ESCMID guideline: diagnosis and treatment of acute bacterial meningitis

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General introduction

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 [1–3]. 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 [1]. 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 among strains of *Streptococcus pneumoniae* (pneumococcus) and *Neisseria meningitidis* (meningococcus). Large differences in resistance rates in Europe exist, and empiric 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 [3]. 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).

Aim of 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 up-to-date scientific evidence for 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 ten 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 microorganisms 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 third-generation cephalosporin improve 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 provided?
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, neuropsychologic evaluation)?

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 recognizing children/patients with developing shock who need acute sepsis management (e.g. NICE guidelines, https://www.nice.org.uk/guidance/cg109).

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.

Composition of 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. After the first meeting the guideline committee was reinforced with two additional members because their specific expertise was originally underrepresented in the committee.

Approach of committee to guideline development

After the guideline preparation project was granted ESCMID funding in Summer 2013, a kickoff meeting was staged in Amsterdam (October 2013) at which the key questions and subquestions 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 held simultaneously with the 2014 ECCMID meeting in Barcelona, Spain. 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.

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 caregivers. To incorporate these factors into the guideline, the United Kingdom–based Meningitis Research Foundation was approached to participate in the guideline development and provide comments.

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://www.sumsearch.org 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, Netherlands) for all PICO formatted questions (Appendix).

Quality of evidence scoring. The literature was selected by the committee members and was graded for quality on the basis of 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.

Strength of recommendation assessment. On the basis of 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 of evidence may result in marginal support for use, while low-quality evidence may result in a strong recommendation for use.

Implementation and assessment of impact

We will disseminate and promote the guideline by publication in a peer-reviewed journal and active promotion of the

TABLE 1.2. Strength of recommendation

Grade	Recommendation
A	ESCMID strongly supports recommendation for use.
B	ESCMID moderately supports recommendation for use.
C	ESCMID marginally supports recommendation for use.
D	ESCMID supports recommendation against use.

guideline to all European national organizations 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 2 years. This will be assessed on a biannual basis and presented at the ESGIB meeting at the ECCMID.

Revision of guideline

Two members of the guideline committee (the chair plus one 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.

Legal status of guideline

Guidelines do not contain legal regulations but provide evidence-based recommendations. Clinicians may strive to provide optimal care by adhering to the guideline. Because 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 on the basis of 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.

Epidemiology of community-acquired bacterial meningitis in Europe

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

TABLE 1.1. Quality of evidence

Class	Conclusions based on:
1	Evidence from at least one properly designed randomized controlled trial.
2	Evidence from at least one well-designed clinical trial, without randomization; from cohort or case–control analytic studies (preferably from >1 centre); from multiple time series; or from dramatic results of uncontrolled experiments.
3	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies.

TABLE 2.1. Causative organisms of neonatal meningitis[a]

Country	United Kingdom [12]	France [13]	Spain [14]	Netherlands [4]	Total
Observation period	2010–2011	2001–2007	1997–1998	2006–2012	
Streptococcus agalactiae	150	258	69	88	565 (58%)
Escherichia coli	41	123	12	27	203 (21%)
Listeria monocytogenes	11	7	0	1	19 (2%)
Streptococcus pneumoniae	28	8	0	3	39 (4%)
Other	72	43	22	14	156 (16%)
Total	302	444	66	133	982

[a]Studies were performed in different time periods, with varying vaccination strategies per country.

The epidemiology of community-acquired meningitis worldwide has changed in the past decades as a result of 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 the age of the patient and predisposing factors.

Bacterial meningitis in neonates

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 weeks [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 1990s [7,8]. However, recent studies from the United Kingdom and the United States showed increased incidence rates in the 2000s [9,10]. A recent epidemiologic study from the Netherlands showed similar incidence rates of GBS meningitis over the past 25 years [11].

Historically *Listeria monocytogenes* has been 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.

Community-acquired bacterial meningitis in children beyond 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*. After vaccination against *H. influenzae* type b was introduced in the 1990s this pathogen has virtually disappeared as a major cause of bacterial meningitis in children [2]. *H. influenzae* meningitis currently occurs incidentally in unvaccinated children or may be due to serotypes other than b [15]. After a peak in incidence of serogroup C meningococcal meningitis in the early 2000s, several countries introduced the Men C vaccine in their vaccination programs [16,17]. This resulted in a sharp decrease in serogroup C meningococcal meningitis cases and provided long-term herd immunity [16,17]. Currently serogroup B causes 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 neonatal age

Country	France [20]	Denmark [21]	France [22]	Netherlands [4]	Total
Observation period	2001–2007	1997–2006	1995–2004	2006–2012	
Neisseria meningitidis	1303	159	35	308	1805 (50%)
Streptococcus pneumoniae	802	195	35	310	1342 (37%)
Haemophilus influenzae	78	8	11	73	170 (5%)
Other	137	56	8	101	302 (8%)
Total	2320	418	89	792	3619

TABLE 2.3. Causative organisms of adult bacterial meningitis

Country	Denmark [25]	Turkey [26]	United Kingdom [27]	Czech Republic [28]	Netherlands [4]	Total
Observation period	1998–2012	1994–2003	1997–2002	1997–2004	2006–2012	
Neisseria meningitidis	42	251	550	75	171	1089 (27%)
Streptococcus pneumoniae	92	457	525	82	1001	2157 (53%)
Haemophilus influenzae	3	2	48	3	56	112 (3%)
Listeria monocytogenes	5	6	48	21	74	154 (4%)
Other	30	68	124	35	291	548 (13%)
Total	172	784	1295	216	1593	4060

Community-acquired bacterial meningitis in adults

The majority of bacterial meningitis cases in adults is caused by *S. pneumoniae* (Table 2.3). After the introduction of PCVs a reduction in cases has been observed as a result of 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 [23]. 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 [18]. *L. monocytogenes* is the third most common cause of meningitis in adults and is commonly associated with old age and an immunocompromised state [24]. *Haemophilus influenzae* and *Staphylococcus aureus* are found in 1–2% of adult cases and are associated with specific underlying conditions such as otitis and sinusitis (*H. influenzae*) or endocarditis (*S. aureus*).

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, which may be iatrogenic (e.g. use of immunosuppressive medication or splenectomy), due to diseases influencing the immune system (e.g. cancer, diabetes mellitus, alcoholism, human immunodeficiency virus (HIV) infection) or hereditary (e.g. hypogammaglobulinaemia, late complement component deficiency, common variable immunodeficiency), increase the risk of bacterial meningitis [2]. The incidence of pneumococcal meningitis is increased in patients after splenectomy or with a hyposplenic state [29], chronic kidney or liver disease [30], HIV infection [31], alcoholism, hypogammaglobulinaemia, diabetes mellitus and patients using immunosuppressive drugs [2]. Patients with complement system deficiencies have been identified to have a strongly increased risk of meningococcal meningitis [32]. Predisposing conditions associated with *H. influenzae* meningitis include diabetes mellitus, alcoholism, splenectomy or asplenic states, multiple myeloma and immune deficiency such as

hypogammaglobulinaemia [2]. *L. monocytogenes* meningitis is more often found in elderly patients (>60 years) and those with acquired immunodeficiencies, such as diabetes, cancer and use of immunosuppressive drugs [24].

Conclusions

Level 2	Most common causative pathogens in neonatal meningitis are *Streptococcus agalactiae* and *Escherichia coli*.

Level 2	Most common causative pathogens in children beyond the neonatal age are *Neisseria meningitidis* and *Streptococcus pneumoniae*.

Level 2	Most common causative pathogens in adults are *Streptococcus pneumoniae* and *Neisseria meningitidis*. Another important causative microorganism in adults is *Listeria monocytogenes*.

Diagnosis of community-acquired bacterial meningitis

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

Clinical characteristics in children with bacterial meningitis

Clinical characteristics of neonatal bacterial meningitis. Neonates with bacterial meningitis often present with nonspecific symptoms such as irritability, poor feeding, respiratory distress, pale or marble skin and hyper- or hypotonia [7,12,13,33]. Fever is present in a minority (6–39%) of cases. Seizures are reported in 9–34% of cases and are more commonly reported among 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 [7,12,13,33]. In neonates with GBS meningitis within 24 hours of birth, respiratory (72%), cardiovascular (69%) and neurologic (63%) symptoms were the predominant initial signs [7]. Concomitant septic shock may be diagnosed in about 25% of the cases of

neonatal meningitis [13]. 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.

Clinical characteristics of bacterial meningitis in children beyond 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) [34−36]. 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 [34,36]. 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 [34−36].

Seizures have been reported at hospital admission in 10−56% of children. Altered mental status was reported in 13−56% of the cases of childhood bacterial meningitis [22,34,38]. 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 [35,37]. In a large study performed in Greece, 511 (61%) of 838 patients with confirmed meningococcal meningitis presented with haemorrhagic rash compared to 17 (9%) of 186 patients with meningitis due to *S. pneumoniae* [35].

TABLE 3.1. Clinical characteristics of paediatric meningitis beyond neonatal age at presentation

Country	Greece [35]	United States [37]	Kosovo [38]	France [22]	Iceland [36]
Observation period	74−05	01−07	97−02	95−04	95−10
No. of patients	1331	231	227	89	140
Fever	93%	93%	—	—	92%
Vomiting	58%	—	—	—	67%
Altered mental status	—	13%	51%	25%	—
Headache	78%	—	—	—	—
Neck stiffness	82%	40%	—	—	60%
Seizures	19%	10%	22%	25%	—
Focal neurologic deficits	—	—	16%	11%	—
Rash	39%	4%	—	—	51%

Diagnostic accuracy of clinical characteristics in children with bacterial meningitis has been assessed in several studies, recently summarized in a meta-analysis [39]. 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-analysis of studies revealed sensitivities of 51% for neck stiffness, 53% for Kernig sign and 66% for Brudzinski sign for the diagnosis of bacterial meningitis, as well as poor test characteristics of other common signs and symptoms in the differentiation between bacterial and viral/ aseptic or no meningitis [39]. These data indicate that clinical characteristics cannot be used to rule out bacterial meningitis [40].

Conclusions

Level 2	Neonates with bacterial meningitis often present with nonspecific 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 nonspecific symptoms. Characteristic clinical signs may be absent. In all children with suspected bacterial meningitis ESCMID strongly recommends cerebrospinal fluid examination, unless contraindications for lumbar puncture are present (see section Imaging before lumbar puncture).

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 at 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 is indicative of meningococcal infection in over 90% of patients [41].

Studies assessing the usefulness of neck stiffness, Kernig sign, and Brudzinski 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 cerebrospinal fluid (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

Country	Netherlands [41]	France [42]	Spain [43]	Iceland [44]	Denmark [25]
Observation period	1998–2002	2001–2004	1996–2010	1975–1994	1989–2010
No. of patients	696	60	295	119	172
Headache	87%	87%	—	—	58%
Nausea/vomiting	74%	—	45%	—	—
Neck stiffness	83%	—	69%	82%	65%
Rash	26%	—	20%	52%	—
Fever (>38.0°C)	77%	93%	95%	97%	87%
Altered mental status	69%	30%	54%	66%	68%
Coma	14%	—	7%	13%	16%
Focal neurologic deficits	34%	23%	15%	—	21%
Triad of fever, neck stiffness and altered mental status	44%	—	41%	51%	45%

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 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.

Diagnostic algorithms

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

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 [45]. 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 on the basis of 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.

None of the published diagnostic algorithms was 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, e.g. 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' judgement should continue to be used to estimate the risk of bacterial meningitis and whether empiric antibiotic and adjunctive therapy needs to be initiated [40].

Conclusion

Level 2	None of the published diagnostic algorithms was 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 empiric antibiotic and adjunctive therapy.

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

TABLE 3.3. Overview of diagnostic algorithms identified by survey

Score	Population	Items	Studies/level of evidence	Lowest reported sensitivity	Lowest reported specificity
Boyer [46]	Children	Score including temperature, rash, neurologic impairment/seizures or altered mental status, CSF protein, glucose and CSF WBC count, PMN count. *If >5 points = bacterial meningitis, 3–4 = unclear, <3 = no bacterial meningitis*	5/2	89%	88%
Oostenbrink [47]	Children	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 <8.5: low risk of bacterial meningitis*	5/2	79%	50%
Bacterial Meningitis Score [48]	Children	Item list including CSF Gram stain, CSF protein, peripheral absolute neutrophil count, seizures before or at admission, CSF absolute neutrophil count. *If all items are absent low risk of meningitis*	8/2	96%	44%
Bonsu [49]	Children	Formula including CSF WBC count, CSF protein concentration and age. *If score is <0.1: low risk of bacterial meningitis*	4/2	92%	28%
Hoen [50]	All ages, except neonates	Formula including CSF PMN count, CSF protein, blood glucose and blood WBC count. *If score is <0.1: low risk of bacterial meningitis*	6/2	77%	70%
Freedman	Children	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. *If all items are absent low risk of meningitis*	3/2	98.7%	12%
Meningitest	All ages, except neonates	Item list including WBC, CSF WBC, CSF PMN, CSF protein, and glucose CSF/blood ratio. *If all items are absent low risk of meningitis*	2/2	79%	51%
Spanos [51]	All ages, except neonates	Formula including age, time of year, glucose ratio, and total CSF PMN count. *Probability of meningitis calculated by nomogram*	6/2	89%	55%
Tokuda	Adults	Item list including disturbed consciousness, CSF gram stain, neutrophil count and percentage. *If all items are absent low risk of meningitis*	2/2	88%	88%
De Cauwer	Children	Item list including CRP, CSF neutrophil count, CSF protein and CSF glucose concentration. *If all items are absent low risk of meningitis*	2/2	99%	40%
Schmidt	All ages, except neonates	Item list including CSF WBC, CSF protein and CSF lactate. *If all items are absent low risk of meningitis*	2/2	59%	100%

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

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 PCR 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 [2].

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, low CSF to blood glucose ratio 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, 95 had culture-proven meningitis, of which 10% had fewer than 3 white blood cells (WBC)/mm^3 in the CSF [5]. The median CSF WBC count was low (6 cells/mm^3; range 0–90 000/mm^3, interquartile range 2–15/mm^3). For culture-proven meningitis, CSF WBC counts of more than 21 cells/mm^3 had a sensitivity of 79% and a specificity of 81%. CSF glucose concentrations varied from 0 to 11 mmol/L or 0 to 198 mg/dL (median, 1.1 mmol/L or 20 mg/dL), and protein concentrations varied from 0.4 to 19.6 g/L (median, 2.7 g/L);

culture-proven meningitis was not diagnosed accurately by CSF glucose or by protein [2,5].

A retrospective study assessed the value of CSF parameters for differentiating between viral and bacterial meningitis in children beyond the neonatal age and adults [51]. 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/mm^3 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 [41,53]. 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 of >100 cells/mm^3 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/mm^3 and five 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 microorganism [2]. In culture-proven pneumococcal meningitis

5% of 153 patients have CSF WBC counts of <10 cells/mm^3, and 17% have less than 100 cells/mm^3 [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 [24]. It is commonly assumed that antibiotic treatment before hospital admission modifies CSF pleocytosis, but one retrospective study in 245 children with bacterial meningitis suggested that the CSF WBC count is not greatly different between patients who have received or have not received lengthy courses of antibiotics before lumbar puncture [57].

The CSF lactate concentration is a widely available, cheap and rapid diagnostic test [40]. 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) [58], and the other included 31 studies with 1885 patients (adults and children) [59]. These meta-analyses concluded that the diagnostic accuracy of CSF lactate is better than that of CSF WBC count. In patients who received antibiotic treatment before lumbar puncture, CSF lactate concentration had a lower sensitivity (49%) compared to those not receiving antibiotic pretreatment (98%) [59]. CSF lactate concentration is less accurate for differentiating patients with other central nervous system diseases from meningitis, such as herpes encephalitis or seizures, as the concentrations may also be raised [60,61]. Therefore, the usefulness of CSF lactate concentrations in patients pretreated with antibiotics, or those with other central nervous system diseases in the differential diagnosis, is probably limited.

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/mm^3 or over 80% polymorphonuclear cells, CSF culture was positive in 85% of patients if not pretreated with antibiotics [62]. CSF culture positivity differed per causative microorganism: 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 [57]. A retrospective study from Brazil including 3973 patients showed a lower yield of CSF cultures: CSF culture was positive in 67% of patients [63]. The yield of CSF culture decreases when a patient is treated with antibiotics before 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 before lumbar puncture [57,62].

The CSF Gram stain is a quick method to identify the cause of bacterial meningitis [40]. Furthermore, the test is cheap and

validated. CSF Gram stains have been shown to have incremental value when the CSF culture is negative, e.g. when a patient is treated with antibiotics before lumbar puncture [2]. In a retrospective study of 875 patients, the Gram stain was the only positive microbiologic finding in 4% of patients [62]. The sensitivity of the Gram stain depends on the causative microorganism. 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 [2]. 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% [64]. The yield of the Gram stain may decrease slightly if antibiotic treatment is initiated before lumbar puncture. A Danish study in 481 children showed that the yield decreased from 56% to 52% [65]. 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) [57].

Several studies have assessed the test characteristics of 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* [40]. Reported specificity was 95−100% for all microorganisms. PCR was shown to have incremental value compared to CSF culture and Gram stain [40,66,67]. A study in 409 bacterial meningitis patients from Burkina Faso showed 33% of patients were diagnosed by PCR only and could not be diagnosed by conventional methods [68]. A study from the meningococcal reference unit in the United Kingdom showed that currently 1099 (57%) of 1925 invasive meningococcal disease patients were confirmed by PCR only [69]. Similar results were shown in children with meningococcal disease in Spain, in whom 46 of 188 cases were confirmed only by PCR [70]. PCR was negative in 5% of culture-positive cases in this study. The availability of rapid CSF PCRs is variable according to country. PCR is particularly useful in patients who received intravenous antibiotic treatment before 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 microorganism: 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 colonized and has no bacteraemia, but this varies according to the test that is used [71]. Finally, 5−26% of bacterial meningitis cases in children and adults (Tables 2.2 and 2.3) are caused by bacteria other than *S. pneumoniae, N. meningitidis* and *H. influenzae* and

are therefore routinely detected by PCR. Therefore, as yet, PCR will not completely usurp CSF culture in the diagnosis of bacterial meningitis, but is a useful additional test, especially if the Gram stain is found to be negative. For suspected meningococcal disease, PCR is considered essential in the diagnosis by the European Monitoring Group on Meningococci (EMGM) [72]. Studies analysing the test characteristics of *L. monocytogenes* PCR in meningitis showed culture-positive CSF samples were positive by PCR as well [73]. However, the incremental value of PCR in *Listeria* meningitis next to culture is currently unclear.

Latex agglutination is a diagnostic method that can be used to determine rapidly the causative microorganism. The reported sensitivity of latex agglutination testing in CSF differs by the causative microorganism: for *H. influenzae* the reported sensitivity varies 78−100%, for *S. pneumoniae* 59−100% and for *N. meningitidis* 22−93% [2]. 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 antibiotics before lumbar puncture, no latex agglutination test was positive [74]. A study of 28 patients with negative CSF cultures but with clinical and CSF characteristics of bacterial meningitis showed a sensitivity of 7% of latex agglutination tests [75]. A third study showed seven positive latex agglutination tests in 478 CSF samples: in all seven the pathogen had been identified by Gram stain as well [76]. 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 [2].

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 [77]. The test was shown to be 100% sensitive and specific for the diagnosis of pneumococcal meningitis; the overall sensitivity of this test ranged 95−100%. 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 [78]. False-positive results have been reported in patients with meningitis due to other streptococcal species [79]. 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.

Serum markers of inflammation. 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 (CRP) and pro-calcitonin are highly discriminatory between paediatric bacterial and viral meningitis [54,80]. The reported sensitivity in a study of 507 children with a CRP level >40 mg/L was 93% with a specificity of 100% [80]. A meta-analysis of several small studies including 198 children showed increased serum pro-calcitonin and CRP concentrations were associated with acute bacterial meningitis [54]. A study in adults showed good sensitivity and specificity of procalcitonin in 105 patients with bacterial meningitis, viral meningitis or no meningitis [81]. 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 CRP and pro-calcitonin may be of little value for the diagnosis of bacterial meningitis.

Blood cultures. Blood cultures are valuable for detection of the causative organism and establish susceptibility patterns if CSF cultures are negative or unavailable, e.g. when lumbar puncture is contraindicated [2]. The rate of blood culture positivity is different for each causative organism and is 75% of pneumococcal meningitis patients, 50−90% for *H. influenzae* meningitis patients and 40−60% of patients with meningococcal meningitis [2]. The yield of blood cultures was shown to decrease by 20% if patients are treated with antibiotics before blood culture [57].

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 magnetic resonance imaging (MRI) or a thermogram can be useful in the diagnosis of bacterial meningitis. Few markers were replicated in independent cohorts or compared to the test characteristics of the marker to standard diagnostics tests. These studies may be valuable for pathophysiologic research but so far have not reached implementation in a clinical setting.

Conclusions

Level 2	In neonatal meningitis, CSF leukocyte count, glucose and total protein levels are frequently within normal range or only slightly elevated.
Level 2	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.

Level 2	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 pretreatment or those with other central nervous system disease in the differential diagnosis.
Level 2	CSF culture is positive in 60–90% of bacterial meningitis patients depending on the definition of bacterial meningitis. Pretreatment with antibiotics decreases the yield of CSF culture by 10–20%.
Level 2	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 lumbar puncture is performed.
Level 2	In patients with a negative CSF culture and CSF Gram stain, PCR has additive value in the identification of the pathogen.
Level 2	Latex agglutination testing has little incremental value in the diagnosis of bacterial meningitis.
Level 2	It is unclear whether immunochromatographic antigen testing has incremental value in the diagnosis of bacterial meningitis.
Level 2	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.
Level 2	In adults and children with bacterial meningitis, blood cultures are useful to isolate the causative microorganism. The yield of blood cultures decreases if the patient is pretreated with antibiotics.

Recommendation

Grade A	In patients with suspected bacterial meningitis, it is strongly recommended to determine CSF leukocyte count, protein and glucose concentration, and to perform CSF culture and Gram stain.
Grade A	In patients with negative CSF cultures, the causative microorganisms can be identified by PCR and potentially by immunochromatographic antigen testing.
Grade A	In patients with suspected bacterial meningitis, it is strongly recommended to perform blood cultures before the first dose of antibiotics is administered.

Imaging before lumbar puncture

Indications for cranial imaging before lumbar puncture. Lumbar puncture is crucial in the diagnosis of bacterial meningitis to confirm the diagnosis, identify the pathogen and determine the

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

resistance pattern to rationalize antibiotic treatment. Before the lumbar puncture is performed, the physician needs to establish whether contraindications exist. Lumbar puncture can be hazardous if brain shift is present due to space-occupying lesions [40]. 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 [40,82]. Cranial imaging, however, was shown to lead to a substantial delay in initiation of antibiotic treatment, which is associated with poor outcome [83,84]. A study in 235 adults with suspected bacterial meningitis showed that intracranial space-occupying lesions are associated with clinical characteristics [82]. Therefore, clinical examination can be used to select patients at risk for lesions causing brain shift in whom CT before lumbar puncture is warranted. On the basis of the above-mentioned study, a set of criteria have been proposed to select patients for cranial imaging [40,85]: focal neurologic deficits (excluding cranial nerve palsies), new-onset seizures, severely altered mental status (defined as a score on the Glasgow Coma Scale of <10) and severely immunocompromised state (e.g. 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 lumbar puncture–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. We found no studies addressing this question for

children 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 contraindications for lumbar puncture, not related to space-occupying intracranial lesions, are coagulation disorders, local skin infections and need for haemodynamic stabilization before further diagnostic procedures.

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

Treatment before or after lumbar puncture. The literature search yielded two prospective and six retrospective studies evaluating the effect of timing of antibiotic treatment on outcome of bacterial meningitis [83,84]. 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 before 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 upon clinical suspicion even if the diagnosis has not been established. In these patients, blood cultures must be drawn to before

initiating antibiotics to increase the chance of identifying the causative pathogen.

Conclusions

Level 2	The risk of cerebral herniation after lumbar puncture in patients with suspected bacterial meningitis is increased compared to normal individuals.

Level 3	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.

Level 2	A delay in antibiotic treatment administration is associated with poor outcome and should therefore be avoided.

Recommendation

Grade A	It is strongly recommended to perform cranial imaging before lumbar puncture in patients with: • Focal neurologic deficits (excluding cranial nerve palsies). • New-onset seizures. • Severely altered mental status (Glasgow Coma Scale score <10). • Severely immunocompromised state. In patients lacking these characteristics, cranial imaging before lumbar puncture is not recommended.

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.

TABLE 4.1. Empiric antibiotic in-hospital treatment for community-acquired bacterial meningitis [3]

Patient group	Standard treatment		Intravenous dose[a]
	Reduced *Streptococcus pneumoniae* antimicrobial sensitivity to penicillin	*S. pneumoniae* susceptible to penicillin	
Neonates <1 month old	Amoxicillin/ampicillin/penicillin plus cefotaxime, or amoxicillin/ampicillin plus an aminoglycoside		Age <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
Age 1 month to 18 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Vancomycin 10–15 mg/kg q6h to achieve serum trough concentrations of 15–20 μg/mL; rifampicin 10 mg/kg q12h up to 600 mg/day; cefotaxime 75 mg/kg q6–8h; ceftriaxone 50 mg/kg q12h (maximum 2 g q12h)
Age >18 and <50 years	Cefotaxime or ceftriaxone plus vancomycin or rifampicin	Cefotaxime or ceftriaxone	Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6 h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 μg/mL; rifampicin 300 mg q12h
Age >50 years, or Age >18 and <50 years plus risk factors for *Listeria monocytogenes*[a]	Cefotaxime or ceftriaxone plus vancomycin or rifampicin plus amoxicillin/ampicillin/penicillin G	Cefotaxime or ceftriaxone plus amoxicillin/ampicillin/ penicillin G	Ceftriaxone 2 g q12h or 4 g q24h; cefotaxime 2 g q4–6h; vancomycin 10–20 mg/kg q8–12h to achieve serum trough concentrations of 15–20 μg/mL; rifampicin 300 mg q12h, amoxicillin or ampicillin 2 g q4h

[a]Diabetes mellitus, use of immunosuppressive drugs, cancer and other conditions causing immunocompromise.

Treatment of bacterial meningitis

Key Question 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?

Antibiotic treatment

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 cefotaxime as empiric treatment instead of vancomycin or rifampicin when true resistance to third-generation cephalosporin (minimum inhibitory concentration (MIC) >2 mg/L) is not to be expected. When risk factors for an infection with *L. monocytogenes* are present in adults under the age of 50 years (e.g. diabetes, use of immunosuppressive drugs, cancer) or in adults over the age of 50 years, 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, four cases of *L. monocytogenes* occurred in adults under the age of 50 without specific risk factors (out of 259 patients aged <50 years without immunocompromised state (1.5%)) [24]. If the physician wishes to cover for this rare possibility, empiric antibiotic treatment should include amoxicillin or ampicillin for all adults with bacterial meningitis.

Specific antibiotic treatment after identification of causative microorganism. After identification of the pathogen through culture and antibiotic susceptibility testing, the antibiotic treatment can be optimized.

Streptococcus pneumoniae—Streptococcus pneumoniae is currently the most common causative microorganism 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 [3]. 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 from 2011 European Centre for Disease Prevention and Control surveillance report). 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).

TABLE 4.2. Specific antibiotic in-hospital treatment for community-acquired bacterial meningitis[a]

Microorganism	Standard treatment	Alternatives	Duration
Streptococcus pneumoniae			
Penicillin susceptible (MIC <0.1 μg/mL)	Penicillin or amoxicillin/ampicillin	Ceftriaxone, cefotaxime, chloramphenicol	10–14 days
Penicillin resistant (MIC >0.1 μg/mL), third-generation cephalosporin susceptible (MIC <2 μg/mL)	Ceftriaxone or cefotaxime	Cefepime, meropenem, moxifloxacin[b]	10–14 days
Cephalosporin resistant (MIC ≥2 μg/mL)	Vancomycin *plus* rifampicin, or vancomycin *plus* ceftriaxone or cefotaxime, or rifampicin *plus* ceftriaxone or cefotaxime[c]	Vancomycin *plus* moxifloxacin,[b] linezolid	10–14 days
Neisseria meningitidis			
Penicillin susceptible (MIC <0.1 μg/mL)	Penicillin or amoxicillin/ampicillin	Ceftriaxone, cefotaxime, chloramphenicol	7 days
Penicillin resistant (MIC ≥0.1 μg/mL)	Ceftriaxone or cefotaxime	Cefipime, meropenem, ciprofloxacin or chloramphenicol	7 days
Listeria monocytogenes	Amoxicillin or ampicillin, penicillin G[d]	trimethoprim-sulfamethoxazole, moxifloxacin,[b] meropenem, linezolid	At least 21 days
Haemophilus influenzae			
β-Lactamase negative	Amoxicillin or ampicillin	Ceftriaxone, cefotaxime or chloramphenicol	7–10 days
β-Lactamase positive	Ceftriaxone or cefotaxim	Cefepime, ciprofloxacin, chloramphenicol	7–10 days
β-Lactamase negative ampicillin resistant	Ceftriaxone or cefotaxime *plus* meropenem	Ciprofloxacin	7–10 days
Staphylococcus aureus			
Methicillin sensitive	Flucloxacillin, nafcillin, oxacillin	Vancomycin, linezolid, rifampicin,[e] fosfomycin,[e] daptomycin[b]	At least 14 days
Methicillin resistant	Vancomycin[f]	Trimethoprim/sulfamethoxazole, linezolid, rifampicin,[e] fosfomycin,[e] daptomycin	At least 14 days
Vancomycin resistant (MIC >2.0 μg/mL)	Linezolid[f]	Rifampicin,[e] fosfomycin,[e] daptomycin[b]	At least 14 days

[a]Recommendations must be in accordance with the results of the susceptibility testing.
[b]Based on case reports.
[c]Ceftriaxone dose 2 g q12h and cefotaxime 2–3g q6h.
[d]Adding an aminoglycoside can be considered.
[e]Must not be used in monotherapy.
[f]Addition of rifampicin can be considered.

Subquestion 5.1. Does the addition of vancomycin or rifampicin to a third-generation cephalosporin improve outcome in pneumococcal meningitis patients in the setting of a high resistance rate of pneumococci?

There is uncertainty regarding the benefit of adding vancomycin or rifampicin to a third-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 third-generation cephalosporins, but only animal studies were identified [86−88]. These showed that ceftriaxone combined with either vancomycin or rifampicin resulted in a higher rate of CSF sterilization after 24 hours compared to monotherapy with ceftriaxone. Another animal study showed the 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 third-generation cephalosporins based on *in vitro* susceptibility patterns [89]. The advised duration of treatment is 10−14 days [3,40,90].

Neisseria meningitidis—In the past decades, a proportional increase in meningococcal strains with reduced susceptibility to penicillin in meningococcal meningitis patients has been observed [91]. A Spanish study described that 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 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 [92].

Therefore, patients with suspected meningococcal meningitis caused by bacterial strains that on the basis of the local epidemiology are likely to be resistant to penicillin, a third-generation cephalosporin should be provided until *in vitro* susceptibility testing is performed. The advised duration of treatment is 7 days [2,3,40].

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 are 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 G [93]. 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 be cautious, however, 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 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 [2]. Vancomycin is recommended for methicillin-resistant staphylococcal meningitis. Linezolid may be chosen in cases of vancomycin resistance (MIC >2 μg/mL) or in cases of 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 therapy in staphylococcal meningitis, the guideline panel recommends at least 14 days of therapy. If staphylococci are identified as the cause of bacterial meningitis, then other sites of infections should be considered, such as endocarditis or spinal epidural abscesses, which may require surgical intervention and prolonged antibiotic therapy [94].

Culture-negative patients—In patients with CSF suggestive of bacterial meningitis in whom the CSF culture and other tests (e.g. PCR) remain negative and the pathogen is not identified from other sites (e.g. blood culture, 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.

Duration of treatment. The optimal duration of antibiotic treatment for bacterial meningitis has been studied in six randomized clinical trials in children. A meta-analysis of these trials concluded that there was insufficient evidence to advise a short course of antibiotics [95]. A large RCT 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 3 days of treatment [96]. Most of the children were resident in Malawi or Pakistan, and a large proportion had *H. influenzae* type b meningitis. Although there was equivalence in the short and long courses of antibiotics, the subgroups for each

causative microorganism were too small to prove equivalence. Because of the substantial differences in epidemiology, clinical characteristics and comorbidity 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. The advised duration of treatment is based on empiric data.

Method of administration of antibiotic treatment. Antibiotics can be administered by continuous infusion or bolus administration (e.g. every 4 hours). Use of constant intravenous infusion of antibiotics is hypothesized to have a beneficial role in treatment of bacterial meningitis. Our literature search yielded 98 articles; six articles were relevant, consisting of three animal studies, two reviews and one RCT [97]. This trial showed no significant differences between continuous and bolus administration of cefotaxime in children with bacterial meningitis. Because of 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) and use of dexamethasone, no recommendation for either continuous or bolus administration can be given at present.

Conclusions

Level 3	The empiric antibiotic treatment in bacterial meningitis patients is based on expert opinion and differentiated for demographic/epidemiologic 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, 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 C	Because of 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?

Adjunctive dexamethasone treatment

Evidence for adjunctive dexamethasone treatment. Experimental animal studies have shown that the outcome of bacterial meningitis is related to the severity of inflammation in the subarachnoid space [98]. Immunomodulation of the inflammatory response with corticosteroids has been evaluated as a treatment strategy in multiple RCTs. A 2013 Cochrane review included 25 RCTs including 4121 bacterial meningitis patients [99]. 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 neurologic sequelae, but did not reduce mortality [99]. No excess of dexamethasone-related adverse 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 a 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 [99,100]. This study did show a beneficial effect of corticosteroids, but it was small and treatment groups were not well balanced for patient age, culture positivity and causative microorganisms. 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 used dexamethasone; this is the most widely used corticosteroid for bacterial meningitis. The advised dexamethasone regimen in children is 0.15 mg/kg every 6 hours and in adults 10 mg every 6 hours, both for a duration of 4 days.

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

Timing of dexamethasone treatment. In the largest RCTs, dexamethasone was provided before or with the first dose of antibiotics in order to prevent the inflammatory response resulting from bacteriolysis by antibiotics [101,102]. Therefore, it is advised to start dexamethasone with the first dose of antibiotics [3]. 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 the timing of corticosteroid therapy [99]. 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 [98]. An individual patient data meta-analysis showed that dexamethasone reduced hearing loss, irrespective of whether the drug was given before or after antibiotics [103].

Because 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.

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

Stopping dexamethasone after pathogen identification. The Cochrane meta-analysis showed that adjunctive dexamethasone is effective in reducing hearing loss and neurologic sequelae in bacterial meningitis caused by all pathogens [99]. 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, because 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 that the use of dexamethasone is safe in meningococcal meningitis patients but that it did not significantly decrease hearing loss or death [53].

The guideline committee concludes that 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 neurologic 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. The use of dexamethasone for neonates is currently not recommended.
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 that 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 (10 mg qid for 4 days) and children (0.15 mg/kg qid for 4 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, 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?

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. antiepileptic drugs for patients presenting with seizures. The section Complications in bacterial meningitis during hospitalization provides details for such cases.

Osmotic therapies. Treatment with osmotic agents has traditionally been used in several neurologic diseases to reduce intracranial pressure. The best-studied osmotic agents in bacterial meningitis is glycerol. The literature search on glycerol in bacterial meningitis yielded 73 articles, eight of which were relevant. Five RCTs were identified, four of which were included in a 2013 Cochrane meta-analysis [104]. One RCT in adults was stopped because of a higher mortality rate in the treatment group, one RCT in children favoured glycerol and three 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 (maximum 100 mL/day or 300 mL/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. Because 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 advice on this treatment.

Paracetamol (acetaminophen). Paracetamol (acetaminophen) has been considered to improve outcome by reducing the inflammatory response and decreasing fever. Observational data in bacteraemic patients showed paracetamol use was associated with improved prognosis [105]. Our literature search identified 19 relevant articles, two of which were RCTs [97,106]. Both trials tested paracetamol in a factorial design with a second intervention. No beneficial effect was observed.

Therapeutic hypothermia. Therapeutic hypothermia is suggested to be neuroprotective and has been extensively studied in severe neurotrauma and postanoxic encephalopathy, with varying results. The literature search yielded one RCT and two observational studies. The RCT was stopped early because of

excess mortality in the hypothermia group [107]. Therefore, hypothermia is not recommended in bacterial meningitis patients.

Antiepileptic treatment. The literature search yielded 320 articles, none of which was relevant. No RCTs have been performed that evaluate the use of standard antiepileptic treatment in bacterial meningitis in the absence of seizures.

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

Intracranial pressure−based treatment. During bacterial meningitis, intracranial pressure is elevated as a result of several factors (e.g. brain swelling or hydrocephalus). Several multistep treatment strategies have been described to reduce intracranial pressure in observational studies [108−110] and have been suggested to improve outcome. However, no RCTs 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.

Other adjunctive treatments. Several other adjunctive treatments were evaluated in bacterial meningitis patients.

- Bacterial meningitis patients included in intensive care RCTs receiving activated protein C showed an increased rate of cerebral haemorrhage in the treatment group, so this treatment is therefore not recommended (and in fact is no longer available) [111].
- Intrathecal and intravenous adjuvant immunoglobulins were tested in a comparative (nonrandomized) 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 [112].

Conclusion

Level 1	The present data do not support the 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.

Prophylaxis

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

Prophylactic treatment of household contacts of meningococcal meningitis patients. The risk of meningococcal disease is increased 400−800-fold in individuals in close contact with meningococcal disease, with the highest risk for household contacts [113]. This risk may be averted by prescribing prophylactic antibiotics. Multiple studies have been performed to determine whether prophylactic antibiotics are beneficial. Our literature search yielded 258 hits, of which eight articles were relevant, including a Cochrane meta-analysis including 24 RCTs. The Cochrane analysis included 19 RCTs including 2531 participants and five cluster RCTs including 4354 participants [113]. 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 provided as a single oral dose, ceftriaxone provided as a single intramuscular dose or rifampicin provided 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 intravenous ceftriaxone do not need additional prophylaxis.

Subquestion 8.1. Is vaccination indicated after community-acquired (pneumococcal) meningitis?

Vaccination of pneumococcal meningitis patients. The risk of a recurrent episode of pneumococcal meningitis is approximately 5% [114,115]. 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 hypogammaglobulinaemia. In one fourth of patients with recurrent meningitis (1% of total cases), no risk factor for recurrent meningitis can be identified [114,115]. On the basis of 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 the vaccination of meningitis patients and recurrence of pneumococcal disease. On the basis of 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 hypogammaglobulinaemia, other existing guidelines apply.

Conclusion

Level 1	Prophylactic antibiotic treatment of household contacts of meningococcal meningitis patients 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 household contacts and other close contacts of meningococcal meningitis patients with antibiotic prophylaxis consisting of ceftriaxone, ciprofloxacin or rifampicin (see 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. Additional vaccination with *H. influenzae* type b and *N. meningitidis* vaccine can be considered in patients with CSF leakage.

TABLE 4.3. Recommended dose of prophylactic antibiotic treatment for household contacts and other close contacts of meningococcal meningitis patients

Antibiotic	Dose	Duration
Rifampicin	Child <3 months of age: 5 mg/kg twice a day orally Child ≥3 months to 12 years of age: 10 mg/kg twice a day orally (max 600 mg) Child >12 years of age: 600 mg twice a day Adult: 600 mg twice a day Pregnancy: 600 mg twice a day—only after first 3 months of pregnancy	2 days
Ciprofloxacin	Adult >16 years: 500 mg oral Pregnancy: Do not use	Once
Ceftriaxone	Child <16 years: 125 mg intramuscular Adult ≥16 years: 250 mg intramuscular Pregnancy: 250 mg intramuscular (first choice during pregnancy)	Once

Key Question 9. What complications occur during community-acquired bacterial meningitis, what ancillary investigations are warranted when complications occur and how should they be treated?

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 EEG. The frequency of complications differs between age groups and causative microorganisms. Common complications reported during neonatal meningitis are shock, convulsions and hydrocephalus (Table 4.4).

Half of the adults with bacterial meningitis develop focal neurologic deficits during their clinical course, and one third of patients develop haemodynamic or respiratory insufficiency [41]. The diagnostic workup in these patients can consist of cranial CT or MRI when intracranial abnormalities are suspected (in which MRI is preferred because of its superior resolution, but the availability and speed of CT are often greater), repeated lumbar puncture and EEG. However, the yield of repeated lumbar puncture is probably limited, and therefore routine repetition of lumbar puncture is not indicated [116]. 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.

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

TABLE 4.4. Common complications of neonatal bacterial meningitis [12,13,33]

Complication	Frequency	Ancillary investigations	Treatment
Seizures	15–34%	EEG (if not clinically evident)	Antiepileptic drugs
Hydrocephalus	5–6%	Transcranial ultrasound or cranial MRI	External ventricular drain
Sepsis	24%	Evaluation of other foci of infection (e.g. pneumonia, endocarditis)	According to guidelines for management of sepsis

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

Level 2	Neurologic and systemic complications occur in a large proportion of children and adults with bacterial meningitis. In patients with neurologic deterioration, cranial imaging (MRI or CT) is often indicated, and repeated lumbar puncture and EEG may be indicated in selected cases.

Level 3	Bacterial meningitis complicated by hydrocephalus, subdural empyema and brain abscess may require neurosurgical intervention.

Recommendations

Grade A	As neurologic 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 (Tables 4.4 and 4.5).

Follow-up care of bacterial meningitis patients

Key Question 10. What follow-up of community-acquired 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 [125]. In this review, the most common cause of meningitis was *H. influenzae* type b, followed by *S. pneumoniae* (20%) and *N. meningitidis* (16%); 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%) [125]. One in five children had multiple sequelae.

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

Hearing loss
Bacterial meningitis is the most common cause of acquired hearing loss in children [126], and hearing loss also occurs in neonates and adults after bacterial meningitis [127]. An estimated 5–35% of patients with bacterial meningitis develop sensorineural 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 [128]. Hearing loss may be present at admission or may develop during the course of the disease. 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 quickly identify hearing loss 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 audiologic expertise for further hearing evaluation using brain

TABLE 4.5. Common complications of bacterial meningitis in adults [117–123]

Complication	Frequency	Ancillary investigations	Treatment
Seizures	17%	Cranial CT or MRI; EEG if not clinically evident	Antiepileptic drugs
Hydrocephalus	3–5%	Cranial CT or MRI	External ventricular drain if clinically relevant
Ischaemic stroke	14–25%	Cranial CT or MRI	No specific treatment
Haemorrhagic stroke	3%	Cranial CT or MRI	Consider neurosurgical intervention
Subdural empyema	3%	Cranial CT or MRI	Consider neurosurgical intervention
Brain abscess	2%	Cranial CT or MRI	Consider neurosurgical intervention
Sinus thrombosis	1%	Cranial CT or MRI	No proven therapy
Severe sepsis	15%	Evaluation of other foci of infection (e.g. pneumonia, endocarditis)	According to guidelines for the management of sepsis [124] including fluid replacement, ICU admission and monitoring
Hearing loss	17–22%	Otoacoustic emission/hearing evaluation	Cochlear implant

CT, computed tomography; ICU, intensive care unit; MRI, magnetic resonance imaging.

stem—evoked response audiometry or speech tone audiometry, depending on the patient's age. In adults, speech tone audiometry has to be performed during admission. In patients with no hearing loss during the initial hospitalization, follow-up testing may be indicated, as hearing loss may become apparent 6—12 months after the meningitis episode. In patients with over 30 dB hearing loss or progressive hearing loss over time, contrast-enhanced MRI, repeated hearing evaluation and consultation with a cochlear implantation specialist are indicated.

Neuropsychologic sequelae

Neuropsychologic 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, language development and social relationships [129]. Half of the patients were followed for 30—40 days after discharge and the other half for 6—24 months after discharge; in both groups, 41% of the patients had significant deficits in cognitive development. Two other studies reported cognitive impairment at discharge in 13% of children after pneumococcal meningitis [130,131]. IQ scores are also reported to be lower in young patients after bacterial meningitis compared to controls. A full-scale IQ score of <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 [132].

In a Dutch study including 155 adult survivors of bacterial meningitis and 72 healthy controls, neuropsychologic examination revealed that 32% had cognitive defects compared to 6% in the control group. The most apparent defect was cognitive slowness [133]. A follow-up study in the same population 9 years after bacterial meningitis found that psychologic functioning and quality of life had returned to normal on a group level, but some cognitive slowness persisted on an individual level [134]. 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.

Neuropsychologic examination is not routinely indicated in bacterial meningitis patients. Patients should be informed about the nature and frequency of cognitive disorders after bacterial meningitis (difficulty with concentration, cognitive slowness, memory deficits). If cognitive defects are suspected, neuropsychologic examination should be performed and referral to a (neuro)psychologist/rehabilitation physician may be indicated. Simple neuropsychologic tests may suffice (e.g. the Montreal

Cognitive Assessment test, MoCA) for screening in experienced hands.

Conclusion

Level 2	Sequelae occur in a substantial proportion of children and adults with bacterial meningitis and most frequently consist of hearing loss, neuropsychologic 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 ear—nose—throat specialist in a medical centre performing cochlear implants.

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

Acknowledgement

Transparency declaration

Appendix.

Search strategies
1 What is the diagnostic accuracy of algorithms in the distinction between bacterial and viral meningitis?

1 exp Meningitis, Bacterial/
2 Bacterial Meningiti*.ti,ab.
3 ((bacterial or meningococcal or pneumococcal or Neisseria or meningitides or Streptococcus or

pneumoniae 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 pneumoniae 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 adrs or (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))).ti,ab.

15 13 or 14

16 12 and 15

17 (CT adj3 (cine or scan* or x?ray* or xray*)).ab,ti.

18 (CT or MDCT).ti.

19 ((electron?beam* or comput* or axial) adj3 tomography).ab,ti.

20 tomodensitometry.ab,ti.

21 exp Tomography, X-Ray Computed/

22 or/17-21

23 16 and 22

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

1 exp Meningitis/

2 meningit*.tw.

3 exp Neisseria meningitidis/

4 exp Haemophilus influenzae/

5 Streptococcus pneumoniae/

6 ("N. meningitidis" or "H. influenzae" or "S. pneumoniae").tw.

7 ("neisseria meningitidis" or "haemophilus influenzae" or "streptococcus pneumoniae").tw.

8 or/1-7

9 exp Adrenal Cortex Hormones/

10 corticosteroid*.tw,nm.

11 glucocorticoid*.tw,nm.

12 exp Steroids/

13 steroid*.tw,nm.

14 exp Dexamethasone/

15 (dexamethasone* or hydrocortisone* or prednisolone* or methylprednisolone*).tw,nm.

16 or/9-15

17 8 and 16

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

1 exp Meningitis/

2 meningit*.tw.

3 exp Neisseria meningitidis/

4 exp Haemophilus influenzae/

5 Streptococcus pneumoniae/

6 ("N. meningitidis" or "H. influenzae" or "S. pneumoniae").tw.

7 ("neisseria meningitidis" or "haemophilus influenzae" or "streptococcus pneumoniae").tw.

8 or/1-7

9 medline.tw.

10 systematic review.tw.

11 meta-analysis.pt.

12 intervention$.ti.

13 9 or 10 or 11 or 12

14 8 and 13

5 Does the use of prophylactic treatment of household contact decrease carriage or secondary cases?

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.

2 limit 1 to ed=20110101-20140301

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