promised, for example by exacerbation of hypoxia due to lung injury, sequential multiple organ failure follows. Organ dysfunction in sepsis is covered in more detail in the accompanying article by Singer.

**Conclusion**

Whilst an infecting organism may produce toxins which injure tissues directly, this is often inadequate to explain the clinico-pathological sequelae in severe sepsis. Instead, the dominant role in pathogenesis may lie with components of the host immune response to infection. The highly conserved responses of the innate immune system comprise sequential activation and amplification of humoral and cellular antimicrobial defence mechanisms which can escape the control of anti-inflammatory regulation, inadvertently causing injury to the host. Further understanding of the immunopathogenesis of severe sepsis may unveil new opportunities for therapeutic intervention.

**References**

1. Rangel-Frausto MS. The epidemiology of bacterial sepsis. Review. *Infect Dis Clin North Am* 1999;13:299–312, vii.
2. Morrison DC, Ryan JL. Endotoxins and disease mechanisms. *Annu Rev Med* 1987;38:417–32.
3. Medshtov R, Janeway C. Innate immunity. *N Engl J Med* 2000;343:338–44.
4. Sriskandan S, Cohen J. Gram-positive sepsis. Mechanisms and differences from gram-negative sepsis. *Infect Dis Clin North Am* 1999;13:397–412.
5. Bernal A, Proff T, Fraser JD, Posnett DN. Superantigens in human disease. *J Clin Immunol* 1999;19:149–57.
6. Takeuchi O, Hoshino K, Kawai T, Sanjo H, et al. Differential roles of TLR2 and TLR4 in recognition of gram-negative and gram-positive bacterial cell wall components. *Immunity* 1999;11:443–51.
7. Brown EJ, Lindberg FP. Leucocyte adhesion molecules in host defence against infection. Review. *Ann Med* 1996;28:201–8.
8. Mammen EF. The haematological manifestations of sepsis. *J Antimicrob Chemother* 1998;41(Suppl A):17–24.
9. Haeney MR. The role of the complement cascade in sepsis. *J Antimicrob Chemother* 1998;41(Suppl A):41–6.
10. van der Poll T, van Deventer SJ. Cytokines and anticytokines in the pathogenesis of sepsis. Review. *Infect Dis Clin North Am* 1999;13:413–26, ix.
11. Mathiak G, Szewczyk D, Abdullah F, Ovadia P, Rabinovici R. Platelet-activating factor (PAF) in experimental and clinical sepsis. *Shock* 1997;7:391–404.
12. Parratt JR. Nitric oxide in sepsis and endotoxemia. *J Antimicrob Chemother* 1998;41(Suppl A):31–9.
13. Dinarello CA. Cytokines as endogenous pyrogens. *J Infect Dis* 1999;179(Suppl 2):S294–304.
14. Brady AJ. Nitric oxide, myocardial failure and septic shock. *Int J Cardiol* 1995;50:269–72.

**Address for correspondence:** Professor J Cohen, Hammersmith Hospital, Du Cane Road, London W12 0NN. E-mail: j.cohen@ic.ac.uk

---

**Pathophysiology and management of meningococcal septicaemia**

**Nazima Pathan** BSc MRCP MRCPCH, Clinical Research Fellow

**Simon Nadel** MRCP MRCPCH, Consultant, Paediatric Intensive Care Unit

**Michael Levin** PhD FRCP FRCPCH, Professor of Paediatrics

Imperial College School of Medicine, St Mary's Hospital, London

*J R Coll Physicians Lond* 2000;34:436–44

**Neisseria meningitidis** (meningococcus) is a major infection risk globally. In the UK, it is the leading cause of death from infection in childhood, with a mortality around 10%. Most deaths from meningococcal infection are due to the development of fulminant septic shock. Yet *N. meningitidis* is a frequent commensal of the human upper respiratory tract. Carriage rates increase from less than 1% in infancy to a maximum of 25% in adolescence, declining to around 10% in adulthood.

The meningococcus is a Gram-negative diplococcus. Pathogenic meningococci possess a polysaccharide capsule, differences in the structure of which form the basis of separation into subgroups. The lack of suitable vaccines for all the meningococcal serogroups is because of a high level of genetic diversity caused by intraspecies recombination and transformation. A single mutation or genetic exchange may lead to an outbreak of clinical disease if associated with a change in an immunologically important surface antigen.

**Epidemiology**

Meningococcal disease is endemic worldwide. Serogroups B and C predominate in the UK with an incidence of 5–6 per 100,000. In sub-Saharan Africa, serogroup A predominates in cyclical epidemics every eight years and can affect up to 1,000 per 100,000 of the population. The reasons for regional variation in disease-causing serogroups are not well defined.

**Immunopathology**

**Transmission**

Transmission is by close contact or respiratory droplet spread.

**Colonisation and invasion of nasopharyngeal epithelium**

The risk of colonisation may be enhanced by disruption of the respiratory epithelial cell layer by irritants (such as cigarette smoke) or by a preceding viral illness, for example influenza A. Binding to epithelial cells is established by pilis and outer membrane proteins. Certain outer...
membrane proteins act as immunoglobulin (IgA) proteases which aid survival of meningococci in the mucosa\(^2\). In addition, the organism displays a high level of antigenic variation during the invasion process\(^13,12\) that may help it to evade host immune mechanisms.

**Survival in the bloodstream**

The IgA proteases reduce the effectiveness of humoral immunity as cleaved inactive IgA monomers may competitively inhibit binding of IgG and IgM\(^19\). The polysaccharide capsule provides protection from both phagocytosis and complement mediated lysis\(^14-16\). Certain sialic acid residues on the capsule activate Factor H, which has an inhibitory effect on C3b activation in the complement system\(^17,18\).

**Endotoxin release**

Once in the bloodstream, the meningococcus triggers an intense inflammatory response, of which endotoxin is thought to be a primary mediator\(^16\). The meningococcus presents an overwhelming immune challenge, due to release of endotoxin-rich membrane blebs from viable bacteria in the bloodstream\(^19\). This, together with the ability to grow to high numbers, results in higher concentrations of endotoxin than in any other infection.

**Host defence against meningococcal infection**

Genetic variation in the host response to meningococcal infection may play an important role in the risk of invasive disease. Complement mediated bacterial lysis is an early step in prevention of infection\(^8\). This is highlighted by the increased risk of meningococcal infection in individuals with complement deficiencies, particularly those of the terminal components of the membrane attack pathway, and properdin deficiency\(^20-22\). However, the population attributable risk from these deficiencies is less than 1%\(^23,24\), suggesting that many different factors are important in determining infection and severity of disease. Furthermore, mannose binding lectin, which binds to the bacterial capsule, also initiates complement activation\(^39\), and genetic polymorphisms in this pathway increase susceptibility to meningococcal disease\(^26\).

Mutations in the promoter region of the tumour necrosis factor (TNF-\(\alpha\)) gene are associated with increased severity and mortality in meningococcal disease\(^27\). Individuals with a polymorphism associated with high TNF-\(\alpha\) secretion have higher mortality. Levels of TNF-\(\alpha\) and other pro-inflammatory cytokines such as interleukin (IL)-1\(\beta\) are strongly associated with disease severity, and correlate with endotoxin levels\(^22-26\).

A key feature of meningococcal septicemia is disseminated intravascular coagulation (DIC). Levels of the fibrinolysis inhibitor, plasminogen activator inhibitor (PAI)-1, are increased in response to endotoxin challenge\(^31\). Levels of PAI-1 in meningococcal sepsis correlate with disease severity\(^32\), with the highest levels found in fatal cases\(^31,32\). A genetic polymorphism in the PAI-1 gene promoter region, associated with increased PAI-1 production, is present in a significantly higher proportion of patients with severe fatal meningococcal septicemia than in those with meningitis or mild disease\(^33\).

**Clinical pathophysiology**

The pathophysiology of meningococcal septicemia has four major components\(^34,35\):

- capillary leak
- intravascular thrombosis (coagulopathy)
- myocardial dysfunction
- metabolic derangements.

**Capillary leak**

A major feature of meningococcal infection is increased vascular permeability. The concomitant leakage of plasma from the intravascular space leads to hypovolaemia and reduced preload\(^16\). This may initially be compensated by an increase in heart rate and cardiac contractility, but these mechanisms may be insufficient if the process continues, with resultant impaired tissue perfusion.

**Coagulopathy**

Coagulopathy in meningococcal septicemia is characterised by raised prothrombin and partial thromboplastin times, increased levels of fibrin degradation products, reduced coagulation factors and thrombocytopenia. In severe disease, this leads to the clinical picture of purpura fulminans. There appears to be an imbalance in the procoagulant and anticoagulant pathways. Levels of anticoagulant factors are reduced, including protein C\(^37,38\), protein S, tissue factor pathway inhibitor, and antithrombin III\(^39\). The procoagulant pathway is upregulated with expression of tissue factor\(^40\) and PAI\(^31\).

**Myocardial dysfunction**

Acute myocardial dysfunction refractory to colloid replacement and inotropes is a consistent feature of severe and fatal cases of meningococcal septicemia\(^41\). Myocardial failure is associated with disease severity and prognosis\(^36\). Studies using invasive monitoring in both adult humans and animal models have shown that cardiac dysfunction in sepsis is due to intrinsic depression of contractility rather than to reduced myocardial perfusion\(^42,43\). Bacterial endotoxin released into plasma leads to the release of many pro-inflammatory substances which inhibit myocardial contractility, including ILs, TNF, oxygen free radicals, eicosanoids, platelet activating factor and nitric oxide\(^44-47\). In addition, the abnormal metabolic environment and low circulating volume may contribute to acute myocardial failure.

**Metabolic derangements**

Impaired tissue perfusion leads to metabolic acidosis secondary to impaired oxidative phosphorylation. In
addition, there is often marked hypokalaemia, hypocalcaemia and hypomagnesaemia. The mechanisms leading to these derangements are not clearly defined.

Clinical presentation and management of meningococcal septicaemia

Consequences of meningococcal infection range from transient bacteraemia to multiorgan failure, refractory shock and death. Other important sequelae include coagulopathy and purpura fulminans, occasionally necessitating amputation of digits or limbs. Early recognition and intervention can reduce the risk of death from meningococcal infection. The guidelines for management presented below represent the practice of a department with extensive clinical and research experience in meningococcal infection. The major principles of treatment are elimination of bacteria using antibiotics, and correction of disordered physiology.

Initial assessment

Care should be taken to adhere to advanced life support guidelines with regard to maintaining support of the airway, breathing and circulation. Resuscitation should be guided by the primary survey of these functions. Management depends on whether shock or raised intracranial pressure predominates at presentation, as shown in Fig 1.

Antibiotics

Although penicillin resistance is rare, a third-generation cephalosporin should be given as soon as the diagnosis of meningococcal infection is suspected. This should not be delayed by diagnostic procedures.

Respiratory support

Initially, high flow oxygen by face mask should be given. Patients requiring large volumes of fluid to restore circulating volume (>40 ml/kg) should be electively intubated as there is a significant risk of pulmonary oedema. Intubation should be performed if there is deterioration in neurological status (Glasgow Coma Score <8) and in patients with raised intracranial pressure.

Fig 1. Validated algorithm for the emergency management of meningococcal disease in children (reprinted with permission of the authors (based on a previous version published in Ref 53)). Note: This protocol will be distributed in leaflet form by the Meningitis Research Foundation.

| Estimate of child’s weight (1–10 years) |
|----------------------------------------|
| Weight (kg) = 2 x (age in years + 4) |
| Systolic blood pressure = 80 + (age in years x 2) |
| NB Low BP is a pre-terminal sign in children |

| Conscious level | Age | Normal Values |
|-----------------|-----|---------------|
| Alert           | <1  | 30–40         |
| Responds to voice | 2–5 | 25–30         |
| Responds to pain | 5–12| 20–25         |
| Unresponsive    | >12 | 15–20         |

| Observe HR, RR, BP, perfusion, conscious level |
|-----------------------------------------------|
| Cardiac monitor and pulse oximetry. Take blood for glucose, FBC, clotting, U&E, Ca++, Mg++, PO4, blood cultures, blood gas (bicarb, base deficit), cross-match |

| Colloid bolus (20ml/kg) |
|-------------------------|
| 4.5% human albumin solution (or fresh frozen plasma or hemaccel/gelofusine) IV or intra-osseous |

| Inotropes |
|----------|
| Dopamine or dobutamine at 10–20mcg/kg/min (make up 3 x weight (kg) mg in 50ml 5% dextrose and run at 10ml/hr = 10mcg/kg/min) (these dilute solutions can be used via a peripheral vein) |

| Intubation (call anaesthetist) |
|-------------------------------|
| Atropine 20mcg/kg (max 600mcg) AND thiopentone 3–5mg/kg AND suxamethonium 2mg/kg (caution, high potassium) ETT size = age/4 + 4, ETT length (oral) = age/2 + 12, then: morphine (100mcg/kg) and midazolam (100 mcg/kg) every 30 min |

| Hypoglycaemia (glucose < 3mmol/l) |
|----------------------------------|
| 5ml/kg 10% dextrose bolus IV and then dextrose infusion at 80% of maintenance requirements over 24 hours |

| Correction of metabolic acidosis pH < 7.2 |
|------------------------------------------|
| 1mmol/kg NaHCO3 IV = 1ml/kg 8.4% NaHCO3 over 20 min or 2ml/kg 4.2% NaHCO3 in neonates |

| If K+ < 3.5mmol/l | – Give 0.25 mmol/kg over 30 min IV with ECG monitoring, Caution if anuric |
|-------------------|----------------------------------------------------------|

| If total calcium < 2mmol/l or ionised Ca++ < 1.0 |
|-----------------------------------------------|
| Give 0.1 ml/kg 10% CaCl2 (0.7mmol/ml) over 30 min IV (max 10ml) or 0.3ml/kg 10% Ca gluconate (0.22mmol/ml) over 30 min (max 20ml) |
| If Mg++ < 0.75mmol/l | Give 0.2ml/kg of 50% MgSO4 over 30 min IV (max 10ml) |

| Prophylaxis of household contacts |
|----------------------------------|
| Inform Public Health Department, give rifampicin (bd for 2 days) <1yr 5mg/kg, 1–12 yrs 10 mg/kg, 12 yrs 600 mg; or ceftriaxone (single im dose) <12 yrs 125mg, >12 yrs 250mg; or ciprofloxacin as single 500mg dose (adults only) |

| Diagnosis |
|-----------|
| Blood cultures, throat swab, whole blood (EDTA specimen) for PCR, rapid antigen test. Aspirations/scrapings from skin showing haemorrhagic rash |

| Serology |
|----------|
| For suspected cases with no isolate or where PCR does not identify serogroup, clotted blood sample to MRU* (acute within 72 hrs and convalescent 10–28 days after presenting symptoms) |

* PHLS Meningococcal Reference Unit

Tel: 0161 291 4628 Fax: 0161 446 2180 Out of hours: 0161 4458111
RECOGNITION
May present with predominant SEPTICAEMIA (with shock), MENINGITIS (with raised ICP) or both. Purpuric/petechial non-blanching rash. Rash may be atypical or absent in some cases.
- Call consultant in A&E, paediatrics, anaesthesia or intensive care
- Initial assessment, looking for features or early shock/raised ICP
- DO NOT ATTEMPT LUMBAR PUNCTURE
- IV cefotaxime (80mg/kg) or ceftriaxone (80mg/kg)

Signs of early compensated shock?
- Tachycardia
- Cool peripheries/pallor
- Increased capillary refill time (> 4 sec)
- Tachypnoea/pulse oximetry < 95%
- Hypoxia on arterial blood gas
- Base deficit (worse than -5mmol/l)
- Confusion/drowsiness/decreased conscious level
- Poor urine output (<1ml/kg/hr)
- Hypotension (late sign)

No

Raised intracranial pressure?
- Decreasing or fluctuating level of consciousness
- Hypertension and relative bradycardia
- Unequal, dilated or poorly reacting pupils
- Focal neurological signs
- Abnormal posturing or seizures
- Papilloedema (late sign)

Yes

ABC and oxygen (10l/min), bedside glucose
Insert 2 large IV cannulae (or intra-osseous)

VOLUME RESUSCITATION
Colloid bolus (20ml/kg 4.5% HAS) and review
Repeat colloid bolus if necessary
Observe closely for response/deterioration
Do not attempt lumbar puncture

No

Repeated review

ABC and oxygen (10l/min), bedside glucose
Give mannitol (0.25g/kg) bolus followed by frusemide (1mg/kg)
Steroids (dexamethasone 0.4mg/kg bd x 2 days)
Treat shock if present
Call anaesthetist and contact (PICU)
Intubate and ventilate to control PaCO₂ (4.4-4.5 kPa)
Urinary catheter and monitor output, NG tube
Do not attempt lumbar puncture

No

CLINICAL FEATURES OF MENINGITIS?

NEUROINTENSIVE CARE
- 30° head elevation, midline position
- Avoid internal jugular lines
- Repeat mannitol and frusemide if indicated
- Sedate (muscle relax for transport)
- Cautious fluid resuscitation (but correct coexisting shock)
- Minimal handling, monitor pupillary size and reaction

Yes

Dexamethasone (0.4mg/kg bd x 2 days)

No

STEPWISE TREATMENT OF SEIZURES
- IV lorazepam (0.1mg/kg) or midazolam (0.1mg/kg) bolus
- Consider paraldehyde (0.4ml/kg PR)
- Phenytoin (18mg/kg over 30 min IV with ECG monitoring)

If persistent seizures
- Thiopentone 4mg/kg in intubated patients (beware of hypotension)
- Midazolam/thiopentone infusion

Close monitoring for signs of raised ICP and repeated review

Repeated review

WILL REQUIRE ELECTIVE INTUBATION AND VENTILATION
Call anaesthetist and contact (PICU)
Continue boluses of 10-20ml/kg of colloid
Consider peripheral inotropes (dopamine, dobutamine)
Nasogastric tube and urinary catheter
Consider cuffed ET tube and CXR
Anticipate pulmonary oedema (consider PEEP)
Central venous access
Consider adrenaline infusion (central) if poor response to volume resuscitation and peripheral inotropes

Anticipate, monitor and correct:
- Hypoglycaemia
- Acidosis
- Hypokalaemia
- Hypocalcaemia
- Anaemia
- Coagulopathy (fresh frozen plasma 10ml/kg)
- Raised intracranial pressure

TRANSFER TO INTENSIVE CARE

After 40 ml/kg fluid resuscitation
STILL SIGNS OF SHOCK?

Yes

No

Repeatead review
Circulatory support

Early and aggressive fluid resuscitation has been shown to improve survival\(^1\). A reduced circulating volume at presentation may make it difficult to establish vascular access. In order to maintain tissue perfusion and oxygenation, cardiac output must be maintained, using inotropes in severe disease.

Initially, a 20 ml/kg bolus of fluid should be given\(^6\). This may be adequate in mild cases, but all patients should be carefully monitored for deterioration due to ongoing capillary leak. Further fluid boluses may be required, using clinical and laboratory signs to assess the fluid resuscitation. These include capillary refill time, heart rate, urine output, central venous pressure, blood pressure and the degree of metabolic acidosis. The optimal fluid for resuscitation is still debated\(^57,58\). It is likely that colloidal solutions remain in the circulation longer than crystalloids. No artificial colloid solution has been adequately assessed in children with sepsis, and 4.5% human albumin solution remains our preferred resuscitation fluid.

In cases of shock unresponsive to 40 ml/kg of fluid, dilute solutions of dopamine and/or dobutamine may be given through a peripheral cannula until central vascular access is obtained. Continued myocardial dysfunction may necessitate infusion of adrenaline or noradrenaline once central access is obtained\(^69\).

**Metabolic corrections**

Hypoglycaemia is common and requires rapid correction. Severe shock is often associated with metabolic acidosis which may be partially corrected by circulating volume and cardiovascular resuscitation. The metabolic acidosis in meningococcal septicaemia is paradoxically associated with hypokalaemia, often profound, and requires close monitoring and correction. Similarly, calcium and magnesium levels commonly fall, and should be corrected in order to improve myocardial performance.

Coagulation support

DIC is a common feature of meningococcal septicaemia. Depletion of coagulation factors, fibrinogen and anticoagulant proteins may be corrected by administration of fresh frozen plasma. This may be given as boluses in place of albumin in continuing shock. Cryoprecipitate is not routinely recommended except in severe and persistent hypofibrinogenaemia. Platelet administration may exacerbate and continue the process of DIC. Thrombocytopaenia is not routinely corrected unless associated with spontaneous haemorrhage, or a platelet count below 20,000/mm\(^3\). Heparin does not help to reverse ischaemia in sepsis\(^60\). Prostacyclin has been anecdotaly useful to reverse severe peripheral vasocostriction in meningococcal sepsis. There is, however, a risk of severe hypotension, and prostacyclin should be considered only after shock has been controlled with volume replacement and inotropes.

Management of raised intracranial pressure in meningococcal infection

Raised intracranial pressure may occur in isolation due to meningitis or coexist with septic shock. This may cause diagnostic difficulties as the signs may be similar to shock and impaired brain perfusion. Clinical features include deteriorating levels of consciousness, pupillary dilatation or changes in pupillary reflexes, hypertension and bradycardia. Papilloedema is a late sign.

Patients with elevated blood pressure, relative bradycardia and deteriorating consciousness should be

---

**Table 1. Novel therapies for septic shock.**

| Anti inflammatory:   | Adult sepsis trials – mortality reduction not significant |
|----------------------|-----------------------------------------------------------|
| Anti-LPS monoclonal antibody | Phase III trial in meningococcal sepsis – no benefit |
| NOS inhibition       | Adult sepsis trials – mortality reduction not significant |
| rBPl21               | A Phase III trial evaluating rBPl21 in children with meningococcal sepsis has been completed. Results will be published soon |
| Recombinant HDL      | Phase II trial pending |

| Fibrinolytic/antithrombotic: | Anecdotal reports – no placebo controlled trials |
|-----------------------------|-------------------------------------------------|
| t-PA, streptokinase         | Data on placebo controlled trial to be released this year |
| Protein C                   | A Phase III trial evaluating recombinant human activated Protein C was stopped prematurely due to a significant beneficial effect on mortality and morbidity of the drug over placebo. The safety and efficacy of this drug in meningococcal disease is currently being evaluated |
| Activated protein C         | Data on placebo controlled trial to be released this year |
| Antithrombin III            | Anecdotal reports – no placebo controlled trials |

| Other:                     |                                               |
|---------------------------|-----------------------------------------------|
| Haemofiltration           |                                               |
| ECMO                      |                                               |

ECMO = extracorporeal membrane oxygenation; HDL = high-density lipoprotein; LPS = lipopolysaccharide; NOS = nitric oxide synthase; rBPl21 = recombinant bacterial permeability increasing protein; TNF = tumour necrosis factor; t-PA = tissue plasminogen activator.
treated for raised intracranial pressure with mannitol, frusemide and elective intubation. In addition, standard neurointensive care practice, such as nursing the patient at 30° to the horizontal and with the head midline, should be maintained.

Normal computed tomography (CT) scans do not exclude raised intracranial pressure. Thus, treatment for raised intracranial pressure should be initiated on clinical grounds without awaiting CT results. Lumbar puncture should be avoided in patients with a clinical diagnosis of meningococcal disease due to the risks associated with concomitant coagulopathy, intracranial hypertension, and cardiac and respiratory insufficiency.

**New therapeutic possibilities (Table 1)**

Patients with meningococcal infection have been given many experimental treatments, including anti-inflammatory/anti-endotoxin strategies (Fig 2) and anticoagulant/fibrinolytic therapies (Fig 3). Until the results of placebo-controlled trials are available, these treatments should be restricted to units specifically undertaking research in the disease.

There have been reports of the use of tissue plasminogen activator and streptokinase, protein C and heparin in patients with purpura fulminans secondary to sepsis. These agents carry a significant risk of haemorrhage. Until their role in sepsis is determined by properly controlled studies, routine use of these agents cannot be recommended.

In experimental models of shock, various anti-cytokine and anti-endotoxin strategies have seemed promising, but have failed to reduce mortality in randomised controlled trials. They included administration of anti-TNF monoclonal antibodies and...
CME Septicaemia – I

Key Points

- Meningococcal septicaemia has a 10% mortality overall in the UK
- The major features of meningococcal septicaemia include capillary leak, coagulopathy, myocardial dysfunction and metabolic derangements
- Management should begin with attention to airway, breathing and circulation problems
- Lumbar puncture should not be performed acutely in patients with a clinical diagnosis of meningococcal disease
- Mass vaccination against group C disease should reduce the incidence of meningococcal disease by 40% in the UK; however, no vaccination exists for serogroup B, so there is a need for continued vigilance

anti-endotoxin (HA-1A) monoclonal antibody\(^{67}\). A trial of the anti-endotoxin agent, recombinant bacterial/ permeability increasing protein (rBPI)\(^{68}\), has been recently completed, and the results will be published soon. Preliminary data suggest that recombinant high-density lipoprotein has anti-endotoxin properties\(^{69,70}\), and further investigation of its clinical benefit is being undertaken.

Prevention

Community prevention of secondary cases

Chemoprophylaxis for household contacts is recommended. Other individuals having close physical contact, such as in day-care centres or kissing contacts, should also receive prophylactic treatment. Rifampicin is the drug of choice. Ciprofloxacin and ceftriaxone are good, but unlicensed, alternatives.

Medical staff prophylaxis

Chemoprophylaxis is recommended for medical personnel exposed to oral secretions, such as during intubation. Other hospital and laboratory personnel do not have an increased risk of infection and prophylaxis is not recommended.

Vaccination

At present, unconjugated polysaccharide vaccines for serogroups A, C, W-135 and Y are available. These confer effective protection for up to three years in children over two years old\(^{69}\). The group B meningococcal polysaccharide closely mimics a human neuronal adhesion molecule\(^{70}\) and is non-immunogenic. A number of outer membrane protein vaccines have been developed which have shown efficacy in outbreaks to specific strains\(^{71,72}\). There is currently no vaccine that protects against the large number of group B strains circulating in the UK.

The introduction in 1999 of a mass vaccination programme using a protein-conjugated group C polysaccharide should reduce the incidence of meningococcal disease in the UK by 40%. However, there remains concern that this vaccine may lead to a shift towards a higher incidence of group B disease. Public awareness of the continued need for vigilance, early identification and management of the disease is therefore of great importance.

Acknowledgements

The authors are grateful to Dr S Faust for help in construction of the coagulation pathway algorithm (Fig 3), also Dr T Ali for helpful advice. Dr N Pathan is funded by a British Heart Foundation Junior Research Fellowship.

References

1. Platt MJ. Child health statistical review. 1997. Arch Dis Child 1997;77:542–8.
2. Invasive meningococcal infections. Commun Dis Rep CDR Wkly 1995;5:5.
3. Riordan FA, Marzouk O, Thomson AP, Sills JA, Hart CA. The changing presenta-
tions of meningococcal disease. Eur J Pediatr 1995;154:472–4.
4. Ramsay M, Kaczmarski E, Rush M, Mallard R, et al. Changing patterns of case ascertainment and trends in meningococcal disease in England and Wales. Commun Dis Rep CDR Rev 1997;7:849–54.
5. Lapeyssonnie L. La méningite cérébro-
spinale en Afrique. Bull WHO 1963; 28(Suppl):1):3–114.
6. Moore PS, Hietholzer J, DeWitt W, Gowan K, et al. Respiratory viruses and mycoplasma as cofactors for epidemic group A meningococcal meningitis. JAMA 1990;264:1271–5.
7. Virji M, Kayhty H, Ferguson DJ, Alexandrescu C, et al. The role of pili in the interactions of pathogenic Neisseria with cultured human endothelial cells. Mol Microbiol 1991;5:1831–41.
8. Stephens DS, McGee Z, Melly MA, Hoffman LH, Gregg CR. Attachment of pathogenic Neisseria to human mucosal surfaces: role in pathogenesis. Infection 1982;10:192–5.
9. de Vries FP, Cole R, Dankert J, Frosch M, van Putten JP. Neisseria meningitidis producing the Opf adhesin binds epithelial cell proteoglycan receptors. Mol Microbiol 1998;27:1203–12.
10. Vitovski S, Read RC, Sayers JR. Invasive isolates of Neisseria meningitidis possess enhanced immunoglobulin A1 protease activity compared to colonizing strains. FASEB J 1999;13:331–7.
11. Nasif X, So M. Interaction of pathogenic neisseriae with nonphagocytic cells. Clin Microbiol Rev 1995;8:376–88.
12. de Vries FP, Van Der Ende A, van Putten JP, Dankert J. Invasion of primary nasopharyngeal epithelial cells by Neisseria meningitidis is controlled by phase variation of multiple surface anti-
gens. Infect Immun 1996;64:2998–3006.
13. Mulks MH, Plaut AG. IgA protease produc-
tion as a characteristic distinguishing pathogenic from harmless neisseriae. N Engl J Med 1978;299:973–6.
14. Virji M, Makepeace K, Peak IR, Ferguson DJ, et al. Opc- and pili-dependent interac-
tions of meningococci with human endothelial cells: molecular mechanisms and modulation by surface polysaccha-
rides. Mol Microbiol 1995;18:741–54.
15. Vogel U, Hammerschmidt S, Frosch M, Stalic acids of both the capsule and the sialylated lipooligosaccharide of Neisseria meningitidis serogroup B are prerequisites for virulence of meningococci in the infant rat. Med Microbiol Immunol (Berl) 1996;185:81–7.
16. Klein NJ, Ison CA, Peakman M, Levin M, et al. The influence of capsulation and lipooligosaccharide structure on neutrophil adhesion molecule expres-
sion and endothelial injury by Neisseria meningitidis. J Infect Dis 1996;173:172–9.
17. Estabrook MM, Griffiss JM, Jarvis GA. Sialylation of Neisseria meningitidis lipooligosaccharide inhibits serum
bacterialcidal activity by masking lacto-N-neotetraose. Infect Immun 1997; 65:4436–44.
18 Jarvis GA, Vedros NA. Sialic acid of group B Neisseria meningitidis regulates alternative complement pathway activation. Infect Immun 1987; 55:174–60.
19 Andersen BM. Endotoxin release from Neisseria meningitidis. Relationship between key bacterial characteristics and meningococcal disease. Review. Scand J Infect Dis 1989; 64(Suppl):1–43.
20 Peter G, Weigert MB, Bissel AR, Gold R, et al. Meningococcal meningitis in familial deficiency of the fifth component of complement. Pediatrics 1981; 67:882–6.
21 Herva E, Leinonen M, Kayhty H, Makela PH, Vetonen-Korhonen SL. Recurrent meningococcal meningitis due to partial complement defects and poor anti-meningococcal antibody response. J Infect 1983; 65:55–60.
22 Sjoholm AG, Bracconier JH, Soderstrom C. Properdin deficiency in a family with fulminant meningococcal infections. Clin Exp Immunol 1982; 50:291–7.
23 Ross SC, Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neiserrial and other infections in an immune deficiency. Medicine (Baltimore) 1994; 63:243–73.
24 Ernst T, Spath P, Aebi C, Schaad UB, Bianchetti MG. Screening for complement deficiency in bacterial meningitis. Acta Paediatr 1997; 86:1009–10.
25 Jack DL, Dodds AW, Anwar N, Ison CA, et al. Activation of complement by mannose-binding lectin on isogenic mutants of Neisseria meningitidis serogroup B. J Immunol 1998; 160:1346–53.
26 Hibberd ML, Sumiya M, Summerfield JA, Booy R, Levin M. Association of variants of the gene for mannose-binding lectin with susceptibility to meningococcal disease. Lancet 1999; 353:1049–53.
27 Nadel S, Newport MJ, Booy R, Levin M. Variation in the tumor necrosis factor-alpha gene promoter region may be associated with death from meningococcal disease. J Infect Dis 1996; 174:878–80.
28 Waage A, Halstensen A, Espevik T. Association between tumour necrosis factor in serum and fatal outcome in patients with meningococcal disease. Lancet 1987;3:355–7.
29 Gardlund B, Spjolin J, Nilsson A, Roll M, et al. Plasma levels of cytokines in primary septic shock in humans: correlation with disease severity. J Infect Dis 1995; 172:296–301.
30 Brandtzæg P, Kierulf P, Gaustad P, Skulberg A, et al. Plasma endotoxin as a predictor of multiple organ failure and death in systemic meningococcal disease. J Infect Dis 1989; 159:195–204.
31 Brandtzæg P, Joo GB, Brusletto B, Kierulf P. Plasminogen activator inhibitor 1 and 2, alpha-2-antiplasmin, plasminogen, and endotoxin levels in systemic meningococcal disease. Thromb Res 1990; 57:271–8.
32 Kornelisse RF, Hazelzet JA, Savelkoul HF, Hop WC, et al. The relationship between plasminogen activator inhibitor-1 and proinflammatory and counterinflammato-ry mediators in children with meningoco-coc septice shock. J Infect Dis 1996;173:1148–56.
33 Westendorp RG, Hottenga JJ, Slagboom PE. Variation in plasminogen-activator-inhibitor-1 gene and risk of meningococ-cal septic shock. Lancet 1999; 354:561–3.
34 Flaegstad T, Kaarelsen PI, Stokland T, Gutteberg T. Factors associated with fatal outcome in childhood meningococcal disease, Acta Paediatr 1995; 84:1137–42.
35 Leclerc F, Beuscatt R, Guillotis B, Diependaelje F, et al. Prognostic factors of severe infectious purpura in children. Intensive Care Med 1985; 11:140–3.
36 Mercier JC, Beaufils F, Hartmann JF, Azema D. Hemodynamic patterns of meningococcal shock in children. Crit Care Med 1988; 16:27–33.
37 Fijnvandraat K, Peters M, Derkx B, Van Deventer S, ten Cate JW. Endotoxin induced coagulation activation and protein C reduction in meningococcal septic shock. Prog Clin Biol Res 1994; 388:247–54.
38 Fijnvandraat K, Derkx B, Peters M, Bijlmer R, et al. Coagulation activation and tissue necrosis in meningococcal septic shock: severely reduced protein C levels predict a high mortality. Thromb Haemost 1995; 73:15–20.
39 Brandtzæg P, Sandset PM, Joo GB, Ovstebro R, et al. The quantitative association of plasma endotoxin, anti-thrombin, protein C, extrinsic pathway inhibitor and fibrinopeptide A in systemic meningococ-cal disease. Thromb Res 1989; 55:459–70.
40 Heyderman RS, Klein NJ, Daramola OA, Hammerschmidt S, et al. Induction of human endothelial tissue factor expression by Neisseria meningitidis: the influence of bacterial killing and adherence to the endothelium. Microb Pathog 1997; 22:265–74.
41 Morsalve F, Rucabador L, Salvador A, Bonastre J, et al. Myocardial depression in septic shock caused by meningococcal infection. Crit Care Med 1984; 12:1021–3.
42 Cunnion RE, Schaer GL, Parker MM, Natanson C, Parrillo JE. The coronary circulation in human septic shock. Circulation 1986; 73:637–44.
43 Dhnahut HF, Huyghhebaert MF, Monsallier JF, Lefevere G, et al. Coronary hemo-dynamics and myocardial metabolism of lactate, free fatty acids, glucose, and ketones in patients with septic shock. Circulation 1987; 75:533–41.
44 Parrillo JE, Burch C, Shellhammer JH, Parker MM, et al. A circulating myocardial depressant substance in humans with septic shock. J Clin Invest 1985; 76:1539–53.
45 Hazelzet JA, van der Voort E, Lindemans J, ter Heerdt P, Neijens HJ. Relation between cytokines and routine laboratory data in children with septic shock and purpura. Intensive Care Med 1994; 20:371–4.
46 van Deuren M, van der Ven-Jongekrijg J, Bartelink AK, van Dalen R, et al. Correlation between proinflammatory cytokines, and anti-inflammatories mediators and the severity of disease in meningococcal infections. J Infect Dis 1995; 172:433–9.
47 Visser J, Scholten RJ, Hoekman K. Nitric oxide synthesis in meningococcal meningi-tis. Ann Intern Med 1994; 120:345–6.
48 Khilnani P. Electrolyte abnormalities in critically ill children. Crit Care Med 1992; 20:241–50.
49 Chemow B. Calcium: does it have a therapeutic role in sepsis? Crit Care Med 1990; 18:969–70.
50 Gauthier B, Trachtmann H, Di Carmine F, Urvetsky M, et al. Hypocalcemia and hypercalcitoninemia in critically ill children. Crit Care Med 1990; 18:1215–9.
51 Mauger DC. Hypocalcaemia as a consistent feature of fulminant meningococcal septicemia. Aust Paediatr J 1971; 7:84–6.
52 Weisinger JR, Bellorin-Font E, Magnus and phosphorus. Lancet 1998; 352:391–6.
53 Pollard AJ, Britto J, Nadel S, de Muncer C, et al. Emergency management of meningococcal disease. Arch Dis Child 1999; 80:290–6.
54 Neu HC. Cephalosporins in the treatment of meningitis. Drugs 1987; 34(Suppl 2):135–53.
55 Carillo JA, Davis AL, Zartinsky A. Role of early fluid resuscitation in pediatric septic shock. JAMA 1991; 266:1242–5.
56 Dula DJ, Lutz P, Vogel MF, Weaver BN. Rapid flow rates for the resuscitation of hypovolemic shock. Ann Emerg Med 1985; 14:303–6.
57 Nadel S, De Muncer C, Britto J, Levin M, Habibi P. Albumin: saint or sinner? Arch Dis Child 1998; 79:384–5.
58 Human albumin administration in critically ill patients: systematic review of randomised controlled trials. Cochrane Injuries Group Albumin Reviewers. Br Med J 1998; 317:235–40.
59 Tobin JR, Wetzel RC. Shock and multi-organ failure. In: Rogers MC (ed). Textbook of pediatric intensive care. Baltimore: Williams and Wilkins, 1996;555–605.
60 Haneberg B, Gutterberg TJ, Moe PJ, Osterud B, et al. Heparin for infants and children with meningococcal septicaemia. Results of a randomized therapeutic trial. NIPH Ann 1983;6:43–7.
61 Zenz W, Muntean W, Zobel G, Grabbauer HM, Gallistl T. Treatment of fulminant meningococcal sepsis with recombinant tissue plasminogen activator. Thromb Haemost 1995; 74:802–3.
62 Keeley SR, Matthews NT, Buist M. Tissue plasminogen activator for gangrene in fulminant meningococcemia. Lancet 1991; 337:1359.
CME Diabetes SAQs

Answers to CME SAQs included in JRCPL July/August 2000:

| Q1 | Q2 | Q3 | Q4 |
|----|----|----|----|
| a) F | a) T | a) F | a) F |
| b) F | b) T | b) F | b) F |
| c) T | c) T | c) T | c) T |
| d) T | d) F | d) T | d) F |
| e) F | e) T | e) T | e) F |

| Q5 | Q6 | Q7 | Q8 |
|----|----|----|----|
| a) F | a) F | a) F | a) F |
| b) F | b) T | b) T | b) F |
| c) T | c) F | c) T | c) F |
| d) F | d) T | d) F | d) T |
| e) T | e) T | e) F | e) F |

| Q9 | Q10 | Q11 | Q12 |
|----|-----|-----|-----|
| a) F | a) F | a) F | a) F |
| b) F | b) T | b) T | b) F |
| c) T | c) T | c) T | c) T |
| d) T | d) F | d) T | d) F |
| e) F | e) F | e) T | e) F |

| Q13 | Q14 | Q15 | Q16 |
|-----|-----|-----|-----|
| a) T | a) T | a) T | a) T |
| b) T | b) T | b) F | b) F |
| c) T | c) F | c) T | c) T |
| d) F | d) F | d) T | d) T |
| e) F | e) T | e) F | e) F |

| Q17 | Q18 | Q19 | Q20 |
|-----|-----|-----|-----|
| a) F | a) T | a) F | a) F |
| b) T | b) F | b) F | b) F |
| c) F | c) F | c) T | c) F |
| d) T | d) T | d) T | d) T |
| e) F | e) T | e) F | e) F |