Bacterial meningitis in adults: Host and pathogen factors, treatment and outcome
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Chapter 8

General discussion

Bacterial meningitis: epidemiology, pathophysiology and treatment

Introduction

Community-acquired bacterial meningitis exacts a heavy toll, even in developed countries. It is a neurological emergency and these patients require immediate evaluation and treatment. The incidence of bacterial meningitis is about 5 cases per 100,000 adults per year in developed countries and may be 10 times higher in less developed countries.\textsuperscript{1,2} The predominant causative pathogens in adults are \textit{Streptococcus pneumoniae} (pneumococcus) and \textit{Neisseria meningitidis} (meningococcus) which are responsible for about 80\% of all cases.\textsuperscript{1,2}

Epidemiology

The incidence of acute bacterial meningitis is 5–10/100,000 persons per year in high income countries, resulting in 15,000–25,000 cases in the USA annually.\textsuperscript{1,3,4} Vaccination strategies have substantially changed the epidemiology of community-acquired bacterial meningitis during the past two decades.\textsuperscript{1,3} The routine vaccination of children against \textit{Haemophilus influenzae} type B has virtually eradicated \textit{H. influenzae} meningitis in the developed world.\textsuperscript{1,6} As a consequence, \textit{S. pneumoniae} has become the most common pathogen beyond the neonatal period and bacterial meningitis has become a disease predominantly of adults. The introduction of conjugate vaccines against seven serotypes of \textit{S. pneumoniae} that are among the most prevalent in children aged 6 months to 2 years has reduced the rate of invasive pneumococcal infections in young children and in older persons.\textsuperscript{5} The integration of the meningococcal protein–polysaccharide conjugate vaccines into vaccination programs in several countries further reduced the disease burden of bacterial meningitis in high- and medium-income countries.\textsuperscript{7} \textit{S. pneumoniae} affects all ages and causes the most severe disease in the very young and the very old.\textsuperscript{8} Of the >90 pneumococcal serotypes, a few dominate as the causes of meningitis. The increase of drug-resistant strains of \textit{S. pneumoniae}, is an emerging problem worldwide. The prevalence of antibiotic-resistant strains in some parts of the US is as high as 50–70\% with important consequences for treatment.\textsuperscript{9} \textit{N. meningitidis} is mainly responsible for bacterial meningitis in young adults; it causes sporadic cases and epidemics.\textsuperscript{10} Its incidence shows a peak in winter
and early spring and varies greatly around the world. Small outbreaks typically occur in young adults living in close quarters, such as dormitories of military camps or schools. Major epidemics have occurred periodically in sub-Saharan Africa (the so-called ‘meningitis belt’), Europe, Asia and South America. During these epidemics, attack rates can reach several hundred per 100,000, with devastating consequences.

Meningococcal serogroups are determined by structural differences in the capsular polysaccharide. Serogroups A, B, C, X, Y and W-135 are most commonly associated with invasive disease worldwide, with regional variation in the distribution.10 In the Netherlands, serogroup B and C account for >95% of disease.10 Serogroup A meningococci cause epidemic disease in the ‘meningitis belt’ every 5-10 years, emphasising the importance of vaccination in these parts of Africa.10 Multilocus sequence typing (MLST) has provided an additional typing method based on the sequencing of 6 meningococcal housekeeping genes.11 This unambiguous method allows for international monitoring of meningococcal epidemiology through an online database (pubmlst.org). In chapter 2, we described the relation of meningococcal clonal complex with clinical characteristics. Meningococcal meningitis caused by meningococci belonging to cc11 was associated with sepsis and poor outcome. Clonal complex 11 was strongly associated with serogroup C and since our study, the implementation of serogroup C vaccination in the Netherlands has all but eradicated serogroup C disease. As serogroup B disease also reduced, the share of meningococcal meningitis in all adult bacterial meningitis has decreased from 37% (1998-2002) to 14% (2006-2009).10

The group B streptococcus (S. agalactiae) is a pathogen of neonates and often causes a devastating sepsis and meningitis.1,12 It colonizes the maternal birth canal, and is transmitted to the child during delivery. The colonized newborn can develop group B streptococcal disease of early onset (developing at less than 7 days of age; median 1 day) or late onset (developing later than 7 days of age). Listeria monocytogenes causes meningitis preferentially in neonates, in adults with alcoholism, immunosupression, or iron overload, pregnant women or the elderly.13 There is often an encephalitic component to presentation, with early mental status alterations, neurologic deficits and seizures. In countries with routine vaccination against H. influenzae type B it has become a rare disease.6 In large parts of the world H. influenzae type b remains a major cause of paediatric meningitis, with high rates of mortality and hearing loss.1
Bacterial meningitis also occurs in hospitalized patients (“physician associated meningitis” or “nosocomial meningitis”). In a large city hospital, almost 40% of cases may be nosocomial. Most cases occur in patients undergoing neurosurgical procedures, including implanting of neurosurgical devices, and in patients with focal infections of the head. Furthermore, patients with cerebrospinal fluid shunts are at continuous risk of developing drain associated meningitis. The organisms causing nosocomial meningitis differ markedly from those causing community-acquired meningitis and include Gram-negative rods (e.g. *Escherichia coli*, *Klebsiella spp.*, *Pseudomonas aeruginosa*, *Acinetobacter spp.*, *Enterobacter spp.*), staphylococci and streptococci other than *S. pneumoniae*. Since the early antibiotic era, the emergence of antimicrobial resistance has been a continuing problem. Pneumococcal resistance to penicillin, due to changes in its penicillin binding proteins, started to appear in the 1960s and has since developed worldwide, often necessitating initial therapy with a combination of a third-generation cephalosporin with vancomycin, instead of monotherapy with penicillin.

**Genetics**

Host genetic factors are major determinants of susceptibility to infectious diseases. A cause of these differences in susceptibility are single base-pair variations, also known as single-nucleotide polymorphisms (SNPs), in genes controlling the host response to microbes. Patients with recurrent or familial meningitis or sepsis due to *S. pneumoniae* or *N. meningitidis* are often found to have rare mutations that cause a substantial increase in susceptibility to infection. These mutations are mostly founding genes coding for the complement system or Toll like receptor (TLR) pathways. In the general population identified alterations include SNPs in the complement system, cytokines and TLRs. A genome wide association study has shown complement factor H SNPs decrease the risk of meningococcal disease. In patients with sepsis due to *N. meningitidis*, SNPs in cytokine and fibrinolysis genes have been reported to influence mortality. In bacterial meningitis research on genetic factors is lacking but may provide important pathophysiological insights. Bacterial meningitis is a complex
disorder in which injury is caused, in part, by the causative organism and, in part, by the host’s own inflammatory response. Recognition of particular subgroups of patients with a genetic predisposition to more severe illness may help to individualize treatment and improve prognosis.

We performed a nationwide genetic association study in adults with bacterial meningitis on common variants in the complement system and selected all SNPs with a minor allele frequency of more than 5% in genes coding for complement components (C1QA, C1QB, C1QC, C2, C3, C5, C6, C7, C8B, C9, CFD, CFH, CFI, and CFP) for which a commercial genotyping assay was available. We identified rs17611 in complement component 5 (C5; GG genotype) to be associated with unfavorable outcome in patients of mixed European descent with pneumococcal meningitis (OR, 2.25; 95% CI, 1.33–3.81; p=0.002). chapter 7

**Pathophysiology and pathology**

Specific bacterial virulence factors for meningeal pathogens include specialized surface components that are crucial for adherence to the nasopharyngeal epithelium, the evasion of local host defense mechanisms and subsequent invasion of the bloodstream. In pneumococcal disease, presence of the polymeric immunoglobulin A receptor on human mucosa, which binds to a major pneumococcal adhesin, CbpA, correlates with the ability of pneumococci to invade the mucosal barrier. Viral infection of the respiratory tract may also promote invasive disease. From the nasopharyngeal surface, encapsulated organisms cross the epithelial cell layer and invade the small subepithelial blood vessels.

Binding of bacteria to upregulated receptors (e.g., platelet activating-factor receptors) promotes migration through the respiratory epithelium and vascular endothelium, resulting in blood stream invasion.

In the bloodstream, bacteria must survive host defenses, including circulating antibodies, complement-mediated bactericidal mechanisms and neutrophil phagocytosis. Encapsulation is a shared feature of the principal meningeal pathogens. To survive the various host conditions they encounter during infection, pneumococci undergo spontaneous and reversible phase variation, which involves changes in the amount of important surface components. The capsule is instrumental in inhibiting neutrophil phagocytosis and
complement-mediated bactericidal activity. Several defense mechanisms counteract the antiphagocytic activity of the bacterial capsule. Activation of the alternative complement pathway results in cleavage of C3 with subsequent deposition of C3b on the bacterial surface, thereby facilitating opsonization, phagocytosis and intravascular clearance of the organism. Impairment of the alternative complement pathway occurs in patients with sickle-cell disease and those who have undergone splenectomy, and these groups of patients are predisposed to the development of pneumococcal meningitis. Functional deficiencies of several components involved in the activation and function of complement-mediated defences have been identified (i.e., mannose-binding lectin, properdin, terminal complement components), which increase the susceptibility for invasive meningococcal infections. In our studies following the discovery of the role of the rs17611-SNP in pneumococcal meningitis, the anaphylatoxin C5a was identified as a crucial complement product in pneumococcal meningitis. Neutralization experiments showed that adjunctive treatment with C5-Ab improved outcome in mice with pneumococcal meningitis.

The blood–brain barrier is formed by cerebromicrovascular endothelial cells, which restrict blood-borne pathogen invasion. Cerebral capillaries, as opposed to other systemic capillaries, have adjacent endothelial cells fused together by tight junctions that prevent intercellular transport. Bacteria are thought to invade the subarachnoid space via transcytosis. Nonhaematogenous invasion of the CSF by bacteria occurs in situations of compromised integrity of the barriers surrounding the brain. Direct communication between the subarachnoid space and the skin or mucosal surfaces as a result of malformation or trauma gives rise to meningeal infection. Bacteria can also reach the CSF as a complication of neurosurgery or spinal anesthesia.

Physiologically, concentrations of leucocytes, antibodies, and complement components in the subarachnoid space are low, which facilitates rapid multiplication of bacteria. In the CSF pneumococcal cell-wall products, pneumolysin, and bacterial DNA induce a severe inflammatory response via binding to Toll-like receptor-2 (TLR). Once engaged, this signaling receptor transmits the activating signal into the cell, which initiates the induction of inflammatory cytokines. In *N. meningitidis*, lipopolysaccharide (LPS) is a major component of the outer membrane. LPS is sensed by mammalian cells through Toll-like receptor 4 (TLR4), in combination with coreceptors MD-2 and
CD14. The host responds to bacterial endotoxin with proinflammatory gene expression and activation of coagulation pathways in sepsis and meningitis.\textsuperscript{10} The discovery of meningococcal \textit{lpxL1} mutants and the associated reduced induction of pro-inflammatory cytokines prompted our investigation of the clinical phenotype caused by meningococcal \textit{lpxL1} mutants in adults with meningococcal meningitis.\textsuperscript{3} Infection with \textit{lpxL1}-mutant meningococcal strains is associated with less systemic inflammation and reduced activation of the coagulant system, reflected in less fever, higher serum platelet counts, and lower numbers with rash.

The subarachnoid inflammatory response is accompanied by production of multiple mediators in the CNS. Tumour necrosis factor \( \alpha \) (TNF\( \alpha \)), interleukin 1\( \beta \), and interleukin 6 are regarded as the major early response cytokines that trigger the inflammatory cascade, which induces various pathophysiological alterations implicated in pneumococcal meningitis (Figure 1).\textsuperscript{20} TNF\( \alpha \) and interleukin 1\( \beta \) stimulate the expression of chemokines and adhesion molecules, which play an important part in the influx of leucocytes from the circulation to the CSF. Upon stimulation with bacterial components, macrophages and granulocytes release a broad range of potentially tissue-destructive agents, which contribute to vasospasm and vasculitis, including oxidants (\textit{e.g.}, peroxynitrite) and proteolytic enzymes such as matrix metalloproteinases (MMP). Matrix metalloproteinases (MMP), zinc-dependent enzymes produced as part of the immune response to bacteria that degrade extracellular matrix proteins, also contribute to the increased permeability of the blood–brain barrier.
Figure 1. Multiple complications in a patient with pneumococcal meningitis

(A) T2-proton-density-weighted MRI of the brain shows a transverse view of a hyperintense signal (arrows) in the globus pallidus, putamen and thalamus that indicates bilateral edema. (B) A postmortem view of the brain of the same patient shows yellowish-colored meninges as a result of extensive inflammation. (C) Confirmation of the bilateral infarction of globus pallidus, putamen and thalamus (arrows). The microscopic substrate in the same patient shows a meningeal artery with (D) lymphocytic infiltration in and around the vessel wall, (E) extensive subpial necrotizing cortical inflammation, and (F) edema in the white matter.
A major contributor to increased intracranial pressure in bacterial meningitis is the development of cerebral oedema, which may be vasogenic, cytotoxic or interstitial in origin. Vasogenic cerebral oedema is a consequence of increased blood–brain barrier permeability.26 Cytotoxic edema results from an increase in intracellular water following alterations of the cell membrane and loss of cellular homeostasis. Cytotoxic mechanisms include ischemia and the effect of excitatory amino acids. Secretion of antidiuretic hormone also contributes to cytotoxic oedema by making the extracellular fluid hypotonic and increasing the permeability of the brain to water. Interstitial oedema occurs by an increase in CSF volume, either through increased CSF production via increased blood flow in the choroid plexus, or decreased resorption secondary to increased CSF outflow resistance.

The exact mechanisms that lead to permanent brain injury are incompletely understood. Cerebral ischemic necrosis probably contributes to damage to the cerebral cortex (Figure 1). Cerebrovascular complications occur in 15–20% of patients with bacterial meningitis.2 Other abnormalities include subdural effusion or empyema, septic sinus thrombosis, subarachnoid hematomas, compression of intracranial structures due to intracranial hypertension, and herniation of the temporal lobes or cerebellum. Gross changes, such as pressure coning, are rare.27

There is diffuse acute inflammation of the pia-arachnoid, with migration of neutrophil leucocytes and exudation of fibrin into the CSF. Pus accumulates over the surface of the brain, especially around its base and the emerging cranial nerves, and around the spinal cord. The meningeal vessels are dilated and congested and may be surrounded by pus (Figure 1). Pus and fibrin are found in the ventricles and there is ventriculitis, with loss of ependymal lining and subependymal gliosis. Infection may block CSF circulation, causing obstructive hydrocephalus or spinal block. In many cases death may be attributable to related septicaemia, although bilateral adrenal haemorrhage (Waterhouse–Friederichsen syndrome) may well be a terminal phenomenon rather than a cause of fatal adrenal insufficiency as was once imagined. Patients with meningococcal septicaemia may develop acute pulmonary oedema.
Clinical presentation

Community-acquired bacterial meningitis

Early diagnosis and rapid initiation of appropriate therapy are vital in the treatment of patients with bacterial meningitis. A recent study provided a systematic assessment of the sequence and development of early symptoms in children and adolescents with meningococcal disease (encompassing the spectrum of disease from sepsis to meningitis) before admission to the hospital. Classic symptoms of rash, meningismus, and impaired consciousness develop late in the pre-hospital illness, if at all. Early signs before admission in adolescents with meningococcal disease were leg pain and cold hands and feet.

Bacterial meningitis is often considered but may be difficult to recognize. The clinical presentation of a patient with bacterial meningitis may vary depending on age, underlying conditions and severity of illness. Clinical findings of meningitis in young children are often minimal and in childhood bacterial meningitis and in elderly patients’ classical symptoms such as headache, fever, nuchal rigidity and altered mental status may be less common than in younger and middle-aged adults. Infants may become irritable or lethargic, stop feeding, and are found to have a bulging fontanel, separation of the cranial sutures, meningism, and opisthotonos, and they may develop convulsions. These findings are uncommon in neonates, who sometimes present with respiratory distress, diarrhoea, or jaundice. In a prospective study on adults with bacterial meningitis, the classic triad of signs and symptoms consisting of fever, nuchal rigidity and altered mental status was present in only 44% of the patients. Certain clinical features may predict the bacterial cause of meningitis. Predisposing conditions like ear or sinus infections, pneumonia, immunocompromise, and dural fistulae are estimated to be present in 68-92% of adults with pneumococcal meningitis. Rashes occur more frequently in patients with meningococcal meningitis, with reported sensitivities of 63–80% and with specificities of 83–92%.

Post-traumatic bacterial meningitis

This is often indistinguishable clinically from spontaneous meningitis. However, in obtunded or unconscious patients who have suffered a recent or previous head injury, few clinical signs may be present. A fever and deterioration
in the level of consciousness or loss of vital functions may be the only signs of meningitis. Finding a CSF leak adds support to the possibility of meningitis in such patients, but this is undetectable in most cases. The range of bacteria causing meningitis in these patients is broad and consideration should be given to broad spectrum antibiotics including metronidazole for anaerobic pathogens.

*Infections of CSF shunts*

Patients may present with clinical features typical of spontaneous meningitis, especially if virulent organisms are involved. The more usual presentation is insidious, with features of shunt blockage such as headache, vomiting, fever, and a decreasing level of consciousness. Fever is a helpful sign, but is not a constant feature and may be present in as few as 20 per cent of cases. Shunts can be infected without causing meningitis, in which event the features of the infection will be determined by where the shunt drains. Infection of shunts draining into the venous system produces a disease similar to chronic right-sided infective endocarditis together with glomerulonephritis (shunt nephritis), while infection of shunts draining into the peritoneal cavity produces peritonitis.

**Management**

Given the high mortality of acute bacterial meningitis, starting treatment and completing the diagnostic process should be carried out simultaneously in most cases (Figure 2). The first step is to evaluate vital functions, obtain two sets of blood cultures, and blood tests which typically should not take more than one or two minutes. At the same time, the severity of the patient’s condition and the level of suspicion for the presence of bacterial meningitis should be determined.

Recommendations for cranial CT and fears of herniation are based on the observed clinical deterioration of a few patients in the several to many hours after lumbar puncture and the perceived temporal relationship of lumbar puncture and herniation, but proving a cause and effect association is very difficult based on the available data. Therefore, it is reasonable to proceed with lumbar puncture without a CT scan if the patient does not meet any of the
following: patients who have new-onset seizures (suggestive of focal brain lesions), an immunocompromised state, signs suspicious for space-occupying lesions (papilledema or focal neurological signs - not including cranial nerve palsy), or moderate-to-severe impairment of consciousness (score on the Glasgow Coma Scale below 11).\textsuperscript{2, 27} Other contraindications to lumbar puncture include local skin sepsis at the site of puncture, a clinically instable patient, and any clinical suspicion of spinal cord compression. Lumbar puncture may also be harmful in patients with coagulopathy, because of the chance of needle-induced subarachnoid hemorrhage or of the development of spinal subdural and epidural hematomas. Contraindications for (immediate) lumbar puncture are provided in Table 1.\textsuperscript{2} In patients with suspected bacterial meningitis who receive a CT scan before lumbar puncture, initial therapy consisting of adjunctive dexamethasone (10 mg iv) and empirical antimicrobial therapy (Figure 2, Table 1) should always be started without delay, even before sending the patient to the CT scanner. Several studies have reported a strong increase in mortality due to a delay in treatment caused by cranial imaging.\textsuperscript{33} In chapter 2 we described adults with meningococcal meningitis and neuroimaging preceded lumbar puncture in 85 of 92 (92%) patients; antibiotics were administered before CT in only 15 of 88 (17%) of these patients. Therefore, 83\% of these patients suffered a delay of administration of adequate therapy.

Table 1. Contra-indications for immediate lumbar puncture

<table>
<thead>
<tr>
<th>Signs suspect for space occupying lesion:</th>
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<tr>
<td>• Papilledema</td>
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<tr>
<td>• Focal neurologic signs (excluding isolated cranial nerve palsies)</td>
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<tr>
<td>Score on Glasgow Coma Scale &lt;10</td>
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<tr>
<td>Severe immunodeficiency (such as HIV)</td>
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<tr>
<td>New onset seizures</td>
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<tr>
<td>Skin infection puncture site</td>
</tr>
<tr>
<td>Coagulopathy, e.g. use of anticoagulant medication or clinical signs of diffuse intravascular coagulation</td>
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<tr>
<td>Septic shock</td>
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Figure 2. Algorithm for the management of the patient with suspected community-bacterial meningitis
Laboratory diagnosis

When CSF analysis shows increased white blood cell counts, confirming a diagnosis of meningitis, it is important to discriminate between the usually harmless viral and the life-threatening bacterial meningitis. The CSF abnormalities of bacterial meningitis include raised opening pressure in almost all patients, polymorphonuclear leukocytosis, decreased glucose concentration, and increased protein concentration. In bacterial meningitis, the white blood cell count is typically $>1000$ cells/$\mu$l, while in viral meningitis it is $<300$ cells/$\mu$l, although there is considerable overlap. The neutrophil count is higher in bacterial than in viral meningitis. More than 90% of cases present with CSF white cell counts of more than $100/\mu$l. In immunocompromised patients, CSF white blood cell counts may be lower, although acellular CSF is exceedingly rare, except in patients with tuberculous meningitis. The normal CSF glucose concentration is between 2.5 and 4.4 mmol/l which is approximately 65% of the serum glucose. In bacterial meningitis the glucose concentration is usually less than 2.5 mmol/l, or $<40\%$ of the serum glucose. The CSF protein in bacterial meningitis is usually increased $>50$ mg/dl.

The CSF Gram stain identifies the causative micro-organism in 50–90% of cases and CSF culture is positive in 80% of untreated patients, depending on the pathogen. Gram's staining of CSF permits the rapid identification of the causative organism (sensitivity, 60–90%; specificity, $>97\%$). The yield of CSF Gram staining is only marginally decreased if the patient received antibiotic treatment prior to the lumbar puncture. Latex particle agglutination tests that detect antigens of $N. meningitidis$, $S. pneumoniae$, $H. influenzae$ and $S. agalactiae$ have been tested in bacterial meningitis patients. No incremental yield of this method was observed in several cohort studies. Therefore these tests are no longer advised. In the past decade PCR has proven to provide additional yield in recognizing the causative pathogen in bacterial meningitis patients from CSF. The reported sensitivities and specificities are high for different organisms and therefore PCR can be used to detect patients in whom cultures remain negative or those who were pre-treated with antibiotics. However, CSF culture will remain the “gold standard” for diagnosis as it is obligatory to obtain the in vitro susceptibility of the causative microorganism and to rationalize treatment.
When to repeat a lumbar puncture

A repeat analysis of the cerebrospinal fluid should only be carried out in patients whose condition has not responded clinically after 48 hours of appropriate antimicrobial and adjunctive dexamethasone treatment. It is essential when pneumococcal meningitis caused by penicillin-resistant or cephalosporin-resistant strains is suspected. Gram staining and culture of the cerebrospinal fluid should be negative after 24 hours of appropriate antimicrobial therapy.

Serum markers of inflammation

In the distinction between viral and bacterial meningitis, serum inflammatory markers may suggest the diagnosis. Retrospective studies showed that increased serum procalcitonin levels (>0.5 ng/ml) and C-reactive protein levels (>20 mg/liter) were associated with bacterial meningitis. Although elevated concentrations can be suggestive of bacterial infection, they do not establish the diagnosis of bacterial meningitis.

Blood Culture

Blood cultures are valuable to detect the causative organism and establish susceptibility patterns if CSF cultures are negative or unavailable. Blood culture positivity differs for each causative organism and varies between 50 and 90%. The yield of blood cultures is decreased by 20% for patients who received pretreatment with antibiotics.

Skin biopsy

Microbiological examination of skin lesions is routine diagnostic work-up in patients with suspected meningococcal infection. It differentiates well between meningitis with and without haemodynamic complications, and the result is not affected by previous antibiotic treatment.

Antimicrobial therapy

The choice of initial antimicrobial therapy is based on the most common bacteria causing the disease according to the patient’s age, the clinical setting
and on patterns of antimicrobial susceptibility (Table 2). Once the pathogen has been isolated, specific treatment based on the susceptibility of the isolate can replace the empirical regimen (Table 3).

The pharmacokinetics and dynamics of antimicrobial agents are important drug characteristics to base the empirical regimen on. Penetration of the BBB into the subarachnoid space is the first pharmacological factor that determines whether an antimicrobial agent is able to clear bacteria from the CSF. BBB penetration is affected by lipophility, molecular weight and structure, and protein-bound fraction. Bacterial meningitis is a dynamic process and CSF penetration of antimicrobials is highly dependent on the breakdown of the BBB. Anti-inflammatory drugs such as dexamethasone might influence the breakdown of the BBB and thereby interfere with CSF penetration of antimicrobial agents.

The activity of antimicrobial drugs in infected purulent CSF depends on a number of factors, such as activity in the environment of decreased pH, protein-bound fraction, bacterial growth rate and density, and clearance in the CSF. Mechanisms of antibiotic action are targeting of the bacterial cell wall, targeting of the bacterial cell membrane or targeting biosynthetic processes. Whereas bacteriostatic activity involves inhibition of growth of microorganisms, bactericidal antimicrobials cause bacterial cell death. Antibiotic-induced lysis of bacteria leads to the release of immunostimulatory cell-wall components and toxic bacterial products, which induce a severe inflammatory response that mainly occurs through binding to Toll-like receptors and the complement system.

Neonatal meningitis is largely caused by group B streptococci, E. coli, and L. monocytogenes. Initial treatment, therefore, should consist of penicillin or ampicillin plus a third-generation cephalosporin, preferably cefotaxime or ceftriaxone, or penicillin or ampicillin and an aminoglycoside.1,26,39

In the community, children are at risk of meningitis caused by N. meningitidis and S. pneumoniae, and, rarely in Hib-vaccinated children, H. influenzae. Antimicrobial resistance has emerged among the three major bacterial pathogens causing meningitis. Although intermediate penicillin resistance is common in some countries, the clinical importance of penicillin resistance in the meningococcus has yet to be established. Because of the resistance patterns of these bacteria third-generation cephalosporins cefotaxime or ceftriaxone should be used in children.1,12,26,39

Spontaneous meningitis in adults is usually caused by S. pneumoniae or N.
meningitidis. Due to the worldwide emergence of multidrug-resistant strains of S. pneumoniae, some experts recommend to add vancomycin to the initial empiric antimicrobial regimen in adult patients. Additionally, in patients aged over 50 years treatment with ampicillin should be added to the above antibiotic regimen for additional coverage of L. monocytogenes, which is more prevalent among this age group. Although no clinical data on the efficacy of rifampin in patients with pneumococcal meningitis are currently available, some experts would recommend the use of this agent in combination with a third-generation cephalosporin, with or without vancomycin, in patients with pneumococcal meningitis caused by bacterial strains that, on the basis of local epidemiology, are likely to be highly resistant to penicillin or cephalosporin. S. suis remains sensitive to the β-lactams and should be treated with penicillin, cefotaxime, or ceftriaxone. Fluoroquinolones may be an alternative.

Nosocomial post-traumatic meningitis is mainly caused by multiresistant hospital-acquired organisms such as K. pneumoniae, E. coli, Pseudomonas aeruginosa, and S. aureus. Depending on the pattern of susceptibility in a given hospital unit, ceftazidime (2 g intravenously, every 8 h), cefotaxime, ceftriaxone, or meropenem should be chosen. If P. aeruginosa infection seems likely, ceftazidime or meropenem is the preferred antibiotic. Device- and shunt-associated meningitis is caused by a wide range of organisms, including methicillin-resistant staphylococci (mostly coagulase-negative staphylococci) and multiresistant aerobic bacilli. Cases with shunts and an insidious onset are probably caused by organisms of low pathogenicity, and empirical therapy is a less urgent requirement. For postoperative meningitis the first-line empirical therapy should be cefotaxime, or ceftriaxone, or meropenem. If the patient has received broad-spectrum antibiotics recently or if P. aeruginosa is suspected, ceftazidime or meropenem should be given. Meropenem should be used if an extended-spectrum, β-lactamase organism is suspected, and flucloxacillin or vancomycin if S. aureus is likely. The infected shunt or drain will almost certainly have to be removed urgently.

Once the aetiological agent has been isolated and its susceptibilities determined, the empirical treatment should be changed, if necessary, to an agent or agents specific for the isolate (Table 4). The optimal duration of treatment has not been determined by rigorous scientific investigation; however, treatment regimens that are probably substantially in excess of the minimum necessary to achieve cure have been based on wide clinical experience.
General recommendations for empirical antibiotic treatment have included ceftriaxone administered intravenously every 12 h or intravenous cefotaxime every 4 to 6 h, and/or ampicillin at 4-h intervals, or penicillin G every 4 h. There are no randomized comparative clinical studies of the various dosing regimens. In general, 7 days of antimicrobial therapy are given for meningitis caused by *N. meningitidis* and *H. influenzae*, 10 to 14 days for *S. pneumoniae*, and at least 21 days for *L. monocytogenes*. As these guidelines are not standardized it must be emphasized that the duration of therapy may need to be individualized on the basis of the patient’s response.\(^1,26,39\)

<table>
<thead>
<tr>
<th>Predisposing factor</th>
<th>Common bacterial pathogens</th>
<th>Initial intravenous antibiotic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 month</td>
<td><em>Streptococcus agalactiae</em>, <em>Escherichia coli</em>, <em>Listeria monocytogenes</em></td>
<td>Ampicillin plus cefotaxime or an aminoglycoside</td>
</tr>
<tr>
<td>1-3 months</td>
<td><em>S. pneumoniae</em>, <em>Neisseria meningitidis</em>, <em>S. agalactiae</em>, <em>Haemophilus influenzae</em>, <em>E. coli</em>, <em>L. monocytogenes</em></td>
<td>Ampicillin plus vancomycin plus ceftriaxone or cefotaxime†</td>
</tr>
<tr>
<td>4-23 months</td>
<td><em>S. pneumoniae</em>, <em>N. meningitidis</em>, <em>S. agalactiae</em>, <em>H. influenzae</em>, <em>E. coli</em></td>
<td>Vancomycin plus ceftriaxone or cefotaxime†</td>
</tr>
<tr>
<td>2-50 years</td>
<td><em>N. meningitidis</em>, <em>S. pneumoniae</em></td>
<td>Vancomycin plus ceftriaxone or cefotaxime†</td>
</tr>
<tr>
<td>&gt;50 years</td>
<td><em>N. meningitidis</em>, <em>S. pneumoniae</em>, <em>L. monocytogenes</em>, aerobic gram-negative bacilli</td>
<td>Vancomycin plus ceftriaxone or cefotaxime plus ampicillin‡</td>
</tr>
<tr>
<td>With risk factor present¶</td>
<td><em>S. pneumoniae</em>, <em>L. monocytogenes</em>, <em>H. influenzae</em></td>
<td>Vancomycin plus ceftriaxone or cefotaxime plus ampicillin</td>
</tr>
<tr>
<td>Posttraumatic</td>
<td><em>S. pneumoniae</em>, <em>H. influenzae</em></td>
<td>Vancomycin plus ceftriaxone or cefotaxime plus ampicillin</td>
</tr>
<tr>
<td>Postneurosurgery</td>
<td>Coagulase-negative staphylococci, <em>Staphylococcus aureus</em>, aerobic gram-negative bacilli (including <em>Pseudomonas aeruginosa</em>)</td>
<td>Vancomycin plus ceftazidime</td>
</tr>
<tr>
<td>CSF shunt</td>
<td>Coagulase-negative staphylococci, <em>S. aureus</em>, aerobic gram-negative bacilli (including <em>Pseudomonas aeruginosa</em>), <em>Propionibacterium acnes</em></td>
<td>Vancomycin plus ceftazidime</td>
</tr>
</tbody>
</table>

†Footnote: †In areas with very low penicillin-resistance rates (as in such as the Netherlands) monotherapy penicillin may be considered. ‡In areas with very low penicillin-resistance and cephalosporin-resistance rates (as in such as the Netherlands) combination therapy of amoxicillin and third-generation cephalosporin may be considered. ¶Alcoholism, altered immune status. General recommendations for intravenous empirical antibiotic treatment have included penicillin, 2 million units every 4 hours; amoxicillin or ampicillin, 2 g every 4 hours; vancomycin, 15 mg/kg every 6-8 hours; third-generation cephalosporin: ceftriaxone, 2 g every 12 hours, or cefotaxime, 2 g every 4-6 hours; ceftazidime, 2 g every 8 hours. This material was published previously by 2 articles by van de Beek et al as part of an online supplementary appendix to reference 1 and 24. Copyright 2006 and 2010 Massachusetts Medical Society. All rights reserved.
Table 3. Recommendations for specific antimicrobial therapy in suspected bacterial meningitis

<table>
<thead>
<tr>
<th>Micro-organism</th>
<th>Antimicrobial therapy</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. influenzae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-lactamase negative</td>
<td>Amoxicilline</td>
<td>7 days</td>
</tr>
<tr>
<td>β-lactamase positive</td>
<td>Ceftriaxone or cefotaxime</td>
<td>7 days</td>
</tr>
<tr>
<td><em>N. meningitidis</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin MIC &lt;0.1 μg/ml</td>
<td>Penicillin G or amoxicilline</td>
<td>7 days</td>
</tr>
<tr>
<td>Penicillin MIC 0.1–1.0 μg/ml</td>
<td>Ceftriaxone or cefotaxime</td>
<td>7 days</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin MIC &lt;0.1 μg/ml</td>
<td>Penicillin G or amoxicilline</td>
<td>10-14 days</td>
</tr>
<tr>
<td>Penicillin MIC 0.1–1.0 μg/ml</td>
<td>Ceftriaxone or cefotaxime</td>
<td>10-14 days</td>
</tr>
<tr>
<td>Penicillin MIC &gt;2.0 μg/ml or cefotaxime / ceftriaxone MIC &gt;1.0 mg/ml</td>
<td>Vancomycin plus ceftriaxone or cefotaxime</td>
<td>10-14 days</td>
</tr>
<tr>
<td><em>L. monocytogenes</em></td>
<td>Penicillin G or amoxicilline</td>
<td>&gt;21 days</td>
</tr>
<tr>
<td><em>S. agalactiae</em></td>
<td>Penicillin G or amoxicilline</td>
<td>7 days</td>
</tr>
</tbody>
</table>

Adjunctive dexamethasone treatment

Animal models of bacterial meningitis showed that bacterial lysis, induced by antibiotic therapy, leads to inflammation in the subarachnoid space. The severity of this inflammatory response is associated with outcome and can be attenuated by treatment with steroids.⁴⁰ On basis of experimental meningitis studies, several clinical trials have been undertaken to determine the effects of adjunctive steroids in children and adults with bacterial meningitis.⁴¹, ⁴² Of several corticosteroids, the use of dexamethasone in bacterial meningitis has been investigated most extensively. Dexamethasone is a glucocorticosteroid with anti-inflammatory as well as immunosuppressive properties and has excellent penetration in the CSF. In a meta-analysis of randomized trials since 1988, adjunctive dexamethasone was shown to reduce meningitis-associated hearing loss in children with meningitis due to *H. influenzae* type B.⁴³ As most available studies on adjunctive dexamethasone therapy in adults with bacterial meningitis were limited by methodological flaws, its value in adults remained a subject of debate for a long time. In 2002, results of a European randomized placebo-controlled trial showed that adjunctive treatment with dexamethasone, given before or with the first dose of antimicrobial therapy, was associated with a reduction in the risk of unfavorable outcome in adults with bacterial meningitis (relative risk [RR] 0.59; 95 per cent confidence interval [CI] 0.37-0.94) and with a reduction in mortality (RR 0.48; CI 0.24-0.96).⁴⁴ This
beneficial effect was most apparent in patients with pneumococcal meningitis, in whom mortality was decreased from 34 to 14%. The benefits of adjunctive dexamethasone therapy were not undermined by an increase of severe neurological disability in patients who survived or by any corticosteroid-induced complication. In a post-hoc analysis, which included only patients with pneumococcal meningitis who died within 14 days after admission, the mortality benefit of dexamethasone therapy was entirely due to reduced mortality from systemic causes such as septic shock, pneumonia or acute respiratory distress syndrome; there was no significant reduction in mortality due to neurological causes.⁴⁵

Results of a subsequent quantitative review on this topic in adults, which included five clinical trials, confirmed that treatment with corticosteroids was associated with a significant reduction in mortality (RR 0.6; CI 0.4-0.8) and in neurological sequelae (RR 0.6; CI 0.4-1). The reduction in case fatality in patients with pneumococcal meningitis was 21% (RR 0.5; CI 0.3-0.8).⁴⁶ In meningococcal meningitis, in which the number of events was smaller, there were favorable point estimates for preventing mortality (RR 0.9; CI 0.3-2.1) and neurological sequelae (RR 0.5; CI 0.1-1.7), but these effects did not reach statistical significance. Adverse events were equally divided between the treatment and placebo groups. Treatment with adjunctive dexamethasone did not worsen long-term cognitive outcome in adults after bacterial meningitis.⁴⁷ Since the publication of these results, adjunctive dexamethasone has become routine therapy in most adults with suspected bacterial meningitis.³¹

Randomized studies in adults with bacterial meningitis from Malawi and Vietnam have been published.⁴⁸,⁴⁹ In the Malawi study dexamethasone was not associated with any significant benefit,⁴⁹ whilst in Vietnam a significant benefit in mortality (RR 0.43, CI 0.2–0.94) was seen in patients with confirmed bacterial meningitis only.⁴⁸ A recent meta-analysis of individual patient data of 5 recent randomized controlled trials showed no effect of adjunctive dexamethasone in meningitis.⁵⁰ Guidelines recommend routine use of adjunctive dexamethasone in adults with pneumococcal meningitis in high-income countries.² ³⁹ Dexamethasone therapy has been implemented on a large scale as adjunctive treatment of adults with pneumococcal meningitis in the Netherlands.³¹ The prognosis of pneumococcal meningitis on a national level has substantially improved after the introduction of adjunctive dexamethasone therapy with a reduction in mortality from 30 to 20%.
Despite these encouraging results, the use of adjunctive dexamethasone in bacterial meningitis remains controversial in certain patients. Clearly the results from studies in children and adults from Malawi suggests that there is no benefit in patients in that setting compared with the results from Europe and Vietnam and further work is needed to determine if these differences in the efficacy of dexamethasone can be explained. Secondly, patients with septic shock and adrenal insufficiency benefit from corticosteroid therapy in physiological doses and for >4 days; however, when there is no evidence of relative adrenal insufficiency, therapy with corticosteroids may be detrimental. Results of a subsequent quantitative review on this topic that included nine studies comparing mortality rates of corticosteroid treatment in sepsis or septic shock showed a trend towards increased mortality associated with their administration.51 As controlled studies of the effects of corticosteroid therapy in a substantial number of patients with both meningitis and septic shock are not available at present, treatment with corticosteroids cannot be recommended unequivocally for such patients. Third, corticosteroids may potentiate ischemic and apoptotic injury to neurons. In animal studies of bacterial meningitis corticosteroids aggravated hippocampal neuronal apoptosis and learning deficiencies in dosages similar to those used in clinical practice. Therefore, concerns existed about the effects of steroid therapy on long-term cognitive outcome. To examine the potential harmful effect of treatment with adjunctive dexamethasone on long-term neuropsychological outcome in adults with bacterial meningitis a follow-up study of the European Dexamethasone Study was conducted.52 In 87 of 99 eligible patients, 46 (53%) of whom were treated with dexamethasone and 41 (47%) of whom received placebo, no significant differences in outcome were found between patients in the dexamethasone and placebo groups (median time between meningitis and testing was 99 months). Therefore, treatment with adjunctive dexamethasone does not worsen long-term cognitive outcome in adults after bacterial meningitis.

By reducing permeability of the BBB, steroids can impede penetration of antibiotics into the CSF, as was shown for vancomycin in animal studies,53 which can lead to treatment failures, especially in patients with meningitis due to drug-resistant pneumococci in whom antibiotic regimens often include vancomycin. However, an observational study, which included 14 adult patients admitted to the intensive care unit because of suspected pneumococcal meningitis, appropriate concentrations of vancomycin in CSF were obtained even when
concomitant steroids were used. The dose of vancomycin used in this study was 60 mg/kg/day. Although these results suggest that dexamethasone can be used without fear of impeding vancomycin penetration into the CSF of patients with pneumococcal meningitis (provided that vancomycin dosage is adequate), it is recommended that patients with bacterial meningitis due to non-susceptible strains, treated with adjunctive dexamethasone, are carefully monitored throughout treatment.

We compared 2 cohorts of adults with culture proven bacterial meningitis: patients from the Dutch Bacterial Meningitis Cohort Study (1998-2002), before routine treatment with dexamethasone, with patients enrolled in the MeninGene study (2006-2009). In adults with meningococcal meningitis, adjunctive dexamethasone did not influence rates of unfavorable outcome. However, there was a favorable trend for death and hearing loss in the meningococcal subgroup in the absence of any excess adverse events. We therefore concluded that when the patient is identified to have meningococcal meningitis there is no obvious reason to discontinue dexamethasone.

In pneumococcal meningitis, the outcome of adults with community-acquired pneumococcal meningitis on a national level has significantly improved over the last few years. We found a decline in unfavorable outcome from 50 to 39%. We used a historical cohort design to evaluate the treatment effect in pneumococcal en meningococcal meningitis. Unknown differences between treatment groups may have existed. However, we have corrected for known prognostic factors and the treatment effect was consistent with the results of the European Dexamethasone Study.

Other adjunctive therapies
Glycerol is a hyperosmolar agent that has been used in several neurological and neurosurgical disorders to decrease intracranial pressure. Although glycerol has no beneficial effect in experimental meningitis models, a small randomised clinical trial in Finland suggested that this drug might protect against sequelae in children with bacterial meningitis. A large study in children with bacterial meningitis in several South American countries showed a significant decrease in sequelae, but there were several questions about the methodology of the trial. A recent trial in Malawi in adults however showed that adjuvant glycerol was harmful and increased mortality. Therefore, there appears to no role for treatment with adjuvant glycerol in bacterial meningitis in adults. For children
the evidence is currently insufficient to justify routine glycerol treatment. The management of adults with bacterial meningitis can be complex and common complications are meningoencephalitis, systemic compromise, stroke and raised intracranial pressure (Figure 2). Various adjunctive therapies have been described to improve outcome in such patients, including anti-inflammatory agents, anticoagulant therapies, and strategies to reduce intracranial pressure (ICP). Few randomized clinical studies are available for other adjunctive therapies than corticosteroids in adults with bacterial meningitis. Recently a randomized controlled trial was published on adjuvant high dose paracetamol in children with bacterial meningitis in Luanda. The trial was performed in a 2x2 design in which simultaneously slow infusion of antibiotics was compared to bolus injection of antibiotics. No benefit on the primary endpoints were observed in any of the treatment groups.

A Dutch cohort study evaluated the effects of complications on mortality in patients with pneumococcal meningitis and compared these findings among different age-groups. In older patients (≥60 years), death was usually a result of systemic complications, whereas death in younger patients (<60 years) was predominantly due to neurological complications such as brain herniation. This observation may be explained by age-related cerebral atrophy, which allows elderly patients to tolerate brain swelling. These findings suggest that supportive treatments that aim to reduce ICP could be most beneficial in younger adults with pneumococcal meningitis. Methods available to reduce intracranial pressure range from simple (e.g., elevation of the head of the bed to 30°) to aggressive strategies (e.g., “Lund concept”). However, there is no evidence that ICP monitoring and treatment of increased ICP is beneficial in patients with bacterial meningitis.

The rationale of hyperventilation in patients with bacterial meningitis is the relation between cerebral arteriolar dilation, increased cerebral blood flow (CBF) and a subsequent rise in ICP. Hyperventilation-induced hypocapnia causes (cerebral) vasoconstriction and a reduction in CBF, resulting in lowering of ICP. This approach has been used in patients with traumatic brain injury as well; however, the enthusiasm for hyperventilation was greatly tempered after a study on prophylactic hyperventilation in patients with severe brain injury showed a worse outcome. In bacterial meningitis, patients are often hypocapneic at the time of admission suggesting that there is spontaneous hyperventilation.
In patients with traumatic brain injury, studies have shown that mannitol decreases blood viscosity and reduces the diameter of pial arterioles in a manner similar to the vasoconstriction produced by hyperventilation. Although osmotic tissue dehydration may still play some role, mannitol works primarily through its immediate rheological effect, by diluting the blood and increasing the deformability of erythrocytes, thereby decreasing blood viscosity ad increased CBF. This sudden increase in CBF causes autoregulatory vasoconstriction of cerebral arterioles, decreasing the intracerebral blood volume and lowering ICP. In bacterial meningitis, because BBB permeability has been increased, the effect of mannitol is uncertain. There is little information from clinical and experimental studies concerning the use of mannitol in bacterial meningitis. A single dose of mannitol reduced ICP for approximately 3 hours in a meningitis model. Continuous intravenous infusion of mannitol attenuated the increases of regional CBF, brain water content and ICP in a pneumococcal meningitis model.

Recurrent bacterial meningitis

Recurrent bacterial meningitis occurs in 5% of community-acquired bacterial meningitis cases, and most patients have a predisposing condition, particularly head injury and CSF leak, only occasionally impairment of humoral immunity. In patients with no apparent cause of recurrent meningitis or known history of head trauma, the high prevalence of remote head injury and CSF leakage justifies an active search for anatomical defects and CSF leakage. Detection of β-2 transferrine in nasal discharge is a sensitive and specific method to confirm a CSF leak and thin-slice CT of the skull base is best to detect small bone defects. It should be kept in mind though that the detection of a small bone defect does not prove CSF leakage. 3D-CISS MRI images may show CSF flow into the nasal cavity or paranasal sinuses and may provide additional evidence for CSF leakage. Surgical repair has a high success rate with low mortality and morbidity.
Outcome

Community-acquired bacterial meningitis in adults is a severe disease with high fatality and morbidity rates. Meningitis caused by *S. pneumoniae* has the highest case fatality rate, reported from 19 to 37%.\(^1\)\(^,\)\(^2\)\(^,\)\(^8\) Whereas neurological complications are the leading cause of death in younger patients, elderly patients die predominantly from systemic complications. Of those who survive, up to 50% develop long-term neurologic sequelae, including cognitive impairment.\(^64\) Hearing loss commonly complicates pneumococcal meningitis and is present in ~25% of patients. Serotype 23F is associated with a significant lower risk of hearing loss, as compared with the serotype 3. Otitis on presentation is a risk factor for developing hearing loss and otolaryngological evaluation in these patients should be performed on admission.\(^{\text{chapter } 6}\)

For meningococcal meningitis mortality and morbidity rates are lower, with rates up to 5 and 7 percent, respectively. The strongest risk factors for an unfavorable outcome in patients with bacterial meningitis are those indicative of systemic compromise, impaired consciousness, low cerebrospinal fluid white-cell count, and infection with *S. pneumoniae*.\(^{30}\) Recently, we have constructed and validated a simple model for predicting outcome, using six variables that are routinely available within one hour of admission.\(^{65}\) This helps to identify high-risk individuals and provides important information for patients and their relatives (Figure 3).

Recommendations for future research

Vaccination strategies have greatly reduced the incidence of meningococcal disease, and the implementation of the PCV7 pneumococcal vaccine has reduced incidence of pneumococcal meningitis in children and is beginning to show effect of herd immunity, reducing invasive pneumococcal disease in adults. The development of additional meningococcal vaccines, such as meningococcal group B vaccine, will further reduce the burden of disease in developed countries. However, access to already existing vaccines in low-income countries is currently the single most important factor for the reduction of the global burden of disease in bacterial meningitis.

The importance of national and international scientific collaboration, as
illustrated in chapters 3 and 7, is essential to the advance of clinical medicine through translational research. Translational medicine is the integration of basic and clinical sciences to improve diagnosis and treatment in patients. Sharing data internationally will contribute to developing new treatments for bacterial meningitis. As bacterial meningitis continues to cause severe disease, further research into elucidating the mechanisms of damage caused by inflammatory response will reveal new strategies for reducing morbidity and mortality in bacterial meningitis. The implementation of dexamethasone in high-income countries has been an important step in this process. Further research into clinical applicability of C5-specific monoclonal antibodies is warranted. Determining of genetic polymorphisms in individual patients may influence vaccination and treatment strategies in the future.

**Figure 3. Prediction rule for risk for unfavorable outcome in adults with bacterial meningitis**

Tachycardia was defined as a heart rate greater than 120 beats/min. Low cerebrospinal fluid (CSF) leukocyte count was defined as <1,000 cells/mm³. Result of CSF Gram’s stain: G⁻ = gram-negative cocci; No = no bacteria; Other = other bacterial species; G⁺ = gram-positive cocci.

Instruction: Locate the age of the patient on the top axis and determine how many points the patient receives. Repeat this for the remaining five axes. Sum the points for all six predictors and locate the total sum on the total point axis. Draw a line straight down to the axis labeled “% unfavorable outcome” to find the estimated probability of an unfavourable outcome for this patient.
References


