# 24.11 Infections of the central nervous system 606

# 24.11 Infections of the central nervous system 6060

# 24.11.1 Bacterial infections 6060 Diederik van de Beek and Guy E. Thwaites

24.11 Infections of the central nervous system CONTENTS 24.11.1 Bacterial infections 6060 Diederik van de Beek and Guy E. Thwaites 24.11.2 Viral infections 6082 Fiona McGill, Jeremy Farrar, Bridget Wills, Menno De Jong,
David A. Warrell, and Tom Solomon 24.11.3 Intracranial abscesses 6097 Tim Lawrence and Richard S.C. Kerr 24.11.4 Neurosyphilis and neuro-AIDS 6100 Hadi Manji 24.11.5 Human prion diseases 6109 Simon Mead and R.G. Will 24.11.1 Bacterial infections Diederik van de Beek and Guy E. Thwaites ESSENTIALS Bacterial meningitis occurs in many clinical situations, including spontaneous (the most important category), post-traumatic, and device-associated (relating to cerebrospinal fluid shunts and drains). Each of these is associated with a particular pattern of infecting organisms, clinical presentation, and outcome, but overall there is high morbidity and mortality. Aetiology (1) Adult spontaneous community-acquired meningitis—80–85% of cases are caused by Neisseria meningitidis or Streptococcus pneumoniae in most countries, with Listeria monocytogenes, aerobic Gram-negative bacilli (e.g. Escherichia coli), Haemophilus influenzae, and Staphylococcus aureus causing most of the others. Streptococcus suis serotype 2 is an im- portant cause in Asia. (2) Post-traumatic meningitis—most hospital- acquired infections are caused by aerobic Gram-negative bacilli; S. pneumoniae causes most community-acquired disease.
(3) Device- associated meningitis—most infections are nosocomial and caused by coagulase-

negative staphylococci or Staph. aureus. Patients with recurrent meningitis frequently have an underlying anatomical or immunological defect (particularly hypogammaglobulinaemia or complement deficiencies). In some parts of the world, HIV infection has altered the pattern of aetiological agents (and presentation and outcome of meningitis),
with Mycobacterium tuberculosis increasingly common. Clinical features (1) Community-acquired meningitis—the classic triad of fever, nu- chal rigidity, and altered mental status is present in just under 50% of patients. Other manifestations include rashes (particularly with men- ingococcal disease), seizures, and focal neurological signs. Clinical tests of 'meningeal irritation' (e.g. Kernig's sign, Brudzinski's signs, and nuchal rigidity) are unreliable to rule out meningitis. Tuberculous, cryptococcal, and other fungal meningitides usually develop more slowly than pyogenic bacterial disease. (2) Post-traumatic bacterial meningitis—often indistinguishable clinically from spontaneous meningitis. (3)  Device-associated meningitis—usual presentation is insidious, with features of shunt blockage such as headache, vomiting, fever, and a decreasing level of consciousness. Investigation and treatment Speed is of the essence—the first step in the management of acute bacterial meningitis is to obtain blood cultures and start antimicro- bial therapy and (when indicated) adjunctive dexamethasone, along with providing any necessary supportive care. In the United Kingdom, family doctors are advised to give parenteral antibiotics before trans- ferring the patient to hospital if meningococcal meningitis is suspected. Lumbar puncture—this is the diagnostic procedure of choice if the diagnosis of bacterial meningitis cannot be ruled out, and can be safely performed without a preceding cranial CT scan to detect brain shift and evidence of herniation provided that the patient does not have any of the following: (1) signs suggesting a space-occupying lesions—papilloedema or focal neurological signs, excluding cranial nerve palsy, (2) new-onset seizure, (3) moderate-to-severe impair- ment of consciousness, or (4) an immunocompromised state. The cerebrospinal fluid—the opening pressure is usually raised. Frank turbidity instantly suggests the diagnosis of pyogenic meningitis.
On microscopic examination the white blood cell count is typic- ally over 1000 cells/μl, and over 100 cells/μl in over 90% of cases, with neutrophils usually predominant, and organisms may be seen after Gram or acridine orange staining. Elevated protein and de- pressed glucose concentrations aid in distinction from viral menin- gitis. Culture of organisms has a sensitivity of about 80% in untreated

24.11.1 Bacterial infections 6061 cases, but this is much reduced in those who have been partially treated, when lumbar puncture results must be interpreted with par- ticular care when attempting to differentiate viral, tuberculous, and bacterial disease. Rapid bacterial antigen tests and tests based on the polymerase chain reaction for bacterial DNA are increasingly used. Antimicrobial therapy—the choice of initial treatment is based on knowledge of which bacteria most commonly cause the disease, based on age and/or clinical circumstances, and on local antimicro- bial susceptibility patterns. Adults with community-acquired disease would typically receive initial treatment with (1) vancomycin, with (2) ceftriaxone or cefotaxime, with (if age >50 years, alcoholism, or altered immune status) (3) ampicillin, which would then be modified based on cerebrospinal fluid culture results and in vitro susceptibility testing. Dexamethasone—this appears to be beneficial in HIV-negative adults with confirmed bacterial meningitis, but there is no evidence for a beneficial effect in those who are HIV-positive and not on antiretroviral drugs.
Complications—these include systemic compromise, stroke, and raised intracranial pressure. Various adjunctive therapies have been described to improve outcome in such patients, including anti- inflammatory agents, anticoagulants, and strategies to reduce intra- cranial pressure, but

there are few randomized clinical studies with which to judge whether they are effective. Prevention The incidence of bacterial meningitis can be reduced by (1) vaccination—this is available against H. influenzae type b, pneumococcal and meningococcal disease; (2) chemoprophylaxis— given to close adult contacts of meningococcal disease (and children of <4 years exposed to H. influenzae type b). Introduction The association of headache and tinnitus with lethal inflammation of the brain was described by Hippocrates. It was not until the 19th century that lumbar puncture was introduced as a diagnostic pro- cedure. Most important in the treatment of bacterial meningitis was the introduction of penicillin in 1940, which reduced the mortality rates of bacterial meningitis to an overall fatality rate of approxi- mately 20%. Despite advances in medical care, the introduction of cranial CT and improvements in intensive care support, the mor- tality from bacterial meningitis remains high. The global spread of multidrug-resistant bacteria has further complicated the treatment of patients with bacterial meningitis. Aetiology, genetics, pathogenesis, and pathology Aetiology Bacterial meningitis occurs in many clinical situations, each of which is associated with a particular pattern of infecting organisms, clinical presentation, and outcome. Spontaneous meningitis is the most important category. It can be divided into neonatal menin- gitis and meningitis of childhood and adulthood. Post-traumatic meningitis follows neurosurgery or fractures of the skull. Device- associated meningitis complicates the use of cerebrospinal fluid shunts and drains. Infection may also be considered as community acquired or nosocomial (hospital acquired or physician associated). The bacterial species that cause meningitis vary by geographical re- gion and according to the categories (Table 24.11.1.1). Age and local social conditions influence the attack rate and mortality of spontan- eous meningitis. Neonatal meningitis is usually caused by three species: group B streptococci (Streptococcus agalactiae), Escherichia coli, and Listeria monocytogenes. Many other organisms have been reported to cause the disease. Infection mostly occurs in the postpartum period, but can occur as late as six weeks after birth. Prolonged rupture of mem- branes and low birth weight are important risk factors. Spontaneous community-acquired meningitis in children (under 14 years of age) is usually caused by Neisseria meningitidis or Strep. pneumoniae. The national implementation of conjugated Haemophilus influenzae type b (Hib) capsular vaccine immunization programmes by many countries during the 1990s has dramatically reduced, or almost eliminated, Hib meningitis; however, meningitis caused by H. influenzae remains common in countries that have not yet implemented a national immunization programme. In most countries, 80–85% of cases of spontaneous community- acquired meningitis in adults are caused by Strep. pneumoniae and N. meningitidis. L. monocytogenes, aerobic Gram-negative bacilli (such as E. coli), H. influenzae, and Staphylococcus aureus cause most of the remaining cases. Strep. suis (group R haemolytic streptococcus) serotype 2 is an important cause of meningitis (and rarely infective endocarditis and septicaemia) in Asia. Hong Kong, Thailand, China, and Vietnam all report Strep. suis as a major cause of adult meningitis. Post-traumatic meningitis occurs in patients with skull or spinal injuries (i.e. skull fractures) or in those who have undergone head and neck or spinal surgery. It usually arises in association with a cerebrospinal fluid leak and soon after injury, but may occur many years after the trauma. In these patients, the risk of developing men- ingitis is as high as 25% with a clinically apparent cerebrospinal fluid leak. The aetiology depends on whether the infection is acquired nosocomially or in the community. Most hospital-acquired infec- tions are caused by aerobic Gram-negative bacilli, such as E. coli, Klebsiella pneumoniae, other Enterobacteriaceae, Acinetobacter spp., and Pseudomonas spp. Less commonly, Strep. pneumoniae, H. influ- enzae, Staph. aureus, and other normal upper respiratory tract flora cause meningitis in patients in hospital. Post-traumatic meningitis acquired in the community is caused mainly by Strep.

pneumoniae. Device-associated meningitis is a well-recognized entity occurring in patients with cerebrospinal fluid drains and shunts. Most infec- tions are nosocomial and caused by coagulase-negative staphylo- cocci (50–60%) and Staph. aureus (15–30%). Aerobic Gram-negative bacilli, streptococci, Corynebacterium spp., and Propionibacterium acnes are encountered. These infections usually present within a few months of inserting the device. Occasionally, Strep. pneumoniae, N. meningitidis, and H. influenzae are responsible. Recurrent meningitis is an unusual (5–10% of meningitis) but well-recognized clinical category (see Chapter 24.11.2). Such cases Acknowledgement: The authors and editors acknowledge the inclusion of material from the chapter by DA Warrell, JJ Farrar, and DWM Crook in the 4th edition of the Oxford textbook of medicine.

 frequently have either an underlying anatomical or an underlying immunological defect. The immune deficiencies that most often predispose to recurrent meningitis are hypogammaglobulinaemia and complement deficiencies. Consideration should be given to im- munizing such patients against the most common pathogens. Genetics Adoption studies have shown that the risk of acquiring bacterial infections is strongly heritable, as is the risk of dying from an in- fection. In recent years there is a growing interest in genetic vari- ation in the host immune system related to susceptibility or severity of infection. For meningococcal diseases, a genome-wide asso- ciation study showed single nucleotide polymorphisms (SNPs) within complement factor H (CFH) to be associated with increased susceptibility to disease. For pneumococcal meningitis, SNPs in complement factor 3 (C3) were associated with reduced suscepti- bility to meningitis. For outcome on bacterial meningitis, a SNP in complement factor 5 (C5) was associated with outcome. In these patients, cerebrospinal fluid levels of C5a and sC5b-9 were sig- nificantly associated with outcome as well. Mice lacking the C5a receptor showed decreased disease severity, and treatment with C5-antibodies completely prevented mortality in a treatment model of pneumococcal meningitis in mice. 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. Particular subgroups of patients with a genetic predis- position to more severe illness, potentially mediated through their innate immune response, is possible, and further work in this area may help design rationale adjunct therapy. Pathogenesis The acquisition of infection and mode of invasion of the cerebro- spinal fluid vary with the type of meningitis. However, once infec- tion is established, the inflammatory injury and pathophysiology are similar in all types of bacterial meningitis. The organisms that cause neonatal meningitis are acquired by the baby from the vagina and perineum during delivery or from the en- vironment soon after birth. The three main infecting species, Strep. agalactiae (group B streptococci), E. coli, and L. monocytogenes, invade the host and cause septicaemia and meningitis. An unusual feature of E. coli and many Strep. agalactiae strains (capsular types K1 and III, respectively) is that their capsules consist of polysialic acid. The association of this unusual type of capsule with two viru- lent strains suggests a role in the pathogenesis of neonatal meningitis. Causative organisms of spontaneous meningitis, Strep. pneumo- niae and N. meningitidis, are acquired by person-to-person spread (see Chapters 8.6.3 and 8.6.5). Nasopharyngeal colonization by bac- teria generally leads to asymptomatic carriage. Invasion of the host is particularly likely to occur early after acquisition of the organism, before the host has developed protective immunity. Carriage is suf- ficient to produce immunity and resistance to disease. The greatest risk of disease, therefore, is in the first few years of life, at a time when the nonimmune host first encounters these pathogens. The precise anatomical site of invasion is not known for these patho- gens. In response to the local generation of inflammatory factors, however, as seen in the presence of viral infections, the

compos- ition of surface components on target epithelial and endothelial cells changes. Binding of bacteria to up-regulated receptors (e.g. platelet- activating-factor receptors) promotes migration through the re- spiratory epithelium and vascular endothelium, resulting in invasive disease. Once the bacterium invades the bloodstream, the host can react with massive activation of inflammatory cascades. The main cascade pathways that are involved are the complement system, in- flammatory response, and coagulation and fibrinolysis pathways. These pathways do not act independently but are able to interact. Genetic polymorphisms among components of these pathways (e.g. complement deficiencies and defects in sensing or opsonophagocytic pathways) are involved in the susceptibility to infection, as well as to severity of disease and outcome. Cytokines coordinate a wide var- iety of inflammatory reactions and play an important role in the

Table 24.11.1.1 Causative organisms in community-acquired adult meningitis in the Netherlands, Malawi, and Vietnam Organism Nationwide study, the Netherlands, 2006–2014 (n = 1412) Queen Elizabeth Central Hospital, Blantyre, Malawi, 1997–1999 (n = 351) Centre for Tropical Diseases, Ho Chi Minh City, Vietnam, 1998–2001 (n = 500) No. % No. % No. % Streptococcus pneumoniae 1017 72 88 25 38 8 Strep. suis 7 <1 – – 65 13 Gram-negative bacilli 13 1 22 6 11 2 Neisseria meningitidis 150 11 64 18 9 2 Streptococcus spp. 80 7 6 2 11 2 Staphylococcus aureus 21 1 – – 3 1 Listeria monocytogenes 74 5 – – – – Haemophilus influenzae 47 3 – – 7 1 Mycobacterium tuberculosis culture confirmed – – – – 46 9 Probable tuberculous meningitis – – 44 13 210 42 Other probable bacterial meningitis – – 59 17 5 1 No confirmation of bacteria – – 68 19 90 19

 initiation, maintenance, and termination of inflammatory reactions. Prominent proinflammatory cytokines include TNFα, IL-1, and IL- 6. Essential parts of the inflammatory response include activation of coagulation and fibrin deposition, shifting the haemostatic balance towards thrombosis. Pathogens can enter the central nervous system (CNS) via the bloodstream and via the blood–brain barrier, or by direct invasion through the external barrier (e.g. invade the cerebrospinal fluid dir- ectly through an anatomical defect). Shunt-associated meningitis is caused mainly by organisms that colonize the skin and contaminate the surgical wound and prosthetic material at the time of surgery. The infected shunt becomes coated with a film of adherent bacteria, commonly referred to as a ‘biofilm’, which is not susceptible to clin- ically achievable levels of antibiotic. Such infections are usually in- curable unless the foreign material is removed. The blood–brain barrier is formed by cerebral microvascular endothelial cells that restrict blood-borne pathogen invasion. Cytokines stimulate cell-surface expression of receptors, which allows binding to activated endothelial cells and invasion of bac- teria into the subarachnoid space. Physiologically, concentrations of leucocytes, antibodies, and complement components in the sub- arachnoid space are low. This condition facilitates multiplication of bacteria, which undergo autolysis under conditions such as growth to stationary phase or exposure to antibiotics. Lysis of bacteria leads to the release of immunostimulatory and/or toxic bacterial products. Bacterial cell-wall products (e.g. lipopolysaccharide and lipoteichoic acid), bacterial toxins (e.g. pneumolysin), and bacterial DNA induce a severe inflammatory response via binding to Toll-like receptors (TLRs). TLRs play a key role in innate immunity by their capacity to recognize conserved molecular patterns shared by sev- eral microorganisms. Once engaged, TLRs transmit the activating signal into the cell and thereby initiate the induction of genes, such as costimulatory molecules and inflammatory cytokines. Thus far, 11 members of the TLR family have been identified in mammals. Whereas TLR2 is considered the key receptor for pneumococci and other Gram-positive bacteria, TLR4 seems to play an important role in meningococcal and other Gram-

negative bacterial infec- tions. TLR-mediated signalling pathways are now being elucidated. Studies in experimental pneumococcal meningitis have demon- strated that the key pathway is dependent on myeloid differenti- ation factor 88, which induces early phase activation of NF-κB. The inflammatory cascade induces various pathophysiological al- terations, such as migration of leucocytes across the blood–brain barrier (leading to cerebrospinal fluid pleocytosis) and increased blood–brain barrier permeability. TNFα and IL-1β stimulate the expression of chemokines and adhesion molecules, which play an important role in the influx of leucocytes from the circulation to the cerebrospinal fluid. Although Fas (CD95) and Fas ligand (FasL, CD95L) have been implicated as being involved in the acute in- flammatory response by attracting neutrophils and regulating their survival, animal studies in pneumococcal meningitis have shown that they are not essential in the regulation of the acute inflamma- tory response during this disease. On stimulation with bacterial components, leucocytes release a broad range of potentially tissue- destructive agents that contribute to vasospasm and vasculitis, including oxidants (e.g. peroxynitrite) and proteolytic enzymes such as matrix metalloproteases. Evidence in animal studies of meningitis suggests that multiple types of programmed cell death play a central role in the complex balance among invading bacteria, the immune system, and host cells, leading to inflammation and tissue damage in infections. In addition, animal studies demon- strated that loss of ependymal cells and ciliary function expose the underlying neuronal milieu to host and bacterial cytotoxins which are likely to contribute to the neuropathology commonly observed in meningitis. The cell walls of Gram-positive bacteria and lipo- polysaccharides of Gram-negative bacteria cause inflammatory change, thereby increasing vascular permeability and leading to the development of cerebral oedema. The inflammatory reaction in meningitis is associated with several severe alterations in the normal physiology of the CNS (Fig. 24.11.1.1). (1)  Permeability of the blood–brain barrier in- creases, which is best measured by the increased penetration of the cerebrospinal fluid by albumin. Also, antibiotic penetration of the cerebrospinal fluid is enhanced. (2)  Increased intracranial pres- sure results from cerebral oedema secondary to an accumulation of interstitial fluid, and communicating hydrocephalus is caused by decreased cerebrospinal fluid reabsorption and cellular swelling sec- ondary to cell injury. (3) A vasculitis may affect mainly the large ves- sels traversing the subarachnoid space. This vascular injury may not only disrupt the normal autoregulation of cerebral blood flow, but, in severe cases, the vessel may become obstructed with thrombus, causing a cerebral infarct. The major impact of increased intracra- nial pressure and vasculitis is decreased cerebral perfusion, causing general hypoxic brain injury. Pathology There is diffuse acute inflammation of the pia arachnoid, with mi- gration of neutrophil leucocytes and exudation of fibrin into the cerebrospinal fluid. 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 con- gested and may be surrounded by pus (see Fig. 24.11.1.1). Pus and fibrin are found in the ventricles and there is ventriculitis, with loss of ependymal lining and subependymal gliosis. Within the sub- arachnoid space and intraventricular system, infection may produce blockages of cerebrospinal fluid circulation, especially at the various foramina or in the aqueduct, causing obstructive hydrocephalus or spinal block. If reabsorption of cerebrospinal fluid across the sub- arachnoid granulations is prevented by a subarachnoid haematoma or empyema or thrombosis of the intracranial veins and venous sinuses, communicating hydrocephalus will result. In patients with meningitis, intracranial hypertension may be the result of cerebral oedema, the ventricular dilatation of hydrocephalus, or subdural or epidural collections of pus. Cerebrovascular complications occur in 15–20% of patients with bacterial meningitis (see Fig. 24.11.1.1). In patients with pneumo- coccal meningitis, brain infarction is the cause of death in 14% of fatal episodes.

Other abnormalities include subdural effusion or empyema, septic thrombosis of the cerebral venous sinuses, sub- arachnoid haematomas, compression of intracranial structures as a result of intracranial hypertension, and herniation of the temporal lobes or cerebellum. Gross changes, such as pressure coning, which would provide an obvious cause of death, are rarely found. In some cases death may be attributable to related septicaemia, although the familiar finding of bilateral adrenal haemorrhage (Waterhouse– Friederichsen syndrome) may well be a terminal phenomenon

section 24 Neurological disorders 6064 rather than a cause of fatal adrenal insufficiency as was once im- agined. Patients with meningococcal septicaemia may develop acute pulmonary oedema. Myocarditis was a common finding in some series of patients. Epidemiology The attack rate of endemic meningitis caused by N. meningitidis is usually low (1–5 cases/105 persons per year), but occasionally the Fig. 24.11.1.1 Multiple complications in a patient with pneumococcal meningitis. (a) proton-density T2-weighted MRI of the brain shows a transverse view of a hyperintense signal in the basal ganglia that indicates bilateral oedema. (b) A postmortem view of the brain of the same patient shows yellowish-coloured meninges as a result of extensive inflammation. (c) Confirmation of the bilateral infarction of the basal ganglia. 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) oedema in the white matter. Published previously by van de Beek et al. (2006). Nature Clin Pract Neurol, 2(9), 504–16.

24.11.1 Bacterial infections 6065 incidence of the infection may increase and even reach epidemic proportions (e.g. >300 cases/105 persons per year). Crowding is thought to play a role in the epidemics occurring in military re- cruits, South African miners, and other groups of people crowded together in closed environments. The attack rate of N. meningiti- dis disease may increase secondarily to epidemics of influenza A. However, the precise origin of the major epidemics affecting re- gions such as sub-Saharan Africa remains unexplained. The bac- terial capsule plays a role in determining the pattern of invasive disease caused by N. meningitidis. Meningococcal virulence is re- lated to capsule expression, expression of other surface structures, and underlying genotype. The attack rate of Strep. pneumoniae meningitis (1–2 cases/105 persons per year) is remarkably constant around the world. The highest attack rate of all three bacterial species is in children under 1 year of age and falls off rapidly with increasing age. The decrease in susceptibility with increasing age results from the acquisition of protective immunity, mainly as a result of nasopharyngeal car- riage. It increases in patients aged over 50 years. A high propor- tion of pneumococcal cases exhibit an associated infective focus. Otitis media or sinusitis is found in approximately 30% of cases and pneumonia in up to 25%. Hypogammaglobulinaemia (primary or secondary, e.g. in nephrotic syndrome and chronic lymphocytic leukaemia), sickle cell disease, splenic dysfunction or splenec- tomy, and previous trauma to the skull (see next) are risk factors for developing pneumococcal meningitis. Strep. suis (group R haemolytic streptococci) serotype 2 infection is related to occupational contact with pigs or pork, but the pre- cise epidemiology remains poorly understood. In the Netherlands the incidence of S.  suis meningitis among abattoir workers and pig breeders was 3/100 000 per year. It is reported to be the most common cause of adult pyogenic meningitis in Vietnam. Possible routes of entry include skin abrasions, found in 40% of patients, and upper respiratory and gastrointestinal tracts. Splenectomized pa- tients are particularly at risk, as with other capsulated Gram-positive organisms. Although rarely fatal, Strep. suis is commonly associated with bilateral permanent deafness. Worldwide, L. monocytogenes accounts for few cases of menin- gitis, with an attack rate of approximately 0.2 to 0.4 cases/105

per- sons per year or 1–5% of the cases of meningitis. Increased attack rates have been associated with contaminated foods such as un- pasteurized soft cheeses, pâté, and poorly refrigerated precooked chicken. Meningitis due to L. monocytogenes is a disease that oc- curs among immunocompromised patients (e.g. attributable to immunosuppressive therapy, immunosenescence, diabetes, or ma- lignancies) and older people. Staph. aureus causes 1–5% of the cases of spontaneous meningitis and usually occurs in association with infective endocarditis. Spontaneous cases of H. influenzae menin- gitis, both capsulate type b and noncapsulate strains, account for up to 5% of adult cases of meningitis. Aerobic Gram-negative (i.e. E. coli) meningitis occurs especially in aged, debilitated, and dia- betic people. The source in these infections is usually thought to be the renal tract. The increasing incidence of HIV infection has altered the presen- tation and pattern of aetiological agents causing meningitis. A large series of adult patients with meningitis who presented to the Queen Elizabeth Central Hospital in Blantyre, Malawi, was reported in 1975. At that time, meningitis comprised 2.5% of medical admissions, the most common pathogens being N. meningitidis and Strep. pneumo- niae. Since then, the population of Malawi has been severely affected by the AIDS pandemic, and the HIV seroprevalence of antenatal women has climbed steadily through the 1980s to the present level of more than 30%. The changed overall pattern in this series is prob- ably due to the influence of HIV infection; in a survey of 153 pa- tients with invasive pneumococcal disease, HIV seroprevalence was 95%. In South Africa, HIV-infected children have more antibiotic- resistant isolates and a different clinical presentation compared with HIV-uninfected children. In adults, the HIV epidemic was found to be responsible for increasing chronic infections such as tuberculous and cryptococcal meningitides. The roll out of antiretroviral therapy is expected to modify this considerably. Another epidemiological trend is emerging of antibiotic-resistant strains of Strep. pneumoniae. Pneumococci resistance to penicillin, due to changes in its penicillin-binding proteins, was first reported in 1965. The prevalence of such resistance was limited until an epi- demic of highly resistant pneumococci occurred in South Africa in 1977. Since then, resistance has developed worldwide and in some regions it occurs in a frequency up to 70%. Reports of reduced sus- ceptibility of pneumococci to several antibiotics, including broad- spectrum cephalosporins, have also been published. In response to this epidemiological trend, recommendations for suspected and confirmed bacterial meningitis have necessarily evolved. Prevention Immunization Vaccines to the three major pathogens causing community-acquired meningitis are available. H. influenzae type b capsular conjugate (Hib) vaccines are now routinely given in the developed world and there has been a dramatic reduction in the incidence of H. influenzae type b meningitis in these countries and invasive disease has been essentially eliminated (see Chapter 8.6.13). However, it remains an important cause of meningitis in mostof the world where vaccine programmes have not been implemented. Current pneumococcal vaccines elicit immune responses to cell- wall polysaccharides of pneumococci (Chapter 8.6.3). The current 23-valent pneumococcal polysaccharide vaccine contains capsular polysaccharides of 23 serotypes responsible for about 90% of inva- sive pneumococcal infections. In the United States of America, the vaccine is recommended for all people aged 65 years and older and for those aged between 2 and 64 years who are at increased risk for invasive pneumococcal disease because of underlying illnesses, such as asplenia or immunodeficiency (e.g. infection with HIV or use of immunosuppressive drugs), or renal failure. However, the vaccine is poorly immunogenic in certain groups at high risk for invasive pneumococcal infection, especially children younger than 2 years old (with relatively immature B cells), older people, and immuno- compromised patients. The immune response in infants and young children can be improved by conjugation of pneumococcal polysac- charides to carrier

proteins that enable activation of T cells, thereby enhancing antibody production and immunological memory. The pneumococcal conjugate vaccines (PCV) consists of seven, ten, or thirteen capsular polysaccharides that are among the most prevalent in children aged 6 months to 2 years, include most antibiotic-resistant types, and are highly represented in

section 24 Neurological disorders 6066 immunocompromised and older patients. In the United States of America, the use of four doses of PCV is recommended for all children aged 23 months and younger and those aged 24– 59 months with chronic illnesses, including sickle cell disease, immunocompromising conditions, and cochlear implants. The introduction of PCV in the United States of America has reduced the burden of invasive pneumococcal disease in children as well as in older age groups through herd immunity. As a consequence, bacterial meningitis has become a disease predominantly of adults rather than of infants and children. Routine vaccination with PCV7 initially decreased the amount of multidrug-resistant pneumococcal strains, but this effect was only temporary. A decline in the incidence of pneumococcal meningitis has been observed in other studies that did not show evidence of an emergence of disease caused by serotype replacement. However, multiple other studies did observe an emergence of all invasive pneumococcal disease caused by serotypes not in the heptavalent vaccine, emphasizing the need for continued surveillance and the development of vaccines with efficacy against these other serotypes; 10-valent and 13-valent vaccines have been developed and may prove efficacious against these emerging serotypes. Patients with anatomical defects leading to an increased risk of invasive pneumo- coccal disease (i.e. previous trauma to the skull) may be at risk of unusual pneumococcal serotypes not commonly associated with invasive disease. In the developing world, invasive pneumococcal disease (including meningitis) remains a leading cause of morbidity and mortality. Since 1905, major epidemics of meningococcal meningitis have occurred in sub-Saharan Africa every few years (see Chapter 8.6.5). For epidemic meningitis control in sub-Saharan Africa, the World Health Organization recommends a strategy of emergency im- munization with meningococcal A/C polysaccharide vaccine when epidemic thresholds are exceeded. Given the relatively poor routine immunization coverage in this region, current strategies of immunization campaigns that achieve higher coverage would generally be more effective and less costly than model routine- scheduled programmes, assuming that campaigns can be rapidly implemented. Routine vaccination also offers herd immunity for the un- vaccinated population. The most illustrative example of such a major impact is the introduction of meningococcal conjugate vaccines. Vaccination against serogroup A  in Africa and sero- group C in Europe have decreased its incidence by 95% or more. More recently, a four-component, recombinant, meningococcal serogroup B vaccine was shown to be immunogenic and safe in two randomized controlled trials testing infants and children. Implementation of this vaccine may further decrease invasive meningococcal disease, but decreasing rates of penicillin suscep- tibility and the possible resurgence of the disease remain a public health threat. Immunization should be considered in all patients with recur- rent meningitis or traumatic head injury, and in splenectomized patients. Chemoprophylaxis The attack rate of meningitis is higher in the immediate contacts of an index case of meningococcal (up to 1000-fold) or H. influenzae type b meningitis (500-fold only in children under 4 years of age) than in the population at large. The administration of rifampicin or ciprofloxacin eliminates the carrier state and is assumed to eliminate the risk of secondary cases of meningitis (see Table 24.11.1.3). Close adult contacts of meningococcal disease are given either rifampicin (300 mg every 12 h for 2 days) or a single oral dose of ciprofloxacin (750 mg). Doctors, nurses, and other healthcare workers need not be given chemoprophylaxis unless they have given

mouth-to-mouth resuscitation. There is no evidence of benefit of antibiotics administered prophylactically to patients with skull fractures and/or cerebro- spinal fluid leakage. Surgical closure of the leak is the only effective means of preventing meningitis in such cases. The prevention of device-associated meningitis relies on rigorous infection con- trol. Ventricular and lumbar drains should be removed as soon as possible. Shunt insertion should be performed while adhering to strict aseptic techniques, and surgical antibiotic prophylaxis may also help to reduce shunt infection. Clinical features Community-acquired bacterial meningitis Early diagnosis and rapid initiation of appropriate therapy are vital in the treatment of patients with bacterial meningitis. A re- cent 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 de- velop late in the prehospital illness, if at all. Early signs before ad- mission 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 men- ingitis may vary depending on age, underlying conditions, and se- verity of illness. Clinical findings of meningitis in young children are often minimal. In childhood bacterial meningitis, and in older patients, classic 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 or stop feeding, and are found to have a bulging fontanelle, 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 of 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 such as ear or sinus infec- tions, 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 menin- gococcal meningitis, with reported sensitivities of 63–80% and with specificities of 83–92%. Rash is occasionally seen in patients with echovirus type 9, leptospirosis, Staph. aureus, Strep. pneu- moniae, Strep. suis, H.  influenzae, Salmonella enterica Serovar Typhi, and other infections, especially in those associated with

24.11.1 Bacterial infections 6067 infective endocarditis. The brownish or reddish geometrical, vasculitic rash of fulminant meningococcaemia is unmistak- able and, characteristically, the toes and fingers become necrotic (Fig. 24.11.1.2). Seizures before admission occur in 5–9% of all cases, and 15–23% of patients develop seizures during their clinical course. Cranial nerve palsy is relatively rare; most commonly affected are cranial nerves VIII (6%), III (4%), IV (3%), and VII (2%). Focal cerebral findings (aphasia, hemiparesis, and monoparesis) on admission occur in approximately 15–23% of patients. Papilloedema is un- common in patients with acute bacterial meningitis (3–4% of patients; however, in most studies the results of fundoscopic exam- ination were not recorded). Systemic manifestations, such as hypo- tension and tachycardia, occur frequently in community-acquired bacterial meningitis. Bilateral sensorineural deafness develops early, two to nine days after the start of symptoms, in most patients with Strep. suis type 2 meningitis. Initially associated with tinnitus this may progress to complete deafness within 24 h. Bacteria probably invade the cochlea via the cochlear aqueduct from the subarachnoid space to produce suppurative labyrinthitis and acute deafness. Associated clinical fea- tures of Strep. suis

meningitis include III nerve palsy, septic arth- ritis, and purpuric skin lesions. Arthritis occurs in 7% of adults with bacterial meningitis, most commonly in meningococcal meningitis, but is also seen in 5% of patients with Strep. suis. Recognition of con- current arthritis is important because prolonged antibiotic therapy is necessary. The presence or absence of meningeal signs such as Kernig's sign, Brudzinski's signs, and nuchal rigidity are physical examination findings often documented when evaluating a patient for possible meningitis. Kernig's sign was first described in the 1880s and was originally done with the patient in the sitting position, but today is frequently done in the supine position. This test involves flexing the hip and extending the knee and a positive result is recorded when pain is elicited in the back and legs. Brudzinski's neck sign is typically done in the supine position where the head is passively flexed and is interpreted as positive when flexion at the hips to lift the legs is elicited in response. Nuchal rigidity is a clinical determination of severe neck stiffness and inability to passively flex and extend the head in a normal fashion. Local causes of neck stiffness, such as local sepsis (i.e. in the nuchal muscles or cervical lymph nodes), cervical spondylitis (particularly common in older people), temporoman- dibular arthritis, dental problems, and pharyngeal lesions, should be considered. A prospective study of 297 adults evaluated Kernig's sign, Brudzinski's sign, and nuchal rigidity and their relationship to men- ingitis diagnosed by lumbar puncture. This study found that none of these signs accurately identified patients with meningitis. There was no correlation with moderate meningeal inflammation or with microbial evidence of infection (such as positive Gram stain or posi- tive cultures), and Kernig's and Brudzinski's signs were found to have poor sensitivity (5%) with high specificity (95%). In this study population, 80 of 297 patients had meningitis, but only 24 had nu- chal rigidity (sensitivity, 30%). Nuchal rigidity was absent in 148 of the 217 patients without meningitis (specificity, 68%). Notably, only 3 of the 297 patients had bacterial meningitis by cerebro- spinal fluid culture, and nuchal rigidity failed to identify 2 of these 3 patients with bacterial meningitis. Post-traumatic bacterial meningitis This is often indistinguishable clinically from spontaneous men- ingitis. 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 cerebrospinal fluid 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 con- sideration should be given to broad-spectrum antibiotics including metronidazole for anaerobic pathogens. Fig. 24.11.1.2 Rashes in a patient with meningococcal meningitis.

 Infections of cerebrospinal fluid shunts Patients may present with clinical features typical of spontan- eous 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 con- stant feature and may be present in as few as 20% 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 endo- carditis together with glomerulonephritis (shunt nephritis), whereas infection of shunts draining into the peritoneal cavity produces peritonitis. Differential diagnosis When a patient presents to an emergency department physician, primary care doctor, neurologist, or infectious disease specialist for an emergent evaluation, the patient history can help to estimate the probability of meningitis. A wide variety of patient complaints may be elicited from patients with meningitis, and a meta-analysis that included 845 patients over a 30-

year period showed poor sen- sitivity and specificity for symptoms such as headache, nausea, and vomiting for the diagnosis of meningitis. This is not surprising since such nonspecific symptoms are found in many patients with a wide variety of clinical conditions. Viral meningitis is important in the differential diagnosis. Meningeal irritation is seen in many acute febrile conditions, especially in children. Local infections of the nasopharynx, cervical lymph nodes, muscles, and spine may produce convincing neck stiffness. Tetanus may be easily confused with meningitis if the persisting rigidity and recurrent spasms go unnoticed. In all these conditions the cerebrospinal fluid will be normal. Subarachnoid haemorrhage can present with sudden headache, neck stiffness, and deteriorating consciousness, and a less dramatic progression of symptoms is seen in patients with some intracranial tumours. Tuberculous and cryptococcal and other fungal meningitides usually develop more slowly than pyogenic bacterial menin- gitis. They may be distinguished by examining cerebrospinal fluid. Cryptococci and free-living amoebae may be mistaken for lymphocytes in the cerebrospinal fluid unless an India-ink preparation is examined to reveal the cryptococcal capsule and the characteristic movements of amoebae. Aseptic meningitis comprises many conditions, many of them caused by viruses, in which there are clinical signs of meningism and the cerebrospinal fluid is found to be abnormal (see Chapter 24.11.2). This group includes partially treated bacterial meningitis and the chemical meningitides, resulting from the introduction of irritants into the subarachnoid space (contrast media, antimicrobial agents, and contaminants of lumbar puncture and spinal anaesthesia). The cerebrospinal fluid glucose concentration may be very low. Discharge of a tuberculoma may produce a sterile tuberculin reac- tion, and the discharge of the contents of a craniopharyngioma or epidermoid cyst into the cerebrospinal fluid can also cause chem- ical meningitis. Clinical investigations Lumbar puncture Once an initial patient evaluation has been completed with history and physical findings, lumbar puncture is the diagnostic procedure of choice if the diagnosis of bacterial meningitis cannot be ruled out. Characteristic findings in the cerebrospinal fluid are typically used to make the diagnosis of meningitis. Indications for CT scan before lumbar puncture In view of the urgent nature of this testing to make the diagnosis of meningitis, one of the issues that physicians are faced with in the hospital emergency department is whether neuroimaging—either CT or MRI—is required before lumbar puncture. Patients with ex- panding masses (e.g. subdural empyema, brain abscess, or necrotic temporal lobe in herpes simplex virus encephalitis) may present with symptoms that appear to be identical with those of bacterial meningitis. In these patients, lumbar puncture may be complicated by brain herniation. The withdrawal of cerebrospinal fluid reduces counterpressure from below, thereby adding to the effect of com- pression from above, increasing the brain shift that may already be present. In patients with suspected bacterial meningitis the inter- pretation of cranial imaging should be focused on brain shift and space around the brainstem, which may result from the pressure effects of a focal space-occupying lesion or severe diffuse brain swelling as illustrated in Fig. 24.11.1.3. 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 tem- poral relationship of lumbar puncture and herniation, but as pre- viously mentioned 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 criteria: patients who have new-onset seizures, an immunocompromised state, signs suggestive of space- occupying lesions (papilloedema or focal neurological signs—not including cranial nerve palsy), or moderate-to-severe impairment of consciousness. Other contraindications to lumbar puncture in- clude local skin sepsis at the site of puncture, a clinically unstable pa- tient, and any clinical suspicion of spinal cord compression.

Lumbar puncture may also be harmful in patients with coagulopathy, be- cause of the chance of needle-induced subarachnoid haemorrhage or of the development of spinal subdural and epidural haematomas. Contraindications for (immediate) lumbar puncture are provided in Box 24.11.1.1. Examination of cerebrospinal fluid (See Chapter 24.3.1.) In patients with bacterial meningitis, the cerebrospinal fluid opening pressure is usually raised (>200 mmCSF), and occasionally it is markedly raised (>500 mmCSF). Frank turbidity of cerebro- spinal fluid instantly suggests the diagnosis of pyogenic meningitis. Microscopic examination of cerebrospinal fluid for white cells, red cells, and organisms, the measurement of glucose and protein, and culture are important investigations in a case of possible menin- gitis. Classically described, the white blood cell count in bacterial meningitis is typically greater than 1000 cells/μl, although in viral

24.11.1 Bacterial infections 6069 meningitis it is less than 300 cells/μl—although considerable overlap exists in these categories. The neutrophil count is typically elevated in bacterial meningitis compared with viral meningitis. A raised cerebrospinal fluid white blood cell (WBC) count is pre- sent in most patients with bacterial meningitis but, rarely, the count may be normal (fewer than 6 WBC/μl, all lymphocytes) but the cerebrospinal fluid may still appear turbid because of the vast num- bers of bacteria. Most cases (more than 90%) present with a count exceeding 100 WBC/μl. The measurement of protein and glucose is an important aspect of cerebrospinal fluid analysis to comple- ment the cell counts because abnormal protein and glucose levels are typically found in bacterial disease but are relatively normal in many cases of viral meningitis. Gram or acridine orange stain of cerebrospinal fluid samples, although having reported sensitivities of only 50–90% can certainly help to make the diagnosis of bac- terial disease with a specificity approaching 100%. Care should be taken in assessment of the cerebrospinal fluid in patients who have been partially treated with antibiotics before being seen. In this case the cerebrospinal fluid may be very difficult to interpret and the cerebrospinal fluid from partially treated pyogenic meningitis and tuberculosis (TB) meningitis can be extremely difficult. An algo- rithm based on readily available clinical and laboratory tests can be useful in deciding whether the patient has pyogenic meningitis or TB meningitis. Culture of organisms has a sensitivity of approximately 80% in untreated cases, and is aided by the culture of good volumes of cerebrospinal fluid and minimizing the delay between the lumbar puncture and setting up of the culture. Organisms are recovered much less often from partially treated cases. Isolation of an or- ganism is not only helpful in establishing the diagnosis, but al- lows the identification and susceptibility testing of the aetiological agent. The culture result can also be used to decide on the need for antibiotic prophylaxis, contact tracing, and other public health control measures. A range of rapid bacterial antigen tests may be helpful in detect ing the presence of bacterial capsular polysaccharide antigens of pneumococci, meningococci, H. influenzae, and group B strepto- cocci. These tests may reach a sensitivity and specificity of 90% or greater for detecting specific causes of bacterial meningitis. However, in our experience these tests seldom add to the diagnostic yield of a good Gram or acridine orange stain performed on an ad- equate volume of cerebrospinal fluid. New molecular techniques for detecting bacteria in the cerebrospinal fluid by polymerase chain re- action (PCR) methods have emerged as powerful tools in the diag- nosis of patients with negative cultures of cerebrospinal fluid; such tools have high sensitivity and specificity. Recurrent bacterial meningitis (See Chapter 24.11.2.) In patients with no apparent cause of recurrent meningitis or known history of head trauma, the high prevalence of remote head injury and cerebrospinal fluid leakage justifies an active search for anatomical defects and cerebrospinal fluid leakage in a patient with recurrent bacterial meningitis. Detection of β2-transferrin in nasal (a) (b) (c) Fig. 24.11.1.3 Cranial imaging to evaluate potential contraindications

for lumbar puncture should be focused on identifying signs of a focal space-occupying lesion, evidence of brain shift, and/or signs of severe diffuse brain swelling. (a) Normal brain, (b) meningitis-associated cerebral infarct causing pronounced brain shift, and (c) diffuse brain swelling associated with severe infection. Initial lumbar puncture should not be done when CT findings of significant brain shift are found, and empirical therapy for meningitis should be continued in such patients. Reprinted from Fitch and van de Beek (2007). Lancet Infect Dis, 7(3), 191–200, Copyright 2007, with permission from Elsevier. Box 24.11.1.1 Contraindications for immediate lumbar puncture Neuroimaging before lumbar puncture to detect brain shift • Signs of brain shift — Papilloedema — Focal neurological signs, not including cranial nerve palsy • Glasgow Coma Score less than 10 • Severe immunocompromised state • New-onset seizures Other contraindications for lumbar puncture • Serious skin infection at site lumbar puncture • Septic shock • Spinal cord compression • Anticoagulant therapy or severe coagulopathy

section 24 Neurological disorders 6070 discharge in cases of rhinorrhoea is a sensitive and specific method to confirm the presence of a cerebrospinal fluid leak. Optimum imaging is done by thin-slice CT of the skull base and is also the ini- tial imaging of choice. It is important to take into account that small bone defects on CT do not prove cerebrospinal fluid leakage. T2- weighted MRI may detect a small cerebrospinal fluid leak, but lacks fine bone detail. As cerebrospinal fluid leaks are often intermittent, the administration of intrathecal contrast will not be more accurate to prove leakage and depends on the timing of imaging. Anatomical defects and cerebrospinal fluid leakage might require consultation of a neurosurgeon or otolaryngologist to evaluate the necessity of surgical repair, which has an overall high success rate and a low mor- tality and morbidity. Emergency management Management algorithm Although some guidelines propose an arbitrary time-based goal for antibiotic administration, others focus on disease severity and immediate antibiotic administration once the diagnosis has been considered. No prospective clinical data have determined the rela- tionship between the timing of antimicrobial treatment and clinical outcome in patients with bacterial meningitis. However, delayed treatment is associated with a bad outcome. A retrospective study in adults with acute bacterial meningitis showed that delayed antibiotic treatment (resulting from cranial imaging or hospital transfer) con- tributed significantly to mortality. Another retrospective study of adults with community-acquired bacterial meningitis also identi- fied delay in treatment with adverse outcome in patients who had deteriorated to the highest stage of prognostic severity before the first dose of antibiotics was administered. A recent prospective study of patients with pneumococcal meningitis who were admitted to the intensive care unit showed that a delay of more than 3 h between hospital admission and initiation of antimicrobial therapy was as- sociated with an increased 3-month mortality. In patients with sus-pected bacterial meningitis whose lumbar puncture is postponed because of coagulopathy (e.g. disseminated intravascular coagu- lation), severe septic shock, or the need for cranial imaging (see Box 24.11.1.1), antimicrobial therapy should be started immedi- ately (Fig. 24.11.1.4). In those who deteriorate clinically or who have cloudy cerebrospinal fluid (suggestive of bacterial meningitis), antibiotic treatment should be started directly after lumbar puncture whereas in those who are clinically stable and whose cerebrospinal fluid is not cloudy treatment can be delayed until cerebrospinal fluid analysis confirms the diagnosis. In the United Kingdom, family doctors are advised to give (paren- teral) antibiotics before transferring the patient to hospital if men-ingococcal meningitis is suspected. However, it may be difficult to identify patients with meningococcal meningitis and to determine whether they will benefit from such prehospital treatment. Several retrospective studies have shown conflicting results. Some patients with

bacterial meningitis are unconscious and should be managed accordingly. Their airway should be maintained and they may need intubation to protect the airway and maintain ventilation. Monitoring in a neurological–neurosurgical intensive care unit is recommended in order to recognize changes in level of consciousness and the development of new neurological signs, monitor for subtle seizures, and effectively treat severe agitation. A urethral catheter should be inserted. Bacterial meningitis may be associated with septic shock, which is an important predictor of outcome. Patients with meningitis and septic shock may require insertion of a Swan–Ganz catheter, to measure cardiac output, the cardiac index, systemic vascular resist- ance, and pulmonary wedge pressures in order to assess intravas- cular volume and cardiac function. Care should be taken to estimate and replace imperceptible fluid loss through the skin and lungs in patients who are febrile. Patients with bacterial meningitis are at risk of acute hyponatraemia, although most cases are mild. This may result from cerebral salt wasting, the syndrome of inappropriate antidiuretic hormone secretion, or ex- acerbation by aggressive fluid resuscitation. Uncertainty about the mechanism creates a clinical dilemma about whether intravenous fluids should be restricted in bacterial meningitis. In children with bacterial meningitis, fluid restriction does not improve either brain oedema or outcome. It seems reasonable to maintain adult patients with meningitis in a normovolaemic state. Patients whose core tem- peratures exceed 40°C should be cooled using physical methods or an antipyretic to avoid brain damage and excessive fluid loss through sweating. Antipyretic treatments are often administered in severely ill patients, but randomized controlled trials (RCTs) of 723 children with bacterial meningitis in Luanda, Angola, and 360 children in Malawi, showed that paracetamol did not increase survival. Case series reported favourable effects of moderate hypothermia in bac- terial meningitis, but one RCT showed that moderate hypothermia did not improve outcome in patients with severe meningitis, and even suggested harm. Antimicrobial treatment The choice of initial antimicrobial therapy is based on which bac- teria most commonly cause the disease, based on age, clinical cir- cumstances, and prevailing antimicrobial susceptibility patterns (Table 24.11.1.2). Once the pathogen has been isolated, specific treatment based on the susceptibility of the isolate can be substi- tuted for the empirical regimen (Table 24.11.1.3). The pharmacokinetics and pharmacodynamics dynamics of anti- microbial agents are highly relevant. Penetration of the blood–brain barrier to reach the subarachnoid space is of paramount import- ance in clearing bacteria from the cerebrospinal fluid. Penetration is affected by lipophilicity, molecular weight, structure, and protein- bound fraction. Bacterial meningitis is a dynamic process and cerebrospinal fluid penetration of antimicrobials is highly de- pendent on the breakdown of blood–brain barrier permeability. Anti-inflammatory drugs such as dexamethasone might influence permeability and thereby interfere with cerebrospinal fluid pene- tration of antimicrobial agents. The activity of antimicrobial drugs in infected purulent cere- brospinal fluid depends on their activity in a low pH environment, protein-bound fraction, bacterial growth rate and density, and clear- ance from the cerebrospinal fluid. Antibiotics target the bacterial cell wall, the bacterial cell membrane, and biosynthetic processes. Bacteriostatic antibiotics merely inhibit growth of microorganisms, whereas bactericidal agents kill the bacteria. Antibiotic-induced lysis of bacteria leads to the release of immunostimulatory cell-wall components and toxic bacterial products, which induce a severe inflammatory response through binding to TLRs.

24.11.1 Bacterial infections 6071 NO NO Assess severity Ventilation Circulation Neurologic examination Stabilization and/or correction coagulopathy Indications for imaging before lumbar puncture? CSF consistent with bacterial meningitis? CSF consistent with bacterial meningitis?

Bacterial meningitis Bacterial meningitis: DXM and empiric therapy DXM and empiric antimicrobial therapy DXM and empiric antimicrobial therapy Cloudy CSF or apparent progress of disease? Shock and/or Coagulopathy? Anticoagulant-use Disseminated intravascular coagulation DXM and empiric antimicrobial therapy Start investigations Blood cultures Blood gases Serum laboratory investigations Chest X-ray Rash: skin biopsy NO Lumbar puncture Indications for imaging before lumbar puncture? Lumbar puncture No lumbar puncture CT/MRI scan brain Significant space-occupying lesion? Reconsider diagnosis Suspicion for bacterial meningitis Typical signs may be absent, prior antibiotics may mask severity of illness YES YES YES YES YES NO YES NO NO NO YES
Fig. 24.11.1.4 Algorithm for the management of patients with suspected community-acquired bacterial meningitis. CSF, cerebrospinal fluid. This material was previously published as part of an online supplementary appendix to van de Beek, et al. (2006).
N Engl J Med, 354(1), 44–53. Copyright 2006 Massachusetts Medical Society. All rights reserved.

section 24 Neurological disorders 6072 Neonatal meningitis This is largely caused by group B streptococci, E.  coli, and L.  monocytogenes. Initial treatment should, therefore, consist of penicillin or ampicillin plus a third-generation cephalosporin, pref- erably cefotaxime or ceftriaxone, or penicillin, or ampicillin and an aminoglycoside. Childhood meningitis In the community, children are at risk of meningitis caused by N.  meningitidis and Strep. pneumoniae, and, rarely in Hib-immunized 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. Adult meningitis Spontaneous meningitis in adults is usually caused by Strep. pneumo-niae or N. meningitidis. Due to the worldwide emerge of multidrug- resistant strains of Strep. pneumoniae, some experts recommend addition of vancomycin to the initial empirical antimicrobial regimen in adult patients. Although no clinical data on the efficacy of rifampicin in patients with pneumococcal meningitis are currently available, some experts would recommend the use of this agent in combin- ation with a third-generation cephalosporin, with or without vanco-mycin, 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. Strep. suis remains sensitive to the β-lactams and should be treated with penicillin, cefotaxime, or ceftriaxone. Fluoroquinolones may be an alternative. In patients aged over 50 years, ampicillin should be added to the aforementioned anti- biotic regimen for additional coverage of L. monocytogenes, which is more prevalent among this age group. Nosocomial post-traumatic meningitis This is caused mainly by multiresistant hospital-acquired organ- isms such as K.  pneumoniae, E.  coli, P.  aeruginosa, and Staph. aureus. Depending on the pattern of susceptibility in a given hos- pital unit, ceftazidime (2 g intravenously, every 8 h), cefotaxime, ceftriaxone, or meropenem should be chosen. If P. aeruginosa in- fection seems likely, ceftazidime or meropenem are the preferred antibiotics. Device- and shunt-associated meningitis This is caused by a wide range of organisms, including meticillin- 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, 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 sus- pected, and flucloxacillin or vancomycin if Staph. aureus is likely. The infected shunt or drain will almost certainly have to be removed urgently. Definitive antibiotic treatment

Once the aetiological agent has been isolated and its suscepti- bilities determined, the empirical treatment should be changed, if necessary, to an agent or agents specific for the isolate (see Table 24.11.1.3). The optimal duration of treatment has not been determined by rigorous scientific investigation; however, treat- ment regimens that are probably substantially in excess of the min- imum necessary to achieve cure have been arrived at through wide clinical experience.
Table 24.11.1.2 Recommendations for empirical antimicrobial therapy in suspected community-acquired bacterial meningitis Predisposing factor Common bacterial pathogens Initial intravenous antibiotic therapy Age <1 month Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes Ampicillin plus cefotaxime or an aminoglycoside 1–3 months Strep. pneumoniae, Neisseria meningitidis, Strep. agalactiae,
Haemophilus influenzae, E. coli, L. monocytogenes Ampicillin plus vancomycin plus ceftriaxone or cefotaximea 3–23 months Strep. pneumoniae, N. meningitidis, Strep. agalactiae,
H. influenzae, E. coli Vancomycin plus ceftriaxone or cefotaximea 2–50 years N. meningitidis, Strep. pneumoniae Vancomycin plus ceftriaxone or cefotaximea

> 50 years N. meningitidis, Strep. pneumoniae, L. monocytogenes, aerobic Gram-negative bacilli Vancomycin plus ceftriaxone or cefotaxime plus ampicillinb With risk factor presentc Strep. pneumoniae, L. monocytogenes, H. influenza Vancomycin plus ceftriaxone or cefotaxime plus ampicillin Post-traumatic Strep. pneumoniae, H. influenzae Vancomycin plus ceftriaxone or cefotaxime plus ampicillin Postneurosurgery Coagulase-negative staphylococci, Staph. aureus, aerobic
> Gram-negative bacilli (including Pseudomonas aeruginosa) Vancomycin plus ceftazidime Cerebrospinal fluid shunt Coagulase-negative staphylococci, Staph. aureus, aerobic Gram-negative bacilli (including P. aeruginosa), Propionibacterium acnes Vancomycin plus ceftazidime General recommendations for intravenous empirical antibiotic treatment have included penicillin 2 MU every 4 h; amoxicillin or ampicillin 2 g every 4 h; vancomycin, 15 mg/kg every 8 h; third-generation cephalosporin: ceftriaxone 2 g every 12 h or cefotaxime 2 g every 4–6 h; ceftazidime 2 g every 8 h. a In areas with very low penicillin resistance rates monotherapy, penicillin may be considered. b In areas with very low rates of penicillin resistance and cephalosporin resistance, combination therapy of amoxicillin and third-generation cephalosporin may be considered. c Alcoholism, altered immune status. Adapted from van de Beek D, et al. (2006). N Engl J Med, 354(1), 44–53. 

24.11.1 Bacterial infections 6073 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 benzylpenicillin every 4 h. There are no randomized comparative clinical studies of the various dosing regimens. In gen- eral, 7 days of antimicrobial therapy are given for meningitis caused by N. meningitidis and H. influenzae, 10–14 days for Strep. pneu- moniae or Strep. suis, 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 Adjunctive dexamethasone treatment Animal models of bacterial meningitis showed that bacterial lysis, induced by antibiotic therapy, leads to inflammation in the sub- arachnoid space. The severity of this inflammatory response is associated with outcome and can be attenuated by treatment with steroids. On the basis of experimental meningitis studies, several clinical trials have been undertaken to determine the effects of ad- junctive steroids in children and adults with bacterial meningitis. 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 im- munosuppressive properties. It has excellent penetration into the cerebrospinal fluid. 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. influ- enzae type b. As the design of most available studies on adjunctive dexa- methasone therapy in adults with bacterial meningitis was flawed, its value in adults was long debated. In 2002, results of a European randomized placebo-controlled trial showed that Table 24.11.1.3 Specific antimicrobial therapy in community-acquired bacterial meningitis based on cerebrospinal fluid (cerebrospinal fluid) culture results and in vitro susceptibility testing; this material was previously published as part of an online supplementary appendix to reference Microorganism, susceptibility Standard therapy Alternative therapies Streptococcus pneumoniae Penicillin MIC < 0.1 mg/l Benzylpenicillin or ampicillin Cefotaxime or ceftriaxone, chloramphenicol 0.1–1.0 mg/l Cefotaxime or ceftriaxone Cefepime, meropenem ≥ 2.0 mg/l Vancomycin + cefotaxime or ceftriaxonea Fluoroquinolonea Cefotaxime or ceftriaxone MIC ≥1.0 mg/l Vancomycin plus cefotaxime or ceftriaxoneb Fluoroquinolonec Neisseria meningitidis Penicillin MIC <0.1 mg/l Benzylpenicillin or ampicillin Cefotaxime or ceftriaxone, chloramphenicol 0.1–1.0 mg/l Cefotaxime or ceftriaxone Chloramphenicol, fluoroquinolone, meropenem Listeria monocytogenes Benzylpenicillin or ampicillind Trimethoprim–sulfamethoxazole, meropenem Group B streptococci Benzylpenicillin or ampicillind Cefotaxime or ceftriaxone Escherichia coli and other Enterobacteriaceae Cefotaxime or ceftriaxoned Aztreonam,d fluoroquinolone, meropenem,d trimethoprim–sulfamethoxazole, ampicillind Pseudomonas aeruginosa Ceftazidimed or cefepimed Aztreonam,d ciprofloxacin,d meropenemd Haemophilus influenzae β-Lactamase negative Ampicillin Cefotaxime or ceftriaxone, cefepime, chloramphenicol, fluoroquinolone β-Lactamase positive Cefotaxime or ceftriaxone Cefepime, chloramphenicol, fluoroquinolone Chemoprophylaxise N. meningitidis Rifampicin, ceftriaxone, ciprofloxacin, azithromycin a Consider addition of rifampicin if dexamethasone is given. b Consider addition of rifampicin if the MIC (minimum inhibitory concentration) of ceftriaxone is ≥2 mg/litre. c Gatifloxacin or moxifloxacin; no clinical data on use in patients with bacterial meningitis. d Consider addition of an aminoglycoside. e Prophylaxis is indicated for close contacts, who are defined as those with intimate contact, which covers those eating and sleeping in the same dwelling as well as those having close social and kissing contacts; or healthcare workers who perform mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management. Patients with meningococcal meningitis who are treated with monotherapy of penicillin or amoxicillin (ampicillin) should also receive chemoprophylaxis, because carriage is not reliably eradicated by these drugs. fGeneral recommendations for intravenous empirical antibiotic treatment have included penicillin 2 MU every 4 h; amoxicillin or ampicillin 2 g every 4 h; vancomycin 15 mg/ kg every 8 h; third-generation cephalosporin: ceftriaxone 2 g every 12 h or cefotaxime 2 g every 4–6 h; cefepime 2 g every 8 h; ceftazidime 2 g every 8 h; meropenem 2 g every 8 h; chloramphenicol 1–1.5 g every 6 h; fluoroquinolone: gatifloxacin 400 mg every 24 h or moxifloxacin 400 mg every 24 h, although no data on optimal dose needed in patients with bacterial meningitis; trimethoprim–sulfamethoxazole

5 mg/kg every 6–12 h; aztreonam 2 g every 6–8 h; ciprofloxacin 400 mg every 8–12 h; rifampicin 600 mg every 12–24 h; aminoglycoside: gentamicin 1.7 mg/kg every 8 h. The preferred dose for chemoprophylaxis: rifampicin 600 mg orally twice daily for 2 days; ceftriaxone 250 mg intramuscular; ciprofloxacin 750 mg orally; azithromycin 500 mg orally. Adapted from van de Beek, et al. (2006). N Engl J Med, 354(1), 44–53. 

section 24 Neurological disorders 6074 adjunctive treatment with dexamethasone, given before or with the first dose of antimicrobial therapy, improved the outcome of adult bacterial meningitis (relative risk (RR) 0.59; 95% con- fidence interval (CI) 0.37–0.94) and reduced its mortality (RR 0.48; 95%CI 0.24–0.96). This beneficial effect was most apparent in patients with pneumococcal meningitis, in whom the mortality rate 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, including only patients with pneumococcal meningitis who died within 14 days of admission, the mortality benefit of dexametha- sone therapy was due entirely to reduced mortality from systemic causes such as septic shock, pneumonia, or acute respiratory dis- tress syndrome; there was no significant reduction in mortality due to neurological causes. Results of a subsequent quantitative review of this topic in adults, which included five clinical trials, confirmed that treatment with corticosteroids was associated with a significant reduction in mor- tality (RR 0.6; 95% CI 0.4–0.8) and in neurological sequelae (RR 0.6; 95% CI 0.4–1). The reduction in case fatality in patients with pneumococcal meningitis was 21% (RR 0.5; 95% CI 0.3–0.8). In meningococcal meningitis, in which the number of events was smaller, there were favourable point estimates for preventing mor- tality (RR 0.9; 95% CI 0.3–2.1) and neurological sequelae (RR 0.5; 95% CI 0.1–1.7), but these effects did not reach statistical signifi- cance. 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. Since the publication of these results, adjunctive dexa- methasone has become routine therapy in most adults with sus- pected bacterial meningitis. In 2007, an updated Cochrane analysis was published on the effi- cacy and safety of adjunctive corticosteroids, including 20 random- ized clinical trials involving 2750 people. In this analysis, adjuvant corticosteroids were associated with lower case fatality (RR 0.83; 95% CI 0.71–0.99), lower rates of severe hearing loss (RR 0.65; 95% CI 0.47 to 0.91), and long-term neurological sequelae (RR 0.67; 95% CI 0.45–1.00). Again, the effect of corticosteroids was evident in adults with bacterial meningitis. In children the beneficial effect was less convincing, although there was a trend towards a beneficial ef- fect on hearing loss in non-H. influenzae meningitis. In the Cochrane meta-analysis, there was a difference in effi- cacy of corticosteroids between high- and low-income countries. For children with bacterial meningitis admitted in high-income countries, corticosteroids showed a protective effect against se- vere hearing loss (RR 0.61; 95% CI 0.41–0.90), favourable point es- timates for severe hearing loss associated with non-H. influenzae meningitis (RR 0.51; 95% CI 0.23–1.13), and short-term neuro- logical sequelae (RR 0.72; 95% CI 0.39–1.33). For children in low- income countries, the use of corticosteroids was not associated with benefit. This difference was mainly caused by inclusion of the Malawian study, which included children in whom treatment began later, children who were more likely to be malnourished, and some HIV-1 positive children. There may be several reasons for the dif- ference in efficacy of corticosteroids, such as delayed presentation, clinical severity, underlying anaemia, malnutrition, the antibiotic used and HIV-1 positivity. A recent study compared characteristics of children with culture-positive bacterial

meningitis treated in the Royal Liverpool Children's Hospital and the Children's Unit, Queen Elizabeth Central Hospital, Blantyre, Malawi; the two cohort studies were derived from time periods before the introduction of vaccines. Children in Malawi presented later and were more often comatose and malnourished, compared with children in Britain. The mortality rate from bacterial meningitis in children in Malawi was much higher than in children in Britain (41% vs. 7%), even when infected with the same organisms. Randomized studies in adults with pyogenic meningitis from Malawi and Vietnam have also been published. In the Malawi study, dexamethasone was not associated with any significant benefit, whereas in Vietnam a significant benefit in mortality (RR 0.43; 95% CI 0.2–0.94) was seen in patients with confirmed pyogenic menin- gitis. These conflicting results are difficult to interpret and further large studies in developing countries may be needed. Despite these encouraging results, the use of adjunctive dexa- methasone in bacterial meningitis remains controversial. Recently a meta-analysis with individual patient data from 2029 adults and children from Malawi, Europe, Chile, and Vietnam was com- pleted. HIV infection was confirmed or likely in approximately a third of all patients and a diagnosis of bacterial meningitis was microbiologically confirmed in 80%, most frequently with Strep. pneumoniae. Dexamethasone was not associated with a significant reduction in deaths (dexamethasone 270/1019 (27%) vs. placebo 275/1010 (27%); odds ratio or OR 1.0; 95% CI 0.8–1.2), death or severe neurological sequelae or bilateral severe hearing loss (dexa- methasone 43% vs. placebo 44%; OR 0.9; 95% CI 0.8–1.1), death or any neurological sequelae or any hearing loss (dexamethasone 54% vs. placebo 57%; OR 0.9; 95% CI 0.7–1.1), and death or severe bi- lateral hearing loss (dexamethasone 54% vs. placebo 57%; OR 0.9; 95% CI 0.8–1.1). However, there was a suggestion that dexametha- sone may reduce hearing loss among survivors (dexamethasone 24% vs. placebo 30%; OR 0.8; 95% CI 0.6–1.0; p = 0.04). There was no effect in any prespecified subgroups including specific causative organisms, pre-dexamethasone antibiotic treatment, HIV status, or age. Pooling of mortality results with all other published trials did not change the conclusions. The use of adjunctive dexametha- sone treatment was not associated with an increased risk of adverse events. Adjunctive dexamethasone in the treatment of acute bac- terial meningitis does not appear to reduce deaths or neurological disability or to produce harm. There were no significant treatment effects in any of the prespecified subgroups. A post-hoc analysis showed that dexamethasone adjuvant therapy may reduce hearing loss in survivors. By reducing permeability of the blood–brain barrier, steroids can impede penetration of antibiotics into the cerebrospinal fluid. This was shown for vancomycin in animal studies and can lead to treatment failures, especially in patients with meningitis caused by drug-resistant pneumococci in whom antibiotic regimens often include vancomycin. However, in a recent observational study, which included 14 adult patients admitted to the intensive care unit because of suspected pneumococcal meningitis, appropriate concentrations of vancomycin in the cerebrospinal fluid were obtained even when concomitant steroids were used. The dose of vancomycin used in this study was 60 mg/kg per day. Although these results suggest that dexamethasone can be used without fear of impeding vancomycin penetration into the cerebrospinal fluid

24.11.1 Bacterial infections 6075 of patients with pneumococcal meningitis (provided that vanco- mycin dosage is adequate), it is recommended that patients with bacterial meningitis due to nonsusceptible strains, treated with adjunctive dexamethasone, are carefully monitored throughout treatment. Treatment of complications The management of adults with bacterial meningitis can be com- plex and common complications are meningoencephalitis, systemic compromise, stroke, and raised intracranial pressure (ICP) (see Fig. 24.11.1.1). Various adjunctive

therapies have been described to improve outcome in such patients, including anti-inflammatory agents, anticoagulant therapies, and strategies to reduce ICP. Few randomized clinical studies are available for other adjunctive ther- apies in adults with bacterial meningitis. The inflammatory response in the CNS results in blood–brain bar- rier permeability, cerebral oedema, and increased ICP. Classically, there are two types of brain oedema: vasogenic due to blood–brain barrier disruption, resulting in extracellular water accumulation, and cytotoxic or cellular oedema due to sustained intracellular water collection. A third type, osmotic brain oedema, results from osmotic imbalances between blood and tissue. A Dutch cohort study evaluated the effects of complications on mortality in patients with pneumococcal meningitis and com- pared 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 predomin- antly due to neurological complications such as brain herniation. This observation may be explained by age-related cerebral atrophy, which allows older patients to tolerate brain swelling. These find- ings suggest that supportive treatments that aim to reduce ICP could be most beneficial in younger adults with pneumococcal menin- gitis. 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’), although there is no evidence that ICP monitoring and treatment of increased ICP are beneficial in pa- tients with bacterial meningitis. Some have advocated early intra- cranial pressure monitoring, aggressive treatment of brain oedema with high doses of corticosteroids, osmotic diuretics, decompressive craniectomy, and ventriculostomy when there is hydrocephalus, but there is no conclusive evidence of improved outcome except in anecdotal cases. In bacterial meningitis, as blood–brain barrier permeability has been increased, the effect of mannitol is uncertain. There is little in- formation from clinical and experimental studies concerning the use of mannitol in bacterial meningitis. A single dose of mannitol re- duced ICP for approximately 3 h in a meningitis model. Continued intravenous infusion of mannitol attenuated the increases of re- gional coronary blood flow (CBF), brain water content, and ICP in a pneumococcal meningitis model. Initial RCTs suggested that gly- cerol could reduce hearing loss and neurologic sequelae in children with bacterial meningitis. However, an RCT in Malawian adults with bacterial meningitis was stopped early because of higher mortality in the glycerol-treated patients as compared to placebo.
A subsequent study from Malawi, including 360 children with bacterial menin- gitis, also showed no benefit of glycerol with comparable mortality, rates of hearing loss, and sequelae in glycerol- and placebo-treated patients. Prognosis In Europe and North America, the overall mortality rate of patients with meningitis caused by N. meningitidis is about 7–14%, by Strep. pneumoniae 15 to 40%, and by group B streptococci and L. monocy- togenes meningitis above 20%. The mortality is much higher in very young and old people, and in patients with debilitating illnesses. A study in Zaria, Nigeria demonstrated that the mortality rate of pneumococcal meningitis was 32% in patients who were fully con- scious on admission, 40% in those who were confused, 54% in semiconscious patients, and 94% in those who were comatose. In Vietnam, in a prospective study of 250 cases of adult bacterial men- ingitis, the overall mortality rate was 13%. Permanent neurological sequelae include intellectual impairment, deafness and other cranial nerve deficits, and hydrocephalus. The re- ported incidence of sensorineural deafness after meningitis ranges from 5% to 40%. A large proportion of patients recover within a few months. N. meningitidis and H. influenzae are the main causes of this complication. Permanent deafness occurs in more than 50% of patients with Strep. suis meningitis. It may be bilateral, complete, and associated with vestibular involvement. Even in patients with apparently good recovery, cognitive impair- ment occurs frequently. In a prospective study, cognitive impair- ment was detected in 27% of adults

who made a good recovery from pneumococcal meningitis. Results of a more recent study showed that about a third of adult survivors of bacterial meningitis experi- ence subtle long-term cognitive impairment, which consists mainly of slight mental slowness. In this study the prevalence of cognitive impairment in patients after pneumococcal and meningococcal meningitis was similar. Tuberculous meningitis Epidemiology Tuberculous meningitis (TBM) kills or disables half those who have the condition and is the most dangerous form of infection with Mycobacterium tuberculosis. Fortunately, it is a relatively uncommon manifestation of TB and represents around 1% of all forms of the disease. In Western countries, its incidence has fallen in parallel with TB as a whole, but for those in the less developed world TBM re- mains a common cause of bacterial meningitis, particularly in popu- lations with a high prevalence of HIV infection. Before the arrival of HIV, most cases of TBM were in young chil- dren and occurred as a complication of primary infection. Now an increased proportion of cases occur in adults with HIV coinfection. HIV infection greatly increases the risk of all forms of TB, but in particular the extrapulmonary forms such as TBM, and the risk in- creases as the CD4 count declines. Pathogenesis Understanding of the pathogenesis of TBM has progressed little since the studies of Rich and McCordock in the 1920s and 1930s. They demonstrated, through post-mortem examinations of chil- dren and experiments on rabbits, that the pathogenesis of TBM requires two steps. During the first step the meninges and brain parenchyma are seeded by blood-borne bacteria with the formation

section 24 Neurological disorders 6076 of small subpial or subependymal foci of infection (or the Rich foci). In children the bacteraemia usually occurs during primary pulmonary infection and may be subclinical, whereas in adults this step may occur after new pulmonary infection or reactivation of old foci. The second step requires the rupture of a Rich focus with re- lease of bacteria into the subarachnoid space. This heralds the onset of meningitis, which, if left untreated, will result in severe and ir- reversible neurological pathology. In 75% of children the onset of TBM is less than 12 months after the primary infection. Pathology Three processes are responsible for the neurological pathology of TBM. An adhesive exudate develops around the basal cisterns and can obstruct cerebrospinal fluid causing hydrocephalus and com- promise efferent cranial nerves (Fig. 24.11.1.5). Granulomas can coalesce to form tuberculomas, or an abscess in unusual cases, causing diverse clinical consequences dependent on their anatom- ical location (Fig. 24.11.1.6). And an obliterative vasculitis can cause infarction and stroke syndromes, commonly involving the basal ganglia, internal capsule, and territory of the middle cerebral artery (Fig. 24.11.1.7). The severity of these complications is believed to depend on the intracerebral inflammatory response and strongly predicts outcome. Spinal cord involvement occurs in around 10% of patients and is often overlooked. Clinical manifestations include very high cerebrospinal fluid protein concentrations, limb weakness, and pain. Vertebral tuberculosis (Pott’s disease) accounts for around a quarter of cases (Fig. 24.11.1.8) and may be associated with fusiform paravertebral abscesses (Fig. 24.11.1.9) or a gibbus (Fig. 24.11.1.10). Extradural cord tuberculomas cause more than 60% of cases of non- osseous paraplegia, although tuberculomas can occur in any part of the cord (Fig. 24.11.1.11). Tuberculous radiculomyelitis is a rare accompaniment to TBM, characterized by a subacute paraparesis, radicular pain, and bladder dysfunction. MRI reveals loculation and obliteration of the spinal subarachnoid space with nodular intradural enhancement (Fig. 24.11.1.12). Fig. 24.11.1.5 CT scan of the head with contrast showing intense basal meningeal enhancement and dilated ventricles. Fig. 24.11.1.6 CT of the head with contrast showing gross hydrocephalus and multiple ring-enhancing tuberculomas. Fig. 24.11.1.7 MRI of the brain with contrast, showing intense basal enhancement with large left middle cerebral artery territory

infarction and mass effect. Fig. 24.11.1.8 MRI of the spine showing destruction of vertebrae and displacement of the cord.

24.11.1 Bacterial infections 6077 Clinical features If left untreated, TBM follows a slowly progressive course that leads to death in almost all cases. The first symptoms are nonspecific and unlikely to raise the suspicion of TBM. Infants may become irrit- able or go off their feeds, whereas older patients may complain of malaise, insomnia, lethargy, anorexia, and gradually worsening headache. These prodromal symptoms can last from 2 weeks to 8 weeks until the classic features of meningitis become more ap- parent. Patients commonly present to hospital at this stage, when the infection is well established. They will usually complain of headache and vomiting; many will present confused or comatose. Examination reveals neck stiffness in most, although it is rarely as marked as in acute pyogenic bacterial meningitis. Cranial nerve palsies are found in 25% of patients, with nerves VI, III, and VII being most commonly affected. Ten per cent of patients will present with a mono- or hemiparesis. Fundoscopy reveals papilloedema in half of patients and, occasionally, choroidal tubercles. Rarely, TBM presents as an acute meningoencephalitis that can be difficult to distinguish from pyogenic bacterial or viral meningitis. Seizures are rare in adults with TBM, but more common in children. HIV infection does not appear to alter the clinical presentation of TBM, although evidence of other extrapulmonary disease is more likely in HIV-infected patients (Fig. 24.11.1.13). Coma occurs in advanced disease and is strongly correlated with outcome. It is usually caused by raised ICP as a result of cerebro- spinal fluid obstruction and cerebral oedema. Hydrocephalus is found in 90% of children at diagnosis and 50% of adults, and is strongly associated with delayed treatment and prolonged coma. Reduced conscious level may also be caused by metabolic disturb- ance. Hyponatraemia affects more than 50% of patients with TBM, although why it occurs is uncertain. Some patients have a classic syndrome of inappropriate antidiuretic hormone secretion (SIADH) but many others have reduced plasma volumes and persistent natri- uresis with normal concentrations of antidiuretic hormone. Indeed, some have suggested that ‘hyponatraemic natriuretic syndrome’ is a better descriptive term for this common complication of TBM. Unusual neurological manifestations of TBM are well described, particularly in the older literature. Movement disorders may follow Fig. 24.11.1.9 MRI of the spine showing vertebral destruction and large, bilateral, paravertebral abscesses. Fig. 24.11.1.10 Spinal deformity or ‘gibbus’ in patient with vertebral tuberculosis. Fig. 24.11.1.11 MRI of the spine with contrast showing cavitating cervical tuberculoma. Fig. 24.11.1.12 MRI of the spine from patient with tuberculous radiculomyelitis showing meningeal thickening.

section 24 Neurological disorders 6078 basal ganglia infarction: tremor is the most common problem, but chorea, ballismus, and myoclonus are all reported. Tuberculomas can affect the hypothalamus and pituitary and cause disordered tem- perature regulation, diabetes insipidus, and panhypopituitarism on rare occasions. More controversial are cases that present with evi- dence of diffuse cerebral involvement but without clinical or cere- brospinal fluid signs of meningitis. ‘Tuberculous encephalopathy’ was first described in Indian children with disseminated TB and was characterized by coma, convulsions, involuntary movements, and pyramidal signs but with normal cerebrospinal fluid examin- ation. It has not been reported in adults. Post-mortem examinations revealed diffuse cerebral oedema, demyelination, and sometimes haemorrhage—features more typical of a postinfectious allergic dis- seminated encephalomyelitis. Diagnosis The diagnosis and treatment of TBM before the onset of coma are the greatest contribution that a physician can make to improve out- come. However, making the diagnosis is challenging because the clinical features

of the disease are nonspecific, small numbers of bacteria in the cerebrospinal fluid reduce the sensitivity of conven- tional bacteriology, and alternative diagnostic methods are incom- pletely assessed. The presenting clinical features of TBM are insufficiently specific to enable the diagnosis to be made on the history and examination alone. Recall of recent exposure to TB may be helpful, particularly in children, as may evidence of active extrameningeal TB on examin- ation. Chest radiography reveals active or previous TB infection in 50%; the appearance of miliary TB is particularly useful as it strongly suggests multiorgan involvement. Skin testing with the purified pro- tein derivative of M. tuberculosis is probably of limited value, except in infants. Examination of the cerebrospinal fluid is an essential part of diagnosing TBM and is a safe procedure for most patients with TBM. Hydrocephalus is not a contraindication to lumbar punc- ture. Cerebrospinal fluid pressures are usually raised (mean 30 cmH2O) and the cerebrospinal fluid is typically clear and slightly xanthochromic. Much is made in the older literature of the formation of a spider's web clot in the cerebrospinal fluid from pa- tients with TBM but the diagnostic utility of this phenomenon has never been systematically tested and is probably exaggerated. The total number of white cells in the cerebrospinal fluid varies from fewer than 5/µl to 1500/µl. Most patients will have 300 to 500 cells/ µl cerebrospinal fluid but older and immunosuppressed people may have low or even normal counts. The cells are a mixture of neutrophils and lymphocytes, although lymphocytes usually form 70–90% of the total. Occasionally, TBM can present with a short history with 1500–2500 WBCs/µl in the cerebrospinal fluid, most of which are neutrophils. Cerebrospinal fluid total protein concen- trations are raised in 95%, typically between 1 and 2 g/l; concen- trations of more than 3 g/l suggest spinal involvement and possibly spinal block. The ratio cerebrospinal fluid:blood glucose concen- tration is less than 0.5 in 95% and is a useful way of distinguishing TBM from other lymphocytic meningitides, especially viral men- ingitis, in which cerebrospinal fluid:blood glucose is usually more than 0.5. Attempts have been made to identify the clinical and cerebro- spinal fluid findings predictive of TBM. In children, a history longer than 6 days, optic atrophy, focal neurological deficit, abnormal movements, and neutrophils forming less than half the total cere- brospinal fluid leucocytes were independently associated with TBM. A diagnostic rule developed in Vietnamese adults to distin- guish TBM from bacterial meningitis calculated weighted scores for the variables predictive of TBM (score in brackets): age less than 36 years (0), 36 years or more (+ 2); peripheral blood white cell count fewer than 15 000 × 103/ml (0), 15 000 × 103/ml or more (+ 4); dur- ation of symptoms more than 6 days (− 5), 6 days or less (0); cerebro- spinal fluid white cells fewer than 900/µl (0), 900/µl or more (+ 3); and cerebrospinal fluid neutrophils less than 75% of total cells (0), 75% or more (+ 4). A total score of less than 4 indicated TBM, and a score of 4 or more indicated bacterial meningitis; when applied pro- spectively the rule was 86% sensitive and 79% specific. However, the performance differs where TB prevalence is lower and HIV preva- lence higher than in Vietnam. CT and MRI of the brain provide diagnostic information, but there are few data to indicate whether the findings can help discrim- inate TBM from other cerebral disorders. Basal meningeal enhance- ment, hydrocephalus, tuberculoma, and infarction are the cardinal neuroradiological features of TBM (see Figs. 24.11.1.1–24.11.1.3). Indeed, the presence of basal meningeal enhancement, tuberculoma, or both, was 89% sensitive and 100% specific for the diagnosis of TBM in one study. Pre-contrast hyperdensity in the basal cisterns may be a highly specific radiological sign of TBM in children. Cranial MRI is better at defining brainstem and cerebellum pathology, tuberculomas, infarcts, and the extent of inflammatory exudates, but there are no data to suggest that MRI is better than CT in discriminating TBM from other disorders. Cryptococcal meningitis, viral encephalitis, sarcoidosis, meningeal metastases, and lymphoma may all produce similar radiographic findings. The major role of neuroradiology has been in the

management and follow-up of the complications of TBM requiring neurosurgery. The culture of M. tuberculosis from the cerebrospinal fluid is the gold standard diagnostic test for TBM, but takes 2–6 weeks and is therefore too slow to aid clinical decision-making. Demonstrating acid-fast bacilli of M. tuberculosis in the cerebrospinal fluid after Ziehl–Neelsen staining is the oldest and most widely available rapid diagnostic test (Fig. 24.11.1.14), but the performance varies widely depending upon the volume of cerebrospinal fluid examined, the Fig. 24.11.1.13 Tuberculous, suppurating, inguinal lymphadenopathy with sinus tract formation in an HIV-infected woman with tuberculous meningitis.

24.11.1 Bacterial infections 6079 duration of microscopy, and the skill of the operator. Most laboratories find acid-fast bacilli in the cerebrospinal fluid of only 10–20% of those with TBM. Meticulous microscopy and the examination of large (>5 ml) volumes of cerebrospinal fluid can improve the sensi- tivity of both staining and culture to more than 60% and 80%, re- spectively. HIV infection is also associated with better performance of bacteriology because there are higher concentrations of bacteria in the cerebrospinal fluid. Commercial nucleic acid amplification tests, such as those based on PCR, have helped improve TBM diagnosis, but have important limitations. The GeneXpert MTB/RIF assay is now widely avail- able worldwide, utilizing a cartridge-based real-time PCR to detect Mycobacterium tuberculosis, and the genetic mutations which confer rifampicin resistance, within 3 hours. Several studies from different settings indicate it has high diagnostic specificity (approaching 100%), but sensitivity is 50–60% when used on cerebrospinal fluid for the diagnosis of TBM. Therefore, it can be used to ‘rule in’ the diagnosis of TBM, and gives very useful information on likely rifam- picin susceptibility, but cannot be used to ‘rule out’ the diagnosis. Unfortunately, there is still no single test that will allow the physician to confidently rule out TBM and empirical therapy, based on clinical features alone, is often required. Many other approaches to the diagnosis of TBM have been at- tempted and shown preliminary promise, but none has proved suffi- ciently reproducible, sensitive, specific, and practical for widespread clinical use. Commercial immunological assays based on the produc- tion of interferon-γ after stimulation with M. tuberculosis-specific antigens (ESAT6 and CFP10)—the T-SPOT and QuantiFERON-TB assays—have been a major advance in the diagnosis of latent TB infection, but their potential role in TBM diagnosis has not been established. Current data suggest these assays have reasonable specificity (80–100%) when used on cerebrospinal fluid for TBM diagnosis, but they lack sensitivity. Unless additional data become available, these assays cannot be recommended for the routine laboratory diagnosis of TBM. In summary, a high index of clinical suspicion is required to diag- nose TBM and, given the fatal consequences of delayed treatment, clinicians should be encouraged to initiate ‘empirical’ therapy in the setting of compatible clinical, epidemiological, and laboratory findings. Differential diagnosis TBM usually presents as a subacute lymphocytic meningitis and the differential diagnosis will depend on the age of the patient, geographical location, and immune status. In immunocompetent individuals the major differential diagnoses are partially treated pyogenic bacterial meningitis and viral meningoencephalitis. Various neoplastic infiltrations of the meninges (e.g. carcinomas, leukae- mias, and lymphomas) may be more common at the extremes of age. Neurosarcoidosis can be very difficult to distinguish from TBM, as may neurosyphilis. Geographical region can suggest specific alter- native diagnoses, for example, meningitis caused by Angiostrongylus cantonensis or Gnathostoma spinigerum in south-east Asia, or by Coccidioides spp., Histoplasma spp., or cysticercosis in the Americas, can all mimic TBM. The immunosuppressed patient represents an important group often at high risk for diseases caused by mycobac- teria, fungi, and herpesviruses. Cryptococcal meningitis is the major differential

diagnosis of TBM in HIV-infected patients but can usu- ally be distinguished on the basis of a cerebrospinal fluid Indian ink stain, fungal culture, or a cryptococcal antigen test. Cerebral toxo- plasmosis can be difficult to differentiate from cerebral tuberculosis, especially when multiple tuberculomas are present, and cyto- megalovirus (CMV) and herpes simplex virus (HSV) 1 and 2 men- ingoencephalitis can also cause diagnostic confusion with TBM. In most of these cases careful microbiological examination of the cere- brospinal fluid (for fungi and mycobacteria, in particular), selected use of nucleic acid amplification assays (M. tuberculosis, Toxoplamsa gondii, CMV, and HSV), and serological tests (syphilis) will allow a diagnosis to be made. Treatment The treatment of TBM follows the model of a short course of chemo- therapy for pulmonary TB: an ‘intensive phase’ of treatment with four drugs, followed by a prolonged ‘continuation phase’ with two drugs. The first two months of treatment should be with isoniazid, rifam- picin, pyrazinamide, and streptomycin, ethambutol, or ethionamide. The British Thoracic Society (BTS) and the Infectious Disease Society of America (IDSA) favour ethambutol as the fourth drug, al- though they acknowledge the lack of evidence from controlled trials. Others, particularly in South Africa, advocate ethionamide, which penetrates healthy and inflamed meninges more effectively than eth- ambutol or streptomycin, but can cause severe nausea and vomiting. In adults, daily single doses of 300 mg isoniazid, 600 mg rifampicin, and 2000 mg pyrazinamide probably provide adequate levels in the sera and cerebrospinal fluid of patients with TBM. There is some evidence higher dose rifampicin given intravenously may increase survival, but a large trial that compared the standard regimen with orally administered higher dose rifampicin (15 mg/kg), in addition to levofloxacin as a fifth drug for the first 2 months of treatment, found no benefit. Higher drug doses are recommended in young children, and have been used with success, notably in South Africa, but this approach cannot yet be recommended in adults. Unlike the treatment of pulmonary TB, interruptions in anti-TB chemotherapy are an independent risk factor for death from TBM. British and American guidelines suggest between 9 and 12 months of total anti-TB treatment for TBM, although a systematic review concluded that 6 months might be sufficient provided that the likelihood of drug resistance is low. Isoniazid and rifampicin are Fig. 24.11.1.14 Acid-fast bacilli of Mycobacterium tuberculosis stained by Ziehl–Neelsen stain in cerebrospinal fluid.

 considered mandatory in the continuation phase and the BTS sug- gests that therapy should be extended to 18 months in those unable to tolerate pyrazinamide in the intensive phase. Others recommend that pyrazinamide be given throughout treatment because of its ex- cellent penetration across the blood–brain barrier, although there is no supporting evidence from controlled trials. TBM caused by M. tuberculosis resistant to one or more first- line anti-TB drugs is an increasingly common problem. Isoniazid resistance alone does not appear to have a major impact on out- come from TBM, except in HIV-infected individuals. However, the combination of rifampicin and isoniazid resistance (multidrug re- sistance) has a major impact such that most patients will die un- less second-line therapy is started early. Detecting TBM caused by multidrug-resistant organisms is difficult: patients are likely to be dead before the results of conventional susceptibility tests (which take 6–8 weeks) are available. The rapid molecular detection of ri- fampicin resistant Mycobacterium tuberculosis in cerebrospinal fluid (CSF) by GeneXpert MTB/RIF has proved very useful, although the limited sensitivity of the assay (50–60%) means a high clinical sus- picion is still required. Furthermore, the best combination, dose, and duration of second-line agents for the treatment of multidrug- resistant TBM are not known. Until more data become available the treatment of multidrug-resistant TBM should follow the prin- ciples of treating drug-resistant pulmonary disease: never add a single agent to a failing

regimen; use at least three previously unused drugs, one of which should be a fluoroquinolone and the other an injectable agent (e.g. amikacin or capreomycin); and treat for at least 18 months. Adjunctive corticosteroids The use of adjunctive corticosteroids has been controversial ever since they were first suggested for the management of TBM more than 50 years ago. A meta-analysis and systematic review of all con- trolled trials published before 2000 concluded that corticosteroids probably improved survival in children, but small trial sizes, poor treatment allocation concealment, and possible publication bias did not support clear treatment recommendations. In 2004, a con- trolled trial of adjunctive dexamethasone in 545 Vietnamese adults with TBM revealed that dexamethasone treatment was strongly as- sociated with a reduced risk of death after 9 months of treatment (RR 0.69, 95% CI 0.52–0.92, p = 0.01), but did not prevent severe disability in the survivors. The effect of dexamethasone was con- sistent across all grades of disease severity, dispelling a previously held belief that corticosteroids benefited only those with more se- vere disease, but did not demonstrate a significant effect on death or disability in those infected with HIV. Current evidence suggests that all HIV-uninfected patients with TBM should be given dexametha- sone, regardless of age or disease severity. A clear benefit of dexa- methasone in HIV-infected patients has not been demonstrated, but the trial in Vietnam suggested that it was safe and might improve survival. There are no data from controlled trials comparing different cor- ticosteroid regimens, so the choice of regimen should be based on those used in the published controlled trials. In adults, the following regimen was shown to improve outcome in Vietnam: those with a Glasgow Coma Scale (GCS) score of less than 15 or focal neuro- logical deficit at the start of treatment received intravenous drug for 4 weeks (0.4 mg/kg per 24 h week 1, 0.3 mg/kg per 24 h week 2, 0.2 mg/kg per 24 h week 3, and 0.1 mg/kg per 24 h week 4) followed by 4 mg total oral drug, reducing each week by 1 mg until 0. Those without coma or neurological signs received intravenous drug for 2 weeks (0.2 mg/kg per 24 h week 1, 0.1 mg/kg per h week 2), fol- lowed by the same oral reducing course just described. In children, the South African trial demonstrated improved survival with 4 mg/kg per day of prednisolone for the first month of treatment. Response to therapy and treatment of complications Ninety per cent of deaths from TBM occur in the first month of treatment. The response to therapy is slow and can follow a fluc- tuant course. Indeed, a rapid and sustained response over a few days suggests an alternative diagnosis. Headache is often present for many weeks, even in uncomplicated cases. Fever rarely disap- pears within a week, and pyrexia is often observed for 6–8 weeks. The degree of neck rigidity at presentation varies considerably and can take 4–6 weeks to resolve. The cerebrospinal fluid mirrors the slow clinical response: cell counts remain elevated for 1–2 months, cerebrospinal fluid glucose remains low for a similar duration, and total cerebrospinal fluid protein can rise before falling slowly over many months. Transient episodes of high fever, worsening headache, and increased nuchal rigidity can occur during the first 2 months of treatment, particularly in those with more severe dis- ease. Distinguishing self-limiting events from the onset of more serious complications is difficult. New focal neurological signs, or a fall in conscious level, rarely accompanies these transient deterior- ations. Cranial imaging should be arranged urgently if new clinical signs develop during treatment. Hydrocephalus, cerebral infarc- tion, the expansion of intracranial tuberculoma, hyponatraemia, and poor adherence to therapy are the foremost reasons for severe acute deterioration. The expansion of intracranial tuberculoma after the start of treatment is a widely reported complication and frequently labelled as a ‘paradoxical’ treatment reaction. Recent data suggest that 75% with TBM develop tuberculomas during therapy but only small proportions are symptomatic. Most au- thors suggest treatment with prolonged high-dose corticosteroids if the tuberculoma causes clinical deterioration, although there are no controlled trials to support these recommendations. There are

case reports to suggest that adjunctive thalidomide may help in the management of symptomatic expanding tuberculomas. Rarely, tuberculomas coalesce to form an abscess and neurosurgical drainage may be indicated. Hydrocephalus is a common and serious complication of TBM and can be treated with diuretics (furosemide and/or acetazolamide), serial lumbar punctures, or ventriculoperitoneal/ atrial shunting. There are no data from controlled trials that de- termine which method of treatment is best. Some advocate early shunting in all patients with hydrocephalus, whereas others recom- mend shunting only for patients with noncommunicating hydro- cephalus. External ventricular drainage has been used to predict response to ventriculoperitoneal shunting but without success; others suggest that monitoring lumbar cerebrospinal fluid pressure can predict response to medical treatment. Without clear evidence physicians must balance possible benefit with the resources and ex- perience of their surgical unit and the significant complications of shunt surgery. Severe hyponatraemia is a common and often overlooked cause of deterioration on therapy. With the pathogenesis unclear, the

24.11.1 Bacterial infections 6081 best way of correcting the plasma sodium is uncertain. Sodium and fluid replacement are probably indicated in hypovolaemic hyponatraemia, whereas fluid restriction may be more appro- priate in those who are euvolaemic with evidence of SIADH. There is anecdotal evidence to suggest that fludrocortisone replacement therapy and demeclocycline may be useful. Prognosis and sequelae TBM kills or severely disables half of the people who have the con- dition. Outcome is even worse in those coinfected with HIV as more than half die. Whether highly active antiretroviral therapy can im- prove survival is uncertain. A  recent trial comparing immediate versus 2-month delayed antiretroviral therapy found no difference in survival between the treatment arms. The immediate treatment arm had more drug-related adverse events, therefore delayed treat- ment is currently recommended. The severity of TBM has been divided into three grades, a cat- egorization that takes its name and definitions from the 1948 British Medical Research Council (MRC) study of streptomycin in TBM treatment (Table 24.11.1.4). The grades are still used because they are good predictors of outcome: less than 10% of patients die with grade I disease, whereas 50% with grade III will not survive. Indeed, extremes of age, high MRC grade, HIV in- fection, and multidrug resistance have all been confirmed as the strongest independent predictors of death from TBM in nu- merous studies. Permanent sequelae occur in 10–30% of survivors: intellectual impairment is common in infants and young children and a quarter of all patients will have cranial nerve deficits, including blindness, deafness, and squints. Ten per cent (10%) will have permanent mono-, hemi-, or paraparesis. Prevention (See Chapter 8.6.26.) Although the efficacy of Bacillus Calmette–Guérin (BCG) im- munization to prevent pulmonary TB is controversial, its ability to prevent disseminated TB (including TBM) in young children is widely accepted. Meta-analyses have shown that BCG immuniza- tion at birth prevents around 70% of all cases of childhood TBM and is a highly cost-effective intervention in settings with a high prevalence of TB. Whether the protection lasts into adulthood is uncertain. TBM can also be prevented by treating the household contacts of newly diagnosed cases of pulmonary TB. The BTS recommend either 6 months of isoniazid or 3 months of isoniazid and rifam- picin for Mantoux-positive contacts to prevent progression to active disease. Possible future developments Immunization Widespread introduction of vaccines, especially where disease burden is greatest, is likely to further decrease the global burden of acute bacterial meningitis. The efficacy of the 23-valent pneumo- coccal polysaccharide vaccine has been extensively studied and, in a meta-analysis, its efficacy was estimated to be 38–53% for the prevention of invasive pneumococcal disease in adults. Although PCV are highly effective in children, the high costs of this vaccine limit its implementation in healthcare in less devel- oped countries. A possible alternative or

complementary approach is to develop vaccines directed against noncapsular antigens common to all pneumococcal species. Potential targets for future pneumococcal protein vaccines are neuraminidase, autolysin, pneumolysin, pneumococcal surface protein, and pneumococcal surface adhesion A. The high variability of N. meningitidis emphasizes the need for a permanent global follow-up, so that public health decision-makers and vaccine manufacturers can plan the most relevant vaccine strategies and development according to the most recent epidemio- logical trends, while taking into account the cost and logistical hur- dles that are the major limitations for the less developed world. Genetic factors Large prospective multinational studies have been performed to determine the role of genetic factors contributing to suscep- tibility and outcome in bacterial and tuberculous meningitis. Findings may have several implications for therapy and preven- tion. Existence of subgroups of patients with genetic variations (e.g. leukotriene A4 hydrolase gene and TBM susceptibility and treatment response) or deficiencies in innate immunity that es- pecially benefits from immunomodulatory therapy is likely. In addition, genotypes may be used to identify patients at high risk for the development of disease and those with high risk for com- plications. Physicians may, in the future, be able to use genetic information to dedicate immune-based therapy to modulate the response in a given patient. Randomized clinical trials Large trials of adjuvant dexamethasone in adults and children with acute bacterial meningitis are still needed and randomized comparative studies of various treatment regimens should be per- formed. The role of adjunctive dexamethasone for HIV-infected patients with TBM also needs defining by large trials. New adjunctive therapies The growing emergence of drug resistance as well as shifts in sero- type incidence is fuelling further development of novel antibiotic and adjuvant treatment strategies. In addition to the widespread introduction of dexamethasone, other options for adjuvant drugs may lie in modulating ROS/RNS-mediated damage, in caspase in- hibition, or in drugs targeting specific mediators in the inflamma- tory, complement, or coagulation cascades. Potentially, the efficacy of therapeutic interventions may be enhanced by simultaneous intervention at several levels of the inflammatory cascade. Despite the benefits of these strategies in experimental models, clinical trials Table 24.11.1.4 The British Medical Research Council disease severity grades for tuberculous meningitis Grade Clinical criteria I Alert and oriented without focal neurological deficit II GCS score 14–10 with or without focal neurological deficit or GCS 15 with focal neurological deficit III GCS score <10 with or without focal neurological deficit GCS, Glasgow Coma Scale.

---

Revision #1
Created 2026-01-22 16:43:18 UTC by Omar Ayman
Updated 2026-01-22 16:43:18 UTC by Omar Ayman