

Meningitis and meningococcal septicaemia

Extended Review

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Neisseria meningitidis accounted for over half the 2,360 notified cases of meningitis in England and Wales in 1997¹ and is the leading infectious cause of death in childhood²⁻⁴. There were twice as many notifications of meningococcal

disease in 1997 as in 1994 and the mortality remained at around 10% (ca 240 deaths)^{1,2}. This article focuses on the presentation and management of meningococcal disease. Other common causes of bacterial meningitis are listed in Table 1 and mentioned in appropriate places in the text. Viral meningitis and HIV-related disease are not considered here.

Clinical presentation of invasive meningococcal infection

Notifications of *N. meningitidis* infections give the misleading impression that the organism causes two distinct diseases,

meningitis and septicaemia. In fact, 30–50% of cases have meningitis alone, 7–10% have features of septicaemia alone, and 40% present a mixed picture^{7,8}. The differentiation between septicaemia and meningitis is important because management differs for patients presenting with shock from those whose major problem is raised intracranial pressure (ICP). Isolated meningococcal meningitis (mortality 5%) has a better prognosis than meningococcal septicaemia (mortality 20–40%)⁹⁻¹⁰.

Meningitis

Meningitis is associated with headache, fever, vomiting, photophobia, lethargy and neck stiffness, often with rash. Early symptoms may be non-specific, but some patients develop a rapidly progressive fall in conscious level, focal neurological deficits, coma and signs of raised ICP including bradycardia, hypotension, asymmetric pupils and decerebrate posturing. Classic signs of

Table 1. Incidence, mortality and first-choice antibiotic treatment for meningitis in the UK where aetiology is known.

Organism	Age of peak incidence	No. of notifications	Year	No. of Deaths	Antibiotic treatment
<i>Neisseria meningitidis</i>	6 months–2 years	1,848 2,646	1995 1997	196 NA	3rd generation cephalosporin
<i>Streptococcus pneumoniae</i>	<5 years and >50 years	241	1995	57	3rd generation cephalosporin +\– vancomycin
<i>Escherichia coli</i>	0–4 weeks	NA	1995	3	3rd generation cephalosporin
<i>Listeria monocytogenes</i> *	<3 months and >50 years	90**	1995	11	Amoxycillin and gentamicin
Group B and other streptococci	0–4 weeks	NA	1995	13	Penicillin and gentamicin or 3rd generation cephalosporin
<i>Haemophilus influenzae</i>	<4 years	60 38	1995 1997	0 NA	3rd generation cephalosporin
<i>Mycobacterium tuberculosis</i>	Adults (UK)	98	1995	9	Isoniazid and rifampicin and streptomycin and pyrazinamide
Staphylococci	Premature infant and shunt-associated	NA	1995	5	Flucloxacillin
Unspecified	–	NA	1995	55	Depends on age†

Deaths and notifications given for all ages (includes neonatal deaths). *N. meningitidis* figures include meningitis and septicaemia cases¹⁻⁶

* Includes cases classified as listeriosis as well as listeria meningitis

** Laboratory reports, notifications not available

† See Table 2

NA = data not available

meningitis may be absent in infants. Presentation in the very young is with fever, poor feeding, irritability, high pitched cry and a tense or bulging fontanelle.

Septicaemia

Meningococcal septicaemia is characterised by fever, rash (see below), vomiting, headache, myalgia, abdominal pain, tachycardia, hypotension, cool peripheries and initially normal conscious level. Early in the disease, symptoms are indistinguishable from a viral illness and, when myalgia is prominent, may be confused with influenza. Progression of disease may take only a few hours. Confusion, cold peripheries, poor capillary refill time and increasing tachycardia may herald a precipitous fall in blood pressure. Rising respiratory rate suggests the development of pulmonary oedema or shock. Generalised oedema develops as a result of the capillary leak syndrome and myocardial depression further impairs tissue perfusion.

Rash in meningococcal disease

Although early meningococcal infection is often associated with a maculopapular rash, a non-blanching rash, petechial or purpuric (Figs 1 and 2), subsequently develops in 80% of children with meningococcal disease. In 13%, a maculopapular rash remains, while 7% have no rash at all¹¹.

Laboratory findings in meningococcal disease

White cell count and C-reactive protein may be raised on presentation or rise over the subsequent 24 hours but are not reliable markers of infection. Only 14% of 128 consecutive children with meningococcal sepsis admitted to our paediatric intensive care unit had a white cell count over $20 \times 10^9/l$ and 71% had a count less than $15 \times 10^9/l$ ¹². Low white cell count is a poor prognostic feature, and its presence suggests rapidly progressive disease. Coagulation is often disturbed in septicaemia

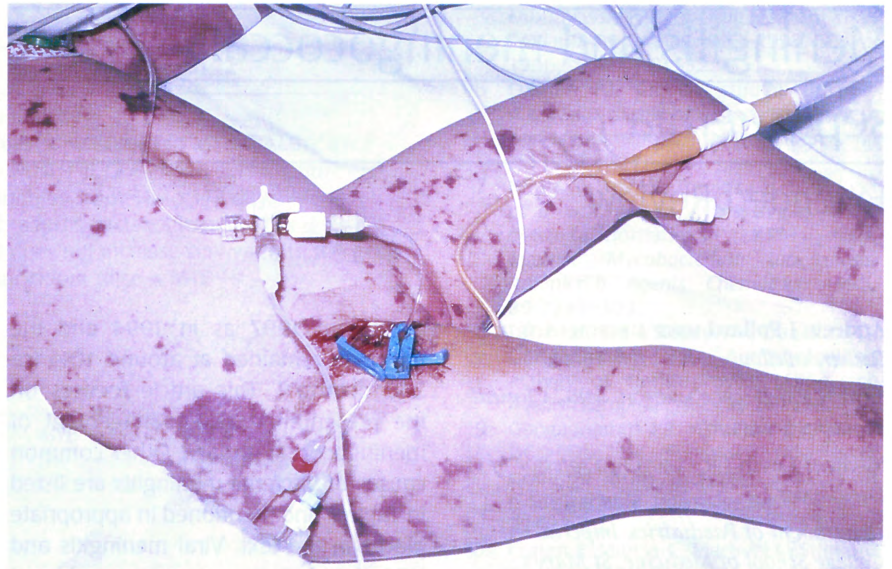


Figure 1. Child with purpuric rash of meningococcal septicaemia shortly after transfer to a specialist paediatric intensive care unit.

because of consumption and loss of clotting factors. Biochemical disturbance is usual in shocked children and may include impaired renal function, hypokalaemia, hypocalcaemia, hypomagnesaemia and metabolic acidosis. Rapid latex antigen tests may assist with diagnosis, but have a high false negative rate; exposing the sample to

ultrasound may increase detection¹³. Rapid diagnosis by polymerase chain reaction (PCR) of blood or cerebrospinal fluid (CSF) is currently being evaluated¹⁴. Blood, throat, CSF and skin aspirate cultures may help with diagnosis, but may be negative after community administration of antibiotics. Convalescent serology may also be useful^{15,16}.

Figure 2. Hand of a child with purpura fulminans due to meningococcal septicaemia (note oedema: capillary leak syndrome). This child's hand was cold and had very prolonged capillary refill time.



Table 2. Cerebrospinal fluid findings in meningitis.

Type of meningitis	White cells (cells/ μ l)	Protein (g/l)	Glucose (mmol/l)
Acute bacterial	100–60,000 (neutrophils)	0.5–5	0.2–2.2
Mycobacterial	25–100 (lymphocytes/monocytes)	1–2	<2.5
Viral	5–200 (lymphocytes, may be >1,000)	Normal or slight elevation but <1	Normal (except mumps/HSV)
Cryptococcal	0–800 (lymphocytes, average 50)	0.2–5	decreased (average 1.7)

Lumbar puncture

Lumbar puncture (LP) is useful to establish the presence of meningitis and to identify the organism and its antibiotic sensitivity. CSF findings are characteristic (Table 2) in 90% of cases. CSF Gram-stain is positive in 40–60% of acute bacterial meningitis cases even after initial antibiotic treatment, but may be negative if antibiotics have been given in the community. Following antibiotics, CSF cultures are positive in fewer than 50%. Newer diagnostic techniques are helpful, for example, latex agglutination (50–100% sensitivity, high specificity) and PCR (91% sensitivity and specificity).

Although LP is usually required to confirm the diagnosis of meningitis, some of the deaths in meningococcal

meningitis are from brain stem herniation (coning), related in time to lumbar puncture. There are clearly defined contraindications to LP (Table 3), including suspected septicaemia and shock and raised ICP¹⁷. In a patient with any of the features in Table 3, lumbar puncture should be avoided and treatment instituted without delay. Furthermore, a normal head computed tomography (CT) scan does not mean it is safe to do a lumbar puncture in a child with bacterial meningitis as CT is an unreliable method for diagnosis of raised ICP¹⁸. In the presence of a purpuric or petechial rash the LP adds little to the clinical diagnosis of meningococcal disease.

Differential diagnosis of meningococcal disease

Since the introduction of *Haemophilus influenzae* type b (Hib) vaccine in 1992 and the decline of Hib meningitis, half

the childhood cases of bacterial meningitis are now caused by *N. meningitidis* and a majority of the rest are pneumococcal¹. Most diagnostic confusion is with other causes of petechiae or purpura (Table 4). In children with fever and petechiae, 2–11% of those with a petechial rash have invasive meningococcal disease^{19–21}, and a majority of the others probably have viral infections. However, because of the high fatality rate, and the difficulty in distinguishing meningococcal disease from other causes of a petechial rash in a febrile child, antibiotic therapy should always be commenced without awaiting additional information.

Management

Community management
(see Table 5)

Since mortality may be reduced by early antibiotic therapy¹⁵, patients with a

Table 3. Contraindications to lumbar puncture. (Reproduced from Ref 17 by permission of the BMJ Publishing Group.)

- Prolonged or focal seizures
- Focal neurological signs
- Widespread purpuric or petechial rash
- Glasgow Coma Scale score of <13
- Pupillary dilatation or asymmetry
- Impaired oculocephalic (doll's eye) reflexes
- Abnormal posture or movement – decerebrate or decorticate movement or cycling
- Signs of impending brain herniation (inappropriate low pulse, raised blood pressure, irregular respirations)
- Coagulation disorder
- Papilloedema
- Arterial hypertension
- Shock

Key Points

- ▶ *N. meningitidis* is the most common cause of bacterial meningitis in the UK and the leading infectious cause of death in childhood
- ▶ Early recognition of shock and/or signs of raised intra-cranial pressure are the keys to successful management
- ▶ Rapid volume replacement is imperative in shock
- ▶ Lumbar puncture should be avoided in shock, cardiovascular compromise and coagulopathy
- ▶ Novel therapies and vaccination are key areas of research
- ▶ Up to half of cases could be prevented by new Group C protein-polysaccharide conjugate meningococcal vaccines in the next few years

Table 4. Other causes of petechial or purpuric rash.

<p>Bacterial infections</p> <ul style="list-style-type: none"> ● pneumococcal septicaemia ● group A streptococcal septicaemia ● other Gram +ve or Gram -ve sepsis ● syphilis <p>Viral infections</p> <ul style="list-style-type: none"> ● Epstein-Barr virus ● enterovirus ● measles ● rubella ● herpes simplex virus ● cytomegalovirus ● haemorrhagic viral fevers (eg dengue) <p>Other infections</p> <ul style="list-style-type: none"> ● mycoplasma (usually maculopapular) ● Rocky Mountain spotted fever ● epidemic typhus ● ehrlichiosis ● leptospirosis <p>Platelet disorders</p> <ul style="list-style-type: none"> ● idiopathic thrombocytopenia ● leukaemia ● other causes of bone marrow failure ● Bernard-Soulier disease ● Glanzmann disease 	<p>Clotting disorders</p> <ul style="list-style-type: none"> ● haemophilia ● von Willebrand disease ● vitamin K deficiency ● protein C or S deficiency <p>Vasculitis</p> <ul style="list-style-type: none"> ● Henoch-Schönlein purpura ● other vasculitides ● haemolytic uraemic syndrome ● Kawasaki disease <p>Trauma</p> <ul style="list-style-type: none"> ● accidental injury ● non-accidental injury ● violent coughing or emesis <p>Connective tissue disorders</p> <ul style="list-style-type: none"> ● osteogenesis imperfecta ● Marfan syndrome ● vitamin C deficiency <p>Miscellaneous</p> <ul style="list-style-type: none"> ● Cushing's syndrome ● drug ingestion ● erythema nodosum ● erythema multiforme
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meningococcal rash should receive parenteral benzylpenicillin by the intravenous or intramuscular route as soon as the diagnosis is suspected. The latter route may be less effective in a shocked patient with poor tissue perfusion. Patients allergic to penicillin may be given cefotaxime, ceftriaxone or chloramphenicol instead²². There

should be immediate transfer to an accident and emergency unit.

Antimicrobial treatment

Meningococcal infection is the commonest bacterial cause of a petechial/purpuric rash and meningitis, but other organisms (including

H. influenzae type b and *Streptococcus pneumoniae*) can cause shock and a non-blanching rash. Therefore, even where the presentation is with classical features of meningococcal disease, a third-generation cephalosporin is the appropriate choice of antibiotic until cultures are available. If no rash is present, the aetiology of meningitis is uncertain and immediate microbiological diagnosis unavailable, empirical antibiotic therapy should aim to ensure coverage of the likely meningeal pathogens (Table 6). Treatment can be modified when the organism is grown or sensitivities become available (Table 1).

Although Hib is now an uncommon cause of meningitis in the UK, initial antibiotic therapy should continue to cover this organism as well as *N. meningitidis* and *S. pneumoniae*. Currently, only 2.9% of pneumococcal strains reported to the Public Health Laboratory Service (PHLS) are penicillin resistant²³. Resistance of pneumococci to high-dose third-generation cephalosporins is unusual in the UK, but increasingly reported in the US and some European countries²⁴. It is likely that resistance will also increase in the UK in the near future. For this reason, and because of the poor outcome of untreated or only partially treated bacterial meningitis, we recommend the use of vancomycin in combination with a third-generation cephalosporin for suspected pneumococcal meningitis until sensitivities are available.

Table 5. Community antibiotic therapy for suspected meningococcal disease²².

Benzyl penicillin (IV or IM)		Chloramphenicol (IV) (penicillin allergic)	
Age (years)	Dose (mg)	Age	Dose
<1	300	<12 years	25 mg/kg
1-9	600	Adult	1.2 g
>10	1,200	-	-

IV = intravenous

Table 6. Empirical antibiotic therapy for meningitis based on age.

Age	Antibiotic choice	Most likely aetiology
Neonates	Ampicillin + cefotaxime	GBS, EC, LM, SP
1-3 months	Ampicillin + cefotaxime (+/- vancomycin)	NM, SP, LM
Older infants, children and adults	Cefotaxime or ceftriaxone (+/- vancomycin)	NM, SP

EC = *Escherichia coli*
 GBS = group B streptococci
 LM = *Listeria monocytogenes*
 NM = *Neisseria meningitidis*
 SP = *Streptococcus pneumoniae*

Emergency management of meningococcal meningitis and septicaemia (see Fig 3)

Many cases of meningococcal infection treated with antibiotics improve rapidly, but in some cases meningococcal disease progresses rapidly from first symptoms to death in a few hours. One in 10 patients with meningococcal disease still die, so all patients with fever and petechial rash warrant urgent initial assessment and treatment, followed by careful and repeated reassessment.

Several scoring systems¹⁶ help identify severely ill patients who are likely to need intensive care. Shock, absence of meningitis, rapidly extending rash, low white cell count, coagulopathy, and deteriorating conscious level predict deterioration.

Death in meningococcal disease is caused by shock and/or raised intracranial pressure, with the latter more common in patients presenting with meningitis alone.

Shock. After considering basic life support and giving antibiotics, the first priority is the treatment of shock. Any patient with cool peripheries (Fig 2), prolonged capillary refill time, decreased urine output, hypotension and tachycardia should be considered to have shock. The initial therapy is volume replacement (20 ml/kg colloid over 10–15 min); this may need to be repeated. A satisfactory response to volume replacement is a reduction in heart rate and improved peripheral perfusion. Patients who stabilise will require close monitoring and reassessment to detect signs of shock reappearing and for signs of pulmonary oedema (from capillary leak syndrome).

In patients who do not respond to initial volume replacement, further volume replacement is required and inotropic support may be needed, starting with dopamine or dobutamine (10–20 µg/kg/min). If hypotension persists, an adrenaline infusion

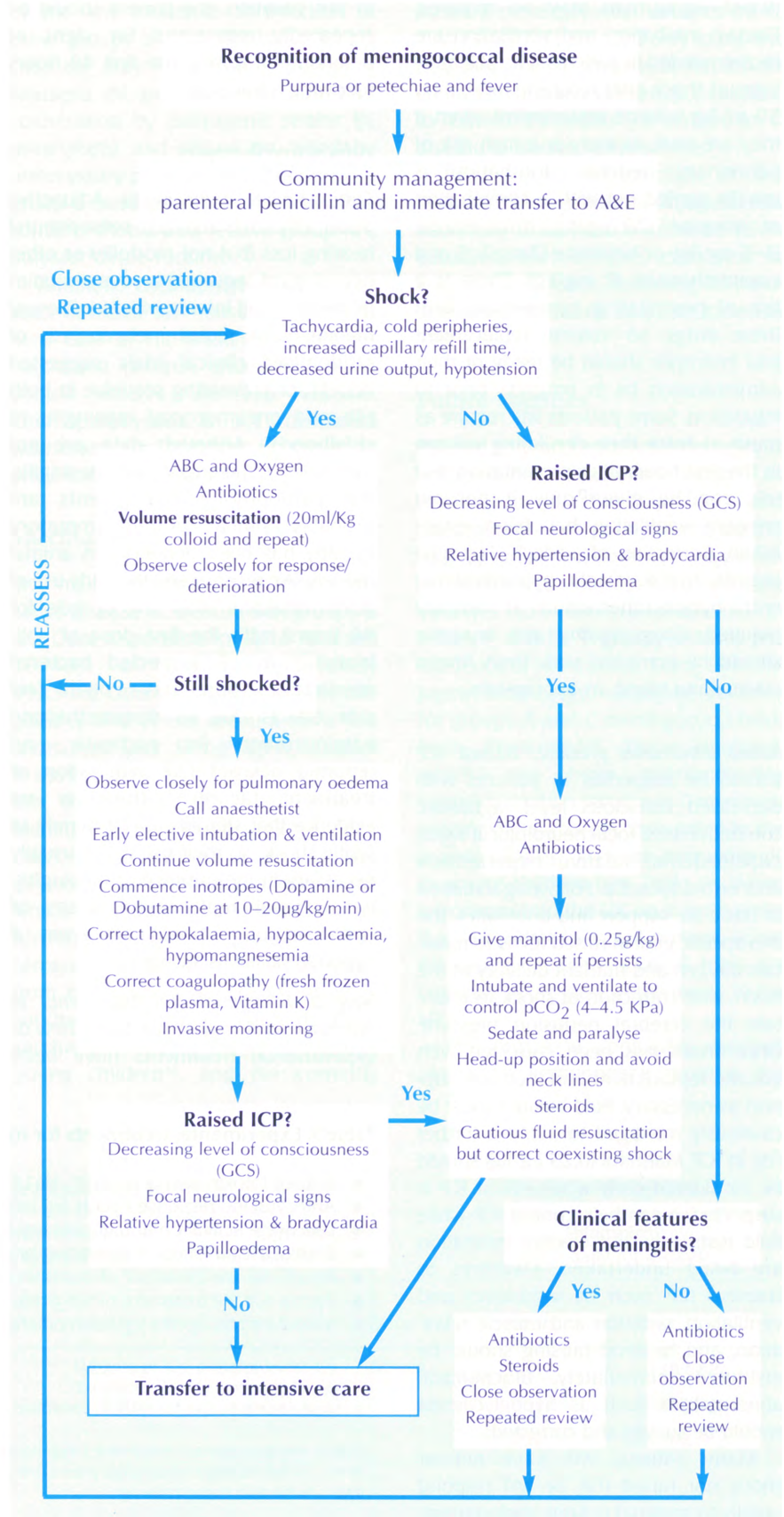


Figure 3. Management of meningococcal disease^{16,17} (ICP = intracranial pressure; GCS = Glasgow coma score).

(0.1–2 µg/kg/min) may be required. Elective intubation and ventilation are recommended in patients who still have signs of shock after receiving more than 50 ml/kg volume replacement, even if they are alert, as there is a high risk of pulmonary oedema. Intubation is usually carried out with a combination of atropine (20 µg/kg), thiopentone (3–5 mg/kg) or ketamine (2 mg/kg), and suxamethonium (2 mg/kg). There is a risk of precipitating hypotension with these drugs, so volume replacement and inotropes should be ready or their administration be in progress prior to intubation. Some patients will require as much as twice their circulating volume in the first hours after presentation, but this can be given only if positive pressure ventilation has been established. Correction of acidosis, hypoglycaemia, hypokalaemia, hypocalcaemia and hypomagnesaemia is usually required. Coagulopathy and anaemia should be corrected with fresh frozen plasma and blood, as appropriate.

Raised intracranial pressure. Raised ICP should be suspected in patients with decreased conscious level, agitation, combativeness, focal neurological signs, papilloedema, relative hypertension and/or bradycardia. Following initiation of basic life support and antibiotics, the therapeutic goal in raised ICP is to maintain oxygen and nutrient delivery to the brain, with correction of shock to maintain the cerebral perfusion pressure. Once shock has been corrected with volume replacement and inotropic support as necessary, fluid balance must be cautiously managed to avoid a further rise in ICP. Mannitol (0.25 µg/kg) should be considered early when raised ICP is suspected; it can help control ICP while fluid restriction and elective intubation are being undertaken. Measures to stabilise ICP such as intubation and ventilation, sedation and muscle relaxation, and head-up nursing should be instituted immediately. Biochemical abnormalities such as hypoglycaemia should be sought and corrected.

Many patients will have neither shock nor raised ICP, or will respond rapidly to minimal volume replacement.

In this situation, the patient should be repeatedly reassessed for signs of deterioration during the first 48 hours following admission.

Adjunctive therapies

Corticosteroids in meningitis. Adjunctive dexamethasone reduced sensorineural hearing loss (but not mortality or other neurological sequelae) in several studies in children and infants with *H. influenzae* meningitis. A recent meta-analysis of randomised clinical trials suggested benefit for preventing sequelae in both Hib and pneumococcal meningitis in childhood²⁵. Although data are not available for meningococcal meningitis, the pathophysiological events are probably similar. Anti-inflammatory therapy has been beneficial in animal models. We recommend the early use of dexamethasone (0.15 mg/kg qds for 48 hours) with the first dose of antibiotic^{16,26} in all suspected bacterial meningitis. There have been few side effects due to dexamethasone administration (in particular, no reported delayed CSF sterilisation or treatment failure)¹⁶. There is no evidence that steroids are of benefit in septic shock, so their use is not usually necessary in the absence of meningitis, but adrenal replacement doses of hydrocortisone should be given if hypoadrenalism is suspected.

New and experimental treatments in meningococcal septicaemia. Many new or experimental treatments have been

proposed in the management of meningococcaemia, with as yet no proven benefit in the reduction of mortality or morbidity (see Table 7). A randomised trial of the anti-endotoxin monoclonal antibody HA1A in children with meningococcaemia showed a reduction in mortality of 32%, but failed to reach statistical significance ($n=269$, $p=0.110$)²⁷. Recently, on the basis of small series, others have proposed using extracorporeal membrane oxygenation (ECMO)²⁸, protein C²⁹ or haemodiafiltration³⁰, but these have not yet been subjected to randomised controlled trials. An international multi-centre randomised controlled trial of the anti-endotoxin recombinant bactericidal permeability-increasing protein (rBPI) is currently underway at centres in the UK and USA. Randomised placebo-controlled trials are needed to determine the efficacy of these new agents and to establish their place in the management of this disease.

Transmission and immunity

Immunity to *N. meningitidis* is probably acquired through intermittent nasal carriage of meningococci and antigenically cross-reacting enteric flora during the first two decades of life. Up to 30% of teenagers and 10% of adults carry meningococci in the upper respiratory tract at any one time³¹, although pathogenic strains are found in only 1% of carriers³². Disease usually occurs less than 10 days after colonisation with a

Table 7. Experimental treatments for meningococcal septicaemia¹⁶.

- Anti-endotoxin agents eg rBPI*, Ha1A**
- Anti-cytokine response agents (eg monoclonal antibody against TNF)
- Leucocyte activation antagonists (eg corticosteroids)
- Cardiovascular support agents (eg prostacyclin)
- Agents for the treatment of disseminated intravascular coagulation (eg protein C)†
- Agents for the treatment of the acute respiratory distress syndrome (eg ECMO)
- Miscellaneous agents (eg haemodiafiltration)

* placebo-controlled trial in progress

** placebo-controlled trial completed

† dose-finding studies for placebo-controlled trial in progress

ECMO = extracorporeal membrane oxygenation

rBPI = recombinant bactericidal permeability increasing protein

TNF = tumour necrosis factor

pathogenic strain in a susceptible individual. The non-immune of any age are susceptible, but the peak incidence is in children from three months to two years of age, with most cases occurring under the age of five years. A second smaller peak occurs in teenagers. Risk factors for meningococcal disease include close contact with a carrier or case, recent viral respiratory illness (influenza), smoking, passive smoking and complement deficiency³³.

Both *S. pneumoniae* and *H. influenzae* colonise the respiratory tract and are disseminated by the respiratory route. The neonatal pathogens which cause meningitis are acquired from the genital tract during childbirth.

Prevention of secondary cases

Household contacts of cases with meningococcal disease are up to 100–800 times more likely to develop disease than the general population^{34,35}. Risk of secondary cases in contacts decreases with time since the index case. Chemoprophylaxis (Table 8) with rifampicin, ciprofloxacin (500 mg as a single dose in adults) or ceftriaxone is currently offered to household and 'kissing-contacts' of children who are suspected clinically to be suffering from meningococcal disease²². Ceftriaxone is preferred in children who refuse oral medication, and it may also be used in pregnancy. Current guidelines do not advise the use of chemoprophylaxis in non-household contacts both because

of the low incidence of infection in these groups and also because young children may carry other types of *Neisseria* (*N. lactamica*) which prevent colonisation by pathogenic strains (*N. meningitidis*) and would be killed by unnecessary prophylaxis²². After proven group C meningococcal infection, close contacts should also receive group A/C polysaccharide vaccine.

Antibiotic chemoprophylaxis is also recommended for household contacts of a case of Hib meningitis, and unvaccinated children under four years should receive the Hib vaccine. Chemoprophylaxis is not considered warranted for contacts of cases of pneumococcal meningitis.

Vaccination

Two main serogroups of meningococci cause disease in the UK. Serogroups B and C are responsible for up to 70% and 30–40% of disease, respectively (PHLS 95). Other serogroups of *N. meningitidis* (Y and W135) account for a few cases each year. Serogroup A, unusual in the UK, is responsible for epidemics in the 'meningitis belt' in the tropics. Meningococci are Gram-negative diplococci. The pathogenic strains are enveloped in a polysaccharide capsule which facilitates invasion and is an obvious vaccine candidate. The serogroup of the organism is assigned from the reaction of sera to the polysaccharide capsule. Purified polysaccharide is not a good immunogen in young children³⁶, and the currently

licensed meningococcal vaccines (A, C, Y, W135 or A/C) are used only to protect travellers, for prophylaxis of household contacts of proven serogroup C cases or to control outbreaks of serogroup C disease in discrete communities³⁷.

Prior to the introduction of the polysaccharide-protein conjugate Hib vaccine in 1992, there were about 1,500 cases of Hib meningitis each year in England and Wales. Following its introduction there were only 38 cases in 1997¹.

Future vaccines

Purified polysaccharide vaccines against encapsulated bacteria (such as meningococci, haemophilus and pneumococci) are poorly immunogenic in young children. However, protein-polysaccharide conjugate vaccines for Hib are protective in infants³⁸ and have greatly reduced the incidence of Hib disease. Using Hib conjugate technology, conjugate vaccines for groups A and C meningococci have been developed³⁹. These vaccines, which also have polysaccharide capsules, contain serogroup C meningococcal polysaccharide conjugated to the protein CRM197. They are immunogenic in young children (see Table 9). When introduced into the UK on a large scale, it is likely that they will prevent about 60 deaths per year. Clinical trials are currently in progress in teenagers in the UK.

Pneumococcal conjugate vaccines also show immunogenic promise, but

Table 8. Antibiotic chemoprophylaxis²².

<i>Neisseria meningitidis</i>						<i>Haemophilus influenzae</i>	
Rifampicin (bd for 2 days)		Ceftriaxone (single IM injection)		Ciprofloxacin (single dose)		Rifampicin (once daily for 4 days)	
Age (years)	Dose	Age (years)	Dose	Age	Dose	Age (years)	Dose
<1	5 mg/kg	<12	125 mg	Adults	500 mg	<1	5 mg/kg
1–12	10 mg/kg	>12	250 mg	–	–	1–12	20 mg/kg
>12	600 mg	–	–	–	–	>12	600 mg

IM = intramuscular

Table 9. Group A/C conjugate meningococcal A/C CRM197 vaccine trials.

Year	Country	No. of vaccinees	Age	Regimen	Post-vaccination C Bactericidal GMT (pre-vaccination)	Post-vaccination C ELISA GMT (pre-vaccination)	Ref
1993	Philippines	16	Adult	2 doses	–	2,021 U/ml (35)	39
1995	Gambia	304	Infants	2 doses	–	818 U/ml (63)	40
1994	USA	50	18–50 years	1 dose	1/7,761 (1/5)	–	41
1996	USA	90	18–24 months	2 doses	1/3,198 (1/4.1)	17 µg/ml (0.2)	42
1996	UK	58	Infants	3 doses	1/3,082 (<1/4)	39 µg/ml (0.6)	43, 44

Post-vaccination titres are given for samples drawn after the last dose of vaccine

Pre-vaccination titres are given in brackets

ELISA = enzyme-linked immunoadsorbent assay

GMT = geometric mean titre to group C meningococci

Table 10. Recent trials of group B vaccines.

Year	Country	Vaccine strain	Vaccine	No. of doses	No. of subjects (x 10 ³)	Age of vaccinees	% with bactericidal activity	Efficacy %	Ref
1991	Cuba	B:4:P1.15 + C poly	OMV	2	>200	5 months–24 years	–	80	46
1995	Chile	B:15:P1.3 + C poly	OMPC	2	41	1–21 years <4 years	83 (5–21 years) 41	51 non-protective	47
1992	Brazil	B:4:P1.15 + C poly	OMV	2	2,400	3 months–7 years <2 years	–	54–74 non-protective	48 49
1996	Netherlands	P1.7,16;P1.5,2;P1.5c,10 P1.12,13;P1.19,15;P1.(7),4	OMV	1	20	Adults	50	–	51
1991	Norway	B:15:P1.7,16	OMV	2	172	13–21 years	–	57	52
1998	Iceland	B4:P1.15, B:15:P1.7,16	OMV OMV	2 2	0.2 0.2	15–20 years 15–20 years	15 47	– –	53 53
1996	Chile	B:15:P1.7,16 B:4:P1.15 + Cpoly	OMV OMV	3 3	0.053 0.023	infants Adults	100 65	– –	50 50
1995	UK	P1.7,16;P1.5,2;P1.5c,10 P1.12,13;P1.19,15;P1.(7),4	OMV	3	0.1	Infants	Data awaited	–	54

Strains are typed according to the nature of their polysaccharide (eg B), Class 2/3 OMP (eg B:4) and Class 1 outer membrane protein (eg B:4:P1.15)

C poly = meningococcal group C polysaccharide

OMPC = outer membrane protein complex

OMV = outer membrane vesicle vaccine

the many polysaccharide types of *S. pneumoniae* will require production of an expensive polyvalent vaccine.

Unfortunately, the polysaccharide capsule of the group B meningococcus, which causes up to 70% of disease in the UK²², is chemically and antigenically identical to human brain and foetal antigens. It is therefore poorly immunogenic in man and its use might induce

autoimmunity⁴⁵. Other bacterial components such as bacterial outer membrane proteins (OMP) are being sought as vaccine candidates. Vaccines have been prepared using simple complexes of OMPs, but recent interest has been directed towards outer membrane vesicle vaccines which contain OMP in spheres of the bacterial lipid membrane. Although some of the serogroup B

vaccine trials have demonstrated overall efficacy in excess of 50%, protection in the most vulnerable age group has not been demonstrated^{46–49}. In those individuals in whom an immune response has been detected, serum bactericidal activity following vaccination seems to have been limited to the vaccine strain⁵⁰. Recent trials of group B vaccines are outlined in Table 10.

Conclusion

Immunisation against Hib in infants prevents about 1,500 cases of invasive Hib disease each year. Safety and immunogenicity data for group C meningococcal conjugate vaccines are encouraging, and it is likely that they will be introduced into the UK in the near future. Pneumococcal conjugate vaccines are also being evaluated in clinical trials. Meningococcal vaccines against group B meningococci still seem a long way off.

Early recognition, optimal resuscitation and specialist intensive care can improve the outcome in meningococcal disease⁵⁵. A number of new therapies currently undergoing trials may in future reduce the mortality and morbidity still further.

Patient organisations

- 1 The Meningitis Research Foundation, 13 High Street, Thornbury, Bristol BS12 2AE (Tel: 01454 281811).
- 2 The National Meningitis Trust, Fern House, Bath Road, Stroud, Gloucestershire GL5 3TJ (Tel: 01453 751738).

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Community acquired pneumonia

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pneumonia (CAP) as it presents to hospital.

Overview

Infections of the chest include a diverse range of conditions such as acute and chronic bronchitis, bronchiectasis, pneumonia, lung abscess, pleurisy and empyema, whilst recurrent respiratory infections characterise those with cystic fibrosis. Because of its relative frequency, complexity and occasional fulminant and fatal nature, the focus of this article is community acquired

The reported incidence of CAP in adults is 1–3 per 1,000 adults per annum. It affects all ages, although the incidence rises rapidly beyond 50 years of age. Risk factors include chronic disease, particularly of the lungs, smoking, alcoholism, institutional care and HIV infection. Approximately 80% of cases are managed in the community. Among

Key Points

- ▶ **Pneumonia is a common cause of hospitalisation and has a mortality ranging from 5–10% to 50% in those requiring intensive care**
- ▶ **The microbial aetiology is diverse and unknown in the majority of patients; *Streptococcus pneumoniae* remains the leading cause**
- ▶ **Initial assessment should include clues to the aetiology, risk factor and severity assessment – crucial to optimising management and directing initial empirical therapy**
- ▶ **Antibiotic resistance among respiratory pathogens is increasing and may in future affect the choice of penicillins and macrolides in treating community acquired pneumonia**
- ▶ **Prevention includes immunisation of risk groups against influenza and pneumococcal infection, health education to control tobacco and alcohol abuse, and optimising the control of any underlying predisposing condition**