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**


**Pathophysiology and management of meningococcal septicemia**

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*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 carrier rate of 0.5% 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) by a preceding viral illness, for example influenza A. Binding to epithelial cells is established by pilic and outer membrane proteins. Certain outer
membrane proteins act as immunoglobulin (Ig)A proteases which aid survival of meningococci in the mucosa\textsuperscript{10}. In addition, the organism displays a high level of antigenic variation during the invasion process\textsuperscript{11,12} that may help it to evade host immune mechanisms.

Survival in the bloodstream

The IgA\textsubscript{1} proteases reduce the effectiveness of humoral immunity as cleaved inactive IgA\textsubscript{1} monomers may competitively inhibit binding of IgG and IgM\textsuperscript{13}. The polysaccharide capsule provides protection from both phagocytosis and complement mediated lysis\textsuperscript{14–16}. Certain sialic acid residues on the capsule activate Factor H, which has an inhibitory effect on C3b activation in the complement system\textsuperscript{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\textsuperscript{16}. The meningococcus presents an overwhelming immune challenge, due to release of endotoxin-rich membrane blebs from viable bacteria in the bloodstream\textsuperscript{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\textsuperscript{19}. 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\textsuperscript{20–22}. However, the population attributable risk from these deficiencies is less than 1\%\textsuperscript{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\textsuperscript{25}, and genetic polymorphisms in this pathway increase susceptibility to meningococcal disease\textsuperscript{26}.

Mutations in the promoter region of the \textit{tumour necrosis factor} (TNF-\textalpha) gene are associated with increased severity and mortality in meningococcal disease\textsuperscript{27}. Individuals with a polymorphism associated with high TNF-\textalpha secretion have higher mortality. Levels of TNF-\textalpha and other pro-inflammatory cytokines such as interleukin (IL)-1\textbeta are strongly associated with disease severity, and correlate with endotoxin levels\textsuperscript{28–30}.

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\textsuperscript{31}. Levels of PAI-1 in meningococcal sepsis correlate with disease severity\textsuperscript{32}, with the highest levels found in fatal cases\textsuperscript{31,32}. A genetic polymorphism in the \textit{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\textsuperscript{33}.

Clinical pathophysiology

The pathophysiology of meningococcal septicemia has four major components\textsuperscript{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\textsuperscript{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\textsuperscript{37,38}, protein S, tissue factor pathway inhibitor, and antithrombin III\textsuperscript{39}. The procoagulant pathway is upregulated with expression of tissue factor\textsuperscript{40} and PAI\textsuperscript{31}.

Myocardial dysfunction

Acute myocardial dysfunction refractory to colloid replacement and inotropes is a consistent feature of severe and fatal cases of meningococcal septicemia\textsuperscript{41}. Myocardial failure is associated with disease severity and prognosis\textsuperscript{16}. 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\textsuperscript{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\textsuperscript{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 multi-organ 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 1.53

Antibiotics

Although penicillin resistance is rare, a third-generation cephalosporin should be given as soon as the diagnosis of meningococcal infection is suspected54. 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.

<table>
<thead>
<tr>
<th>Estimate of child’s weight (&lt;10 years)</th>
<th>Weight (kg) = 2 x (age in years + 4)</th>
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<tbody>
<tr>
<td>Systolic blood pressure = 80 + (age in years x 2)</td>
<td></td>
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<tr>
<td>NB</td>
<td>Low BP is a pre-terminal sign in children</td>
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<table>
<thead>
<tr>
<th>Conscious level</th>
<th>Age</th>
<th>Normal Values</th>
<th>Heart rate</th>
</tr>
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<tbody>
<tr>
<td>Alert</td>
<td>&lt;1</td>
<td>30–40</td>
<td>110–160</td>
</tr>
<tr>
<td>Responds to voice</td>
<td>2–5</td>
<td>25–30</td>
<td>95–140</td>
</tr>
<tr>
<td>Responds to pain</td>
<td>5–12</td>
<td>20–25</td>
<td>80–120</td>
</tr>
<tr>
<td>Unresponsive</td>
<td>&gt;12</td>
<td>15–20</td>
<td>60–100</td>
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<table>
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<tr>
<th>Observe HR, RR, BP, perfusion, conscious level</th>
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</thead>
<tbody>
<tr>
<td>Cardiac monitor and pulse oximetry, take blood for glucose, FBC, clotting, U&amp;E, Ca++, Mg++, PO₄, blood cultures, blood gas (bicarb, base deficit) cross-match</td>
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<tr>
<th>Colloid bolus (20ml/kg)</th>
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<tr>
<td>4.5% human albumin solution (or fresh frozen plasma or hemocollagenosine) IV or intra-osseous</td>
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<tr>
<th>Inotropes</th>
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<tr>
<td>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)</td>
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<tr>
<th>Intubation (call anaesthetist)</th>
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<tbody>
<tr>
<td>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</td>
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<thead>
<tr>
<th>Hypoglycaemia (glucose &lt; 3mmol/l)</th>
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<tr>
<td>5ml/kg 10% dextrose bolus IV and then dextrose infusion at 80% of maintenance requirements over 24 hours</td>
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<tr>
<th>Correction of metabolic acidosis pH &lt; 7.2</th>
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</thead>
<tbody>
<tr>
<td>1mmol/kg NaHCO₃ IV = 1ml/kg 8.4% NaHCO₃ over 20 min or 2ml/kg 4.2% NaHCO₃ in neonates</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>If total calcium &lt; 2mmol/l or ionised Ca++ &lt; 1.0</th>
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<tbody>
<tr>
<td>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)</td>
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<tr>
<th>If Mg++ &lt; 0.75mmol/l</th>
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<tr>
<td>Give 0.2ml/kg of 50% MgSO₄ over 30 min IV (max 10ml)</td>
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<tr>
<th>Prophylaxis of household contacts</th>
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<tbody>
<tr>
<td>Inocum Public Health Department, give rifampicin (bd for 2 days) &lt; 1yr 5mg/kg, 1–12 yrs 10mg/kg, 12 yrs 600 mg or ceftriaxone (single im dose) &lt;12 yrs 125mg, &gt;12 yrs 250mg; or ciprofloxacin as single 500mg dose (adults only)</td>
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<tr>
<th>Diagnosis</th>
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<tr>
<td>Blood cultures, throat swab, whole blood (EDTA specimen) for PCR, rapid antigen test, Aspirations/scratchings from skin showing haemorrhagic rash</td>
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<tr>
<th>Serology</th>
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<tr>
<td>For suspected cases with no isolate or where PCR does not identify serogroup, clot on blood sample to MRU* (acute within 72 hrs and convalescent 10–28 days after presenting symptoms)</td>
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</table>

* MHLs 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. Pupillary and/or cranial nerve palsies. Rash may be atypical or absent in some cases.

- Call consultant in A&E, paediatrics, anaesthesia or intensive care
- Initial assessment, looking for features of early shock/raised ICP
- **DO NOT ATTEMPT LUMBAR PUNCTURE**
- IV cefotaxime (60mg/kg) or ceftriaxone (60mg/kg)

---

**-signs of early compensated shock?**
- Tachycardia
- Cool peripheries/pallor
- Increased capillary refill time (> 4 sec)
- Tachypnoea/pulse oedema < 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)

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**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)

---

**VOLUME RESUSCITATION**
- Collated bolus (20ml/kg 4.5%) and review
- Repeat collated bolus if necessary
- Observe closely for response/deterioration
- Do not attempt lumbar puncture

---

ABC and oxygen (10l/min) bedside glucose
- Insert 2 large IV cannulae (or intravenous)
- **WILL REQUIRE ELECTIVE INTUBATION AND VENTILATION**
- Call anaesthetist and contact (P)ICU
- Continue boluses of 10-20ml/kg of colloids
- Consider peripheral isotopes (ex: dopamine, dobutamine)
- Nasogastric tube and urinary catheter
- Consider cuffed ET tube and CVP
- Anticipate pulmonary oedema (consider PECP)
- Central venous access
- Consider adrenaline infusion (central)
- If poor response to volume resuscitation and peripheral isotopes

---

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

---

**TRANSFER TO INTENSIVE CARE**

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

---

**STEPSWISE 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

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**CLINICAL FEATURES OF MENINGITIS?**

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Dexamethasone (0.4mg/kg bd x 2 days)

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Repeated review
Circulatory support

Early and aggressive fluid resuscitation has been shown to improve survival. 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. 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.

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.

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 septicemia 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 septicemia. 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. Thrombocytopenia is not routinely corrected unless associated with spontaneous haemorrhage, or a platelet count below 20,000/mm³. Heparin does not help to reverse ischaemia in sepsis.

Prostacyclin has been anecdotally useful to reverse severe peripheral vasoconstriction 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...
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...
anti-endotoxin (HA-1A) monoclonal antibody. A trial of the anti-endotoxin agent, recombinant bactericidal/permeability increasing protein (rBPI), has been recently completed, and the results will be published soon. Preliminary data suggest that recombinant high-density lipoprotein has anti-endotoxin properties, 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. The group B meningococcal polysaccharide closely mimics a human neuronal adhesion molecule and is non-immunogenic. A number of outer membrane protein vaccines have been developed which have shown efficacy in outbreaks to specific strains. 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.

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.

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