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Pathophysiology and treatment of bacterial meningitis

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***Abstract*:** Bacterial meningitis is a medical emergency requiring immediate diagnosis and immediate treatment. *Streptococcus pneumoniae* and *Neisseria meningitidis* are the most common and most aggressive pathogens of meningitis. Emerging antibiotic resistance is an upcoming challenge. Clinical and experimental studies have established a more detailed understanding of the mechanisms resulting in brain damage, sequelae and neuropsychological deficits. We summarize the current pathophysiological concept of acute bacterial meningitis and present current treatment strategies.

***Keywords*:** bacterial meningitis, meningoencephalitis, pneumococci, meningococci, dexamethasone

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Introduction

Despite modern antibiotics and improved critical care, bacterial meningitis (BM) is still an unresolved problem in clinical medicine. Although highly effective antibiotics kill bacteria efficiently, mortality rates are still up to 34% [van de Beek *et al.* 2006]. Up to 50% of the survivors suffer from long-term sequelae [Weisfelt *et al.* 2006; de Gans and van de Beek, 2002; Schuchat *et al.* 1997; Bohr *et al.* 1984]. This review focuses mostly on the typical and most common causes of community acquired bacterial meningitis such as meningococci and pneumococci.

Two landmark studies suggested an approach to improve the outcome of acute BM by decreasing inflammation using dexamethasone as an adjunctive treatment to antibiotics [de Gans and van de Beek, 2002; Odio *et al.* 1991]. In contrast to these clinical data collected in the USA or Western Europe, several studies performed in resource poor countries did not detect any positive effect. Potential reasons for this difference may include other underlying diseases, in particular AIDS [Scarborough *et al.* 2007; Molyneux *et al.* 2002], tuberculosis [Nguyen *et al.* 2007], malnutrition and the fact that patients in these studies presented to emergency rooms at more advanced stages of the disease [Scarborough and Thwaites, 2008].

Consequently, the widening gap between wealthier societies and countries with limited resources presents an equally important issue beside the scientific and medical challenges in unraveling the molecular basis of bacterial meningitis, developing new treatments and meeting new upcoming challenges such as increasing resistance of pathogens to currently used antibiotics; for example, pneumococci up to 35% [Richter *et al.* 2002; Doern *et al.* 2001; Whitney *et al.* 2000]. It is important to state that the proportion of resistant isolates is extremely dependent on geographical and other factors.

Definition of bacterial meningitis

Bacterial meningitis is an inflammation of the meninges, in particular the arachnoid and the pia mater, associated with the invasion of bacteria into the subarachnoid space, principles known for more than 100 years [Flexner, 1907]. The pathogens take advantage of the specific features of the immune system in the CNS, replicate and induce inflammation [Simberkoff *et al.* 1980]. A hallmark of bacterial meningitis is the recruitment of highly activated leukocytes into the CSF. Beside bacteria, viruses, fungi and non-infectious causes as in systemic and neoplastic disease as well as certain drugs can induce meningeal inflammation. Usually the inflammatory process is not limited to the meninges surrounding the brain but also affects the brain parenchyma (meningoencephalitis) [Swartz, 1984], the ventricles (ventriculitis) and spreads along the spinal cord [Kastenbauer *et al.* 2001].

In recent years the damage of neurons, particularly in hippocampal structures, has been identified as a potential cause of persistent neuropsychological deficits in survivors [Zysk *et al.* 1996; Nau *et al.* 1999b]. Bacterial meningitis is a medical emergency requiring immediate diagnosis and subsequent treatment.

Epidemiology

During the last 20 years, the epidemiology of bacterial meningitis has dramatically changed. *Haemophilus influenzae*, formerly a major cause of meningitis, has disappeared in developed countries and serves as a remarkable example of a successful vaccination campaign. Nowadays, pneumococci are the most important cause of bacterial meningitis in children and adults in the US as well as in Europe. The incidence of the disease varies from 1.1 to 2 in the US [Schuchat *et al.* 1997; Wenger *et al.* 1990] and in Western Europe [Berg *et al.* 1996] up to 12 in 100 000 per year in Africa [O'Dempsey *et al.* 1996]. The risk of disease is highest in individuals younger than 5 years and older than 60 years. Some predisposing factors such as a former splenectomy, malnutrition or sickle cell disease are known [Kastenbauer and Pfister, 2003; Fraser *et al.* 1973]. The use of conjugate pneumococcal vaccines has led to a significant decline in invasive pneumococcal disease, including meningitis, in those regions promoting this approach [Hsu *et al.* 2009; Whitney *et al.* 2003]. An emerging problem is the growing prevalence of pneumococci resistant to beta-lactam antibiotics [Stanek and Mufson, 1999]. Prolonged persistence of pneumococci in the cerebrospinal fluid (CSF) may result in higher mortality as well as in pronounced neurological damage in survivors [Fiore *et al.* 2000; McCullers *et al.* 2000]. These effects of living bacteria urge us to understand in detail the effects of bacterial toxins and released cell wall and surface components and their contribution to neuronal damage.

With *Haemophilus* on the decline, *Neisseria meningitides* has become the leading meningitis pathogen in developing countries, but it continues to pose a major health problem in the US and Europe. In addition to classical meningitis, meningococci frequently cause systemic disease including fulminant gram-negative sepsis and disseminated intravascular coagulopathy. WHO estimates at least 500 000 newly symptomatic infections per year worldwide, leading to at least 50 000 deaths [Stephens *et al.* 2007]. The highest incidence is observed in the sub-Sahara meningitis belt where cyclic epidemics occur at least once per decade.

Pathogenesis

Bacterial invasion

The current assumption is that high-grade bacteremia precedes meningitis and that bacteria invade from the blood stream to the central nervous system (CNS). Alternatively, direct accesses to the CNS through dural defects or local infections are potential entrance routes. In the clinical setting, such defects should be identified by CCT or MRI scans.

The anatomical site of bacterial invasion from the bloodstream remains unidentified. Experimental evidence suggests that the choroid plexus may be a site of invasion [Daum *et al.* 1978]. Meningococci are found in the choroid plexus as well as in the meninges [Pron *et al.* 1997] and pneumococci infiltrate the leptomeningeal blood vessels [Zwijnenburg *et al.* 2001; Rodriguez *et al.* 1991] in meningitis. These data suggest that several highly vascularized sites are potential entry locations. In order to cross the blood–brain or the blood–CSF barrier and to overcome sophisticated structures such as tight junctions, meningeal pathogens must carry effective molecular tools.

Streptococcal proteins such as CbpA interact with glycoconjugate receptors of phosphorylcholine with platelet activating factor (PAF) on the eukaryotic cells and promote endocytosis and crossing the blood–brain barrier [Radin *et al.* 2005; Orihuela *et al.* 2004; Ring *et al.* 1998; Cundell *et al.* 1995]. Meningococci's PilC1 adhesin interacts with CD46 and the outer membrane protein connects to vitronectin and integrins [Unkmeir *et al.* 2002; Kallstrom *et al.* 1997]. Bacteria causing meningitis in newborns, most importantly group B streptococcal (GBS) and *E. coli*, are also well equipped with adhesive proteins allowing them to invade the CNS [Maisey *et al.* 2007; Prasadarao *et al.* 1997]. Detailed knowledge of how bacteria activate and invade cells may allow to block these interactions and therefore to prevent disease progression.

Inflammatory response

Inflammatory activation of endothelial cells seems to be a prerequisite for bacterial invasion but also results in the regulation of adhesion

molecules as ICAM-1 [Freyer *et al.* 1999]. Subsequently, these molecules promote the multistep process of leukocyte invasion. Leukocytes, in particular the presence of granulocytes in the CSF, are the diagnostic hallmark of meningitis. Early inflammatory response and bacterial invasion seem to progress in parallel and products of activated leukocytes such as MMPs [Kieseier *et al.* 1999] and NO [Koedel *et al.* 1995] and others contribute to early damage of the blood–brain and blood–CSF barrier. Once bacteria have entered the subarachnoidal space, they replicate, undergo autolysis and cause further inflammation.

Several cell types seem to be involved and as mentioned endothelial cells, perivascular macrophages and mast cells may play a crucial role [Polfliet *et al.* 2001; Weber *et al.* 1997]. Heat killed bacteria and pathogen-associated molecular patterns (PAMP) of meningitis pathogens as lipoprotein (LP), lipoteichoic acid (LTA), peptidoglycan (PG), and lipopolysaccarid (LPS) cause meningitis indistinguishable from living bacteria [Hoffmann *et al.* 2007a; Ivey *et al.* 2005; Tuomanen *et al.* 1985]. Immune pattern recognition molecules as CD14 and LBP function as sensors in identifying PAMPs [Beutler, 2003]. Pneumococcal PG and LP are recognized by TLR2 [Weber *et al.* 2003; Aliprantis *et al.* 1999] whereas LPS, and interestingly the pneumococcal toxin pneumolysin, signal through TLR4 [Malley *et al.* 2003]. TLR signals are conveyed by the intracellular adapter protein MyD88 downstream to a multitude of inflammatory signaling cascades including NFkB and MAP kinases leading to a rapid inflammatory response in meningitis [Lehnardt *et al.* 2006].

Neuronal damage

Up to 50% of survivors of bacterial meningitis suffer from disabling neuropsychological deficits [van de Beek *et al.* 2002; Merkelbach *et al.* 2000]. Clinically as well as experimentally, the hippocampus seems to be the most vulnerable area of the brain [Nau *et al.* 1999a; van Wees *et al.* 1990]. Neuronal loss translates into hippocampal atrophy and has been reported on MRI scans in survivors of bacterial meningitis [Free *et al.* 1996].

The predisposition of the hippocampus for neuronal damage remains unclear. The extracellular fluid around brain cells is contiguous with the CSF and the proximity to the ventricular system allows diffusion between these compartments [Rennels *et al.* 1985] that could deliver soluble bacterial and inflammatory toxic mediators.

Neuronal damage in meningitis is clearly multifactorial, involving bacterial toxins, cytotoxic products of immune competent cells, and indirect pathology secondary to intracranial complications (Figure 1). In the case of *S. pneumoniae*, the pathogen associated with the highest frequency of neuronal damage, two major toxins have been identified, H_2O_2 and pneumolysin, a pore-forming cytolysin. In experimental meningitis induced by toxin-deficient pneumococcal mutants, neuronal damage was reduced by 50% compared to wild-type bacteria [Braun *et al.* 2002]. The proof of direct bacterial toxicity underlines the critical importance of rapid antibiotic elimination of living bacteria and their metabolism. In insufficiently treated patients or resistant bacteria toxic activity may be significantly prolonged and harm neuronal functions. Mechanistically, these toxins seem to cause programmed death of neurons and microglia by inducing rapid mitochondrial damage.

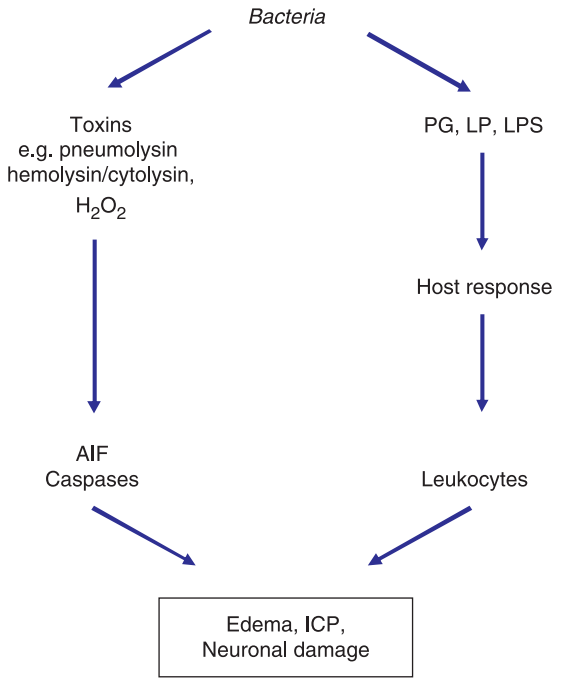

Figure 1. Two major routes involving bacterial toxins and cytotoxic products of the inflammatory response lead to intracranial complications and brain damage. Peptidoglycan (PG), bacterial lipopeptide (LP), lipopolysaccharide (LPS), apoptosis inducing factor (AIF), intracranial pressure (ICP).

In particular, pneumolysin was shown to translocate to mitochondria and induce pore formation in mitochondrial membranes [Braun *et al.* 2007; Bermpohl *et al.* 2005; Braun *et al.* 2001]. Release of apoptosis inducing factor (AIF) from damaged mitochondria leads to large-scale fragmentation of the DNA and apoptosis-like cell death. This type of cell death is executed in a caspase-independent manner. As a consequence, cells exposed to live pneumococci or pneumolysin *in vitro* cannot be rescued by caspase inhibitors [Bermpohl *et al.* 2005; Braun *et al.* 2001]. *In vivo*, however, intrathecal application of the broad spectrum caspase inhibitor, z-VAD-fmk, prevents about 50% of neuronal damage in experimental meningitis [Braun *et al.* 1999]. Further studies in caspase-3 deficient mice revealed that late but not early neuronal damage is dependent on caspase activity [Mitchell *et al.* 2004]. The interpretation of these findings is that early caspase-independent cell death may be induced by bacterial toxins while delayed, caspase-mediated apoptosis occurs as a consequence mostly of the host immune response. The *in vivo* findings can be modeled in cell culture systems, and the coexistence of different forms and time courses of cell damage has been confirmed *in vitro* [Bermpohl *et al.* 2005; Colino and Snapper, 2003].

Antibiotic treatment results in an increase of bacterial debris, including bacterial DNA and extremely powerful stimuli of the immune response such as PG and LPS [Fischer and Tomasz, 1984]. The concentration of PG in the CSF correlates with the clinical outcome of pneumococcal meningitis [Schneider *et al.* 1999], just as LPS concentrations in body compartments are linked to the severity of meningococcal disease [Brandtzaeg *et al.* 1992]. While they are extremely potent inflammatory stimuli [Hoffmann *et al.* 2007a], these bacterial cell wall components have no direct toxic effect on cultured neurons [Lehnardt *et al.* 2006, 2003]. This resistance of neurons to TLR ligands can be explained by the absence of TLR4 and TLR2 on these cells. Instead, PAMPs induce indirect neurotoxicity by activation of pattern recognition receptors (PRRs) present on microglia, as has been shown elegantly in coculture systems. Neuronal death is efficiently induced by TLR ligands in the presence of microglia, and it is strictly dependent on the presence of the exact matching TLR and an intact downstream MyD88 pathway in microglia [Lehnardt *et al.* 2006, 2003].

Taken together, bacterial components activate microglia in a TLR-dependent fashion and microglia releases cell death signals such as NO to neighboring neurons. Bacterial and host-derived reactive oxygen and nitrogen species coalesce to form highly reactive, tissue damaging intermediates [Hoffmann *et al.* 2006]. Moreover, dying parenchymal cells release TLR ligands as endogenous 'danger signals', leading to a vicious circle of inflammatory tissue damage [Lehnardt *et al.* 2008]. These mechanisms are important and clearly add to our understanding of how activated microglia can damage surrounding neurons and expand the importance of the findings beyond meningitis.

Leukocyte influx as the hallmark of acute meningitis contributes to neuronal damage and may in fact be more detrimental than beneficial to the host [Tuomanen *et al.* 1989]. Neutrophils, which form the first line of defense in bacterial meningitis, are equipped with cytotoxic and proinflammatory activity, placing these cells both as direct effectors of tissue damage and as orchestrators of further immune activation. Granulocyte depletion is neuroprotective in experimental meningitis, while persistence of granulocytes was associated with more pronounced neuronal damage [Hoffmann *et al.* 2007b]. Especially in the context of sufficient antibiotic therapy, it may therefore be desirable to limit granulocyte activity and to speed up granulocyte clearance from the CSF. The cytokine TRAIL was recently identified as a factor that reduces the life span of activated granulocytes [Renshaw *et al.* 2003]; TRAIL deficient mice displayed prolonged CSF pleocytosis and increased neurotoxicity in experimental meningitis, while therapeutic application of recombinant TRAIL reversed this effect and provided neuroprotection [Hoffmann *et al.* 2007b].

Clinical features and diagnosis

Clinical features

Early clinical features of bacterial meningitis are nonspecific and include fever, malaise and headache; and later on, meningismus (neck stiffness), photophobia, phonophobia and vomiting develop as signs of meningeal irritation [van de Beek *et al.* 2004]. Headache and meningismus indicate inflammatory activation of the trigeminal sensory nerve fibers in the meninges and can be blocked experimentally by 5-$HT_{1B/D/F}$ receptor agonists (triptans) [Hoffmann *et al.* 2002]. However the

role of triptans for headache control in patients with bacterial meningitis remains to be clarified [Lampl *et al.* 2000].

Meningismus may be absent very early in the disease, in deeply comatose patients, in children and in immunocompromised patients such as in liver cirrhosis [Cabellos *et al.* 2008]. It is important to consider that the classical triad of fever, neck stiffness and altered mental state is present in less than 50% of adults with proven bacterial meningitis [Heckenberg *et al.* 2008; van de Beek *et al.* 2004]. Approximately 33% of patients develop focal neurological signs, such as epileptic seizures or paresis of a limb, and up to 69% present with impaired consciousness or 14% with coma [van de Beek *et al.* 2004].

Inspection of the integument may reveal petechiae suggestive of meningococcal infection or Osler's nodes indicative of bacterial endocarditis. Meningitis occurs in about 7% of patients with bacterial endocarditis, often as a presenting symptom [Angstwurm *et al.* 2004; Jones *et al.* 1969]. The most frequent pathogens in this context are *S. aureus*, otherwise uncommon in bacterial meningitis, and pneumococci. Occasionally, pneumococcal meningitis, endocardits and pneumonia may be diagnosed simultaneously (Austrian's syndrome) [Dalal and Ahmad, 2008]. Meningococcal disease may present as a fulminant gram-negative sepsis with prominent cardiovascular insufficiency and disseminated intravascular coagulation, threatening ischemic tissue damage. Notably, a petechial skin rash is not unique to meningococcal disease but may also be present in septicemia caused by, amongst others, streptococci or *S. aureus*.

Laboratory tests

The key to the diagnosis of bacterial meningitis is the proof of bacteria in the CSF by Gram-staining (Figure 2) or a positive bacterial culture. Detection rates in the CSF may be as high as 90%, while about 50% positive results are observed in blood cultures. The diagnostic yield of CSF microscopy can be improved by centrifugation of a larger sample and experience. Polymerase chain reaction (PCR) may be attempted if microscopic and cultural identification of the pathogen fail but is not yet a routine test. PCR has an important role in strain identification mostly in meningococcal disease [Fox *et al.* 2007]. Latex agglutination-based rapid tests are available for major meningitis pathogens, but imperfect sensitivity and specificity argue against routine clinical use at this time [Hayden and Frenkel, 2000].

The CSF in bacterial meningitis is characterized by a strongly elevated white blood cell count (>500 cells/μl) with predominant neutrophils and a strongly elevated protein (>1 g/l), indicating severe blood–CSF barrier disruption. Increased lactate (>0.3 g/l) and decreased glucose CSF/blood ratio (<0.4) support the diagnosis of acute bacterial meningitis [Straus *et al.* 2006]. Use of urine dipsticks for semiquantitive detection of glucose and leukocyte concentrations in the CSF has been suggested for resource-limited conditions when elaborated CSF studies and microscopy are not available [Moosa *et al.* 1995].

Lower cell counts and a mixed pleocytosis are observed with *L. monocytogenes*, *M. tuberculosis* and fungi; also, they may be found in partially or insufficiently treated meningitis. Cerebral malaria, an important clinical differential diagnosis in endemic regions, is not usually associated with pronounced CSF pleocytosis. As a caveat, low-CSF white blood cell counts may confound the diagnosis in bacterial meningitis of immunocompromised, leukopenic patients or in overwhelming bacterial infection ('apurulent bacterial meningitis'), further emphasizing the importance of Gram stains.

Peripheral white blood cells, erythrocyte sedimentation rate, serum C-reactive protein,

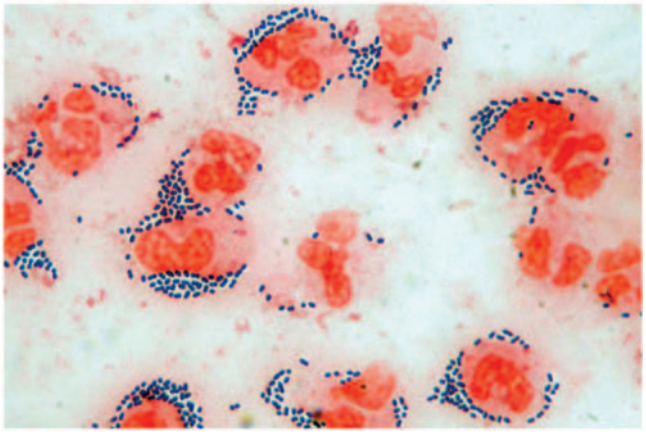

Figure 2. Diagnostic Gram stain of CSF from a patient with pneumococcal meningitis. Neutrophils (stained red) are surrounded by Gram-positive dipolcocci (stained blue).

procalcitonin [Hoffmann *et al.* 2001] and other acute phase proteins are usually elevated in bacterial meningitis but are of limited diagnostic value especially in atypical cases. Additionally, the above-mentioned typical CSF results can be different very early in the disease and in patients insufficiently treated by antibiotics.

CT

A cranial CT provides information concerning intracranial complications such as brain edema, hydrocephalus and infarcts. Moreover, bone window imaging identifies parameningeal foci such as sinusitis, mastoiditis or odontogenic abscess. Local infections are especially frequent in pneumococcal meningitis and may require surgical treatment.

There is an ongoing controversy about a cranial CT before lumbar puncture, the concern being the risk of cerebral herniation due to raised intracranial pressure. In particular, those patients who present with focal neurological deficits or seizures and those who have a disturbed consciousness should have a cranial CT before lumbar puncture. If the technique is not available treatment must be initiated based on clinical suspicion and without CSF examination. Of those patients without focal signs or seizures and with a normal level of consciousness, CT abnormalities are found in less than 3% [Joffe, 2007; Hasbun *et al.* 2001]; here, CSF can be drawn without prior CT scanning. However, a normal CT does not rule out intracranial hypertension and a residual risk of herniation [Oliver *et al.* 2003].

Treatment

Antibiotics

Immediate antibiotic therapy is imperative and must not be postponed by diagnostic delays; for example, waiting for a CT scan. Prehospital antibiotic treatment is advised in cases of suspected meningococcal disease but depends on local resistance situation and the medical environment [Sudarsanam *et al.* 2008]. Prior to treatment, a blood culture should be obtained. Since microbiological identification of the pathogen is not immediately available, the initial choice of antibiotics is usually empirical. Factors to consider include regional antibiotic resistance rates, patient age, predisposing conditions and resources (Table 1).

Microbiological identification and susceptibility testing of the causative agent are key determinants of successful antibiotic therapy. In view of emerging resistances, antibiotic chemotherapy should be adjusted according to the cultural results in order to provide highly active yet narrowly targeted coverage. However, penicillin G monotherapy for meningococci or pneumococci is advisable only after susceptibility has been confirmed. Treatment durations of 10–14 days are adequate for most pathogens; a shorter course of 5–7 days will be sufficient for uncomplicated meningococcal disease, while 3–4 weeks of treatment are recommended for *L. monocytogenes* and Enterobacteriacae. The data for treatment durations are very limited and mostly based on expert opinion [Tunkel *et al.* 2004]. Suspected or proven meningococcal meningitis requires patient isolation during the first 24 h of treatment; chemoprophylaxis is recommended for close contacts (Table 1). Cerebral imaging and repeat lumbar puncture should be considered in patients who fail to improve clinically after 48 h of treatment to assess antibiotic failure.

Corticosteroids

Corticosteroids reduce brain edema, intracranial hypertension and meningeal inflammation in experimental models of bacterial meningitis. Subsequent clinical studies have led to conflicting results concerning potential benefits of steroid use in patients with meningitis. Currently available evidence supports a reduced incidence of severe hearing loss in children with *H. influenzae* meningitis [Odio *et al.* 1991; Lebel *et al.* 1988], while information on other pediatric pathogens is incomplete. In adults, a single double-blind RCT of 301 adult patients reported reduced mortality and lower frequency of hearing loss and neuropsychological sequelae [de Gans and van de Beek, 2002]. Subgroup analysis suggested that protective effects of dexamethasone are limited to pneumococcal meningitis (death: 34% *versus* 14%; unfavorable outcome: 52% *versus* 26%) [van de Beek *et al.* 2006]. Expert opinion and several societal guidelines recommend routine treatment with dexamethasone for community-acquired meningitis of children (0.15 mg/kg every 6 hours for 2–4 days) and adults (10 mg every 6 hours for 4 days). Discontinuation of this therapy is advisable if *H. influenzae* (children) and *S. pneumoniae* (adults and children) can be ruled out as the underlying pathogen. Notably, *H. influenzae* and *S. pneumoniae* infections are declining in the pediatric population in those

Table 1. Empirical antibiotic therapy.

	Probable pathogens	Empirical therapy
Neonates	Gram-negative Enterobacteriacae (*E. coli*, Klebsiella, Enterobacter, Proteus) Group B streptococci	Cephalosporin[1] + ampicillin
Infants and children	*N. meningitides, S. pneumoniae* (*H. influenzae* [2])	Cephalosporin[1] (+ vancomycin or rifampin[3])
Adults	*S. pneumoniae, N. meningitidis, L. monocytogenes*[4], Aerobic streptococci (*H. influenzae*)	Cephalosporin[1] (+ ampicillin[4])
Nosocomial, trauma, ventriculitis, shunt infection	Staphylococci, Gram-negative, Enterobacteriacae *P. aeruginosa*	Meropenem or cephalosporin[5] + vancomycin (or rifampicin or fosfomycin or linezolid)
Immunocompromised patients	*L. monocytogenes,* Gram-negative Enterobacteriacae, *S. pneumoniae, P. aeruginosa*	Cephalosporin[1] + ampicillin (+ vancomycin[3])
Resource-limited countries	*N. meningitidis, S. pneumoniae, H. influenzae, L. monocytogenes*	Ceftriaxone[6] chloramphenicol[7], penicillin G[7], ampicillin/amoxicillin[7] rifampicin[8]
Chemo-prophylaxis of close contacts	*N. meningitidis*	Adult doses[9]: rifampicin (600 mg b.i.d., 2 days), ciprofloxacin (500 mg single dose), ceftriaxone (250 mg single dose)

[1]Cephalosporins group 3 a (e.g. ceftriaxone or cefotaxime) or group 4 (e.g. cefepime) are recommended.
[2]*H. influenzae* is unlikely if the child has been vaccinated.
[3]Cephalosporin- and penicillin-resistant pneumococci are increasingly frequent (e.g. in areas of the US, Australia, South Africa and Spain). In these regions, vancomycin or rifampicin should be included in the initial antibiotic regimen.
[4]Listeriae may occasionally cause meningitis in immunocompetent patients. Addition of ampicillin should be considered especially in patients with atypical CSF findings (mixed pleocytosis).
[5]Cephalosporins with activity against *P. aeruginosa* include (e.g. ceftazidime and cefepime).
[6]Ceftriaxone may be administered i.m. or i.v. WHO recommends a single dose for epidemic meningococcal disease. At least 5 days of treatment are recommended for uncomplicated courses of bacterial meningitis in immunocompetent patients, and longer durations in immunocompromised patients or with persistent fever, seizures or coma.
[7]Emerging resistance of *S. pneumoniae* and *H. influenzae* in certain regions.
[8]Avoid first-line use to prevent resistance of *M. tuberculosis*.
[9]Rifampicin and ciprofloxacin are not recommended in pregnancy. Recommended dose of rifampicin is 5 mg/kg for neonates and 10 mg/kg for children older than 1 month; alternatively, 125 mg ceftriaxone can be used. Ciprofloxacin should not be given below age 18.

countries promoting immunization. The first steroid dose should be administered 10–20 min before initiating antibiotic treatment, or at least concomitantly. Delayed treatment is not beneficial as dexamethasone does not reverse existing brain edema or intracranial hypertension in later stages of meningitis. Conversely, there is concern about aggravated neurotoxicity which seems to have no clinically relevance [Weisfelt *et al.* 2006; Zysk *et al.* 1996] and may impair antibiotic penetration into the CSF [Paris *et al.* 1994] as a consequence of dexamethasone treatment. Current data do not support the routine use of corticosteroids in countries with limited resources [Scarborough and Thwaites, 2008].

Other symptomatic therapy

Severe headache requires generous analgesia, often including opioids. Antiepileptic treatment is indicated if seizures occur; prophylactic treatment is not recommended.

Complications

Mortality from bacterial meningitis may reach 34% [van de Beek *et al.* 2006] and is highest with *S. pneumoniae* and *L. meningitidis*. Long-term neurological sequelae are found in up to 50% of survivors [Weisfelt *et al.* 2006; de Gans and van de Beek, 2002; Bohr *et al.* 1984; Schuchat *et al.* 1997]. Both intracranial and systemic complications contribute to this negative outcome. Complications are most likely to occur during the first few days of therapy. Sensorineural hearing loss or vestibular dysfunction are the most frequent problems. They are most frequent with *H. influenzae* and *S. pneumoniae*. As outlined above, the incidence of these complications is reduced by adjunctive dexamethasone therapy. The most threatening intracranial complications are brain edema, vascular alterations and hydrocephalus, which all contribute to increased intracranial pressure and parenchymal damage [Pfister *et al.* 1992]. Clinically, patients may display prolonged or progressive alteration of their mental state or level of consciousness. CT imaging should be performed if patients fail to improve within 48 h of antibiotic treatment or if new focal signs develop. In general, a head elevation (30°) of the bed is recommended in patients with meningitis.

Treatment options for brain edema include osmotherapy. Therapeutic hypothermia, which is effective in experimental models of bacterial meningitis [Angstwurm *et al.* 2000], has not been investigated in patients but lowering of increased body temperature seems advisable.

Hydrocephalus develops in up to 15% of patients, usually in the form of malresorption due to increased outflow resistance of the CSF. Patients with hydrocephalus and impaired consciousness should be closely monitored on follow-up CTs; eventually, they may require external ventricular drainage (EVD). EVD offers the additional benefit of ICP monitoring. The amount of drainage is determined using ICP, clinical improvement and CT follow up. With normalization of CSF protein and leukocyte concentrations, EVD usually becomes expendable; otherwise, a ventriculoperitoneal shunt should be placed.

Invasive ICP monitoring should be considered in comatose patients with generalized brain edema. Vascular complications include vasculitis, vasospasm and septic thrombosis of dural sinuses and cortical veins [Haring *et al.* 1998, 1993; Pfister *et al.* 1992], often leading to the infarction of large cerebral territories. Clinically new focal neurological deficits in the course of meningitis should lead to such diagnostic considerations. MR, CT and MR or CT angiograms are of specific diagnostic use. The risks and benefits of anticoagulation in septic sinus thrombosis are uncertain in the absence of controlled trials. Likewise, no evidence-based therapies exist for meningitis-associated vasculitis or vasospasm. Hemodilution and nimodipine may be given in analogy to subarachnoid hemorrhage, and dexamethasone has been suggested for suspected vasculitis. Extracranial complications include sepsis, disseminated coagulopathy, multiorgan failure, arthritis and electrolyte imbalance, usually due to the syndrome of inappropriate antidiuretic hormone (SIADH) secretion.

Neuropsychological deficits are frequently found in survivors of bacterial meningitis. In adults, long-lasting cognitive impairment is most prominent after pneumococcal meningitis, with lower incidence after meningococcal meningitis [van de Beek *et al.* 2002]. Short-term and working memory, executive functions, and associative learning of verbal material were specifically affected in adults 1–12 years after bacterial meningitis [Schmidt *et al.* 2006]; other authors emphasize psychomotor slowing as a primary feature [Hoogman *et al.* 2007; Merkelbach *et al.* 2000]. Children may show persistent difficulties in learning, impaired short-term memory and behavioral deficits, leading to poorer academic performance [Grimwood *et al.* 2000].

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Conflict of interest statement

None declared.

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