow Coma Scale below 10)
- severely immunocompromised state (for example in organ transplant recipients and HIV infected patients)

In the absence of the aforementioned features, CT is not recommended before lumbar puncture in suspected bacterial meningitis patients as it is unlikely to provide new information on the risk of LP-associated herniation in this patient population. In these patients, cranial imaging for other diagnostic purposes such as the detection of mastoiditis or sinusitis should be performed after the lumbar puncture.

The studies described above were all performed in adults. Studies addressing this question for children have not been found in our search. The guideline committee’s consensus is to use the same indications to perform CT before lumbar puncture in children (beyond the neonatal age) as in adults. For neonates, no data are available to guide daily practice on the use of ancillary investigations before lumbar puncture.

Other contra-indications for lumbar puncture, not related to space-occupying intracranial lesions, are coagulation disorders, local skin infections and need for hemodynamic stabilisation prior to further diagnostic procedures.

3.5.2. Treatment before lumbar puncture

The literature search yielded 2 prospective and 6 retrospective studies evaluating the effect of timing of antibiotic treatment on outcome of bacterial meningitis. These studies showed that delayed initiation of antibiotic treatment in bacterial meningitis patients is strongly associated with death and poor outcome. The delay in treatment was often due to cranial imaging prior to the lumbar puncture. Therefore, antibiotic treatment in patients with acute bacterial meningitis should be started as soon as possible and the time period from entering the hospital to initiation of antibiotic treatment should not exceed 1 hour. Whenever lumbar puncture is delayed, e.g. due to cranial CT, empiric treatment must be started immediately on the clinical suspicion; even if the diagnosis has not been established. In these patients blood cultures must be drawn to prior to start of antibiotics to increase the chance of identifying the causative pathogen.

Conclusions
The risk of cerebral herniation after lumbar puncture in patients with suspected bacterial meningitis is increased compared to normal individuals.

Clinical characteristics can be used to identify patients with an increased risk for space-occupying lesions associated with increased risk of cerebral herniation due to lumbar puncture.

A delay in antibiotic treatment administration is associated with poor outcome and should therefore be avoided.

Recommendation

<table>
<thead>
<tr>
<th>Grade A</th>
<th>It is strongly recommended to perform cranial imaging before lumbar puncture in patients with:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- focal neurologic deficits (excluding cranial nerve palsies),</td>
</tr>
<tr>
<td></td>
<td>- new-onset seizures</td>
</tr>
<tr>
<td></td>
<td>- severely altered mental status (defined as a score on the Glasgow Coma Scale below 10)</td>
</tr>
<tr>
<td></td>
<td>- severely immunocompromised state</td>
</tr>
<tr>
<td></td>
<td>In patient lacking these characteristics, cranial imaging before lumbar puncture is <strong>NOT</strong></td>
</tr>
<tr>
<td></td>
<td>recommended.</td>
</tr>
</tbody>
</table>

| Grade A | It is strongly recommended to start antibiotic therapy **as soon as possible** in acute bacterial meningitis patients. The time period until antibiotics are administered should not exceed 1 hour. Whenever lumbar puncture is delayed, *e.g.* due to cranial CT, empiric treatment must be started immediately on clinical suspicion, even if the diagnosis has not been established. |
Chapter 4 Treatment of bacterial meningitis

4.1. Antibiotic treatment

**Sub-question 5.1:** What is the optimal type, duration and method of administration of antibiotic treatment, whether given empirically or non-empirically?

4.1.1. Empiric antibiotic treatment

The choice of empiric antibiotic treatment is conditional on the age of the patient and the regional rate of decreased susceptibility to penicillin and third generation cephalosporins of *S. pneumoniae* (Table 4.1). The spectrum of pathogens in neonates is considerably different to that of children beyond the neonatal age and adults, which is reflected by the empiric antibiotic treatment for this age group. When there is a risk of decreased susceptibility of *S. pneumoniae*, empiric treatment should include vancomycin or rifampicin. However, some experts advise the use of ceftriaxone or cefotaxim as empiric treatment instead of vancomycin or rifampicin when true resistance to third-generation cephalosporin (MIC > 2 Mg/L) is not to be expected.

When risk factors for an infection with *L. monocytogenes* are present in adults below the age of 50 years (e.g. diabetes, use of immunosuppressive drugs, cancer), or in adults over 50 years of age, empiric antibiotic treatment should include amoxicillin or ampicillin to cover for *L. monocytogenes*. A recent nationwide Dutch study revealed that during a period of 6 years 4 cases of *L. monocytogenes* occurred in adults below the age of 50 without specific risk factors (out of 259 patients <50 years without immunocompromised state [1.5%]).

If the physician wishes to cover for this rare possibility, empiric antibiotic treatment should include amoxicillin or ampicillin for all adults with bacterial meningitis.

4.1.2. Specific antibiotic after identification of the causative micro-organism

Following identification of the pathogen through culture and antibiotic susceptibility testing the antibiotic treatment can be optimized.

**Streptococcus pneumoniae**

The pneumococcus is currently the most common causative micro-organism in adults and the second-most common in children beyond the neonatal age. Reduced susceptibility to penicillin and third generation cephalosporins of *S. pneumoniae* is a growing problem in Europe, although resistance rates vary considerably between countries. For example, rates of reduced susceptibility to penicillin in the Netherlands, England, Denmark and Germany are <1%, while reduced susceptibility rates of 20-50% have been reported for Spain, France and Romania (data ECDC Surveillance report 2011). When *S. pneumoniae* has been identified and susceptibility testing is pending or not available, treatment should be based on local resistance rates (table 4.2).

**Key question 5**: Does the addition of vancomycin or rifampicin to a 3rd generation cephalosporin improve outcome in pneumococcal meningitis patients in the setting of lower antimicrobial sensitivities of pneumococci.

There is uncertainty regarding the benefit of adding vancomycin or rifampicin to a 3rd generation cephalosporin in pneumococcal meningitis patients in the setting of decreased susceptibility rates of pneumococci. We systematically evaluated the literature for studies of the efficacy of vancomycin and rifampicin in infections caused by pneumococci resistant to 3rd generation cephalosporins, but only animal studies were identified. These showed that ceftriaxone combined with either vancomycin or rifampicin resulted in a higher rate of CSF sterilisation after 24 hours compared to monotherapy with ceftriaxone. Another animal study showed superiority of ceftriaxone combined with either rifampicin or rifampicin and vancomycin compared to ceftriaxone combined with vancomycin. Although there is no clinical evidence for adding vancomycin or rifampicin in the setting of lower pneumococcal susceptibility rates, the committee advises addition of vancomycin or rifampicin to 3rd generation cephalosporins based on *in vitro* susceptibility patterns. The advised duration of treatment is 10-14 days.

**Neisseria meningitidis**

In the past decades a proportional increase in meningococcal strains with reduced susceptibility to penicillin in meningococcal meningitis patients has been observed. A Spanish study described up to 80% of
meningococcal strains had reduced susceptibility to penicillin. The majority of patients with *N. meningitidis* strains of intermediate susceptibility to penicillin described in the literature have responded well to penicillin therapy. However, a study in children with meningococcal meningitis described higher mortality and risk of sequelae when infected with strains with reduced susceptibility.88 Therefore, patients with suspected meningococcal meningitis caused by bacterial strains that, on basis of the local epidemiology, are likely to be resistant to penicillin, a third generation cephalosporin should be given until in vitro susceptibility testing is performed. The advised duration of treatment is 7 days.2,3,40

Table 4.1. Empiric antibiotic in-hospital treatment for community acquired bacterial meningitis.3

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Standard treatment Reduced <em>S. pneumoniae</em> antimicrobial sensitivity to penicillin</th>
<th><em>S. pneumoniae</em> susceptible to penicillin</th>
<th>Intravenous dose3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates &lt;1 month</td>
<td>Amoxicillin/ampicillin/penicillin plus cefotaxime, or amoxicillin/ampicillin plus an aminoglycoside</td>
<td>Age &lt;1 week: cefotaxime 50 mg/kg q8h; ampicillin/amoxicillin 50 mg/kg q8h; gentamicin 2.5 mg/kg q12h Age 1–4 weeks: ampicillin 50 mg/kg q6h; cefotaxime 50mg/kg q6–8h; gentamicin 2.5 mg/kg q8h; tobramycin 2.5 mg/kg q8h; amikacin 10 mg/kg q8h</td>
<td></td>
</tr>
<tr>
<td>Age 1 months –18 years</td>
<td>Cefotaxime or ceftriaxone plus vancomycin or rifampicin</td>
<td>Cefotaxime or ceftriaxone</td>
<td>Vancomycin 10–15mg/kg q6 h to achieve serum trough concentrations of 15–20μg/mL; rifampicin 10mg/kg q12h up to 600mg/day; cefotaxime 75 mg/kg q6–8h; ceftriaxone 50 mg/kg q12h (maximum 2g q12h)</td>
</tr>
<tr>
<td>Age &gt;18 and &lt;50 years</td>
<td>Cefotaxime or ceftriaxone plus vancomycin or rifampicin</td>
<td>Cefotaxime or ceftriaxone</td>
<td>Ceftriaxone 2g q12h or 4gr q24h; cefotaxime 2g q4–6 h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 μg/mL; rifampicin 300mg q12h</td>
</tr>
<tr>
<td>Age &gt;50 years, or Age &gt;18 and &lt;50 years plus risk factors for <em>L. monocytogenes</em>1</td>
<td>Cefotaxime or ceftriaxone plus vancomycin or rifampicin plus amoxicillin/ ampicillin / penicillin</td>
<td>Cefotaxime or ceftriaxone plus amoxicillin/ ampicillin / penicillin</td>
<td>Ceftriaxone 2g q12h or 4gr q24h; cefotaxime 2g q4–6 h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 μg/mL; rifampicin 300mg q12h, amoxicillin or ampicillin 2 g q4h</td>
</tr>
</tbody>
</table>

1Diabetes mellitus, use of immunosuppressive drugs, cancer, other conditions associated causing immunocompromise.
Table 4.2. Specific antibiotic in hospital treatment for community acquired bacterial meningitis.\(^a\)

<table>
<thead>
<tr>
<th>Micro-organism</th>
<th>Standard treatment</th>
<th>Alternatives</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S. pneumoniae</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin susceptible (MIC &lt;0.1 (\mu)g/ml),</td>
<td>Penicillin or amoxicillin/ampicillin</td>
<td>Ceftriaxone, ceftaxime, chloramphenicol</td>
<td>10-14 days</td>
</tr>
<tr>
<td>Penicillin resistant (MIC &gt;0.1(\mu)g/ml), 3rd generation cephalosporin susceptible (MIC &lt;2 (\mu)g/ml)</td>
<td>Ceftriaxone or ceftaxime</td>
<td>Cefepime, meropenem, moxifloxacin(^b)</td>
<td>10-14 days</td>
</tr>
<tr>
<td>Cephalosporin resistant (MIC (\geq )2 (\mu)g/ml)</td>
<td>Vancomycin plus rifampicin, or vancomycin plus ceftaxime, or rifampicin plus ceftaxime(^c)</td>
<td>Vancomycin plus moxifloxacin(^b), linezolid,</td>
<td>10-14 days</td>
</tr>
<tr>
<td><strong>N. meningitidis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin susceptible (MIC&lt;0.1(\mu)g/ml)</td>
<td>Penicillin or amoxicillin/ampicillin</td>
<td>Ceftriaxone, ceftaxime, chloramphenicol</td>
<td>7 days</td>
</tr>
<tr>
<td>Penicillin resistant (MIC (\geq )0.1(\mu)g/ml)</td>
<td>Ceftriaxone or ceftaxime</td>
<td>Cefepime, meropenem, ciprofloxacin or chloramphenicol</td>
<td>7 days</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Amoxicillin or ampicillin, Penicillin G(^d)</td>
<td>trimethoprim-sulfamethoxazole, moxifloxacin(^b), meropenem, linezolid</td>
<td>At least 21 days</td>
</tr>
<tr>
<td><strong>H. influenzae</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>beta-lactamase negative</td>
<td>Amoxicillin or ampicillin</td>
<td>Ceftriaxone, ceftaxime, or chloramphenicol</td>
<td>7-10 days</td>
</tr>
<tr>
<td>beta-lactamase positive</td>
<td>Ceftriaxone or ceftaxim</td>
<td>Cefepime, ciprofloxacin, chloramphenicol,</td>
<td>7-10 days</td>
</tr>
<tr>
<td>beta-lactamase negative ampicillin resistant</td>
<td>Ceftriaxone or ceftaxim plus meropenem</td>
<td>Ciprofloxacin</td>
<td>7-10 days</td>
</tr>
<tr>
<td><strong>S. aureus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methicillin sensitive</td>
<td>Flucloxacillin, nafcillin, oxacillin</td>
<td>Vancomycin, linezolid, rifampicin(^e), fosfomycin(^e), daptomycin(^b)</td>
<td>at least 14 days</td>
</tr>
<tr>
<td>Methicillin resistant</td>
<td>Vancomycin(^f)</td>
<td>Trimethoprim-sulfamethoxazole, linezolid, rifampicin(^e), fosfomycin(^e), daptomycin</td>
<td>at least 14 days</td>
</tr>
<tr>
<td>Vancomycin resistant (MIC&gt;2.0 (\mu)g/ml)</td>
<td>Linezolid(^f)</td>
<td>Rifampicin,(^e) fosfomycin,(^e) daptomycin(^b)</td>
<td>at least 14 days</td>
</tr>
</tbody>
</table>

Footnote table 4.2  \(^{a}\)Recommendations must be in accordance with the results of the susceptibility testing.\(^a\)\(^b\)

\(^b\)Based on case reports \(^c\)Ceftriaxone dose 2g q12h and ceftaxim 2-3g q6h. \(^d\)Adding an aminoglycoside can be considered, see text. \(^e\)Must not be used in monotherapy. \(^f\)The addition of rifampicin can be considered.
Listeria monocytogenes

Linezolid, penicillin, ampicillin, gentamicin, quinolones, meropenem, chloramphenicol and vancomycin were shown to be effective against Listeria species in *in vitro* studies. However, there is limited clinical data to make strong recommendations for one of these agents in Listeria meningitis. Standard therapy for *L. monocytogenes* meningitis has been amoxicillin, ampicillin or penicillin. There is controversy on adding aminoglycosides to the regimen as two retrospective series showed addition of an aminoglycoside was associated with renal failure. In these studies however, several biases made direct comparison of treatment groups difficult. Adding aminoglycosides (gentamicin) could be considered as a treatment regimen for *L. monocytogenes* meningitis. Treating physicians should however be cautious about adding gentamicin especially in terms of renal failure.

There is no study assessing the optimal duration of the therapy in *L. monocytogenes* meningitis; the guideline panel recommends at 21 days of therapy or longer.

Staphylococcus aureus

For staphylococcal meningitis flucloxacillin, nafcillin, oxacillin or a combination therapy including fosfomycin or rifampicin are the recommended agents. Vancomycin is recommended for methicillin resistant staphylococcal meningitis. Linezolid may be chosen in cases with vancomycin resistance (MIC > 2 μg/ml) or contraindications to vancomycin. Rifampicin could also be considered as supplementary therapy together with vancomycin or linezolid. Trimethoprim-sulfamethoxazole or daptomycin may be used as salvage therapy options although only case reports support their use in staphylococcal meningitis. Rifampicin and fosfomycin must not be used as monotherapy to avoid the development of resistance. Although there is no study comparing the durations of the therapy in staphylococcal meningitis, the guideline panel recommends at least 14 days of therapy. If staphylococci are identified as the cause of bacterial meningitis, other sites of infections should be considered such as endocarditis or spinal epidural abscesses which may require surgical intervention and prolonged antibiotic therapy.

Culture negative patients

In patients with CSF suggestive of bacterial meningitis in whom the CSF culture and other tests (e.g. PCR) remains negative and the pathogen is not identified from other sites (e.g. from blood culture, or petechial rash culture) the committee’s advice is to continue empiric treatment for a duration of at least 2 weeks. However, depending on the clinical condition of the patient this may need to be extended.

4.1.3 Duration of treatment

The optimal duration of antibiotic treatment for bacterial meningitis has been studied in 6 randomized clinical trials in children. A meta-analysis of these trials concluded that there was insufficient evidence to advise a short course of antibiotics. A large randomized controlled trial showed a 5-day regimen was as effective as 10 days of antibiotics in children with bacterial meningitis who were in a stable condition after three days of treatment. Most of the children were resident in Malawi or Pakistan and a large proportion had *H. influenzae* type b meningitis. Although there was equivalence of the short and long course of antibiotics, the subgroups per causative micro-organism were too small to prove equivalence. Because of the substantial differences in epidemiology, clinical characteristics and co-morbidity between the study population and children in the European situation, the results of this trial cannot be extrapolated to the European situation and therefore the duration of treatment remains as advised in table 4.2.

4.1.4 Method of administration of antibiotic treatment

Antibiotics can be administered by continuous infusion or bolus administration (e.g. every 4 hours). Use of constant iv infusion of antibiotics is hypothesized to have a beneficial role in treatment of bacterial meningitis. Our literature search yielded 98 articles, 6 articles were relevant consisting of 3 animal studies, 2 reviews and 1 randomized controlled trial. This trial showed no significant differences between continuous and bolus administration of cefotaxime in children with bacterial meningitis. Due to the results of this trial and other concerns such as CSF pharmacokinetic/pharmacodynamic-parameters (e.g. long antibiotic elimination half-life, poor bacterial growth rate), use of dexamethasone, no recommendation for either continuous of bolus administration can be given at present.
## Conclusions

### Level 3

The empiric antibiotic treatment in bacterial meningitis patients is expert opinion based and differentiated for demographic/epidemiological factors (age and rate of reduced antibiotic susceptibility).

### Level 3

The specific antibiotic treatment in bacterial meningitis patients is based on antimicrobial susceptibility testing.

### Level 2

There is insufficient evidence to support a short course of antibiotics in children and adults with bacterial meningitis in the European setting.

### Level 1

There is no evidence of superiority of either continuous or bolus administration of antibiotics in bacterial meningitis patients.

## Recommendation

### Grade A

The recommended empiric treatment for bacterial meningitis patients is based on age and local resistance rates as displayed in table 4.1.

### Grade A

The recommended specific treatment for bacterial meningitis patients should be determined by the antibiotic susceptibility pattern and is as displayed in table 4.2.

### Grade A

The recommended treatment for bacterial meningitis patients in whom no pathogen can be cultured should be according to the empiric regimen for a minimum duration of 2 weeks.

### Grade D

The committee does not recommend a short course of antibiotics in children and adults with bacterial meningitis.

### Grade

Due to a lack of evidence the committee does not provide a recommendation on the use of continuous or bolus administration of antibiotics in bacterial meningitis patients.
Key question 6: Does dexamethasone have a beneficial effect on death, functional outcome and hearing loss in adults and children with bacterial meningitis.

4.2. Adjunctive dexamethasone treatment

4.2.1. Evidence for adjunctive dexamethasone treatment

Experimental animal studies have shown that outcome of bacterial meningitis is related to the severity of inflammation in the subarachnoid space.94 Immunomodulation of the inflammatory response with corticosteroids has been evaluated as treatment strategy in multiple RCTs. A 2013 Cochrane review included 25 RCTs including 4121 bacterial meningitis patients.95 The guideline update of the literature search did not identify additional RCTs that were published after the publication of this meta-analysis.

In the Cochrane meta-analysis corticosteroids were found to decrease overall hearing loss and neurological sequelae, but did not reduce mortality.95 No excess of dexamethasone related side effects was observed compared to the placebo group. A subgroup analysis showed that corticosteroids reduced mortality in pneumococcal meningitis, but not in meningitis due to other pathogens. Further subgroup analyses showed that use of corticosteroids was beneficial in studies performed in high income countries with high standard of medical care, but no effect was observed in studies performed in low income countries.

Only one RCT was published on the use of adjunctive corticosteroids in neonatal meningitis.95,96 This study did show a beneficial effect of corticosteroids, but was small and treatment groups were not well balanced with regards to patient age, culture positivity and causative micro-organisms. Therefore, additional RCTs evaluating corticosteroids in neonatal meningitis need to be performed before definitive conclusions can be drawn on the role of dexamethasone treatment in neonatal meningitis. The use of dexamethasone for neonates is currently not recommended.

Most studies included in the meta-analysis use dexamethasone and this is the most widely used corticosteroid for bacterial meningitis. The advised dexamethasone regimen in children is 0.6 mg/kg/day in 4 doses and in adults 10 mg every 6 hours, both for a duration of 4 days.

Sub-question 6.1.: If adjunctive dexamethasone therapy is indicated, what is the maximal delay for administering dexamethasone after the start of antibiotics?

4.2.2. Timing of dexamethasone treatment

In the largest RCTs dexamethasone was given before or with the first dose of antibiotics, in order to prevent the inflammatory response resulting from bacteriolysis by antibiotics.97,98 Therefore, it is advised to start dexamethasone with the first dose of antibiotics.9 When dexamethasone has not been started with the first dose of antibiotics it is unclear at what point adjunctive dexamethasone ceases to be beneficial. No RCTs have been performed that address timing of corticosteroid therapy.95 In experimental pneumococcal meningitis, CSF bacterial concentrations at the start of treatment seemed to be a more important factor affecting the antimicrobial induced inflammatory response than the time when dexamethasone therapy was started.94 An individual patient data meta-analysis showed that dexamethasone reduced hearing loss, irrespective of whether the drug was given before or after the antibiotics.99 As there are no data supporting a specific time, the guideline committee has reached consensus (based on expert opinion) that dexamethasone treatment can still be started up to 4 hours after initiation of antibiotic treatment.

Sub-question 6.2.: Should dexamethasone be stopped if pathogens other than S. pneumoniae are identified?

4.2.3. Stopping dexamethasone after pathogen identification

The Cochrane meta-analysis showed adjunctive dexamethasone is effective in reducing hearing loss and neurological sequelae in bacterial meningitis caused by all pathogens.95 In subgroup analyses it was shown that the effect of dexamethasone was most apparent in pneumococcal meningitis, and also reduced mortality in this group. Furthermore, for H. influenzae meningitis a strong effect on hearing loss was identified. For N. meningitidis, subgroup analysis showed no effect on any of the outcome measures. However, as the event rate (mortality, hearing loss) in meningococcal meningitis is substantially lower than in pneumococcal meningitis, no
conclusions can be drawn on the efficacy of dexamethasone owing to the small number of meningococcal meningitis patients included in the meta-analysis. An implementation study showed the use of dexamethasone is safe in meningococcal meningitis patients, but did not significantly decrease hearing loss or death. The guideline committee concludes dexamethasone should be stopped if the patient is discovered not to have bacterial meningitis or if the bacterium causing the meningitis is a species other than *H. influenzae* or *S. pneumoniae*, although some experts advise that adjunctive treatment should be continued irrespective of the causative bacterium.

### Conclusions

| Level 1 | Corticosteroids significantly reduced hearing loss and neurological sequelae, but did not reduce overall mortality. Data support the use of corticosteroids in patients with bacterial meningitis beyond the neonatal age in countries with a high level of medical care. No beneficial effects of adjunctive corticosteroids have been identified in studies performed in low-income countries. |
| Level 3 | In the absence of scientific evidence the committee has reached consensus that, when antibiotic treatment has already been started, adjunctive dexamethasone treatment can still be started up to 4 hours after initiation of antibiotic treatment. |
| Level 3 | In the absence of scientific evidence the guideline committee concludes dexamethasone should be stopped if the patient is discovered not to have bacterial meningitis or if the bacterium causing the meningitis is a species other than *H. influenzae* or *S. pneumoniae*, although some experts advise that adjunctive treatment should be continued irrespective of the causative bacterium. |

### Recommendation

| Grade A | Empiric treatment with dexamethasone is strongly recommended for all adults (10mg QID for 4 days) and children (0.6mg/kg/day in 4 doses for four days) with acute bacterial meningitis in the setting of high income countries. |
| Grade A | Treatment with dexamethasone is strongly recommended to be initiated with the first dose of antibiotic treatment. |
| Grade C | If intravenous antibiotic treatment has already been started, dexamethasone can still be administered up to 4 hours after start of the first dose of intravenous antibiotics. |
| Grade B | It is recommended to stop dexamethasone if the patient is discovered not to have bacterial meningitis or if the bacterium causing the meningitis is a species other than *H. influenzae* or *S. pneumoniae*, although some experts advise that adjunctive treatment should be continued irrespective of the causative bacterium. |
Key question 7: Do glycerol, mannitol, paracetamol (acetaminophen), hypothermia, antiepileptic drugs, hypertonic saline and other adjunctive treatments have a beneficial effect on death, functional outcome and hearing loss in adults and children with bacterial meningitis?

4.3. Other adjunctive treatments

This section considers routine use of adjunctive treatment strategies in unselected patients. In individual patients treatment with one on the described agents may be indicated, e.g. anti-epileptic drugs for patients presenting with seizures. Please see section 4.5 for details in such cases.

4.3.1 Osmotic therapies

Treatment with osmotic agents has traditionally been used in several neurological diseases to reduce intracranial pressure. The most well studied osmotic agents in bacterial meningitis is glycerol. The literature search on glycerol in bacterial meningitis yielded 73 articles of which 8 were relevant. Five RCTs were identified of which four were included in a 2013 Cochrane meta-analysis. One RCT in adults was stopped because of higher mortality rate in the treatment group, one RCT in children favoured glycerol, and 3 RCTs showed no difference. There were substantial differences between the studies regarding geography (South-America, Europe or Africa), age group (adults or children) and study medication dose (max 100ml/day or 300ml/day) and duration of treatment (2 or 4 days). The study performed in Europe showed no effect. No studies were performed in neonates with bacterial meningitis. As there is no clear benefit of glycerol it should not be given to adults or children with bacterial meningitis.

Other osmotic agents such as mannitol or hypertonic saline have not been studied in RCTs or comparative studies of bacterial meningitis patients. Therefore there is insufficient evidence to guide an advice on this treatment.

4.3.2. Paracetamol (acetaminophen)

Paracetamol (or Acetaminophen) has been considered to improve outcome by reducing the inflammatory response and decreasing fever. Observational data in bacteraemic patients showed acetaminophen use was associated with improved prognosis. Our literature search identified 19 relevant articles of which 2 RCTs. Both trials tested paracetamol (acetaminophen) in a factorial design with a second intervention. No beneficial effect was observed.

4.3.3. Therapeutic hypothermia

Therapeutic hypothermia is suggested to be neuroprotective and has been extensively studied in severe neurotrauma and post-anoxic encephalopathy with varying results. The literature search yielded 1 RCT and 2 observational studies. The RCT was stopped preliminary because of excess mortality in the hypothermia group. Therefore, hypothermia is not recommended in bacterial meningitis patients.

4.3.4. Anti-epileptic treatment

The literature search yielded 320 articles of which none were relevant. No RCTs have been performed that evaluate the use of standard anti-epileptic treatment in bacterial meningitis in the absence of seizures.

4.3.5. Hypertonic saline

The literature search yielded 21 articles of which none were relevant. No RCTs have been performed that evaluate the use of hypertonic saline treatment in bacterial meningitis.

4.3.6. Intracranial pressure based treatment

During bacterial meningitis the intracranial pressure is elevated due to several factors (e.g. brain swelling or hydrocephalus). Several multi-step treatment strategies have been described to reduce the intracranial pressure in observational studies, and have been suggested to improve outcome. However, no RCT’s have been performed and results varied considerably between observational studies. As the described interventions may also cause harm, further studies are needed before these treatment strategies can be advised for routine use in patients with bacterial meningitis.

4.3.7. Other adjunctive treatments
Several other adjunctive treatments were evaluated in bacterial meningitis patients. Bacterial meningitis patients included in intensive care RCT's on activated protein C showed increase rate of cerebral haemorrhage in the treatment group and is therefore not recommended (the treatment is no longer available). Intrathecal and intravenous adjuvant immunoglobulins were tested in a comparative (non-randomized) study in children with bacterial meningitis. No significant difference was observed in outcome or death, but groups were small. Adjuvant heparin was tested in a study of 15 patients with bacterial meningitis. A higher risk of bleeding and mortality was found in the treatment group, and therefore heparin is not recommended.

Conclusion

Level 1 Present data do not support use of glycerol in adults with acute bacterial meningitis. Although potential beneficial effect exists in children, no recommendation can be made because strong evidence is not available.

Level 1 Therapeutic hypothermia is associated with a higher mortality rate in bacterial meningitis patients.

Level 1 Paracetamol (acetaminophen) use in bacterial meningitis patients did not improve outcome.

Level 3 Use of mannitol, antiepileptic drugs and hypertonic saline needs further evaluation to make conclusive recommendations on its routine use in bacterial meningitis patients.

Level 2 Use of intracranial pressure/cerebral perfusion pressure monitoring and treatment needs further evaluation to make a conclusive recommendation on its use in bacterial meningitis patients.

Recommendations

Grade D Routine adjuvant therapy with mannitol, acetaminophen, antiepileptic drugs or hypertonic saline is not recommended. Hypothermia and glycerol are contraindicated in bacterial meningitis.

Grade C Use of intracranial pressure/cerebral perfusion pressure monitoring and treatment can be life-saving in selected patients, but cannot be recommended as routine management, because solid evidence is lacking and harm may occur.

Grade D Adjuvant therapy with immunoglobulins, heparin and activated protein C is not recommended.
4.4. Prophylaxis

**Key question 8:** Does the use of prophylactic treatment of household contacts (of meningococcal meningitis patients) decrease carriage or secondary cases?

4.4.1. Prophylactic treatment of household contacts of meningococcal meningitis patients

The risk of meningococcal disease is increase 400-800 fold in individuals in close contact with meningococcal disease, with the highest risk for house-hold contacts.\(^{109}\) By prescribing prophylactic antibiotics, this risk may be averted. Multiple studies have been performed to determine whether prophylactic antibiotics are beneficial. Our literature search yielded 258 hits of which 8 articles were relevant, including a Cochrane meta-analysis including 24 RCTs. The Cochrane analysis included 19 RCTs including 2531 participants and 5 cluster randomized controlled trials including 4354 participants.\(^{109}\) Ceftriaxone, rifampicin and ciprofloxacin were found to be the most effective to prevent secondary cases and to achieve eradication of *N. meningitidis* from the nasopharynx. Therefore, antibiotic prophylaxis should be given to all close contacts of the patient with invasive meningococcal disease to prevent secondary cases and to decrease carriage. Close contacts are defined as household members, child-care centre contacts and anyone directly exposed to oral secretions. Ciprofloxacin single oral dose, ceftriaxone single intramuscular dose or rifampicin orally for 2 days are the drugs of choice and should be commenced within 24 hours of identification. Patients treated with penicillin should also receive clearance-effective antibiotics before discharge; those who have received their meningitis therapy in the form of IV ceftriaxone/cefotaxim do not need additional prophylaxis.

**Sub question 8.1:** Is vaccination indicated after pneumococcal meningitis?

4.4.2. Vaccination of pneumococcal meningitis patients

The risk of a recurrent episode of pneumococcal meningitis is approximately 5%.\(^{110,111}\) Of the cases of recurrent meningitis the majority have a risk factor for meningitis such as a CSF leak due to trauma or prior surgery, or immunodeficiency such as splenectomy or hypogammaglobulinemia. In one fourth of patients with recurrent meningitis (1% of total cases) no risk factor for recurrent meningitis can be identified.\(^{110}\) Based on the identified recurrence rate in pneumococcal meningitis patients, this population can still be considered to be at high risk and therefore vaccination may be warranted. In a literature search we did not identify RCTs or case control studies on vaccination of meningitis patients and recurrences of pneumococcal disease. Based on expert opinion the committee recommends vaccination in all patients with pneumococcal meningitis. Along with reconstruction of the dural barrier patients with CSF leakage should receive pneumococcal vaccination, and *H. influenzae* and meningococcal vaccination can be considered as well. For patients with other risk factors, such as splenectomy, hyposplenism or hypogammaglobulinemia, other existing guidelines apply.

**Conclusion**

**Level 1**

Prophylactic antibiotic treatment of household contacts prevents secondary cases and eradicates meningococcal carriage.

**Level 3**

Based on the recurrence risk of 1-5% of pneumococcal meningitis, the committee sees substantial benefits in vaccination with pneumococcal vaccines after an episode of pneumococcal meningitis. Vaccination with pneumococcal vaccines is deemed beneficial in bacterial meningitis patients with CSF leakage to reduce recurrences. Vaccination with *H. influenzae* type B and a meningococcal vaccine (either serogroup C, serogroup B or quadrivalent A/C/Y/W135 depending on local epidemiology) can be considered in bacterial meningitis patients with CSF leakage.
Recommendations

**Grade A**

It is strongly recommended to treat house-hold contacts and other close contacts with antibiotic prophylaxis consisting of ceftriaxone, ciprofloxacin or rifampin (table 4.3 for dose).

**Grade B**

It is recommended to vaccinate with pneumococcal vaccine patients after an episode of pneumococcal meningitis and persons with CSF leakage along with the reconstruction of the dural barrier. Vaccination with *H. influenzae* type b and *N. meningitidis* vaccine can be considered in patients with CSF leakage.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifampin</strong></td>
<td>Child &lt; 3 months of age: 5mg/kg twice a day orally</td>
<td>2 days</td>
</tr>
<tr>
<td></td>
<td>Child ≥3 months to 12 years of age: 10mg/kg twice a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Child &gt;12 years of age: 600mg twice a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adults: 600mg twice a day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnancy: 600mg twice a day – only after first three months of pregnancy</td>
<td></td>
</tr>
<tr>
<td><strong>Ciprofloxacin</strong></td>
<td>Adults &gt;16 years: 500 mg oral</td>
<td>Once</td>
</tr>
<tr>
<td></td>
<td>Do not use during pregnancy</td>
<td></td>
</tr>
<tr>
<td><strong>Ceftriaxone</strong></td>
<td>Child &lt;16 years: 125mg intramuscular</td>
<td>Once</td>
</tr>
<tr>
<td></td>
<td>Adults &gt;16 years: 250mg intramuscular</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregnancy 250 mg intramuscular (first choice during pregnancy)</td>
<td></td>
</tr>
</tbody>
</table>

4.5 Complications in bacterial meningitis during hospitalization

The clinical course of bacterial meningitis can be complicated by both neurologic and systemic complications. Patients may develop a decrease in mental status, focal neurologic deficits, haemodynamic instability or respiratory insufficiency. The cause of deterioration will need to be determined by physical and neurologic investigation and ancillary investigations may become necessary, such as laboratory investigations, cranial imaging and electroencephalography (EEG). The frequency of complications differs between age groups and causative micro-organisms. Common complications reported during neonatal meningitis are shock, convulsions and hydrocephalus (Table 4.4).

<table>
<thead>
<tr>
<th>Complication</th>
<th>Frequency</th>
<th>Ancillary investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>15-34%</td>
<td>EEG (if not clinically evident)</td>
<td>Anti-epileptic drugs</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>5-6%</td>
<td>Transcranial ultrasound or cranial MRI</td>
<td>External ventricular drain</td>
</tr>
<tr>
<td>Sepsis</td>
<td>24%</td>
<td>Evaluation of other foci of infection (e.g. pneumonia, endocarditis)</td>
<td>According to guidelines for management of sepsis</td>
</tr>
</tbody>
</table>

Half of the adults with bacterial meningitis develop focal neurologic deficits during their clinical course, and one third of patients develops haemodynamic or respiratory insufficiency. The diagnostic work-up in these patients can consist of cranial CT or MRI when intracranial abnormalities are suspected (in which MRI is preferred due to superior resolution, but availability and speed of CT is often greater), repeated lumbar puncture and EEG. However, the yield of repeated lumbar puncture is probably limited and therefore routine repetition of the LP is not indicated. When hydrocephalus or space occupying lesions, such as subdural empyema, brain abscess or intracerebral haemorrhages, are detected on cranial imaging, neurosurgical
intervention may be warranted to prevent cerebral herniation and sometimes remove the lesion. In most patients with obstructive hydrocephalus, placement of an external ventricular drain is indicated. In patients with communicating hydrocephalus who are awake and can be monitored clinically, invasive measures such as repetitive lumbar punctures or placement of an external lumbar drain can be considered but might not be necessary at all.

Table 4.5 Common complications of bacterial meningitis in adults

<table>
<thead>
<tr>
<th>Complication</th>
<th>Frequency</th>
<th>Ancillary investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>17%</td>
<td>Cranial CT or MRI EEG (if not clinically evident)</td>
<td>Anti-epileptic drugs</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>3-5%</td>
<td>Cranial CT or MRI</td>
<td>External ventricular drain if clinically relevant</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>14-25%</td>
<td>Cranial CT or MRI</td>
<td>No specific treatment</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>3%</td>
<td>Cranial CT or MRI</td>
<td>Consider neurosurgical intervention</td>
</tr>
<tr>
<td>Subdural empyema</td>
<td>3%</td>
<td>Cranial CT or MRI</td>
<td>Consider neurosurgical intervention</td>
</tr>
<tr>
<td>Brain abscess</td>
<td>2%</td>
<td>Cranial CT or MRI</td>
<td>Consider neurosurgical intervention</td>
</tr>
<tr>
<td>Sinus thrombosis</td>
<td>1%</td>
<td>Cranial CT or MRI</td>
<td>No proven therapy</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>15%</td>
<td>Evaluation of other foci of infection (e.g. pneumonia, endocarditis)</td>
<td>According to guidelines for the management of sepsis including fluid replacement, ICU admission and monitoring</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>17-22%</td>
<td>Oto-acoustic emission / hearing evaluation</td>
<td>Cochlear implant</td>
</tr>
</tbody>
</table>

Cerebrovascular complications occur frequently during bacterial meningitis and can consist of cerebral infarctions, subarachnoid haemorrhage, intracranial haemorrhage and venous sinus thrombosis. The development of intracerebral haemorrhage has been associated with the use of anticoagulant medication and therefore discontinuation of this medication should be considered in bacterial meningitis patients. In patients with bacterial meningitis and venous sinus thrombosis, the guideline committee considers the increased risk of cerebral haemorrhage higher than the benefit of anticoagulants, at least during the acute phase of meningitis.

Conclusion

<table>
<thead>
<tr>
<th>Level 2</th>
<th>Neurologic and systemic complications occur in a large proportion of children and adults with bacterial meningitis. In a patient with neurologic deterioration cranial imaging (MRI or CT) is often indicated, and repeated lumbar puncture and EEG may be indicated in selected cases.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 3</td>
<td>Bacterial meningitis complicated by hydrocephalus, subdural empyema, and brain abscess may require neurosurgical intervention.</td>
</tr>
</tbody>
</table>

Recommendations

<table>
<thead>
<tr>
<th>Grade A</th>
<th>As neurological and systemic complications frequently occur during bacterial meningitis, physicians should be alert for recognition of these complications, perform ancillary investigations upon deterioration and initiate specific treatment when required (table 4.4; 4.5)</th>
</tr>
</thead>
</table>
Chapter 5 Follow-up care of bacterial meningitis patients

Key question 9: What follow-up care of bacterial meningitis patients should be provided (e.g. testing for hearing loss, neuropsychological evaluation)?

It is estimated that one third of patients surviving an episode of bacterial meningitis will have persisting complaints. A systematic review has been performed on the sequelae of bacterial meningitis in children, including 18,183 patients surviving bacterial meningitis included in 132 studies. In this review the most common cause of meningitis was H. influenzae type b, followed by S. pneumoniae (20%), N. meningitidis (16%) while other bacteria were identified in 12% of patients. Median follow-up was 24 months. The most common severe sequelae were hearing loss (34%), seizures (13%), motor deficits (12%), cognitive defects (9%), hydrocephalus (7%) and visual loss (6%). One in five children had multiple sequelae.

Common sequelae in adults are neurological deficits due to cerebral infarctions, hearing loss and cognitive slowness. It is important to recognize patients in whom neuropsychological investigation is indicated upon discharge from the hospital. Patients, family members and care-givers should be informed about the potential sequelae and when to contact their physician.

5.1 Hearing loss

Bacterial meningitis is the most common cause of acquired hearing loss in children and hearing loss occurs also in neonates and adults following bacterial meningitis. An estimated 5-35% of patients with bacterial meningitis develop sensorineuronal hearing loss and 4% of patients have severe bilateral hearing loss. In a study on hearing loss in pneumococcal meningitis survivors, including patients with no clinical suspicion of hearing loss, 54% of patients had audiometric evidence of hearing loss. Hearing loss may be present on admission or develop during disease course. Especially in young children it may go undetected for a period of time. This can negatively influence the speech development of these children. A cochlear implant can prevent this, when placed in a timely fashion. If implantation is delayed, cochlear fibrosis and calcification may occur, limiting the function of the implant.

Because of the necessity to identify hearing loss quickly in both children and adults with bacterial meningitis, hearing evaluation should be performed during admission. In children, otoacoustic emission can be used as a screening test. If the otoacoustic emission test fails children need to be referred to a centre with audiological expertise for further hearing evaluation using brainstem evoked response audiometry (BERA) or speech tone audiometry depending on the patients age. In adults speech tone audiometry has to be performed during admission. In patients with no hearing loss during initial hospitalisation, follow-up testing may be indicated as hearing loss may become apparent 6-12 months after the meningitis episode. In patients with over 30dB hearing loss or progressive hearing loss over time contrast enhance MRI, repeated hearing evaluation and consultation with a cochlear implantation specialist are indicated.

5.2. Neuropsychological sequelae

Neuropsychological sequelae in children often consist of failure to learn in school and poor development of cognitive abilities for their age. A follow-up study on the short- and long-term impacts of pneumococcal meningitis among 102 Bangladeshi children, aged 2 – 59 months, found high rates of cognitive delay that affected their ability to learn, their language development and social relationships. Half of the patients were followed up 30 to 40 days after discharge, the other half 6 to 24 months after discharge and in both groups 41% of the patients had significant deficits of cognitive development. Two other studies reported cognitive impairment at discharge in 13% of children after pneumococcal meningitis. IQ scores are also reported to be lower in young patients after bacterial meningitis compared with controls. A full-scale IQ score < 85 is reported in 10-36% of patients after pneumococcal meningitis. Learning problems were found in 10-20% of children and 12-33% of children had to repeat school years or required referral to a special-needs school after pneumococcal meningitis in one Dutch follow-up study.

In a Dutch study including 155 adult survivors of bacterial meningitis and 72 healthy controls, neuropsychological examination revealed that 32% had cognitive defects compared to 6% in the control group.
The most apparent defect was cognitive slowness. A follow-up study in the same population 9 years after bacterial meningitis found that psychological functioning and quality of life had returned to normal on a group level, but some cognitive slowness persisted on an individual level. A German study comparing 59 patients with bacterial meningitis and 30 controls showed that 37% of bacterial meningitis patients had short term memory and working memory problems.

Neuropsychological examination is not routinely indicated in bacterial meningitis patients. Patients should be informed about the nature and frequency of cognitive disorders following bacterial meningitis (difficulty with concentration, cognitive slowness, memory deficits). If cognitive defects are suspected neuropsychological examination should be performed and referral to a (neuro)psychologist / rehabilitation physician may be indicated. Simple neuropsychological tests may suffice (Montreal cognitive assessment test - MOCA) for screening in experienced hands.

**Conclusion**

**Level 2**

Sequelea occur in a substantial proportion of children and adults with bacterial meningitis and most frequently consist of hearing loss, neuropsychological defects and focal neurologic deficits.

**Level 2**

Hearing loss needs to be detected early during the disease course to facilitate effective cochlear implantation in the case of severe hearing loss.

**Recommendations**

**Grade A**

In children with bacterial meningitis, testing for hearing loss should be performed during admission (otoacoustic emission). In adults with bacterial meningitis testing for hearing loss should be performed during admission. In the case of hearing loss, patients should be referred to an ENT specialist in a medical centre performing cochlear implants.

**Grade B**

Routine neuropsychological examination is not recommended. If cognitive defects occur neuropsychological examination should be performed and referral to a (neuro)psychologist / rehabilitation physician may be indicated.
References


56. 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.


Appendix 1 Search strategies

1. What is the diagnostic accuracy of algorithms in the distinction between bacterial en viral meningitis?
   1. exp Meningitis, Bacterial/
   2. Bacterial Meningiti*.ti,ab.
   3. ((bacterial or meningococcal or pneumococcal or Neisseria or meningitides or Streptococcus or pneumiae or Haemophilus or Hib or influenzae or Listeria or monocytogenes or Escherichia or coli or agalactiae or pyogenes or Staphylococcus or aureus or Cryptococcus or neoformans) adj5 meningiti*).ti,ab.
   4. or/1-3
   5. (rule$ or model$ or (decision adj5 (support or rule$)) or logistic model$ or ("Stratification" or "Discrimination" or "Discriminate" or "c-statistic" or "c statistic" or "Area under the curve" or "AUC" or "Calibration" or "Indices" or "Algorithm" or "Multivariable").tw. or exp algorithms/
   6. 4 and 5
   7. exp Meningitis, Viral/
   8. ((virus or viral) adj5 meningitis).tw.
   9. exp Enterovirus/
   10. exp Enterovirus Infections/
   11. enterovir$.tw.
   12. exp Virus Diseases/
   13. Meningitis/
   14. 12 and 13
   15. 7 or 8 or 9 or 10 or 11 or 14
   16. 4 and 15
   17. 5 and 16
   18. exp "sensitivity and specificity"/ or exp "mass screening"/ or "reference values"/ or "false positive reactions"/ or "false negative reactions"/ or specificit$.tw. or screening.tw. or false positive$.tw. or false negative$.tw. or accuracy.tw. or predictive value$.tw. or reference value$.tw. or roc$.tw. or likelihood ratio$.tw.
   19. 16 and 18
   20. 17 or 19

2. Can we use clinical characteristics to predict the absence of intracranial abnormalities associated with increased risk of lumbar puncture?
   1. exp Meningitis, Bacterial/
   2. Bacterial Meningiti*.ti,ab.
   3. ((bacterial or meningococcal or pneumococcal or Neisseria or meningitides or Streptococcus or pneumiae or Haemophilus or Hib or influenzae or Listeria or monocytogenes or Escherichia or coli or agalactiae or pyogenes or Staphylococcus or aureus or Cryptococcus or neoformans) adj5 meningiti*).ti,ab.
   4. or/1-3
   5. Spinal Puncture/
   6. ((lumbar or spinal) adj3 (puncture or tap)).tw.
   7. exp Cerebrospinal Fluid/
   8. spinal fluid.tw.
   9. cerebrospinal fluid.tw.
   10. CSF.tw.
   11. or/5-10
   12. 4 and 11
   13. (ae or de or co).fs.
   14. (safe or safety or side-effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adverse or adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.
3. Does dexamethasone has a beneficial effect on death, functional outcome and hearing loss in adults and children with bacterial meningitis

4. Do glycerol, mannitol, acetaminophen, hypothermia, antiepileptic drugs, hypertonic saline have a beneficial effect on death, functional outcome and hearing loss in adults and children with bacterial meningitis.
5. Does the use of prophylactic treatment of household contact decrease carriage or secondary cases?

1473
1474
1475 1 ((exp "Meningitis, Bacterial"/ or bacterial meningitis*.ti,ab. or pneumococcal meningitis*.ti,ab. or meningococcal meningitis*.ti,ab. or staphylococcal meningitis*.ti,ab. or nosocomial meningitis*.ti,ab. or hospital acquired meningitis*.ti,ab. or e coli meningitis*.ti,ab. or escherichia coli meningitis*.ti,ab. or neonatal meningitis*.ti,ab.) and (exp "Anti- Bacterial Agents"/ or antibiotic*.ti,ab. or antimicrobial*.ti,ab.) and Humans/) not (tuberc* or anthra*).ti. not (case reports or editorial).pt.
1478
1479
1480 2 limit 1 to ed=20110101-20140301