Chapter 36

Bacterial Meningitis

HANS-WALTER PFISTER and KAREN L. ROOS

Introduction

The earliest clinical and pathological description of meningococcal meningitis appeared in 1806 in a medical and agricultural journal. The remarkable features of the pathological process were recognized and described, including the purulent exudate between the dura and pia mater over the cerebrum and cerebellum, and the turgidity of the blood in the veins and sinuses of the brain.

The recognition of the characteristic pathological process of this infection – the production of a purulent exudate in the subarachnoid space (SAS) – resulted in the earliest form of therapy, which was the removal or "washing out" of the cerebrospinal fluid. The advent of antimicrobial therapy altered the management of this infection, focusing the therapeutic process on the eradication of the micro-organisms in the SAS. With increasing understanding of the pathopysiology of this infection, management is again directed toward altering the primary pathological process, i.e., inflammatory exudation in the SAS, and managing the complications that arise as a result.

The incidence of bacterial meningitis is estimated at five to ten cases per 100 000 persons per year. There are approximately 25 000 cases of bacterial meningitis annually in the United States, 80% of which occur in children under the age of 10. This disease is much more common in developing countries and in specific geographic areas, such as the meningitis belt of Africa, where there is an estimated incidence of 70 cases per 100 000 persons per year.

Before the advent of antimicrobial agents, bacterial meningitis was almost exclusively a fatal disease with a case fatality rate of 95–100% for pneumococcal meningitis, 90% for *Haemophilus influenzae* meningitis, and 70–90% for meningococcal meningitis. However, despite further progress in antimicrobial therapy the fatality rate of meningitis due to pneumococcus, which is the organism most often responsible for bacterial meningitis in adults, has remained unchanged (20–30%) during the past

Section Editor: Thomas P. Bleck

W. Hacke et al. (eds.), *Neurocritical Care*

several decades. The incidence of neurological sequelae, including sensorineural hearing loss, focal neurological deficits, and seizure disorders, remains high. The chance to improve the outcome of bacterial meningitis lies in a better management of the complications arising during the acute phase of the disease.

Definition

The diagnosis of bacterial meningitis is based on the presence of symptoms and signs of meningitis and detection of the bacterial micro-organisms in the cerebrospinal fluid (CSF). The symptoms of bacterial meningitis are stiff neck, headache, fever, photophobia, vomiting, and lethargy or an altered level of consciousness. The classic sign of meningeal irritation is nuchal rigidity. The neck resists flexion but can be passively rotated from side to side. There may be a history of a recent upper respiratory tract infection or an acute or chronic otitis media. Focal or generalized seizures, signs of increased intracranial pressure, and cranial nerve palsies are also common at the time of presentation. The laboratory diagnosis of bacterial meningitis is made by at least one or both of the following: (a) detection of the bacterial microorganism in the CSF by microscopic examination of a Gram-stained smear, culture for bacterial pathogens, or detection of bacterial antigen using the latex agglutination method; or (b) CSF pleocytosis >1000 white blood cells per microliter with >60% polymorphonuclear leukocytes, a low CSF glucose concentration, and exclusion of other causes of meningitis.

Pathophysiology

Most of the knowledge on pathophysiological mechanisms of bacterial meningitis has been derived from rabbit and rat models. These experimental studies have shown that components of bacterial cell walls initiate the local production of cytokines, including tumor necrosis factor alpha and interleukin-1β, within the CSF that subsequently elicit inflammatory changes in CSF. Cerebral edema formation, alterations in cerebral blood flow, increased intracranial pressure (ICP), and obstruction to CSF outflow and resorption have been demonstrated in animal models of bacterial meningitis. An increase of regional cerebral blood flow (rCBF) occurs early in experimental bacterial meningitis, while in advanced stages of the disease, rCBF was reduced. Morphological alterations of the blood-brain barrier result in increased blood-brain barrier permeability. The complex pathophysiological mechanisms of the major intracranial complications, i.e., cerebrovascular complications, brain edema, and increased ICP, are not completely understood; however, a number of phenomena have been observed during experimental bacterial meningitis which may contribute to the ultimate brain injury. These factors include leukocytes and their products, endothelial adhesion of leukocytes, cytokines, reactive oxygen intermediates, cyclo-oxygenase metabolites, and platelet-activating factor.

Clinical Features

The spectrum of meningeal pathogens is dependent on a patient's age, concomitant or underlying diseases, or clinically predisposing factors. Such factors include a parameningeal infectious source (e.g., otitis, sinusitis, mastoiditis, brain abscess, subdural empyema), recent intracranial surgery, a history of head trauma with or without a dural sinus fistula, a distant infectious focus (e.g., pneumonia, endocarditis), immunodeficiency, or malignancy.

The three major etiologic agents causing bacterial meningitis are *Haemophilus influenzae* (30–40% of all bacterial meningitis cases), *Neisseria meningitidis* (20–30%), and *Streptococcus pneumoniae* (15–20%). *Listeria monocytogenes* is emerging as a frequent pathogen as well. Gram-negative bacilli are responsible for 10% of cases of bacterial meningitis overall; however, they are responsible for 60–70% of all cases of meningitis in postneurosurgery patients and are a common cause of meningitis in the elderly adult and in adults debilitated by chronic illness. The meningeal pathogen cannot be detected in approximately 10–30% of patients with purulent meningitis.

The presence of a purpuric or petechial rash is suggestive of meningococcal infection or, more rarely, *Staphylococcus aureus* infection. Ten percent of meningococcal infections have an overwhelming course with development of the Waterhouse-Friderichsen syndrome. This syndrome is characterized clinically by fever, large petechial hemorrhages in the skin and mucous membranes, cardiovascular insufficiency, and disseminated intravascular coagulation.

The clinical presentation of bacterial meningitis is usually rapidly progressive over several hours; however, bacterial meningitis may also have a more subacute presentation evolving over 24–72 h. Because of the characteristic clinical presentation of this infection, antibiotic therapy is started within the first 48 h of the disease in approximately 50% of patients. With adequate therapy, clinical symptoms usually improve within several days. If the patient's clinical condition does not improve, a change of antibiotics may be considered; however, the possibility of a persistent infectious focus or complications of bacterial meningitis should be investigated.

Approximately 10% of patients with bacterial meningitis develop focal cerebral signs, e.g., hemi- or tetraparesis, ataxia, aphasia, and hemianopia. Seizures occur in 30–40% of patients. Approximately 10% of the patients develop cranial nerve palsies, usually of the third, sixth, seventh, or eighth cranial nerve. Sensorineural hearing loss develops in 10–30% of patients with bacterial meningitis.

Predictors for an unfavorable course of the disease are: apurulent bacterial meningitis, i.e., high bacterial density in the CSF combined with a low cell count; age over 40 years; underlying or concomitant disease, e.g., splenectomy or endocarditis; type of bacterial pathogen (e.g., gram-negative bacteria or pneumococci); and a long time between onset of neurological symptoms and initiation of therapy.

Differential Diagnosis

The differential diagnosis in the acute phase of bacterial meningitis includes: (a) viral meningitis or meningoencephalitis, (b) rickettsial infection, (c) Lyme disease, (d) subarachnoid hemorrhage, (e) fungal meningitis, (f) focal infectious mass lesions, and (g) neuroleptic malignant syndrome.

The clinical presentation of viral meningitis is headache, fever, nuchal rigidity, and lethargy. Patients with viral meningitis are typically awake and alert, although they complain of incapacitating, throbbing headache. On examination the cerebrospinal fluid is clear, and the opening pressure is either normal or only slightly elevated. The CSF cell count ranges from 50 to 2000 white blood cells per cubic millimeter with a predominance of lymphocytes. CSF protein concentration is only mildly elevated, and the glucose concentration is usually normal.

The term meningoencephalitis is used when there are signs of brain parenchymal inflammation by the infectious process. When this occurs, the clinical presentation is characterized by focal neurological deficits, such as hemiparesis, an altered level of consciousness, and focal or generalized seizure activity.

In herpes simplex virus type-I (HSV-1) encephalitis, initial symptoms are fever, hemicranial headache, confusion, or a change in behavior. The headache may be present for several days prior to the onset of the confusional state. As the infection progresses, focal neurological deficits and seizure activity develop. HSV-1 has a predilection for the temporal and orbitofrontal areas; as such, the abnormalities on neurological examination suggest infection in these localized areas of the brain. The following abnormalities are typical of HSV-1 meningoencephalitis on examination of the CSF: (a) elevated opening pressure, (b) white blood cell counts ranging from 50 to 500 cells per μl, with a lymphocytic predominance, (c) red blood cells and/or xanthochromia, (d) elevated protein concentration (averaging approximately 200 mg/dl), and (e) normal or moderately low glucose concentration. Electroencephalographic (EEG) abnormalities are very specific for this infection and often very useful, in addition to the abnormalities on CSF examination, in making the diagnosis. The characteristic EEG abnormalities in HSV-1 encephalitis are periodic sharp wave complexes that arise from one or both temporal regions and recur every 1–5 s.

Rocky Mountain spotted fever (RMSF) may present like bacterial meningitis. The initial symptoms of RMSF are fever, headache, myalgias, and gastrointestinal disturbances. The neurologic manifestations of RMSF include focal deficits, stupor, delirium, coma, and seizure activity. The rash of RMSF is maculopapular and/or purpuric, typically diffuse, and involves the palms and soles; it may be difficult to distinguish clinically from the rash of meningococcemia. The rash of RMSF usually does not involve the mucous membranes, while the rash of meningococcemia may appear on them. The diagnosis of RMSF may be made by biopsy of the skin lesions. Examination of the CSF can also distinguish RMSF from bacterial meningitis. In RMSF, the white blood cell count in the CSF is typically less than

100/mm^3 (cells may be absent), the protein concentration is mildly to moderately elevated, and the glucose concentration is normal.

A clinical presentation typical of viral meningitis may also be a manifestation of CNS involvement by *Borrelia burgdorferi*, the etiologic organism of Lyme disease. The CSF inflammatory changes are much less pronounced in Lyme disease than in bacterial meningitis, and the clinical presentation is more typically subacute. There is a mild CSF mononuclear pleocytosis, a mild elevation in protein concentration, and a normal glucose concentration. In the majority of cases, intrathecal production of anti-*B. burgdorferi* antibodies can be detected in CSF.

The typical presentation of a subarachnoid hemorrhage is a severe, explosive headache with vomiting or a sudden transient loss of consciousness followed by a severe headache. Nuchal rigidity is usually present within a few hours of onset. Subarachnoid hemorrhage may be visualized on computerized tomographic (CT) scan; however, in 5–10% of cases the CT scan is negative, and the diagnosis is made by finding red blood cells or xanthochromia in the CSF.

Fungal meningitides may resemble bacterial meningitis; however, fungal meningitides tend to have a more insidious onset of fever, headache, and increasing confusion over several days or weeks. The CSF usually shows a mononuclear pleocytosis, an elevated protein concentration, and a low glucose concentration. India ink examination of CSF is positive in approximately 50% of cryptococcal meningitis cases; this percentage increases in the setting of HIV infection. The diagnosis of fungal meningitis is established by a positive culture, although fungal cultures are typically slow growing. When coccidioidal meningitis is suspected, culture of CSF obtained from a cisternal, rather than a lumbar, puncture is recommended. The detection of fungal antigen in serum and CSF and complement-fixing antibodies are useful in the diagnosis of fungal meningitis.

Brain abscess and subdural empyema may have a clinical presentation similar to that of bacterial meningitis. The presentation of either of these mass lesions is dominated by hemicranial headache that becomes increasingly more severe and generalized, focal neurological deficits, and seizure activity. Either of these lesions can be readily visualized by CT or magnetic resonance (MR) scan. The similarity between the initial presentation of these mass lesions and that of bacterial meningitis has prompted the use of neuroimaging prior to lumbar puncture in patients with fever and headache; however, careful neurological examination can often distinguish a focal mass lesion from meningitis.

The diagnostic criteria of neuroleptic malignant syndrome are fever, generalized lead-pipe rigidity, fluctuating level of consciousness, autonomic instability, and a marked elevation in the serum creatine kinase concentration.

Complications

Major determinants of the prognosis of bacterial meningitis are based on the occurrence of the following com-

plications: (a) central nervous system complications including cerebral arterial or venous ischemia or infarction, cerebral edema, hydrocephalus, brain abscess, subdural empyema, or subdural effusion (noted in 15–45% of cases of bacterial meningitis in infants <18 months of age), and, rarely, central diabetes insipidus, or the syndrome of inappropriate secretion of antidiuretic hormone, and spinal vasculitis; (b) systemic complications including septic shock, disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (ARDS), septic or reactive arthritis and rhabdomyolysis; and (c) typical complications arising during intensive care therapy including pneumonia, deep venous thrombosis, pulmonary embolism, pharmacogenic or alcoholic withdrawal syndrome, electrolyte disturbances (e.g., central diabetes insipidus or the syndrome of inappropriate secretion of antidiuretic hormone), and adverse effects of drug or surgical therapy.

Cerebral arterial or venous complications should be investigated in patients with bacterial meningitis who have focal neurological deficits or persistent unexplained coma despite 3 days of adequate antibiotic therapy. Such vascular involvement became evident from (a) autopsy studies showing arteritis and thrombophlebitis; (b) angiographic evidence of vasculitis (Fig. 1) or thrombosis of the superior sagittal sinus and cortical veins; (c) observations of altered cerebral blood flow and blood velocity; and (d) CT studies revealing cerebral infarctions.

Vascular complications may raise ICP by different mechanisms, including: (a) vasogenic brain edema from endothelial damage, (b) cytotoxic brain edema from brain infarction, and (c) failure of autoregulation. There is a risk of cortical necrosis when the cerebral perfusion pressure decreases as a result of increased ICP.

In Pfister and colleagues' prospective study of 86 adult patients with

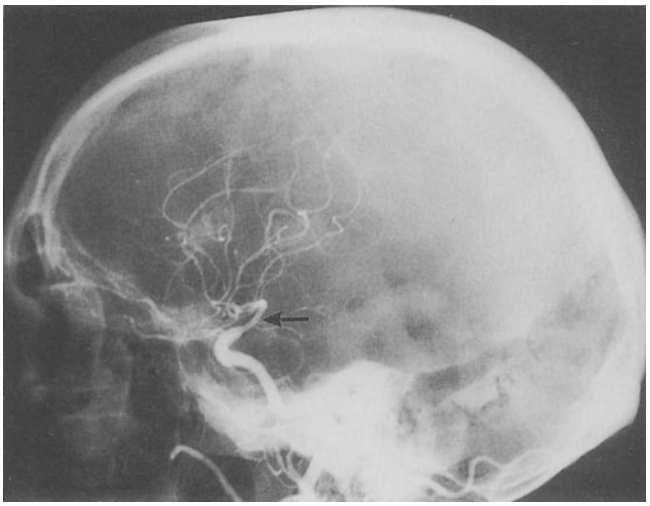


Fig. 1. Right carotid angiography (lateral view from a common internal carotid artery injection) in a 66-year-old patient with pneumococcal meningitis revealed marked narrowing in the supraclinoid portion of the right internal carotid artery (*arrow*)

bacterial meningitis, 43 developed complications. The major CNS complications were vascular involvement (15.1% of the patients), cerebral edema (14.0%), and hydrocephalus (11.6%). The systemic complications were dominated by septic shock (11.6%), ARDS (3.5%), and DIC (8.1%). Seven patients had cerebral herniation, three with a fatal outcome. Likewise, in a retrospective study of children with bacterial meningitis performed by Horwitz et al., 18/302 children (6.0%) had cerebral herniation during the acute phase of the disease, three died, and four had severe disability.

An autopsy study done by Dodge and Swartz revealed that ten of 30 patients who died during the acute phase of bacterial meningitis had diffuse brain edema. Because of the efficiency of the pia as a barrier, brain abscess is a very rare complication of bacterial meningitis.

Ancillary Tests

After admission of the patient and clinical examination, a cranial CT should be performed to identify the following:

1. Parameningeal infectious foci via the bone window technique, e.g., sinusitis, mastoiditis (Fig. 2)
2. Intracranial free air due to a dural leak (Fig. 3)
3. Brain abscess or subdural empyema (Fig. 4)
4. Early complications of bacterial meningitis, e.g., venous sinus thrombosis, hydrocephalus, or infarction

MR is superior to CT for detecting parenchymal ischemic changes. Vascular involvement can be detected by cerebral angiography, transcranial Doppler sonography, and SPECT investigation. Transcranial Doppler sonography may be useful in diag-

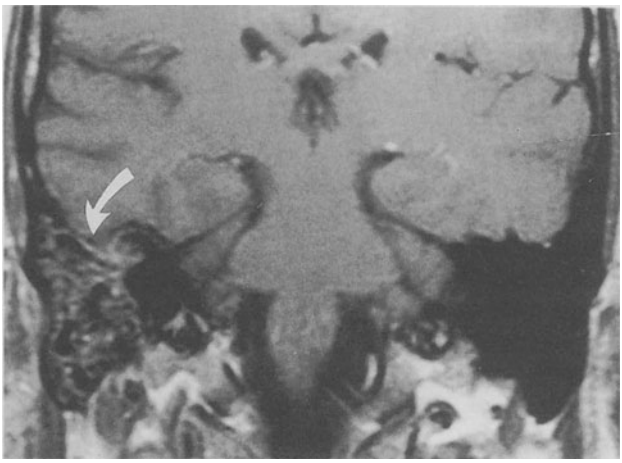


Fig. 2. Acute mastoiditis with dural involvement in a 53-year-old man. T1-weighted coronal MR image obtained after IV administration of paramagnetic contrast agent shows abnormal enhancement of both thickened mucosa of right mastoid air cell system and dura above tegmen tympani (*arrow*). (Courtesy of Klaus Sartor and Marius Hartmann, Heidelberg)

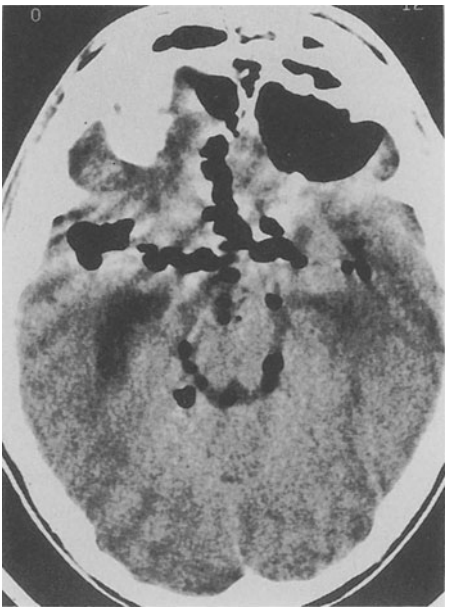
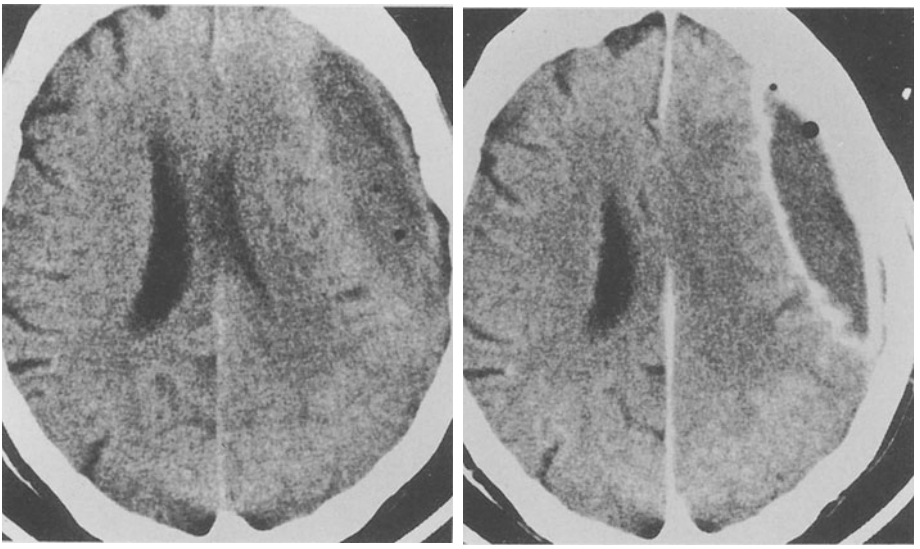


Fig. 3. Pneumocephalus in a 33-year-old man which was due to a craniocerebral injury caused by a shooting device used to kill cattle (suicide attempt). Axial CT scan shows multiple smaller and larger collections of air, most of which are located extra-axially, which have entered the intracranial cavity through leaks in the frontobasal dura. (Courtesy of Klaus Sartor and Marius Hartmann, Heidelberg)



a **b**

Fig. 4a,b. Subdural empyema in a 70-year-old man with a changed mental status occurring 4 weeks after drainage of a chronic subdural hematoma through a burr hole. Axial CT scans obtained before (**a**) and after (**b**) IV administration of iodinated contrast material reveal extraaxial mass lesion of low density compared with normal brain parenchyma that is biconvex and enhances peripherally, with short extensions of the enhancement into several sulci. The ipsilateral ventricle is largely compressed due to the mass effect. (Courtesy of Klaus Sartor and Marius Hartmann, Heidelberg)

nosing involvement of great arteries at the base of the brain. However, vasculitis or thrombosis of small vessels, major sinuses, and cortical veins cannot be detected by this technique. Cerebral angiography may be considered if at least one of the following criteria is fulfilled: the development of focal neurological deficits or focal seizure activity; evidence of a focal lesion on cranial CT or MR (e.g., infarction, focal brain edema); or no improvement in coma (Glasgow Coma Scale score less than eight) after 3 days of adequate antibiotic therapy, provided that other causes for coma, e.g., metabolic or pharmacologic causes, hydrocephalus or brain abscess, have been excluded. In addition, MR angiography can diagnose sinus thrombosis.

Cerebrospinal fluid typically shows a pleocytosis with more than 1000 cells/μl. There is a predominance of polymorphonuclear leukocytes (PMNs); 80–90% of patients with bacterial meningitis have more than 80% PMNs in their CSF. A cell count below 1000 cells/μl may be found in the following conditions:

- Very early stage of bacterial meningitis
- Partially treated bacterial meningitis
- Overwhelming bacterial meningeal infection usually due to pneumococci (so-called apurulent bacterial meningitis), characterized by a very low cellular response but a high density of bacteria in the CSF
- Leukopenic or immunosuppressed patients

Certain bacterial pathogens such as Listeria monocytogenes may not induce a purulent CSF.

The protein concentration in the CSF usually exceeds 120 mg/dl, and the glucose concentration is normally below 30 mg/dl. The CSF/serum glucose ratio is typically less than 0.31. Gram's stain discloses bacteria in approximately 80–90% of patients with a positive CSF culture. The likelihood of a positive culture of Gram's stain result decreases to 5–40% in patients treated with antibiotics prior to examination of the CSF. An elevated CSF lactate concentration or C-reactive protein may be useful in differentiating bacterial from viral meningitis, especially in patients who have been partially treated with antibiotics prior to examination of the CSF.

Management

General Aspects

Clinical suspicion of bacterial meningitis (high fever, headache, stiff neck, impairment of consciousness) should prompt a cranial CT, including the bone window technique, and examination of the CSF. Only clinical signs of cerebral herniation or a focal mass lesion constitute a clear contraindication to lumbar puncture. In the case of suspected raised ICP, hyperosmolar agents (e.g., 0.25 g/kg body wt. of mannitol) may be infused intravenously, just before lumbar puncture. CSF should be immediately examined for cell count with differential, protein, and glucose concentration, Gram's stain, and bacterial antigen detection by latex agglutination; in addition, agar plates should be inoculated for routine

culture for bacteria. Thereafter, intravenous antibiotic therapy should be started. If CT scan is delayed, antibiotic therapy should be initiated and CT scan and CSF examination obtained as soon as possible. The goal should be to limit the period from examination of the patient to the initiation of antibiotic therapy to less than 1 h. The possibility of an extracranial infectious focus should be investigated. Surgical intervention for parameningeal infections, such as otitis or mastoiditis, should be performed as soon as possible when indicated. CSF leaks are surgically corrected once the meningeal infection is under control, not during the acute phase of bacterial meningitis.

If the meningeal pathogen is known, an antibiotic is chosen with bactericidal activity against the pathogen, good blood-CSF barrier penetration, and effective concentrations in the CSF, with a relatively low incidence of adverse effects (Table 1). Experimental studies have demonstrated that the best response is achived with CSF antibiotic concentrations that exceed the minimal bactericidal concentration (MBC) of the infecting organism by 10- to 20-fold. If the meningeal pathogen is unknown, empiric therapy is started based on the age of the patient, predisposing factors, and the most likely meningeal pathogen (Table 2). The total daily dosages of the most frequently used antibiotics in bacterial meningitis are listed in Table 3. The susceptibility of the identified meningeal pathogen to several antibiotics should be determined. The CSF cultures usually become sterile within 24–48 h after starting therapy; however, enteric gram-negative rods and *Pseudomonas aeruginosa* may remain culturable for 2–3 days after the initiation of antibiotic therapy. If the CSF is not sterile within 3 days, a change in the antibiotic regimen should be considered; in addition, a persistent source of infection should be investigated. Within 24 h of the onset of antibiotic therapy, almost 50% of samples of CSF from patients with bacterial meningitis have an increase in cell count in the CSF. This has no prognostic significance.

Antibiotics Most Often Used in the Therapy of Bacterial Meningitis

Penicillin G is very effective against gram-positive and gram-negative cocci and anaerobic bacilli, with the exception of penicillinase-producing staphylococci, enterococci, and *Bacteroides fragilis*. Penicillin G is insufficiently effective against *Haemophilus influenzae*, gram-negative Enterobacteriaceae, and *Pseudomonas aeruginosa*. The blood-CSF penetration is adequate in inflamed meninges but very poor in intact blood-CSF barrier (<1%).

Ampicillin is less effective than penicillin against streptococci and pneumococci, equally effective against meningococci, and more effective against *L. monocytogenes, H. influenzae*, and enterococci. Ampicillin is insufficiently effective against gram-negative Enterobacteriaceae and *P. aeruginosa*.

The broad-spectrum penicillins such as piperacillin, azlocillin, and mezlocillin are mainly effective against *P. aeruginosa*, Enterobacteriaceae, and enterococci, but they are inferior to cefotaxime against enteric gram-

Table 1. Recommended treatment of bacterial meningitis

Meningeal pathogen	Antibiotic	Alternatives
N. meningitidis	Penicillin G *or* ampicillin	Third-generation cephalosporin[a]
S. pneumoniae	Penicillin G *or* third-generation cephalosporin[a]	Ampicillin
H. influenzae type b	Third-generation cephalosporin[a]	Ampicillin plus chloramphenicol
Streptococci (group B)	Penicillin G *or* third-generation cephalosporin[a]	Ampicillin
Enterobacteriaceae	Third-generation cephalosporin[a]	Broad-spectrum penicillin[c] plus aminoglycoside[b]
Pseudomonas aeruginosa	Ceftazidime plus aminoglycoside[b]	Piperacillin plus aminoglycoside[b]
S. aureus (methicillin sensitive)	Oxacillin	Nafcillin *or* vancomycin *or* fosfomycin
S. aureus (methicillin resistant)	Vancomycin	
Coagulase-negative staphylococci	Vancomycin	
L. monocytogenes	Ampicillin (plus aminoglycoside[b])	Trimethoprim-sulfamethoxazole

[a] Cefotaxime or ceftriaxone
[b] Gentamicin or tobramycin
[c] Piperacillin or mezlocillin

negative rods. Since the CSF concentrations usually do not exceed the minimal bactericidal concentration for *P. aeruginosa*, a combination with an aminoglycoside is recommended because of the synergistic effect. The penicillinase-resistant oxacillins exhibit a high binding to plasma proteins (97%) and a moderate blood-CSF penetration in inflamed meninges. They are used in the treatment of staphylococcal meningitis.

The first-generation cephalosporins such as cefalotin and most second-generation cephalosporins such as cefamandol and cefoxitin have been shown to provide relatively poor CSF penetration with achieved CSF concentrations below the minimal bactericidal concentration of most meningeal pathogens, and are therefore inappropriate for the treatment of bacterial meningitis. A marked advancement in the therapy of bacterial meningitis was achieved with the development of the third-generation cephalosporins, such as cefotaxime, latamoxef, ceftizoxime, ceftriaxone, ceftazidime, and cefsulodine. The most frequently employed and best studied antibiotics in this group are cefotaxime and ceftriaxone.

Cefotaxime has a sufficient CSF penetration rate and has been used successfully in the therapy of pneumococcal, meningococcal, and *H. influenzae* meningitis and meningitis due to enteric gram-negative rods (reaching CSF concentrations of 10–500 times the minimal inhibitory concentration of *Escherichia coli* and *Klebsiella*). However, cefotaxime is only minimally effective or not ef-

Table 2. Initial empiric antibiotic therapy of bacterial meningitis

Age-groups	Frequent etiologic agents	Recommended antibiotic regimen
Neonates (≤2 months old)	Enteric gram-negative rods Group-B streptococci *Listeria monocytogenes*	Cefotaxime plus ampicillin
Infants and children (>2 months old)	*Haemophilus influenzae* *Streptococcus pneumoniae* *Neisseria meningitidis*	3rd-generation cephalosporin[a]
Adults		
• healthy, immunocompetent, community-acquired	*Streptococcus pneumoniae* *Neisseria meningitidis*	3rd-generation cephalosporin or penicillin G or ampicillin
• nosocomial (e.g., postneurosurgical) or recent head injury	*Staphylococcus aureus* *Staphylococcus epidermidis* Enteric gram-negative rods *Streptococcus pneumoniae*	3rd-generation cephalosporin plus oxacillin[b] plus aminoglycoside[c]
• immunocompromised	*Streptococcus pneumoniae* *Listeria monocytogenes* Enteric gram-negative rods	3rd-generation cephalosporin plus ampicillin
• shunt-related meningitis	*Staphylococcus epidermidis* *Staphylococcus aureus* Enteric gram-negative rods	3rd-generation cephalosporin plus vancomycin plus aminoglycoside

[a] Cefotaxime or ceftriaxone
[b] Alternatives: nafcillin or vancomycin
[c] Gentamicin or tobramycin

fective against *L. monocytogenes*, *P. aeruginosa*, enterococci, *S. aureus*, *Acinetobacter*, and *Clostridium difficile*.

Ceftriaxone has an activity comparable to that of cefotaxime and the advantage of a long serum half-life of about 8 h; therefore, ceftriaxone can be administered in a once- or twice-daily dose. In childhood bacterial meningitis, ceftriaxone has been proven to be superior to cefuroxime.

Ceftazidime is very effective against *P. aeruginosa* and is superior in vitro to cefsulodine and piperacillin. However, ceftazidime is less effective against gram-positive bacteria than cefotaxime. Ceftazidime's level of beta lactamase stability is high, and its CSF penetration rate is comparable to that of cefotaxime.

Latamoxef is not recommended for initial therapy of bacterial meningitis because it is insufficiently effective against gram-positive cocci; however, it has been used successfully in combination with ampicillin in the treatment of meningitis due to these organisms. The use of latamoxef is limited because of the potential adverse effects of hypoprothrombinemia, thrombopathy, and thrombocytopenia associated with this agent.

The aminoglycosides such as gentamicin, tobramycin, netilmicin, and amikacin are especially effective against gram-negative bacteria (enteric

Table 3. Recommended antibiotics in bacterial meningitis[a]

Antibiotic	Total daily dose (dosage interval)				Serum half-life (h)	CSF/serum ratio (%)[b]
	Adults	Infants	Neonates			
			1–4 weeks	<1 week		
Penicillin G	24–30 mega U/day (every 4 h)	250 000–400 000 U/kg/day (every 4 h)	150 000–200 000 U/kg/day (every 6 h)	50 000–150 000 U/kg/day (every 8 h)	0.6–1	3–5
Ampicillin	12 g/day (every 4 h)	150–200 mg/kg/day (every 4 h)	100–200 mg/kg/day (every 6 h)	50–100 mg/kg/day (every 12 h)	0.5–1	5–10
Cefotaxime	6 g/day (every 8 h)	200 mg/kg/day (every 6 h)	150 mg/kg/day (every 8 h)	100 mg/kg/day (every 12 h)	~1	6–16
Ceftriaxone	2(–4) g/day (every 24 h)	100 mg/kg/day (every 24 h)	–	–	6–8	4–9
Ceftazidime	6 g/day (every 8 h)	150 mg/kg/day (every 8 h)	100–150 mg/kg/day (every 8 h)	60 mg/kg/day (every 12 h)	1.8	~20
Gentamicin/ tobramycin	240–360 mg/day (every 8 h)	5 mg/kg/day (every 8 h)	7.5 mg/kg/day (every 8 h)	5 mg/kg/day (every 8 h)	2–3	<10
Trimethoprim-sulfamethoxazol	10 mg/kg/day[c] (every 8 h)	10 mg/kg/day (every 8 h)	10 mg/kg/day (every 8 h)	10 mg/kg/day (every 8 h)	11	30–50
Chloramphenicol	4 g/day (every 6 h)	100 mg/kg/day (every 6 h)	50 mg/kg/day (every 12 h)	25 mg/kg/day (every 12 h)	1.5–3.5	40–90
Vancomycin	2 g/day (every 6 h)	40 mg/kg/day (every 6 h)	40 mg/kg/day (every 6 h)	20–30 mg/kg/day (every 12 h)	6	10–30
Oxacillin	9–12 g/day (every 4 h)	200 mg/kg/day (every 6 h)	100–200 mg/kg/day (every 6 h)	50–100 mg/kg/day (every 6 h)	0.7	<10
Piperacillin	12 g/day (every 8 h)	200–300 mg/kg/day (every 8 h)	200–300 mg/kg/day (every 8 h)	200–300 mg/kg/day (every 8 h)	1.3–1.5	~15
Fosfomycin	15 g/day (every 8 h)	200–300 mg/kg/day (every 8 h)	100 mg/kg/day (every 12 h)	100 mg/kg/day (every 12 h)	2	20–30

[a] Reduction of dosage of all antibiotics except ceftriaxone is necessary in renal failure.
[b] With inflamed meninges.
[c] Based on trimethoprim.

gram-negative rods and *P. aeruginosa*) and staphylococci. They are not effective or only insufficiently effective against meningococci, pneumococci, streptococci, enterococci, *L. monocytogenes*, *H. influenzae*, and anaerobic bacteria. The serum concentrations of the aminoglycosides should be monitored regularly (e.g., gentamicin concentration $<10\,\mu g/ml$). The CSF concentrations of the aminoglycosides, whose activity is decreased in acid milieu, usually do not attain the minimal bactericidal concentrations for most gram-negative bacteria because of their poor and variable CSF penetration, even in inflamed meninges. Therefore, especially during the 1970s, intraventricular administration of the aminoglycosides was recommended. However, with the advent of sufficient CSF-penetrating third-generation cephalosporins, this strategy has increasingly receded into the background. Currently, the intraventricular administration of gentamicin (dosage 5–10 mg/day in adults, 1–2 mg/day in children) is indicated only if gram-negative meningitis is unquestionable, the clinical picture is severe (coma), and clinical or bacteriological improvement does not occur during intravenous antibiotic therapy.

Once-daily Aminoglycoside Therapy

All aminoglycosides can potentially cause reversible and irreversible vestibular, cochlear, and renal toxicity, and, because of the narrow therapeutic range and wide pharmacokinetic variability among patients, optimal dosage regimens are often difficult to attain. In general, low serum trough levels of aminoglycosides are associated with decreased antibiotic accumulation in the renal cortex and endolymph and perilymph of the inner ear, and high serum peak levels correlate with increased bactericidal effect. Recently, it has been reported that toxicity can be reduced and efficacy can be improved when aminoglycosides are given only once daily compared with the conventional regimen of multiple times daily (that is, a single total dose of aminoglycosides results in higher peak levels and lower trough levels). Aminoglycosides should always be given intravenously because of the variable rate of absorption after intramuscular injection.

Fosfomycin has an effective CSF penetration and may be useful in staphylococcal meningitis; however, staphylococci may become resistant to this antibiotic during therapy. In addition, it is active against *H. influenzae*, meningococci, and gram-negative enterobacteria (*E. coli*, *Citrobacter*, *Serratia*). It is less effective against pneumococci, *Enterobacter*, *Klebsiella*, and *Proteus* and ineffective against *Bacteroides* species.

Vancomycin is an alternative antibiotic for bacterial meningitis due to oxacillin- or fosfomycin-resistant staphylococci. Vancomycin is often required in shunt infections or ventriculitis. In addition, vancomycin is effective against streptococci, including enterococci and pneumococci.

Trimethoprim-sulfamethoxazol (TMP-SMZ) has good CSF penetration and is used as an alternative antibiotic in the therapy of *Listeria* meningitis in cases of allergy to ampicillin. Furthermore, TMP-SMZ has been successful in the therapy of bacterial

meningitis due to *Enterobacter*, *Acinetobacter*, and *Serratia*.

Metronidazole adequately penetrates into the CSF and is employed in the therapy of brain abscess and the very rare condition of anaerobic meningitis (e.g., meningitis caused by *Bacteroides fragilis*, *Fusobacterium*, *Peptococcus*, *Veillonella*, and *Peptostreptococcus*).

Chloramphenicol is not a first-choice antibiotic because of its possible side effects. It has a good degree of CSF penetration, even in intact meninges, and is very effective against meningococci, pneumococci, and *H. influenzae*. Chloramphenicol has a high failure rate in gram-negative meningitis because in this condition it reaches only bacteriostatic concentrations in the CSF. The serum concentrations of chloramphenicol have to be monitored regularly, and the maximum levels should not exceed 15–20 μg/ml.

Empiric Antibiotic Recommendations

The most common bacterial pathogens causing neonatal meningitis are enteric gram-negative rods, group-B streptococci, and *Listeria monocytogenes*. Therefore, a combination of ampicillin and cefotaxime or of ampicillin and an aminoglycoside is recommended (Table 2). A third-generation cephalosporin is recommended for initial empiric antibiotic therapy in infants and children (over 2 months of age). In controlled studies, cefotaxime or ceftriaxone were as effective as ampicillin and chloramphenicol. Moreover, an increasing number of strains of *Haemophilus influenzae*, the most frequent bacterial pathogen of meningitis in infants and children, have been identified in recent years that are resistant to ampicillin and chloramphenicol.

The most frequent agents of bacterial meningitis in previously healthy adults are meningococci and pneumococci. Initial treatment with a third-generation cephalosporin (e.g., cefotaxime or ceftriaxone) is recommended before the meningeal pathogen is identified. Penicillin G or ampicillin may be substituted in cases of meningococcal infection as demonstrated by Gram's stain. CSF isolates of pneumococci and meningococci should be tested for penicillin and ampicillin susceptibility. A third-generation cephalosporin can be used for penicillin-resistant meningococci or relatively penicillin-resistant pneumococci, and vancomycin is recommended for highly penicillin-resistant pneumococci.

Initial therapy of bacterial meningitis associated with recent head trauma or a neurosurgical procedure should include a combination of a third-generation cephalosporin, such as cefotaxime or ceftriaxone, oxacillin (alternatively fosfomycin), and an aminoglycoside to treat staphylococci and enteric gram-negative rods. Ventriculitis associated with an external intraventricular drainage device should be treated with a combination of a third-generation cephalosporin, vancomycin (alternatively oxacillin or fosfomycin), and an aminoglycoside. When meningitis develops in association with a ventriculoperitoneal shunt, the shunt should be removed and a temporary external ventricular drainage device inserted. The latter will control hydrocephalus while the infection is being treated. Some clini-

cians have attempted antibiotic treatment without shunt removal, with limited success. Antibiotic therapy should include a combination of a third-generation cephalosporin, vancomycin (alternatively flucloxacillin or fosfomycin), and an aminoglycoside. If the shunt infection is caused by enteric gram-negative rods, which are susceptible to aminoglycosides, then gentamicin should be given intravenously and intraventricularly (dosage in infants and children 1–2 mg/day, in adults 5–10 mg/day). If there is a known underlying immunocompromised state or malignancy, the initial antibiotic therapy should be directed against a broad spectrum of bacterial pathogens, including *L. monocytogenes*; therefore, a combination of a third-generation cephalosporin and ampicillin is recommended.

Treatment Duration

The treatment duration of bacterial meningitis depends on the response to therapy and the type of bacterial pathogen. In meningitis caused by meningococci, pneumococci, *H. influenzae* and group-B streptococci, a 10–14 day course of antibiotic therapy is recommended. Alternatively, antibiotics should be continued for 7 days after the patient's fever has disappeared. Meningitis due to *L. monocytogenes* and enteric gram-negative rods is usually treated for 3–4 weeks.

Isolation

Patients with meningococcal meningitis should be isolated for the first 24 h after the onset of antibiotic therapy.

Chemoprophylaxis

The risk of secondary disease for close contacts of patients with *H. influenzae* type b or meningococcal meningitis is approximately 200–1000 times the risk for the general population. Chemoprophylaxis for eradication of the bacteria from the nasopharynx is recommended for family and household members, persons who have had close contact with the index case for more than 4 h daily during the week prior to the onset of the disease, and hospital staff members who have had potential contact with secretory products of the respiratory tract of the index case prior to the onset of antibiotic therapy. In contrast to meningococcal meningitis, the risk of infection in *H. influenzae* meningitis seems to exist only for children younger than 6 years of age. Since the bacterial pathogens are usually not eradicated from the upper respiratory tract in a patient with *H. influenzae* meningitis or meningococcal meningitis despite successful systemic antibiotic therapy, the patient is a potential carrier. Therefore, it is recommended that the index patient also receives chemoprophylaxis before discharge from the hospital. The recommended antibiotic for chemoprophylaxis is rifampicin (Table 4). Rifampicin usually has no toxic effects when administered for a short period of time; however, it should not be prescribed to pregnant women.

Up to 70% of meningococci were resistant to sulfadiazine in reported series in the 1970s; therefore, sul-

Table 4. Chemoprophylaxis of bacterial meningitis

Etiologic agent	Total daily dosage of rifampicin		
	Adults	Infants and children (>1 month)	Neonates (<1 month)
Haemophilus influenzae	600 mg/day orally over 4 days	20 mg/kg/day orally (maximum 600 mg/day) over 4 days	10 mg/kg/day orally over 4 days
Neisseria meningitidis	2 × 600 mg/day orally over 2 days	2 × 10 mg/kg/day orally over 2 days	2 × 5 mg/kg/day orally over 2 days

fadiazine is not recommended for chemoprophylaxis of meningococcal disease. Rifampicin is currently the recommended agent. An alternative to rifampicin, ciprofloxacin, has been given successfully as chemoprophylaxis in meningococcal infection (500 or 750 mg in a single oral dose).

Immunophrophylaxis (Vaccination)

The efficacy of the 23-valent preparation of pneumococcal vaccine against pneumococcal meningitis has not been proven. However, this preparation is usually recommended for high-risk patients over 2 years of age. The dose of the vaccine is 0.5 ml, intramuscularly, which is usually well tolerated. Booster injections should be given every 5 years. There is no effective vaccine against meningococci of the serogroup B, which accounts for the most frequent cases of meningococcal infection. A tetravalent meningococcal vaccine (serogroups A,C,Y, and W 135) is currently recommended for high-risk patients, including patients with terminal complement component deficiency or dysfunction, asplenic patients, and travelers to areas with hyperendemic or epidemic meningococcal disease (e.g., Nigeria, Cameroon). *H. influenzae* type b conjugate vaccine is recommended for all infants at the age of 2, 4, and 6 months.

Management of Special Problems and Complications

Experimental studies on the pathophysiological mechanisms of pneumococcal meningitis have shown that the cell wall of the pneumococcus elicits an inflammatory response in the subarachnoid space. Since bacterial lysis by antibiotics releases cell-wall components, which in turn initiate the inflammatory cascade, adjunctive therapy to alter the inflammatory cascade may be more promising than further development of lytic antibiotics.

Two placebo-controlled double-blind studies performend by Lebel et al. and Odio et al. in children with bacterial meningitis showed a beneficial effect of *dexamethasone* on hearing loss and neurological

sequelae. These results may not be applicable to newborns but are most likely applicable to adults with bacterial meningitis. Dexamethasone reduced mortality in adults with pneumococcal meningitis in an open randomized study performed in Egypt. Dexamethasone may also have a beneficial effect in patients with cerebral edema, cerebral arterial complications, or apurulent bacterial meningitis. Recent studies to evaluate the effect of corticosteroids in septic shock do not, however, support the use of high-dose steroids in septic shock. The recommended dose of dexamethasone in children with bacterial meningitis is 0.15 mg/kg every 6 h intravenously for 4 days. The first dose of dexamethasone should be given before the first dose of antibiotic. The concomitant use of an intravenous H_2-receptor antagonist is recommended. For cerebral arterial complications there is no proven therapy. Vasospasm of the large arteries at the base of the brain, with a high risk of cerebral infarction, resembles vasospasm in subarachnoid hemorrhage after aneurysmal bleeding. In these patients, *hypervolemic hypertensive therapy* could be considered to prevent irreversible brain damage, but this has not yet been investigated in bacterial meningitis.

Anticoagulation of septic venous sinus thrombosis in bacterial meningitis is a subject of controversy. Recently, the beneficial effect of dose-adjusted intravenous heparin was reported in patients with aseptic venous sinus thrombosis. Although prospective controlled studies on the treatment of septic venous sinus thrombosis have not been performed, anticoagulation with intravenous heparin seems justified, since the outcome with antibiotic therapy alone is unsatisfactory, with mortality still between 50% and 78%.

Immediate treatment of hydrocephalus by ventricular drainage is easy and very effective. Subdural effusion (sterile) usually spontaneously resolves and does not require surgical therapy. Only in cases of clinical deterioration due to subdural empyema should *stereotactic aspiration* be performed.

Treatment of increased ICP is discussed in Chap. 9.

New Developments

Free-radical scavengers and non-steroidal anti-inflammatory agents such as indomethacin have had beneficial effects in experimental animal studies of bacterial meningitis, but so far they have not been investigated clinically. Further studies are needed to determine whether some of the approaches recently considered, such as application of monoclonal antibodies directed against leukocyte endothelial adhesion molecules, endotoxin, or cytokines (tumor necrosis factor alpha or interleukin 1β), may be applied in clinical practice.

Prognosis and Conclusions

Despite the improvement in antimicrobial therapy during the past few decades, the mortality and number of sequelae due to bacterial meningitis remain high. The unfavorable clinical outcome is often due to intracranial complications such as cerebral edema,

hydrocephalus, and cerebrovascular complications during the acute phase of the disease. The availability of the third-generation cephalosporins has led to a decrease in mortality of gram-negative meningitis from 40–80% to 10–20%; however, the mortality of bacterial meningitis due to pneumococcus, which is the most frequent pathogen in adult bacterial meningitis, is still as high as 20–30%. The overall incidence of sensorineural hearing loss in children with bacterial meningitis is 10–30%. The antibiotics most often used for the treatment of bacterial meningitis are known to induce autolysis, which results in the release of inflammatory cell wall components. Further improvement of antibiotics so that they retain killing without lysis may substantially improve the prognosis of the disease. Likewise, it may also be helpful to identify agents capable of intervening with mediators which are believed to be of major importance in producing secondary brain damage. Thus, in clinical practice, early detection and better management of the complications may be important factors in decreasing mortality and improving prognosis of bacterial meningitis.

Suggested Reading

Arevalo CE, Barnes PF, Duda M, Leedom JM (1989) Cerebrospinal fluid cell counts and chemistries in bacterial meningitis. South Med J 82:1122–1127

Bone RC, Fisher CJ, Clemmer TB et al. (1987) A controlled trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 317:563–568

Cabral DA, Flodmark O, Farrell K, Speert DP (1987) Prospective study of computed tomography in acute bacterial meningitis. J Pediatr 111:201–205

Cohen J, Glauser MP (1991) Septic shock: treatment. Lancet 338:736–739

DiNubile MJ, Boom WH, Southwick FS (1990) Septic cortical thrombophlebitis. J Infect Dis 161:1216–1220

Dodge PR, Swartz MN (1965) Bacterial meningitis – a review of selected aspects. II. Special neurologic problems, postmeningitic complications and clinicopathologic correlations. N Engl J Med 272:954–960

Dodge PR, Davis H, Feigin RD, Holmes SJ, Kaplan SL, Jubelirer DP, Stechenberg BW, Hirsh SK (1984) Prospective evaluation of hearing impairment as a sequela of acute bacterial meningitis. N Engl J Med 311:869–874

Durand ML, Calderwood SB, Weber DJ et al. (1993) Acute bacterial meningitis in adults. N Engl J Med 328:21–28

Einhäupl KM, Villringer A, Meister W et al. (1991) Heparin treatment in sinus venous thrombosis. Lancet 338:597–600

Felgenhauer K, Kober D (1985) Apurulent bacterial meningitis (compartmental leucopenia in purulent meningitis). J Neurol 232:157–161

Geiseler PJ, Nelson KE, Levin S, Reddi KT, Moses VK (1980) Community-acquired purulent meningitis: a review of 11316 cases during the antibiotic era, 1954–1976. Rev Infect Dis 2:725–745

Gilbert DN (1991) Minireview: once-daily aminoglycoside therapy. J Antimicrob Chemother 35:399–405

Girgis NI, Farid Z, Mikhail IA, Farrag I, Sultan Y, Kilpatrick ME (1989) Dexamethasone treatment for bacterial meningitis in children and adults. Pediatr Infect Dis J 8:848–851

Haring HP, Rötzer HK, Reindl H, Berek K, Kampfl A, Pfausler B, Schmutzhard E (1993) Time course of cerebral blood flow velocity in central nervous system infections. A transcranial Doppler sonography study. Arch Neurol 50:98–101

Horwitz SJ, Boxerbaum B, O'Bell J (1980) Cerebral herniation in bacterial meningitis in childhood. Ann Neurol 7:524–528

Igarashi M, Gilmartin RC, Gerald B, Wilburn F, Jabbour JT (1984) Cerebral arteritis and bacterial meningitis. Arch Neurol 41:531–535

Kaplan SL, Fishman MA (1988) Update on bacterial meningitis. J Child Neurol 3: 82–93

Mustafa MM, Lebel MH, Ramilo O, Olsen KD, Reisch JS, Beutler B, McCracken GH (1989) Correlation of interleukin-1β and cachectin concentrations in cerebrospinal fluid and outcome from bacterial meningitis. J Pediatr 115:208–213

Odio CM, Faingezicht I, Paris M et al. (1991) The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. N Engl J Med 324:1525–1531

Paulson OB, Brodersen P, Hansen EL, Kristensen HS (1974) Regional cerebral blood flow, cerebral metabolic rate of oxygen, and cerebrospinal fluid acid-base variables in patients with acute meningitis and with encephalitis. Acta Med Scand 196:191–198

Peltola H, Anttila M, Renkonen OV and the Finnish study group (1989) Randomised comparison of chloramphenicol, ampiciliin, cefotaxime, and ceftriaxone for childhood bacterial meningitis. Lancet 1:1281–1286

Peukonen OV, Sivonen A, Visakorpi R (1987) Effect of ciprofloxacin on carrier rate of *Neisseria meningitidis* in army recruits in Finland. Antimicrob Agents Chemother 31:962–963

Pfister HW, Koedel U, Haberl R, Dirnagl U, Feiden W, Ruckdeschel G, Einhäupl KM (1990) Microvascular changes during the early phase of experimental pneumococcal meningitis. J Cereb Blood Flow Metab 10:914–922

Pfister HW, Borasio GD, Dirnagl U, Bauer M, Einhäupl KM (1992a) Cerebrovascular complications of bacterial meningitis in adults. Neurology 42:1497–1504

Pfister HW, Koedel U, Lorenzl S, Tomasz A (1992b) Antioxidants attenuate microvascular changes in the early phase of experimental pneumococcal meningitis in rats. Stroke 23:1798–1804

Pfister HW, Feiden W, Einhäupl KM (1993) The spectrum of complications during bacterial meningitis in adults: results of a prospective clinical study. Arch Neurol 50: 575–581

Pugsley MP, Dworzack DL, Horowitz EA et al. (1987) Efficacy of ciprofloxacin in the treatment of nasopharyngeal carriers of *Neisseria meningitidis*. J Infect Dis 156: 211–213

Quagliarello V, Scheld WM (1992) Mechanisms of disease: bacterial meningitis: pathogenesis, pathophysiology, and progress. N Engl J Med 327:864–872

Raimondi AJ, DiRocca C (1979) The physiopathologic basis for the angiographic diagnosis of bacterial infections of the brain and its covering in children. Childs Brain 5:1–13

Roos KL, Tunkel AR, Scheld WM (1991) Acute bacterial meningitis in children and adults. In: Scheld WM, Whitley RJ, Durack DT (eds) Infections of the central nervous system. Raven, New York, pp 335–410

Saez-Llorens X, Ramilo O, Mustafa MM, Mertsola J, McCracken GH (1990) Molecular pathophysiology of bacterial meningitis: current concepts and therapeutic implications. J Pediatr 116:671–684

Sagar SM, McGuire D (1991) Infectious diseases. In: Samuels MA (ed) Manual of neurology. Diagnosis and therapy, 4th edn. Little, Brown, Boston, pp 127–182

Saukkonen K, Sande S, Cioffe C, Wolpe S, Sherry B, Cerami A, Tuomanen E (1990) The role of cytokines in the generation of inflammation and tissue damage in experimental gram-positive meningitis. J Exp Med 171:439–448

Schaad UB, Suter S, Gianella-Boradori A, Pfenninger J, Auckthaler R, Bernath O, Cheseaux JJ, Wedgwood J (1990) Comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. N Engl J Med 322:141–147

Scheld WM (1989) Drug delivery to the central nervous system: general principles and relevance to therapy for infections of the central nervous system. Rev Infect Dis 11 [Suppl 7]:1669–1690

Schmutzhard E, Aichner F, Berek K et al. (1989) Akute Komplikationen der Pneumokokken-Meningoenzephalitis. Intensivbehandlung 14:91–95

Smith AL (1988) Neurologic sequelae of meningitis. N Engl J Med 319:1012–1014

Southwick FS, Richardson EP jr, Swartz MN (1986) Septic thrombosis of the dural venous sinuses. Medicine (Baltimore) 65: 82–106

Sprung CL, Caralis PV, Marcial EH et al. (1984) The effects of high-dose corticosteroids in

patients with septic shock. A prospective, controlled study. N Engl J Med 311: 1137–1143

Swartz MN (1984) Bacterial meningitis: more involved than just the meninges. N Engl J Med 311:912–914

Tuomanen E, Liu H, Hengstler B, Zak O, Tomasz A (1985) The induction of meningeal inflammation by components of the pneumococcal cell wall. J Infect Dis 151: 858–868

Tuomanen EI, Saukkonen K, Sande S, Cioffe C, Wright SD (1989) Reduction of inflammation, tissue damage, and mortality in bacterial meningitis in rabbits treated with monoclonal antibodies against adhesion-promoting receptors of leucocytes. J Exp Med 170:959–969

Tunkel AR, Wispelwey B, Scheld WM (1990) Bacterial meningitis: recent advances in pathophysiology and treatment. Ann Intern Med 112:610–623

Tureen JH, Dworkin RJ, Kennedy SL, Sachdeva M, Sande MA (1990) Loss of cerebrovascular autoregulation in experimental meningitis in rabbits. J Clin Invest 85:577–581

Veterans Administration Systemic Sepsis Cooperative Study Group (1987) Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. N Engl J Med 317:659–665