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cohort study. BMJ, 333, 281. Zimmermann B 3rd, Mikolich DJ, Ho G Jr (1995). Septic bursitis. Semin Arthritis Rheum, 24, 391–410. 8.6.5 Meningococcal infections Petter Brandtzaeg ESSENTIALS Neisseria meningitidis is an obligate human Gram-negative diplococcus. It is carried in the nasopharynx by about 3–10% of people, with most strains being harmless and inducing immunity. Pathogenic strains usually belong to specific clones that are en- capsulated, express pili, and the major porin, PorA. Serogroups A, B, and C usually account for more than 90% of all invasive isolates. Epidemiology Asymptomatic young adolescents (Africa) and young adults (in- dustrialized countries) are the main reservoir. Meningococci are transmitted by droplets and susceptible people usually develop the first symptoms within 2 to 4 days. The incidence of disease is highest during the first 4 years of life, with a secondary lower peak in adolescents. Pathogenic strains tend to cause single
cases or small clusters in industrialized countries, whereas they cause large outbreaks in developing countries, particularly in the meningitis belt of Africa. Host factors predisposing to invasive
disease include (1) lack of protective antibodies, (2) defects in the

 complement system, (3) HIV infection and (4) polymorphisms of complement factor H. Clinical features and prognosis Initially, N. meningitidis induces bacteraemia, with growth velocity in the circulation a major determinant of the clinical presentation and outcome. It has the propensity to invade the meninges. Low graded growth in the cerebrospinal fluid is often present in patients lacking distinct symptoms of meningitis. The two major clinical presenta- tions are meningitis and septic shock. Meningitis—the commonest presentation (50%); preceded by low- grade meningococcaemia (<103/ml). After transition to the subarach- noid space the meningococci proliferate to high levels (106–109/ml) in the cerebrospinal

fluid. Clinically the patients develop fever, subse- quently a petechial rash (30–80% of cases) and increasing symptoms of meningitis. If adequately treated with antibiotics, case fatality is less than 1–2% in industrialized countries, but higher in developing countries. Brain oedema leading to herniation of the cerebellum is the main cause of death. Neurosensory hearing loss is the major complication. Septic shock—symptoms develop in 30% of European patients. The septic shock is preceded by high grade meningococcaemia (106–108/ml). The massive bacterial proliferation leads to rapidly escalating endotoxin levels in plasma and large organs. Endotoxin triggers the innate immune system inappropriately. Within 12 h of initial symptoms the patient may have persistent circulatory failure and severe coagulopathy. Subsequently they develop extensive skin haemorrhages, thrombosis of the extremities causing gangrene, and impaired renal, adrenal, and pulmonary function. Mortality is high (16–52%). Mild meningococcaemia—in European countries, 20% of cases present with fever and usually petechial or macular rash, but without marked signs of meningitis or shock. The meningococcaemia is low grade (<104/ml) and often transient. Occasional complica- tions include pericarditis, arthritis, ocular infection, or chronic meningococcaemia. Mortality is low (0–5%) and usually related to late debut of shock or cerebellar herniation. Diagnosis Intra- and extracellular diplococci can be observed in the cerebro- spinal fluid, peripheral blood buffy coat (fulminant septicaemia), and biopsies of haemorrhagic skin lesions using Gram or acridine orange stains. N. meningitidis can be grown from blood culture and swabs from the nasopharynx/tonsils. Polymerase chain re- action methods are increasingly used to detect and classify N. meningitidis in blood, cerebrospinal fluid, other bodily fluids, and skin biopsies. Treatment Aside from supportive care, appropriate antibiotic treatment should be started immediately in suspected cases of meningococcal in- fection: this should not be delayed while the patient is transferred to hospital, or for the results of investigations to become available. Ceftriaxone or benzylpenicillin (intravenously or intramuscularly) re- mains the drugs of choice in most countries; chloramphenicol are also effective. Prevention Vaccination—conjugate vaccines comprising serogroup A, C, Y, and W polysaccharide are effective from 2 months of age. Two vaccines covering most serogroup B strains are marketed; one (Bexsero®) in Europe, Canada, Australia, and United States, the other (Trumenba®) in United States and Europe. A single sero- group A conjugate vaccine (MenAfriVac®) has had a major impact on incidence and carriage in sub-Saharan Africa. Secondary prophylaxis—health authorities in most countries advise that close contacts of cases of meningococcal disease have eradi- cation treatment (e.g. with a single dose of ciprofloxacin 500 mg or ofloxacin 400 mg). During pregnancy a single dose of 250 mg ceftriaxone IM and for children below 12 years of age 125 mg IM is effective. Introduction Neisseria meningitidis infection remains a major public health problem worldwide by causing clusters or epidemics of meningitis and acute lethal sepsis. Case fatality has gradually declined from 70–90% to approximately 7–10% in industrialized countries but has remained at this level since the introduction of antimicrobial chemotherapy in 1937. The bacterium N. meningitidis is an obligate human Gram-negative diplococcus classified as a β-proteobacterium and is a member of the family Neisseriaceae. Meningococci are normally located in the mucous membrane of the nasopharynx and tonsils. Invasive isolates from blood and cerebrospinal fluid or as detected in tissue biopsies are encapsulated and express pili and the major porin PorA. Capsule polysaccharides that inhibit phagocytosis and bacterial adhesion are divided into at least 13 different serogroups (A, B, C, D, E, H, I, K, L, W, X, Y, and Z). Serogroups A, B, and C usually account for more than 90% of all invasive isolates. Less than 10% of clinical isolates are from serogroups X, Y, and W. The cell wall of meningococci consists of an outer lipid bilayer, containing lipopolysaccharides (LPS, endotoxin also denoted lipooligosaccharides, LOS), lipids, and outer membrane proteins, and an inner thin

peptidoglycan layer. LPS is the major inflammatory (toxic) component of N. meningitidis (Fig. 8.6.5.1). Lipoproteins and fragments of peptidoglycan are weaker inflammatory molecules. They activate the innate immune system via CD14 and the Toll-like receptors (TLR 4), (LPS), TLR 2 (lipoproteins, peptidoglycan) and TLR 9 (bacterial DNA) located on monocytes, macrophages, and to a lesser extent neutrophils (Fig. 8.6.5.2). During growth, menin- gococci release many outer membrane vesicles containing LPS and other outer membrane molecules that trigger the innate immune system in a dose-dependent manner. Outer membrane proteins are classified according to elec- trophoretic mobility into five major classes. PorA (class 1 pro- tein) and PorB (class 2 or 3 proteins) are cation-selective and

 anion-selective porins, respectively. PorB and PorA define sero- type and serosubtype. Several surface-exposed proteins including PorA, neisserial adhesion A, factor H binding protein, and neisserial heparin binding antigen induce bactericidal antibodies when exposed to the human immune system. Recombinant variants of these proteins are included in the new serogroup B vaccine (Bexsero® and Trumenba). Meningococci are fastidious bacteria that readily autolyse. They grow well on blood agar, supplemented chocolate agar, trypticase soy agar, Mueller–Hinton agar, and selective GC medium. Optimal Cytoplasmic-membrane proteins Cytoplasmic-membrane Lipooligosaccharide Periplasmic space Outer membrane Pilus Capsule Phospholipid Outer-membrane proteins Fig. 8.6.5.1 Cross-sectional view of N. meningitidis. Reproduced from Rosenstein NE, Bradley BA, Stephens DS, Popovic T, Hughes JM (2001). Meningococcal disease. N Engl J Med, 334, 1378–88. Copyright © 2001 Massachusetts Medical Society. TIRAP IRAK-1 TRAF-6 lαβ MD-2 CD14 ↑NF κB Nuclear transcription MyD88-dependent pathway MyD88 TLR4 TIR LBP LOS sCD14 IRF-3 Tram/Trif IFNb, NO, chemokines (IP-10, MCP-5, RANTES) MyD88-independent pathway TNfα,IL-1β, MCP-1, MIP-3a, IL-6, IL-8 Fig. 8.6.5.2 Activation of Toll-like receptor 4 by endotoxin (lipopolysaccharides or lipooligosaccharides, LOS). Reproduced with permission from Stephens DS, Greenwood B, Brandtzaeg P (2007). Epidemic meningitis, meningococcaemia, and Neisseria meningitidis, Lancet, 369, 2196–210.

 growth occurs at 35–37°C in a humid atmosphere with 5–10% carbon dioxide. The convex colonies (diameter 1–4 mm) are trans- parent, nonpigmented, and nonhaemolytic. They produce cyto- chrome oxidase and ferment glucose and maltose, but not lactose and sucrose, to acid without gas formation. Practical handling of clinical specimens Blood culture (10 ml for adults, 2–4 ml for infants/children) and swabs from the nasopharynx and the tonsils are collected immedi- ately. Media for blood culture and transportation of swabs should be optimal for recovery of meningococci. Cerebrospinal fluid is best cultured by direct plating of 0.1 ml on supplemented chocolate agar or a similar medium. If direct plating is impossible or delayed, the sample should be stored at + 4°C to + 20°C but preferably at refriger- ator temperature. Recovery of live meningococci may increase if some drops of the cerebrospinal fluid are stored on a sterile swab in transport medium or injected into blood culture medium and incu- bated at 35–37°C. Direct visualization of N. meningitidis
in clinical specimens Intracellular and extracellular diplococci can be observed in the cere- brospinal fluid, peripheral blood buffy coat (fulminant septicaemia), and biopsies of haemorrhagic skin lesions using Gram's or acridine orange stains. Polymerase chain reaction Polymerase chain reaction (PCR) is increasingly used to detect and classify N. meningitidis in blood, cerebrospinal fluid, joint fluid, pericardial fluid, and skin biopsies. Real-time PCR has made it possible to quantify the total number of meningococci (i.e. live plus dead bacteria), in plasma and cerebrospinal fluid. In

shock plasma, nonviable meningococci outnumber those that can be cultured by a factor 1000:1. The number of N. meningitidis DNA copies is closely correlated to the LPS levels, clinical presentation, disease severity, and outcome. Blood anticoagulated with ethylenediaminetetraacetic acid is optimal for the PCR reaction but other anticoagulants (hep- arin, citrate) or even serum have been used. Epidemiology Industrialized countries Infection presents as single cases or in small clusters. The inci- dence used to be 1 to 3 per 100 000 inhabitants per year but has declined to 0.77 per 100 000 per year (2011) in Europe and 0.12 per 100 000 per year (2010) in the United States. Strains belonging to specific clonal complexes may cause a hyperendemic situation characterized by a much higher incidence than usually observed (4–30 per 100 000 per year). This epidemiological situation may last for more than a decade in defined geographical areas before slowly declining. Serogroup A has disappeared as a cause of sig- nificant epidemics. Outbreaks in Finland in the 1970s and in New Zealand in the 1980s were exceptions. In Europe 70–80% of the cases are presently caused by serogroup B. Immunization of in- fants with serogroup C conjugate vaccine in United Kingdom and various countries has reduced the incidence significantly. Serogroup Y strains belonging to several clonal complexes are gradually increasing in several European countries. In the United States of America serogroups B, C, and Y accounted for approxi- mately one-third of the cases each (Fig. 8.6.5.3). Presently sero- group Y is declining in the United States. Developing countries Large-scale epidemics are confined to developing countries, pri- marily in sub-Saharan Africa where the incidence approaches 10–25 per 100 000 inhabitants per year. During epidemic peaks in Africa, as many as 500–1000 per 100 000 inhabitants may con- tract meningococcal infections. Serogroup A and to lesser extent serogroups W and C dominate the isolates of large epidemics (Fig. 8.6.5.3). Large-scale vaccination in sub-Saharan Africa with the newly implemented serogroup A conjugate vaccine (MenAfriVac®) has proven very effective virtually eradicating transmission and development of new cases (2014). Two years after mass vaccination it is still very effective. Cases of serogroup C, W, and X might still occur. Meningitis belt in sub-Saharan Africa The area stretches from the Gambia in the west to Ethiopia in the east and includes Senegal, Guinea, Mali, Burkina Faso, Ghana, Togo, Benin, Nigeria, Niger, Chad, Cameroon, the Central African Republic, and Sudan (Fig. 8.6.5.3). Mainly serogroup A strains be- longing to a few clonal complexes cause the increased attack rate. In some of these countries large-scale epidemics occur every 8 to 12 years. Since the 1990s serogroup W has caused epidemics in West Africa. Season In temperate climates most cases occur during the winter and early spring. In the sub-Saharan African meningitis belt the incidence in- creases from the middle of the dry season and reaches its maximum at the end of that season (harmattan). New cases decline rapidly after the start of the rainy season. Preceding infections Preceding infections (≤2 weeks) with influenza A, other airway vir- uses, and mycoplasma have been associated with meningococcal in- fections, assuming that they influenced the nasopharyngeal barrier negatively. Whether this relation is causal or merely temporal has yet to be firmly established. Age distribution Cases are seen in all age groups; however, most occur from 0 to 4 years with a smaller peak from 13 to 20 years. During epidemics the median age appears to increase. Complement-deficient patients may contract the infection at an older age than average. Genetic diversity N. meningitidis can exchange and incorporate DNA from other Neisseria species or closely related bacteria. Meningococci are genetically more diverse than most other human pathogens. However, strains from certain clonal complexes may persist for many decades over wide areas, retaining their pathogenicity. Strains from seven clonal complexes have predominated since the late 1960s.

section 8 Infectious diseases 1014 Nasopharyngeal colonization Upper respiratory tract mucosa is the natural habitat of N. men- ingitidis. It is spread from person to person by droplets and direct mucosal contact. Most colonizing meningococci are nonpathogenic and are genetically and phenotypically different from virulent inva- sive strains. Only a minority of those colonized with virulent strains will develop invasive disease. Based on carriage and incidence data from Norway, ≤1% of those carrying hypervirulent B or C clones developed clinical disease. Colonization is asymptomatic; it induces local and systemic immune responses within 1–2 weeks. Carriage Cross-sectional studies in England and Norway in the 1980s and 1990s indicated that approximately 10% of the population har- boured meningococci in the upper respiratory tract. However, only 1% of the healthy normal population carried strains from typical virulent clones prevalent at the time. The acquisition rate leading to carriage appears to be independent of season. The carriage rate in England is low (2–3%) in the first 4 years of life, rises in children aged 10 to 14 years (9–10%), reaches a maximum among young adults of 15 to 19 years (20–25%), and then gradually declines to less than 15% in persons above 25 years. It increases in closed or semi-closed communities and is particularly high in mili- tary camps where strains change frequently. In university communi- ties with bar and catering facilities the carriage rate is high. Smoking increases the carriage rate. In Burkina Faso the carriage rate among more than 20 000 screened persons below 30 years was 4%. It peaked in 15–19-year-old boys and in 10–14-year-old girls. The most fre- quently carried strains in 2009 were Y (2.3%), X (0.44%), A (0.39%), and W (0.34%) which may change from year to year. Reservoir of virulent meningococci In industrialized countries young adults are the main reservoir. Infants and children are usually infected by a local adult carrier. Household members and kissing contacts of a patient harbour viru- lent strains more often than the average population. Healthy children and young adults carrying virulent strains are the main reservoir in sub-Saharan Africa. Children may infect each other. Spread from patients to medical staff is uncommon. Predisposing factors for invasive disease These are summarized in Box 8.6.5.1. Lack of protective antibodies Antibodies against serogroups A, C, W, and Y capsule polysac- charides are bactericidal and confer protection at concentrations of 1–2 μg/ml of serum. Serogroup B polysaccharide induces a weak transient IgM but no protective IgG response. Bactericidal and opsonophagocytic antibodies recognizing surface-exposed epitopes of the outer membrane protein, in particular PorA, are important for protection. Antibodies to newly discovered outer membrane proteins including factor H binding protein, neisserial adhesion A, neisserial heparin binding antigen (components of two serogroup B vaccines recently licensed) are bactericidal and may contribute to Fig. 8.6.5.3 Outbreaks of different serogroups of N. meningitidis since the 1960s. Purple areas indicate countries with serogroup B epidemics. Reproduced with permission from Stephens DS, Greenwood B, Brandtzaeg P (2007). Epidemic meningitis, meningococcaemia, and Neisseria meningitidis, Lancet, 369, 2196–210 and Caugant DA (1998). Population genetics and molecular epidemiology of Neisseria meningitides. APMIS, 106, 505–10. Box 8.6.5.1 Factors predisposing for meningococcal infections • Lack of bactericidal and/or opsonizing antibodies • Lack of alternative pathway or late complement components • Infection with human immunodeficiency virus • Treatment with complement inhibiting drugs

 protection. Antilipopolysaccharide antibodies, recognizing com- monly shared epitopes among virulent and nonpathogenic neisseria and closely related species, presumably play a role in protection. Defects in the complement system Reduced function of the complement system caused by defects in the alternative or terminal pathways increases the susceptibility up to 6000 times. Defects in the classic pathway appear not to predis- pose to

meningococcal infection. Complement defects are rare; they play a minor role in the development of invasive serogroup A, B, and C infections in Europe. Complement defects were overrepresented in patients with the less common and presumably less virulent sero- groups X, Y, and Z in studies from the Netherlands. Defects in com- plement factors 5 and 6 are well recognized in South Africa. Defects in the terminal complement system are associated with recurrent infections, often with a relatively benign character. Other genetic predisposition for invasive infection and outcome Genetic variants in the complement factor H region are associated with reduced, but possibly also increased, susceptibility to men- ingococcal disease. High serum levels of factor H appear to in- crease the risk of invasive meningococcal infections in England. Polymorphism in tumour necrosis factor (TNF), mannose-binding lectin, Fcγ receptors (CD16, CD32), and Toll-like receptor (TLR)-4 have previously been implicated in increased susceptibility and outcome. The results have not been reproduced in larger studies. TLRs play an important role in protecting the host from intruding microorganisms. Studies from the United Kingdom and Gambia suggest that the most common polymorphism in the TLR4 gene (Asp299Gly) is not overrepresented among cases. Polymorphism in genes coding for plasminogen activator inhibitor 1 (PAI-1), interleukin-1 receptor antagonist (IL-1RA) and interleukin-1 (IL-1) have been associated with increased disease severity but need to be confirmed in larger studies. Invasive infection Most patients appear to develop invasive disease 2–4 days after acquiring the virulent strain in the upper respiratory tract, but some are carriers for up to 7 weeks before invasive infection de- velops. N. meningitidis adheres to specific molecules on non- ciliated epithelial cells in the nasopharynx and on the tonsils (Fig. 8.6.5.4). During a period of adaptation and proliferation, meningococci presumably alter various surface structures (lipopolysaccharides, pili, outer membrane proteins) by phase variation before starting transepithelial migration. They reach submucosal tissue and, via ca- pillaries, gain access to the circulation (Fig. 8.6.5.5). The initial bacteraemic phase Bacteraemia is a prerequisite for systemic meningococcal infection. Meningococci may be eliminated from the blood by lysis induced by bactericidal antibodies and complement and by phagocytosis of op- sonized bacteria. Persistent bacteraemia allows meningeal invasion. Bacterial proliferation and the accompanying inflammatory re- sponse can occur predominantly in either the subarachnoid space, causing meningitis, or in the circulation, causing meningococcaemia with or without shock. (b) (a) (d) (c) Fig. 8.6.5.4 Attachment to and proliferation of meningococci on nonciliated epithelial cells in nasopharynx. Reproduced with permission from Stephens DS, Greenwood B, Brandtzaeg P (2007). Epidemic meningitis, meningococcaemia, and Neisseria meningitidis. Lancet, 369, 2196–210.

 The rash Haemorrhagic skin lesions are the hallmark of systemic meningo- coccal disease, occurring in 60–80% of all cases in industrialized coun- tries. They appear as red or bluish petechiae. These lesions are larger and more irregular in size than the petechiae of thrombocytopenic purpura. Each lesion represents a local nidus of meningococci within the endothelial cells, thrombus formation, and extravasation of erythrocytes. The petechial rash indicates meningococcaemia, not necessarily severe sepsis leading to shock. However, in fulminant meningococcal septicaemia the haemorrhagic lesions are larger (ec- chymoses) with a propensity to locate on extremities (Fig. 8.6.5.6). Some patients develop relatively large nonspecific maculopapular lesions, with or without haemorrhagic lesions, at an early stage (Figs. 8.6.5.7, 8.6.5.8). The petechial lesions are difficult to discover on dark skin but may be observed in the conjunctivae (Fig. 8.6.5.9). Clinical presentations The initial symptoms of systemic meningococcal infection are attrib- utable to meningococcaemia. This may persist as a low-grade bac- teraemia or develop into septic shock in a few hours. Development of persistent shock is the major determinant

of the case fatality rate. According to a recent extensive Dutch study the disease course and outcome depended primarily on age and development of shock and less on clonal complex and serogroup of N. meningitidis. Most com- monly, the patient develops meningococcaemia without circulatory impairment which gradually evolves to meningitis within 12 to 72 hours. Less frequently, patients develop distinct meningitis and persistent shock simultaneously. Based on easily recognizable clin- ical symptoms, meningococcal infections can be classified as: (1) meningitis without shock (50%), (2) shock without meningitis (15%), (3) meningitis and shock (15%), and (4) meningococcaemia Fig. 8.6.5.5 Events leading to the different clinical presentations of meningococcal infections. Reproduced from Rosenstein NE, Bradley BA, Stephens DS, Popovic T, Hughes JM (2001). Meningococcal disease.
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8.6.5 Meningococcal infections 1017 without shock or meningitis (20%). Each clinical presentation is as- sociated with a distinct pathophysiological background and prog- nosis (Table 8.6.5.1). Distinct meningitis without persistent shock Meningism dominates the clinical presentation and the onset is often insidious. The patients, particularly children, may complain of general malaise, nausea, and headache. They vomit and become febrile. The temperature may fluctuate and can be normal at times. Many patients are initially diagnosed as ‘gastric flu’, gastroenter- itis, or upper respiratory tract infection. Gradually, the symptoms of meningitis dominate the clinical picture. The patient com- plains of headache, vomits, and develops nuchal and back rigidity, photophobia, and in more advanced cases altered consciousness; Kernig’s and Brudzinski’s signs become positive. Many patients are lethargic, and some are agitated. The blood pressure is normal or slightly elevated by stress. Occasionally it is low but can be restored to normal by infusion of a limited volume of fluid. In untreated cases brain oedema develops, the intracranial pressure rises, and the central circulation is increasingly compromised. Finally, her- niation of the cerebellum occurs with arrest of the brain circu- lation. The case fatality rate was 0–2% in four European studies comprising 1801 patients classified as given in Table 8.6.5.1. Fig. 8.6.5.6 Massive skin haemorrhage on the extremities of a 4- year-old girl with fulminant meningococcal septicaemia. The infection was caused by Neisseria meningitidis group B. The left leg had to be amputated below the knee. She needed extensive skin transplantation and several fingers had to be amputated. Fig. 8.6.5.7 Macular lesions on the legs, some with a central haemorrhagic spot in a 17-year-old girl with mild meningococcaemia caused by Neisseria meningitidis group C. She recovered completely after 5 days of treatment with benzylpenicillin. Fig. 8.6.5.8 Macular and haemorrhagic lesions on the legs of a 21-year- old man with mild meningococcaemia caused by Neisseria meningitidis group B. He recovered completely after 5 days of penicillin treatment. Fig. 8.6.5.9 Conjunctival petechiae in an African child with meningococcal group A meningitis. Copyright D. A. Warrell. Table 8.6.5.1 Levels of N. meningitidis DNA copies, lipopolysaccharides (endotoxin), and inflammatory mediators related to the clinical presentation No shock Shocka Shock No shock Meningitisb No meningitis Meningitis No meningitis Circulation (+) ++++ ++ (+) Subarachnoid space +++++ (+) +++ (+) a Shock denotes persistent hypotension requiring treatment with volume and pressor for 24 h. b Meningitis denotes 100 × 106/litre or more leucocytes in the cerebrospinal fluid or clinically distinct signs of meningism.

section 8 Infectious diseases 1018 Meningococcal meningitis without persistent shock accounts for more than 50% of all cases of systemic meningococcal infections in industrialized countries and an even higher proportion of cases reaching hospitals in developing countries. The combination of

multiple petechiae and symptoms of meningitis supports a diag- nosis of meningococcal meningitis. Pathophysiological background N. meningitidis multiply in a compartmentalized manner with the main proliferation occurring in the subarachnoid space. Quantitative PCR indicates that the real number of meningococci is usually less than 103/ml in plasma and may increase to 109/ml in the cerebrospinal fluid (Fig. 8.6.5.10). This distribution is re- flected in the levels of endotoxin and various cytokines which are low in plasma and 100–1000 times higher in the cerebrospinal fluid. Meningococci can be cultivated from both compartments in untreated patients. Plasma proteins, mainly albumin, leak into the cerebrospinal fluid, and the influx of mainly neutrophils causes the pleocytosis. The glucose level of the cerebrospinal fluid is reduced mainly as a result of increased central glucose consumption rather than the pleocytosis. Laboratory findings The erythrocyte sedimentation rate, C-reactive protein, and leuco- cyte count in the peripheral blood are markedly elevated with increased numbers of band forms. Sodium, potassium, calcium, and magnesium ions, pH, renal, hepatic, and coagulation param- eters are usually within normal range. Cerebrospinal fluid shows a marked pleocytosis (more than 100 × 106 leucocytes/litre), with increased levels of protein and decreased levels of glucose. Intracellular and extracellular Gram-negative diplococci can be detected by direct microscopy. Persistent septic shock without distinct meningitis Fulminant meningococcal septicaemia (Waterhouse–Friderichsen syndrome) is characterized by shock and persistent circulatory failure and severe coagulopathy leading to thrombosis and extensive haemorrhage of the skin, thrombosis and gangrene of the extrem- ities, and impaired renal, adrenal, and pulmonary function. Symptoms develop very rapidly. Six to 12 hours after recognizing their first symptoms the patients are often desperately ill. Initially, they complain of ‘flu-like’ symptoms such as fever, aching muscle, prostration, abdominal pain, and nausea. The temperature rises rap- idly, commonly to between 39.0 and 41.5°C, but occasionally lower. Diarrhoea may occur during the first few hours. The patient appears worryingly sick to relatives. The parents usually recognize cold extremities indicating impaired circulation before the skin haem- orrhagic lesions appear but misinterpret the acute symptoms as in- fluenza or acute gastroenteritis. The haemorrhagic skin lesions are first seen as bluish petechiae, which rapidly increase in size and number. They are distributed all over the body but are often more pronounced and detected earliest on the extremities. Occasionally they are seen on the conjunctivae and other mucous membranes. The circulation is severely impaired. The extremities are often cold and cyanotic with a capillary refill time of more than 3 sec- onds. The blood pressure is low despite tachycardia. The tissue perfusion remains inadequate despite extensive fluid and pressor therapy. Initially, the circulation is hyperdynamic, but gradually becomes hypodynamic from persistent vasodilatation and grad- ually reduced myocardial performance. The heart becomes dilated with a reduced ejection fraction, as observed by serial ultrasound examinations. Patients usually lack nuchal and back rigidity, and Kernig’s sign is negative. Despite impaired circulation, many patients remain Meningitis Bacteraemia Blood Bacteraemia Bacteraemia Bacteraemia <103 DNA copies/ml endotoxin <0.5 EU/ml 104 DNA copies/ml endotoxin <0.5 EU/ml 106 DNA copies/ml endotoxin 10 EU/ml 107 DNA copies/ml endotoxin 50 EU/ml Fulminant septicaemia Sepsis + meningitis Mild meningo- coccaemia Fig. 8.6.5.10 Median number of N. meningitidis (number of DNA copies) as determined by real-time PCR and median level of endotoxin in plasma in the different clinical presentations of systemic meningococcal disease.

 awake and alert on hospital admission, being able to communi- cate their complaints. They hyperventilate to compensate for the pronounced metabolic acidosis. Urine output gradually dwindles. They may develop acute respiratory distress syndrome,

that is, pul- monary oedema after fluid volume repletion of more than 40 ml/kg. Circulatory collapse dominates the clinical picture during the first 48–96 h. Fifty per cent of the nonsurvivors die within 12 h of hospital admission. Few patients die after 48 h. Later, acute respira- tory distress syndrome, renal failure, and the consequences of the diffuse thrombosis of the extremities and the skin dominate the pic- ture. The case fatality rates ranged from 16 to 53% in four European studies. Rapidly evolving symptoms with fever, circulatory shock, and extensive skin haemorrhages in a person without a history of splenectomy makes the diagnosis of fulminant meningococcal septicaemia likely. The same clinical picture is, however, observed in cases of overwhelming infections caused by Streptococcus pneu- moniae, Haemophilus influenzae, Streptococcus pyogenes, and Capnocytophaga canimorsus (after animal bite) and with viral haem- orrhagic fevers (Fig. 8.6.5.11). Pathophysiological background The pathophysiological changes are explained by the very rapid pro- liferation of N. meningitidis in the circulation. On admission 5 × 105 to 5 × 108 meningococci/ml plasma are detectable by quantitative PCR (Fig. 8.6.5.10). This massive bacterial growth generates very high levels of endotoxin and other bacterial molecules in the blood, lungs, heart, liver, spleen, and kidneys. Few meningococci have yet penetrated into the subarachnoid space, which is explained by the short duration of symptoms. The levels of lipopolysaccharides in the plasma are closely associated with the copy number of meningococcal DNA and predict the devel- opment of persistent septic shock, multiple organ failure, and death. Plasma levels of lipopolysaccharides below 10 endotoxin units/ml were associated with 1% mortality due to circulatory impairment whereas levels above 250 endotoxin units/ml (i.e. 1.4 log higher), were associated with 100% mortality among 150 Norwegian patients (Fig. 8.6.5.12). Coagulopathy Coagulation is activated primarily via the extrinsic (tissue factor, FVIIa) pathway. In patients with fulminant meningococcal septicaemia there are increased levels of bioactive tissue factor in monocytes and on microparticles released from monocytes. The platelets disappear rapidly and remain at a low level for many days due to extensive consumption at the altered endothelial surface. Thrombopoietin increases in plasma without detectable increase of circulating platelets. The activation of the coagulation system, as measured by formation of fibrin, gradually reduces after antibiotic and fluid therapy is initiated (Table 8.6.5.2). Inhibited fibrinolysis Concurrently with activation of coagulation, fibrinolysis is inhibited by high levels of plasminogen activator inhibitor 1 (PAI-1) released from activated endothelial cells and platelets. High levels of PAI-1 are associated with development of persistent septic shock and a fatal outcome. Allelic variations in the promoter region of the PAI-1 gene enhance production and are associated with an increased risk of dying. Thrombus formation Thrombosis occurs particularly in the vessels of the skin, adrenals, kidneys, muscles, choroid plexus, peripheral extremities, and to some extent in the lungs. The thrombomodulin–thrombin complex on the endothelial cells converting protein C to activated protein Fig. 8.6.5.11 The ‘tumbler test’ used to differentiate haemorrhagic skin lesions from viral or drug rash in an infant with meningococcal meningitis caused by Neisseria meningitidis group B. There was complete recovery after 5 days treatment with benzylpenicillin. n = 68 100 80 60 40 20 0 <0.5 Case fatality rate (%) Endotoxin in plasma (endotoxin units/ml) 0.5–10 10–50 50–250

> 250 n = 31 n = 24 n = 20 n = 7 Fig. 8.6.5.12 Relationship between the levels of endotoxin (lipopolysaccharides) in plasma and case fatality rate related to the development of septic shock and multiple organ failure in 150 Norwegian patients with systemic meningococcal disease. Table 8.6.5.2 Factors

> contributing to the coagulopathy in fulminant meningococcal septicaemia Procoagulant factor Tissue factor in monocytes and microvesicles ↑ Anticoagulant factors Antithrombin ↓ Protein C ↓↓ Tissue factor pathway inhibitor ↑ Profibrinolytic factor Tissue plasminogen activator ↑ ↓ Antifibrinolytic factor Plasminogen activator inhibitor 1 ↑↑

section 8 Infectious diseases 1020 C, and the protein C endothelial cell receptor enhancing this activity, are down-regulated. Glycosaminoglycans including heparan sulphate, molecules with an antithrombotic effect, are released from the endothelial surface. Numerous meningococci are present in and around small vessels. These processes facilitate forma- tion of thrombi. Concomitantly natural coagulation inhibitors are consumed. Protein C is reduced to 20% and antithrombin to median 50% of normal functional plasma levels (>70%). Tissue factor pathway inhibitor increases. Proinflammatory and anti-inflammatory mediators A multitude of bioactive proinflammatory and anti-inflammatory mediators are released into the plasma and tissues of the lungs, heart, liver, spleen, and kidneys. The complement and the kallikrein–kinin systems generate anaphylatoxins (C3a, C4a, C5a) and bradykinin, which are potent vasodilators. Proinflammatory cytokines, notably TNF, IL-1β, IL-6, and various chemokines are massively up- regulated. Concomitantly, high levels of soluble receptors of the same cytokines are released. The anti-inflammatory cytokines IL-10 and IL-1 RA are present at high levels partly suppressing the cell- activating effect of the bacterial lipopolysaccharides (endotoxin) and the many proinflammatory cytokines. Nitric oxide production is increased in meningococcal septic shock and is thought to con- tribute to the vasodilation. The subarachnoid space The number of meningococci is very low owing to short onset ad- mission time, if present at all. However, they can be cultured from cerebrospinal fluid in up to 50% of untreated cases. The inflamma- tory response is very limited with a leucocyte count usually in the range of 10 to 100 × 106/litre and normal contents of protein and glucose. Laboratory findings The erythrocyte sedimentation rate and C-reactive protein are only moderately elevated on admission, rising to high levels within 48 h. The leucocyte count is usually low owing to upregulation of adhe- sion molecules with a marked shift to young band forms of neutro- phils. There is evidence of a partly compensated metabolic acidosis with decreased levels of pH and bicarbonate. Hyperventilation reduces Pco2. Creatinine and urea are elevated, serum glucose is variable (high, normal, or low), and potassium, calcium, and magnesium are low. Potassium rises with the renal failure. Serum aspartate aminotransferase and alanine aminotransferase are slightly elevated, whereas γ-glutamyl transferase remains normal. Creatine kinase rises within 1 to 3 days, indicating rhabdomyolysis. Prothrombin, activated partial thromboplastin, and thrombin times are prolonged. The levels of platelets, fibrinogen, coagulation factors VII, X, and V, and prothrombin are low. Antithrombin and protein C are low, whereas tissue factor pathway inhibitor is ele- vated. Fibrin(ogen) degradation products, thrombin–antithrombin complexes, PAI-1, and plasmin-α2-antiplasmin complexes are ele- vated. Lumbar puncture should be avoided since the procedure may deteriorate the general condition of the patient, particularly the unstable circulation. For unknown reasons this clinical picture is uncommon in Africa but occurs among Africans migrating to industrialized countries. The case fatality rate was 14–52% in four European studies. The mortality was highest during the outbreak of a serogroup B epidemic. Distinct meningitis and persistent shock There are meningeal and circulatory symptoms. Usually the symp- toms from the inflamed meninges dominate the picture. On ad- mission there are classic signs and symptoms of

meningitis such as headache and nausea, nuchal and back rigidity, and a positive Kernig's sign. The blood pressure remains low despite fluid volume repletion. Circulating levels of endotoxin and inflammatory mediators are lower than in patients with fulminant septicaemia, and case fatality is lower (Fig. 8.6.5.12). However, it is higher than in patients with meningitis without compromised circulation. The case fatality rate is 7–14% in Europe. Meningococcaemia without distinct meningitis
and persistent shock Twenty to thirty per cent (20–30%) of patients with invasive meningococcal disease are hospitalized because of fever and pe- techial or uncharacteristic rash. They lack distinct signs of men- ingitis although slight cerebrospinal fluid pleocytosis (less than 100 × 106 leucocytes/l) may be present. The circulation is not se- verely compromised. They represent a composite group of pa- tients. Many are admitted to hospital early, 12 to 24 h after their first symptoms. Left untreated they might have developed symp- toms of meningitis or fulminant shock. The endotoxin level in plasma is less than 7 endotoxin units/ml and the number of N. meningitidis DNA copies less than 104/ml (Fig. 8.6.5.10). The case fatality rate was 0–5% in Europe. Transient benign meningococcaemia These patients develop fever and often an uncharacteristic rash, but no meningism. They are diagnosed as most likely having a viral in- fection and receive no antibiotic. When the blood culture results are known, the symptoms have disappeared spontaneously, usually within 1–3 days. This syndrome may occur in all age groups. Subacute meningococcaemia A few patients develop fever, an uncharacteristic maculopapular rash, general malaise, and arthralgia but no signs of meningitis or shock. They feel uncomfortable but are not severely ill. Meningococci are isolated from blood cultures. Untreated the symptoms may last for days to several weeks but disappear within 1–2 days after peni- cillin therapy is initiated. Chronic meningococcaemia The patient develops undulating fever, arthralgia, and maculopapular rash (Fig. 8.6.5.13). The symptoms may last for months, but at times they may disappear completely. Blood cultures are sometimes re- peatedly negative. Patients are often treated with corticosteroids because an underlying autoimmune disease is suspected. The fever disappears temporarily before reappearing and at this stage menin- gococci may well be isolated from blood cultures. Antibiotic treat- ment clears the symptoms within a few days. Meningococci with an abnormal lipopolysaccharide (endotoxin) containing five and not

 six fatty acids in the lipid A moiety have been isolated in many of such patients. Other organ manifestations Pericarditis The pericardium is seeded during a transient meningococcaemia. Subsequent inflammation and exudate may lead to cardiac tam- ponade if left untreated. The patient is febrile, nauseated, and may complain of epigastric pain. The condition is often misdiagnosed as an acute abdominal condition. Blood cultures may be negative. N. meningitidis can be cultured, detected by PCR, and seen in aspir- ated pus by direct microscopy. Treatment consists of evacuating the pus and administering antibiotics. The condition should be followed daily by ultrasound examination. Serogroup C organisms have been particularly implicated in these cases. Arthritis Acute meningococcal arthritis is an uncommon clinical mani- festation of a preceding, often low-grade, meningococcaemia. It is usually located to one, or more rarely, several large joints. If the characteristic petechial rash is absent, detection of meningo- cocci in blood or joint fluid is necessary for a correct diagnosis. Arthritis caused by Neisseria gonorrhoeae is considerably more common than primary meningococcal arthritis. The symptoms disappear rapidly after penicillin treatment and there are no long- term complications. Arthritis induced by immune complexes This is more common than the meningococcal arthritis. One or several large joints become swollen and painful. The symptoms usually develop at the end of the

first week of treatment. Blood and joint cultures are negative. The temperature and inflammatory markers may rise after an initial decline. The symptoms disappear gradually after some days of treatment with nonsteroidal anti- inflammatory drugs. Extended antibiotic therapy is not necessary. Cutaneous vasculitis and episcleritis This appears simultaneously with the immune complex arthritis and is commonly observed in sub-Saharan Africa (Figs. 8.6.5.14, 8.6.5.15). The vasculitis causes multiple blisters that readily rupture leading to multiple superficial skin ulcers. Ocular infections Conjunctivitis or panophthalmitis may precede other symptoms of invasive meningococcal infection. They are primarily observed in infants and children. The patient develops a red eye which in the case of panophthalmitis becomes painful with impaired vision. Formation of microthrombi and haemorrhage in retina and corpus vitreum, leading to blindness, may complicate the infection. Pneumonia Strains belonging to serogroups Y and W or more rarely other sero-groups may cause pneumonia in adults and children. The diagnosis depends on detecting meningococci in a representative specimen from the low respiratory tract or blood culture. It cannot be differ- entiated from pneumonia caused by other agents on the clinical symptoms alone. Treatment Prehospital antibiotic treatment Early antibiotic treatment to stop further bacterial growth is re- garded as vital because as many as 30% of the patients in industri- alized countries infected with N. meningitidis develop septic shock Fig. 8.6.5.14 Vasculitic lesion in an African child with meningococcal group A meningitis. Copyright D. A. Warrell. Fig. 8.6.5.15 Episcleritis in an African child with meningococcal group A meningitis. Copyright D. A. Warrell. Fig. 8.6.5.13 Maculopapular rash and peri-articular swellings in an adult patient with chronic meningococcaemia. Copyright D. A. Warrell.

 characterized by rapidly increasing levels of meningococci and lipo- polysaccharides (endotoxin) in the blood. Consequently, health authorities in many countries advise general practitioners to start prehospital antibiotic treatment with ceftriaxone 100 mg/kg, (max- imum dose is 4 g) or benzylpenicillin in suspected cases of men- ingococcal infection. The doses in Table 8.6.5.3 rapidly lead to bactericidal concentrations in plasma. The ceftriaxone or penicillin is injected intravenously or intramus- cularly (into one or both thighs). The patients most likely to benefit from this strategy, if applied early enough, are those who are distant from the hospital and have rapidly evolving symptoms leading to a compromised circulation and extensive haemorrhagic skin lesions. Initial evaluation in hospital The patients should be regarded as emergency cases. The main clin- ical presentation and severity should be evaluated immediately. A variety of prognostic scores have been developed. The Glasgow Meningococcal Septicaemia Prognostic Score is the one most com- monly used. Scores can be used to select patients for intensive care treatment. They should never be used to justify withholding treat- ment as they may overestimate case fatality. Antibiotic treatment Adequate doses of benzylpenicillin, cefotaxime, ceftriaxone, or chloramphenicol effectively stop further proliferation of N. menin- gitidis in the circulation, cerebrospinal fluid, and other extravascular sites. Induction of an explosive release of bacterial lipopolysac- charides leading to a Jarisch–Herxheimer reaction has never been documented in patients receiving antibiotics for meningococcal infection. Plasma levels of lipopolysaccharides and the levels of important inflammatory mediators decline immediately after treat- ment with antibiotics is initiated in these patients (Table 8.6.5.4). Benzylpenicillin, chloramphenicol, cefotaxime, ceftriaxone, and meropenem are bactericidal to N. meningitidis. Benzylpenicillin remains the drug of choice in most countries. It is effective, cheap, and nontoxic in high doses as long as renal function is normal. High doses are necessary since it penetrates the cerebrospinal fluid rela- tively poorly. In patients with fulminant septicaemia and severe renal

dysfunction the doses should be reduced after 24 to 48 h. Strains whose sensitivity to penicillin is reduced because of altered penicillin-binding protein 2 are an increasing problem. In most industrialized countries they account for less than 5% of all menin- gococcal isolates, but the frequency is higher in Mediterranean countries, particularly Spain. Patients infected with these strains have been adequately treated with benzylpenicillin as long as dosage is adequate. A recent study from the United Kingdom indicated the same outcome among patients infected with fully sensitive strains as compared with strains with reduced sensitivity to penicillin. Penicillinase-producing meningococci remain extremely rare. Chloramphenicol is a good alternative in patients hypersensitive to β-lactam antibiotics. In developing countries, it is the best and cheapest alternative to benzylpenicillin. Meningococcal strains re- sistant to chloramphenicol occur in certain areas. In many industrial- ized countries cefotaxime or ceftriaxone is combined with vancomycin as empirical treatment of bacterial meningitis until the aetiological agent has been identified. Cefotaxime and ceftriaxone are highly ef- fective antibiotics that penetrate the blood–brain barrier better than benzylpenicillin. Meropenem is a carbapenem highly active against N. meningitidis, H. influenzae, and S. pneumoniae. It does not induce seizures as observed with the imipenem–cilastatin combination. In each country the health authorities and microbiological laboratories should recommend the optimal and affordable drug regimen. Antibiotic treatment should be initiated promptly. Therapy should start immediately after the first clinical evaluation and collection of the necessary samples for microbiological diagnosis. If there are contra- indications to lumbar puncture or if it is delayed until after brain imaging, antibiotic treatment should be started immediately. Three to 4 days of treatment is adequate to eradicate sensitive meningococci. Supportive treatment Patients with persistent shock should be given extensive volume replacement, whereas patients with meningitis should receive a mod- erate amount of fluid. All patients should be monitored closely to detect early signs of a deteriorating circulation, renal and pulmonary failure, or increasing intracranial pressure. Volume treatment Patients in industrialized countries with persistent hypotension and signs of inadequate peripheral circulation have routinely been treated with massive fluid volume repletion. The extensive capillary leak syndrome increases the volume required. Children and adults may require an infused volume that is one to several times their circu- lating blood volume in the first 24 h. Sodium chloride 0.9% solution is recommended as basic treatment, later supplemented with Ringer’s solution. However, in a recently conducted clinical controlled trial in several African countries evaluating children with severe febrile illness and impaired circulation, the results showed unexpectedly that an initial bolus infusion with 20–40 ml/kg of 5% albumin or NaCl 0.9% increased the mortality significantly. Whether these re- sults also apply to meningococcal shock in Africa is unknown since the pathophysiology with capillary leakage, cardiac dysfunction, and disseminated intravascular coagulation differs from malaria. In many countries the use of fresh frozen plasma is no longer recommended because of the risk of transmitting pathogens, especially HIV. Table 8.6.5.3 Doses of prehospital antibiotic to be administered in suspected cases of meningococcal infection Age (years) Dose All 100 mg/kg ceftriaxone intramuscularly, maximum single dose is 2 g <2 300 mg (0.5 × 106 IU) benzylpenicillin intramuscularly 2–7 600 mg (1 × 106 IU) benzylpenicillin intramuscularly

> 7 1.2 g (2 × 106 IU) benzylpenicillin intravenously or intramuscularly
> Table 8.6.5.4 Antibiotics in meningococcal meningitis or sepsis Antibiotic

> Dose/24 h Dose interval (h) Adult (g) Child (mg/kg) Benzylpenicillin 14.4 (24 × 106 IU) 200 (300 000 IU/kg) 4–6 Cefotaxime 9 200 6–8 Ceftriaxone 4 100 12–24 Chloramphenicol 3 100 6

8.6.5 Meningococcal infections 1023 Patients presenting with distinct signs of meningitis without shock should receive the basic daily requirement of fluid supple- mented with extra volume for dehydration and loss due to vomiting and fever to ensure a normal diuresis (≥1 ml/kg per hour for chil- dren). Excessive hydration should be avoided since it may precipitate irreversible brain oedema and cerebellar herniation. In patients with persistent shock and meningitis, treatment of shock is the priority. Inotropic support If initial volume repletion fails to improve the circulation, inotropic support should be added. Dopamine, dobutamine, noradrenaline, and adrenaline are used. Most physicians start with dopamine at 3–10 µg/kg per min which at an early stage is combined with noradrenalin at 0.03–3.0 µg/kg per min or dobutamine at 1–10 µg/ kg per min. Ideally, infusions should be via infused a central line. Corticosteroid therapy for shock In adults with septic shock and reduced adrenal function, low doses of cortisol increased survival in one study but was not con- firmed in a larger follow up study. Similar studies do not exist for children. Adrenal haemorrhage is common in patients with ful- minant meningococcal septicaemia. Serum cortisol is lower and adrenocorticotropic hormone higher in nonsurviving than sur- viving children with meningococcal shock; a relative adrenal in- sufficiency may therefore exist. Recently many clinicians have treated meningococcal shock with low doses of cortisol in an at- tempt to reduce inotropic support. Corticosteroid therapy for meningitis The United Kingdom National Institute of Health and Clinical Excellence (NICE) guidelines advocate the use of dexamethasone 0.15 mg/kg × 4/24 h (maximum dose 10 mg × 4/24 h) for 4 days for bacterial meningitis. Dexamethasone should ideally be given 15 min before or at least within 4 h after antibiotic treatment is initiated. However, the benefit of dexamethasone in meningo- coccal meningitis is controversial and has not been documented in randomized clinical controlled trials in Europe and North America. Dexamethasone did not improve the outcome in any type of bacterial meningitis in two large double-blind random- ized clinical controlled trials (children and adults) in Malawi, one (adults) in Vietnam and one (children) in Chile. Corticosteroids reduce the penetration of antibiotics over the blood–brain bar- rier. In developing countries corticosteroids are presently not re- commended as adjunct treatment for meningitis. The American Academy of Pediatrics does not advise any adjunct therapy, given the lack of evidence. Ventilatory support Patients receiving volume treatment for profound shock are in danger of developing acute respiratory distress syndrome. Hyperventilation, increasing oxygen demand, decreased pulmonary compliance, and the appearance of diffuse infiltrates on chest radiograph indicate the development of acute respiratory distress syndrome. At a par- tial oxygen pressure in arterial blood (Pao2) of less than 8 kPa with the fraction of inspired oxygen (Fio2) above 0.6 (60% O2 in the in- spiration air), the patient usually requires intubation and artificial ventilation. Infants and children often require mechanical ventila- tion if the resuscitation fluid volume exceeds 40 ml/kg per 24 h to combat the septic shock, even if the oxygenation is normal. Renal support Patients with persistent septic shock and coagulopathy develop renal dysfunction from acute proximal tubular necrosis. Thrombosis in the small peritubular vessels and in glomeruli, and myoglobinaemia, may contribute to renal dysfunction. Serum creatinine and urea are ele- vated on admission and continue to increase for many days without ad- equate treatment. Hyperkalaemia, which may develop during the first 24 to 48 h, is an immediate threat. Haemodialysis or peritoneal

dialysis and continuous haemofiltration are used to treat the renal failure and remove oedema. The renal failure is usually reversible but may last for weeks. Complete kidney failure is uncommon in survivors. Treatment of disseminated intravascular coagulation The first priority is to stop further bacterial proliferation with anti- biotics. This reduces the thrombin activity by 50% within 2 to 6 h. In the 1970s heparin was extensively used. Two small controlled trials did not document any survival benefit in patients receiving heparin. Infusion of a continuous low-dose unfractionated heparin (10–15 IU/kg per h) has been advocated as supplement to treatment with concentrated protein C. The antithrombin levels should be kept above 35 to 40 IU/ml. Antithrombin does not reduce the fatality rate in other types of severe sepsis. Infusion of the natural anticoagulant protein C (loading dose 100 IU/ kg, followed by 15 IU/kg per h for 4 days to keep the plasma concen- tration between 0.8 and 1.2 IU/ml) may possibly limit thrombus for- mation, skin necrosis, and the need for amputation. If used it should be started early. In the few uncontrolled studies that have been pub- lished, several patients treated with protein C concentrate still needed amputation. Randomized controlled trials are lacking. Recombinant human activated protein C (Xigris) did not improve the outcome in patients with septic shock in a randomized con- trolled trial. The drug was withdrawn from the market (November 2011). Routine transfusion of platelets is controversial. In patients with life-threatening bleeding and thrombocytopenia, massive platelet transfusion can be lifesaving; however, it may also aggravate thrombus formation. Fibrinolysis To overcome inhibition by PAI-1, recombinant human tissue plas- minogen activator (0.25–0.5 mg/kg in 1.5–4 h) has been infused to enhance fibrinolysis. Retrospective studies suggest that it increases the rate of cerebral haemorrhage. It is not recommended for routine use in severe meningococcaemia. Plasmapheresis and blood exchange Plasmapheresis and exchange blood transfusion have been tried to remove pathologically activated plasma and leucocytes; 50 ml plasma/kg body weight has been exchanged with fresh plasma. These techniques do not increase the clearance of bacterial lipo- polysaccharide (endotoxin) substantially. Results suggest improved survival, but adequate control groups are lacking. Even desperately ill patients have tolerated the procedures.

 Extracorporeal membrane oxygenation A limited number of children have been treated with extracorporeal membrane oxygenation in a few centres with apparently good re- sults. However, equally good results have been achieved in another paediatric intensive care unit without using the procedure, sug- gesting that the experience of the intensive care unit is more im- portant than the procedure per se. Neutralization of bacterial lipopolysaccharides Three different antiendotoxin principles, the anti-J5 serum, the human monoclonal IgM (HA-1A) antibody, and the recombinant bactericidal/permeability increasing protein (BPI21) have been evalu- ated in randomized double-blind controlled clinical trials. None in- creased survival significantly; however, fewer patients treated with BPI21 required multiple severe amputations and more patients had a functional outcome similar to that before illness 60 days after treat- ment. None of the principals are presently commercially available. Antimediator therapy Strategies to neutralize TNF, IL-1β, bradykinin, platelet-activating factor, and prostaglandins in patients with septic shock have not increased the 28-day survival rate. They have not been specifically evaluated in meningococcal septic shock. Sequelae Meningitis Sensorineural hearing loss or impaired vestibular function occurs in 4–19% of patients. It develops at an early stage, is usually irreversible, and is more common in adults than children. Epilepsy, hydroceph- alus, and diffuse brain damage are at present rare complications in industrialized countries. Persistent headache, altered sleep pattern, concentration difficul- ties, irritability, and neurasthenia may persist in 5–8% of all patients. Shock and coagulopathy Most long-term complications are related to development of gan- grene of the extremities requiring amputation and necrotic skin

lesions requiring extensive grafting. The renal failure is usually re- versible although reduced function may persist. Permanent adrenal insufficiency (i.e. Addison's disease), develops very rarely in sur- vivors. Acute respiratory distress syndrome may lead to permanent pulmonary fibrosis and reduced function. Prevention Vaccination Conjugate protein capsule polysaccharide vaccines (A, C, Y, and W) Serogroup A, C, W, Y conjugate vaccines are immunogenic from 2 months of age. They are very effective, reduce transmission, and induce immunological memory. Booster doses are required for those vaccinated in the first year of life. In United Kingdom babies are offered the C conjugate vaccine at 3 and 12 months. Combined conjugate vaccines containing serogroups A, C, Y, and W have been licensed in many countries for children and adults. Menveo® has been licensed in the United Kingdom for use in infants ≥2 months of age. In babies 2–12 months old, two doses given 1 month apart are required. In United Kingdom students are presently offered A, C, W, and Y conjugate vaccine. Menactra® is licensed for use for ages ≥9 months to 55 years in the United States and other coun- tries. Booster doses are recommended. Mass vaccination of 1–29-year-olds in sub-Saharan Africa with serogroup A conjugate vaccine MenAfriVac® has proven to be very effective. It induces bacteri- cidal anticapsule antibodies and reduces carriage profoundly in the first two years after mass vaccination, resulting in heard immunity. Serogroup A, combined A–C, and various other combinations of conjugate vaccines are marketed or under development, and will be licensed in the near future for use in infants. Capsule polysaccharide vaccine (A, C, Y, and W) The protective effect of these vaccines in infants below 2 years of age is uncertain. When vaccination is required to prevent serogroup A infection, infants of less than 24 months should receive two doses with at least a 1-month interval, whereas those above 2 years should receive one dose. For serogroup C infection, one dose should be given from 18 months. Revaccination with serogroup C polysac- charide may reduce the antibody level. Malaria reduces the immune response. They do not induce immunological memory. An antibody level of 1–2 μg/ml appears to be necessary for protection which lasts for 3–5 years. The vaccines are cheap and have for many years been used successfully to contain outbreaks for those above 2 years of age. Outer membrane vesicle vaccine (B) Since the capsule polysaccharide of serogroup B strains induces a short-lived IgM but no lasting IgG response, several countries (Cuba, Norway, New Zealand) have developed and used an outer membrane vesicle vaccine protecting against outbreaks of one viru- lent clone. The protection rate in adolescents after two doses is lower (57–80%) than for the non-B polysaccharide and conjugate vaccines and is relatively strain specific. The immunodominant epitope is the outer membrane protein PorA. Three doses given 6 weeks apart and a fourth dose 8 months later induce a significantly better immune re- sponse than two doses. Studies in New Zealand with a strain-specific vaccine resulted in 73% protection. The duration of the protection is not known. The Norwegian and New Zealand vaccines are presently not on the market. Serogroup B vaccines Two new serogroup B vaccines are available. The method known as 'reverse vaccinology' has identified genes in the N. meningitidis DNA coding for previously unknown surface-exposed outer mem- brane proteins present in most of the invasive strains. Bexsero® was granted marketing authorization by the European Medicines Agency in November 2012. It contains three cloned proteins: neisserial ad- hesion A (NadA), factor H binding protein (fHbp) and neisserial heparin binding antigen. These are produced in E. coli, purified, and, combined with outer membrane vesicles from the New Zealand epi- demic strain (exposing PorA P1.4). The vaccine induces bactericidal antibodies in all age groups from 2 months. The United Kingdom is the first country to include Bexsero® in its immunization programme starting in September 2015 and vaccinating at 2, 4, and 12 months. If starting after 6 months of age 2 doses are given 2 months apart with a

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