Diagnosis and management of meningococcal disease: the need for centralized care

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Abstract
Meningococcal infection remains a significant health problem in children, with a significant mortality and morbidity. Prompt recognition and aggressive early treatment are the only effective measures against invasive disease. This requires immediate administration of antibiotic therapy, and the recognition and treatment of patients who may have complications of meningococcal infection such as shock, raised intracranial pressure (ICP) or both. Encouragingly, its mortality has fallen in recent years. This is the result of several factors such as the centralization of care of seriously ill children in paediatric intensive care units (PICUs), the establishment of specialized mobile intensive care teams, the development of protocols for the treatment of meningococcal infection, and the dissemination by national bodies and charities of guidance about early recognition and management. We will review the pathophysiology and management of the different presentations of meningococcal disease and examine the possible role of adjunctive therapies.

Introduction
Meningococcal infection remains a significant health problem in children, with a significant mortality and morbidity. Since the widespread introduction of the conjugated meningococcal serogroup C vaccine, there has been a substantial and sustained reduction in the incidence of serogroup C meningococcal disease. However, in the absence of an effective serogroup B vaccine and without widespread use of vaccines against group A, W135 and Y meningococci, these remain an important cause of morbidity and mortality worldwide.

Prompt recognition and aggressive early treatment are the only effective measures against this invasive disease. This requires the immediate administration of antibiotic therapy, and recognition and treatment of patients who may have complications of meningococcal infection such as shock, raised intracranial pressure (ICP) or both. Encouragingly, mortality due to meningococcal infection has fallen in recent years. This is the result of several factors such as centralization of the care of seriously ill children in paediatric intensive care units (PICUs), the establishment of specialized mobile intensive care teams, the development of protocols for the treatment of meningococcal infection, and the dissemination by national bodies and charities of guidance about its early recognition and management.

Susceptibility to infection and severity of disease
Approximately 10% of the population carry meningococci in their upper respiratory tract at any time, with higher rates amongst teenagers and young adults (Caugant et al., 1994; Maiden & Stuart, 2002). Not all carriage is of highly virulent clones, and many commensal Neisseria are nonpathogenic and may confer an element of protection against highly virulent strains. By contrast, less than 1% of children under 4 years of age are colonized with Neisseria meningitidis (Gold et al., 1978).

Although cases are reported of invasive disease following a prolonged period of carriage with a pathogenic strain, disease usually occurs less than 10 days after colonization with a pathogenic strain in a susceptible individual (American Academy of Pediatrics (Meningococcal Infections), 2000). Risk factors for invasive disease include young age (Kaczmarski, 1997; Rosenstein et al., 1999), winter or dry season (Greenwood, 1987), close contact with a carrier or case (De Wals et al., 1981), overcrowding (Moodley et al., 1999; Baker et al., 2000), moving into new communities (Berild et al., 1980; Neal et al., 1999), active or passive smoking (Haneberg et al., 1983; Fischer et al., 1997; Yusuf et al., 1999), and exposure to respiratory infection (Cartwright et al., 1991; Moodley et al., 1999).
Whilst most individuals are colonized by meningococci at some time in their lives, very few suffer invasive disease. Even in those who do develop invasive infection, its severity varies considerably. These observations suggest that various host factors influence both susceptibility to infection and severity of disease. This is confirmed by the finding that complement deficiency (Fijen et al., 1989; Nielsen et al., 1989), hypogammaglobulinaemia (Salit, 1981) and hypoplasmenism (Locker et al., 1995) all predispose to invasive meningococcal infection, while variations in cytokine responses and coagulation pathway control may lead to variations in severity (Nadel et al., 1996; Haralambous et al., 2003). These observations have led to extensive investigations directed at identifying genetic associations in meningococcal disease (Emons et al., 2003).

In addition, real-time PCR techniques have shown that the number of meningococci in plasma and CSF appears to be the main determinant of lipopolysaccharide levels, which have been shown to be associated with clinical presentation and outcome (Ovstebo et al., 2004).

**Presentation and clinical features**

The classical presenting features of meningococcal disease include fever and a characteristic haemorrhagic rash, with features of meningitis and/or septicemia. A recent study on the clinical recognition of meningococcal disease in children and adolescents noted that the classical features developed later on in disease progression (median time of onset 13–22 h after symptoms began), whereas early, less-specific features of sepsis such as leg pain, cold hands and feet and abnormal skin colour first developed after a median period of 8 h in the majority of children (Thompson et al., 2006). This suggests that recognition of these early symptoms of sepsis could increase the proportion of children identified by primary-care clinicians as likely to have sepsis, shorten the time to hospital admission, and potentially, save lives.

It seems that patients with meningitis are likely to present following a longer period of lower-grade bacteremia than patients with fulminant meningococcal septicemia who will have higher levels of bacteraemia and thus higher levels of cytokinaemia than patients with a compartmentalized infection such as meningitis (van Deuren et al., 2000).

Occult bacteraemia with *N. meningitidis* may occur (Edwards et al., 1985). In one study, febrile children who were evaluated as outpatients and then discharged home (being considered at low risk of invasive infection) were termed cases of ‘unsuspected meningococcal disease’ (UMD) when *N. meningitidis* was subsequently isolated from blood or cerebrospinal fluid cultures obtained during these outpatient visits (Kuppermann et al., 1999). They constituted fully 12% of all children diagnosed with meningococcal disease on the basis of a positive culture. These children were compared to a large number of febrile outpatients from 3–36 months old with negative blood cultures. The children with UMD were significantly younger and had significantly higher immature neutrophil (band cell) counts. There were no significant differences however, in temperature, total white blood cell counts, and absolute neutrophil counts.

Multivariate analyses identified young age and the band count as independent predictors of UMD. The conclusion from this study was that children ultimately diagnosed with meningococcal disease have not infrequently been evaluated as outpatients and discharged to home before diagnosis. Of the haematologic parameters frequently used in the evaluation of fever, only the band count differed significantly between young febrile children with UMD and those with negative cultures. Because UMD is uncommon in young febrile pediatric outpatients however, the predictive value of the band count is poor. It is clearly impossible to quantify the risk of progression to meningococcal septicemia or meningitis in these children, but the potential for it is certainly present. Of children who progress to invasive meningococcal disease, 30–50% have meningitis alone (mortality 5%), 7–10% have features of septicemia alone (mortality 5–40%) and 40% present a mixed picture of meningitis with septicemia (Havens et al., 1989; Kirsch et al., 1996).

In the UK, mortality from meningococcal disease has fallen over the past 10 years. Even in the most severe cases, mortality rates are now reported to be around 5% for those treated in specialist PICUs (Booy et al., 2001; Thorburn et al., 2001). Children with the highest risk of death include those with a rapidly progressive purpuric rash, absence of meningism, coma, hypotension (mean arterial blood pressure ≤2 SD below mean for age), low peripheral blood white cell count (≤10 × 10⁹/L), low platelet count (≤100 × 10⁹/L) and young age (Lodder et al., 1996).

**Symptoms and signs of meningitis**

In patients with meningococcal meningitis the following symptoms and signs predominate: headache, fever, vomiting, photophobia, neck stiffness, positive Kernig’s and Brudzinski’s signs, and lethargy. In infants and younger children, poor feeding, irritability, a high pitched cry and a bulging fontanelle are typical findings. Seizures may occur in up to 20% of cases and meningitis is a cause of the first episode of convulsive status epilepticus in 12% of cases (Chin et al., 2006).

**Symptoms and signs of septicemia**

Patients with meningococcal septicemia may present with fever, rash, headache, flu-like symptoms (especially myalgia), vomiting or abdominal pain. Clinical signs of shock...
including tachycardia, poor peripheral perfusion, tachypnoea, oliguria, confusion and hypotension may be present. Rarely, invasive disease may take the form of focal infection, such as arthritis, pneumonia, conjunctivitis, pericarditis or endophthalmitis.

**Rash**

The presence of a characteristic haemorrhagic rash is highly variable, however, 80% of bacteriologically proven cases of meningococcal disease develop a rash at some stage in their illness. Typically this is haemorrhagic (petechial or purpuric) in character (Marzouk et al., 1991), but around 15% of patients will present with an atypical, blanching, maculopapular rash, which may evolve into the more typical nonblanching form over anything from minutes to hours. A small percentage (around 7%) never develops a rash and their presentation is indistinguishable from other causes of sepsis.

The extent and description of the rash does not always correlate with the severity of disease and some children with severe disease will have no rash, or minimal rash.

Whilst the presentation of a fulminant case of meningococcal disease should be unmistakeable, many children present to primary care physicians, or to Accident and Emergency Departments, febrile, with a petechial rash but with no other features of severe infection. While a significant proportion of children are sent to primary care physicians, or to Accident and Endophthalmitis.

**Laboratory features**

Meningococcal disease should be suspected in the face of suggestive clinical features, and initial treatment with antimicrobials, and the recognition and management of shock or raised ICP, should not be delayed whilst waiting for the results of laboratory investigations. In any case, they may be misleading. Elevated white cell count and C-reactive protein are common features of invasive bacterial diseases. However, these acute phase reactants may take 12–24 h to respond following the onset of invasive meningococcal infection and are therefore not commonly raised early in the course of the disease, especially in severe or rapidly progressive cases (Stiehm & Damrosch, 1966; Pollard et al., 1997). In severe cases, biochemical and haematological derangements are common.

Microbiological confirmation is important for guiding public health management and in excluding other possible causes. Cultures of blood, secretions from the throat, CSF (in the absence of contraindications) and skin lesion aspirates may confirm a diagnosis and allow for antimicrobial sensitivity testing. Latex agglutination assays on blood, CSF or urine have been used as adjunctive diagnostic tests but have a poor sensitivity and specificity (Perkins et al., 1995). In many countries, the PCR from samples of blood or CSF is now used to detect meningococcal DNA. This is particularly useful in patients who have received antimicrobial therapy prior to cultures being taken (Cartwright & Kroll, 1997; Carrol et al., 2000; Pollard et al., 2002). It is likely that PCR-based techniques will replace serological methods for serotyping meningococcal outbreaks for epidemiological analysis and routine surveillance in the near future (Gray et al., 2006).

**Progression of disease**

Meningococcal disease may progress rapidly, even after the appropriate treatment has commenced. All children admitted to hospital with suspected meningococcal disease should be closely monitored for signs of deterioration. Their outcomes may critically depend on the prompt recognition of two important complications: shock or raised ICP. While children with comparatively mild disease may have neither, these two clinical problems may coexist in some cases, and present a formidable treatment challenge.

**The presence of shock**

Shock in meningococcal disease is multi-factorial and results from a combination of hypovolaemia caused by capillary leak syndrome, myocardial dysfunction, altered vasomotor tone and impaired cellular metabolism (Nadel et al., 1995).

The increased vascular permeability results from endothelial cell injury, causing leakage of water and plasma proteins out of the intravascular compartment. The clinical features of shock arise because perfusion of the vital organs (such as the brain or heart) is maintained at the expense of
perfusion of nonvital organs (e.g., skin, kidneys and gut). In the early phases of shock these processes compensate for hypovolaemia and maintain central circulating blood volume and cardiac output.

The vasoconstriction that occurs in shock reduces blood flow to the skin, to the peripheries and to some organs, especially the kidneys and gut. As a result, patients with meningococcal septicaemia may present with cold peripheries and prolonged capillary refill time, with sluggish or even absent blood flow to the skin, as well as oliguria. In the most severe cases, ischaemia of the skin or even a whole limb may occur, particularly if there is thrombosis in areas of vascular stasis. In addition, many patients with septic shock will develop renal dysfunction, often leading to acute renal failure.

Despite severe shock, preservation of brain perfusion and function is often present until decompensation occurs, so that the child’s relatively alert state may make observers underestimate the degree of cardiovascular collapse. Eventually a decreased level of consciousness indicates a loss of cerebral vascular homeostasis and reduced brain perfusion.

The onset of hypotension signifies a failure of the compensatory mechanisms. It should be remembered that the diagnosis of shock in children is not dependent on the presence of arterial hypotension. Children are able to compensate for the loss of up to 40% of their circulating volume without developing hypotension, and may therefore have a normal blood pressure until shock is advanced (Zaritsky et al., 2002).

The presence of a haemorrhagic rash is pathognomonic of meningococcal disease and reflects coagulopathy. Coagulopathy is universal in severe sepsis, regardless of the cause. Both pro-coagulant and anticoagulant pathways of haemostasis are dysregulated as a consequence of activation of the inflammatory and coagulation cascades, in addition to endothelial dysfunction (Pathan et al., 2003). It is likely that the disturbed coagulation seen in meningococcal sepsis arises from a combination of the loss of anticoagulant proteins such as proteins C and S from the plasma, and the failure of anticoagulant mechanisms on the endothelial surface. The endothelial receptors required for protein C activation (endothelial protein C receptor and thrombomodulin) are down-regulated on the endothelium of patients with meningococcal septicaemia (Faust et al., 2001). In addition, levels of circulating activated protein C and antithrombin III are reduced, the normal fibrinolytic mechanisms are suppressed due to the reduced production of endothelial tissue plasminogen activator, and the production of plasminogen activator inhibitor-1 (PAI-1) and other fibrinolysis inhibitors such as thrombin-activatable fibrinolysis inhibitor (TAFI). This results in intravascular clot formation, with a suppression of the normal mechanisms which degrade intravascular thrombi, and the clinical syndromes of disseminated intravascular coagulopathy (DIC) and Purpura fulminans (Esmon, 2005).

Myocardial dysfunction arises as a result of a number of the different pathological processes that are activated in septic shock (Parrillo, 1993). Hypovolaemia causes decreased ventricular filling, and metabolic derangements including hypoxia, acidosis, hypokalaemia, hypocalcaemia, hypophosphataemia, hypomagnesaemia, hypoglycaemia and disturbed fatty acid metabolism may also affect myocardial contractility (Mercier et al., 1988). Bacterial products and inflammatory cytokines also directly suppress myocardial contractility (Kumar et al., 1996). Interleukin 6 (IL–6) in plasma has recently been identified as a specific myocardial depressant factor in meningococcal disease, which may offer a new approach to management (Pathan et al., 2002, 2004).

Myocardial contractility improves with volume resuscitation and correction of metabolic derangements, but patients with signs of ongoing shock despite adequate volume resuscitation require inotropic support to improve their myocardial function. Most patients who survive will regain their normal cardiac function in convalescence despite evidence of myocardial cytotoxic injury in the acute phase of disease (Thiru et al., 2000).

Initial assessment and management

The use of prehospital parenteral antibiotic therapy is recommended in many countries following a provisional diagnosis of meningococcal disease. Observational studies that have attempted to assess the impact of such use in clinical practice, however, have reported conflicting results. In 1992 Cartwright et al. reported a 40% reduction in case fatality in children given parenteral penicillin before admission (Cartwright et al., 1992). In contrast, two more recent studies from Denmark reported a two to threefold increase in mortality associated with antibiotics given before admission (Sorensen et al., 1998; Norgard et al., 2002).

A recent study from Harnden et al. confirmed the Danish data, showing that the administration of parenteral penicillin by general practitioners was associated with increased odds ratios for death (7.4, 95% confidence interval 1.5–37.7) and complications in survivors (95% CI = 5.0, 1.7–15.0) (Harnden et al., 2006). However, as hypothesized in the Danish studies, the children who had received penicillin had more severe disease on admission (median Glasgow meningococcal septicaemia prognostic score (GMSPS) 6.5 vs. 4.0, P = 0.002). It is therefore likely that prehospital antibiotics are given to more severely ill children, and theoretically should be beneficial: Brandtzæg et al. have shown that antibiotic therapy reduces endotoxin level on admission (Brandtzæg et al., 1989).

The initial assessment of any individual with potentially life-threatening illness follows the standard ‘ABC’
Management of Meningococcal Disease in Children

**Fig. 1.** Early management algorithm for children with meningococcal disease.
algorithms that are widely taught in acute life support training: A, airway; B, breathing; C, circulation (Zaritsky et al., 2002) (Fig. 1). Unless consciousness is impaired, the airway is usually patent in meningococcal disease, but breathing may be compromised by pulmonary oedema due to capillary leakage in the lungs, and hypoxia may be present. Circulation is affected as described above.

Many prognostic scoring systems have been evaluated for use in patients with acute meningococcal disease. They all lack precision in their predictions of outcome, but the clinically based GMSPS has proven beneficial in determining whether patients are at high risk of poor outcome (GMSPS > 8) and should therefore be managed in an area which can offer a high level of support and monitoring (i.e., a high dependency or intensive care area) (Riordan et al., 2002).

**Management of shock**

The goal of circulatory support in shock is the maintenance of oxygenation and adequate tissue perfusion. The priority in achieving this goal is fluid resuscitation to restore intravascular volume. Early and aggressive fluid resuscitation is associated with an improved survival in paediatric septic shock (Carcillo et al., 1991). In addition, inotropic support is frequently necessary in order to maintain cardiac output and organ perfusion.

The establishment of central venous access is a priority in the critically ill patient. This will aid and guide fluid resuscitation, and the measurement of central venous oxygen saturation (ScvO2) has been a useful guide to the adequacy of oxygen delivery in shock, with the goal of achieving a central venous pressure (CVP) of 8–12 mmHg, and ScvO2 > 70% (Rivers et al., 2001). An initial bolus of 20 mL·kg−1 of fluid should be given over 5–10 min to children with signs of shock. The expected response to volume replacement is a reduction in heart rate, a warming of the peripheries and a decrease in capillary refill time. In mild cases, shock is rapidly reversed by this initial fluid bolus, but repeated review is mandatory as the disease may progress due to ongoing capillary leakage.

Another marker of improvement in perfusion is increased urine output, and bladder catheterization should be performed early to allow this to be accurately assessed.

When signs of shock persist after an initial 20 mL·kg−1 of fluid, further 20 mL·kg−1 fluid boluses should be given until signs of circulatory compromise improve (Carcillo & Fields, 2002). If signs of shock persist after 40–60 mL·kg−1 of fluid resuscitation, there is a significant risk of pulmonary oedema developing. Elective tracheal intubation and mechanical ventilation is recommended at this stage, even in the absence of overt signs of respiratory failure. If performed early enough, before signs of pulmonary oedema are manifest, this procedure is associated with an improvement in outcome (Ledingham & McArdle, 1978). Early intubation and ventilation is thought to be beneficial by its reduction of myocardial and respiratory muscle oxygen consumption and by allowing the delivery of positive end expiratory pressure (PEEP) to aid oxygenation. The sedation and muscle relaxation used in these circumstances additionally facilitates the placement of arterial and central venous catheters.

Fluid resuscitation therapy should be monitored continuously using heart rate, blood pressure, central venous pressure, urine output, metabolic status and peripheral perfusion as indicators. There is evidence to suggest that the monitoring of mixed venous or central venous oxygen saturation may provide a surrogate indicator of cardiac output and help to guide fluid and inotrope requirements (Rivers et al., 2001).

Some children with severe capillary leak syndrome are only stabilized after resuscitation with twice or more times their circulating volume of fluid, together with concurrent inotropic support.

Although, there is controversy about the use of human albumin solution (HAS) for volume replacement, 4.5% HAS has been our preferred resuscitation fluid in meningococcal sepsis, and its use has been associated with a reduction in morbidity and mortality (Booy et al., 2001; Thorburn et al., 2001). A large randomized controlled study comparing 4% HAS with normal saline in critically ill adult patients in Australia and New Zealand has suggested that HAS may be beneficial in a subgroup analysis of patients with septic shock (Finfer et al., 2004). However, no such studies have been performed in children.

As myocardial depression is invariably a contributory feature of persistent shock, inotropic support with adrenalin or noradrenaline should be initiated early, via a central vein. It is usually impractical to gain central venous access in children before intubation. Dilute solutions of these vasoactive agents or less potent inotropes such as dopamine or dobutamine can be given as an infusion through a peripheral vein until central venous access is obtained.

In patients who are unresponsive to high doses of catecholamines, there are some anecdotal data that vasoressin or its analogues may be valuable in raising blood pressure (Matok et al., 2005). However, the use of vasconstrictors, while increasing blood pressure, may not always be associated with improvement in cardiac output, and the use of some vasconstrictors in shock, such as nonspecific inhibitors of nitric oxide synthase, has previously been associated with a worsening of outcome (Lopez et al., 2004).

**Respiratory support**

High flow facial oxygen should be delivered routinely from the outset during initial assessment. If no major problem
in airway or breathing is present, priority is given to the assessment and treatment of circulatory failure. Indications for immediate endotracheal intubation are hypoxia, with severe respiratory distress indicating a progression of pulmonary oedema, severe persistent shock, fluctuating or decreasing conscious level (Glasgow Coma Score ≤ 8, or a decrease of 3 points within 1 h) or other signs of raised ICP.

Biochemical and haematological derangements

Children with meningococcal sepsis may have profound derangements in blood chemistry including acidosis, hyperglycaemia, hyponatraemia, hypokalaemia, hypomagnesaemia or hypophosphataemia (Khilnani, 1992; Nadel et al., 1995). These can be detected by repeated blood testing and treated if present.

Hyperglycaemia may occur following resuscitation and stabilization. Data from critically ill adults indicate that the control of blood glucose using insulin to maintain blood glucose within strictly defined limits is associated with a reduction in mortality (van den Berghe et al., 2001). However, there are no data yet available in children.

DIC is common. As described above, a procoagulant state occurs in sepsis due to a combination of loss of anticoagulant proteins, C, S and antithrombin III, together with an inability to activate protein C on the endothelial surface, and upregulation of antifibrinolytic proteins Plasminogen Activator Inhibitor and Thrombin-Activatable Fibrinolysis Inhibitor. This leads to a consumptive coagulopathy, with an inability to contain bleeding points where required, as the coagulation factors are consumed in the microvasculature. There may be bleeding from mucosal surfaces and venepuncture sites. In addition, spontaneous pulmonary, gastric or cerebral haemorrhage may occur, particularly if there is associated thrombocytopenia. Correction of coagulopathy with fresh frozen plasma, platelets and in severe cases, cryoprecipitate, may prevent life-threatening haemorrhage.

Recombinant activated protein C (aPC) has been shown to reduce mortality in adults with severe sepsis and septic shock and there is rationale for its use in children with meningococcal disease (Bernard et al., 2001; Esmon, 2005). A retrospective analysis of the use of aPC in adults and children with meningococcal meningitis, septicaemia and purpura fulminans has suggested that it is safe, but as yet there are no data to suggest that it may be beneficial (Vincent et al., 2005). A recently completed study on the use of aPC in children with severe sepsis, including some with purpura fulminans and meningococcal disease, has not shown a similar benefit to that seen in adults (Giroir et al., 2006). There is some suggestion that the use of aPC may be more beneficial in the subgroup of patients with DIC, but this remains to be confirmed.

The skin may be severely compromised in meningococcal disease through inadequate perfusion as a result of vasoconstriction and DIC. Decreased skin perfusion may predispose pressure areas to ischaemic damage, and tissue oedema from capillary leak may cause a compartment syndrome. The role of fasciotomy to treat ischaemic limbs is not clearly established, but has been used in circumstances where there is evidence of an increase in compartment pressure (Davies et al., 2000). Multi-disciplinary input from orthopaedic, vascular and plastic surgeons may be needed for limb salvage. Amputation should not be considered until it is felt to be absolutely necessary and only performed following extensive discussion.

Raised Intracranial Pressure

Raised ICP occurs due to inflammation of the meninges and capillary leak leading to cerebral oedema (Tunkel & Scheld, 1993). Most patients with meningococcal meningitis have a mildly raised ICP (Odio et al., 1991), but clinically significantly raised ICP is uncommon. Although most critically ill children with meningococcal infection have shock as their primary clinical problem, a small proportion present primarily with signs of raised ICP as their predominant clinical manifestation.

Signs of raised ICP include a declining level of consciousness, focal neurological signs including unequal, dilated or poorly responsive pupils, relative hypertension and bradycardia. Papilloedema is a late finding in acutely raised ICP. Patients without significant meningeal inflammation who have profound shock may also present with impaired consciousness as a result of cerebral hypoperfusion. Conversely, patients without shock who have a raised ICP may have peripheral vasoconstriction and these signs may be confused with compensated shock. In this case, poor peripheral perfusion is associated with the absence of a metabolic acidosis in blood gases, together with relative bradycardia, normal or high blood pressure and a decrease in level of consciousness or other neurological signs. In these circumstances, it should be assumed that the abnormal neurology is due to raised ICP, and aggressive fluid resuscitation should be avoided, as excess fluid will exacerbate any cerebral oedema (Kirkham, 2001). If raised ICP is suspected, an intravenous infusion of mannitol (0.25–0.5 g kg⁻¹ over 5 min, or 3% saline 3 mL kg⁻¹ over 5 min), may prevent brain-stem herniation and may be life-saving (Wakai et al., 2005). Urgent tracheal intubation to protect the airway and control blood gases is indicated.

In the child with raised ICP from meningococcal infection, an initial assessment may reveal coexistent shock. In this case the priority is to correct the shock before addressing specific measures to control the ICP (Sarnaik & Lieh-Lai, 1993). An adequate or high blood pressure is necessary...
in order to maintain cerebral perfusion. In this situation fluid resuscitation may result in improved levels of consciousness. In the absence of shock, cautious fluid restriction may be useful, but the fluid balance requires careful monitoring.

Sedation is essential following tracheal intubation in order to prevent acute rises in ICP caused by agitation and coughing, but muscle relaxants should generally be avoided as they may mask seizures. Seizures should be aggressively managed to avoid any further increases in ICP.

Neuro-intensive care should be instituted using a 30° head-up position, head midline, minimal suction, deep sedation, normo- or moderate hypothermia and strict avoidance of hypercapnia.

**Lumbar puncture**

Lumbar puncture can yield rapid microbiological confirmation of meningococcal meningitis and exclude other causes of meningeal irritation. However, the procedure may cause deterioration in patients who have a raised ICP or who are shocked, as it may cause cerebral herniation or a further compromise of cardiovascular function (Rennick et al., 1993).

The following are contraindications to lumbar puncture: cardiorespiratory insufficiency, raised ICP (evidence for which includes fluctuating or deteriorating levels of consciousness; normal or high blood pressure in the presence of a slow or normal heart rate; unequal, dilated or poorly reacting pupils; focal neurological signs or abnormal posturing; seizures; and papilloedema), and coagulopathy (Anon., 1997). In view of the rapid and unpredictable progression of the disease in some children, we have previously argued that lumbar puncture should be avoided or deferred in the initial assessment of patients with clinically obvious meningococcal disease (Nadel, 2001). This is because the additional information provided by the LP adds little to the diagnosis. Clearly, microbiological confirmation is important, but with use of molecular diagnostics with a high sensitivity that can be deployed even after treatment has begun, it is unlikely that an LP at the outset will add vital information that will otherwise be lost. In a child with a haemorrhagic rash, with the most likely diagnosis of meningococcal infection, the routine use of broad-spectrum antibiotics such as the third generation cephalosporins (which have excellent CSF penetration and little reported meningococcal resistance) further reduces the absolute dependence on early microbiological diagnosis. However, where the diagnosis is unclear, or in areas where resistant meningococci are emerging, important information may be obtained by carrying out a lumbar puncture, but this should only be done in the absence of any of the contraindications described above (Manchanda & Bhalla, 2006).

Computed tomographic (CT) brain imaging is frequently used in patients with a depressed consciousness, and is particularly recommended in adult practice where there is a broader differential diagnosis in patients with presumed meningitis. However, urgent cranial imaging is rarely justified in children with meningitis and a haemorrhagic rash, unless there is abnormal focal neurology or a suspicion of neurosurgical emergency. It is hazardous to take a critically ill patient to a radiology department before they have been adequately stabilized and monitored, and unjustifiable if it is unlikely that the scan will significantly alter clinical management. In any case, cranial CT scanning is not a sensitive way of ruling out raised ICP, and cannot therefore help in making the decision to perform a lumbar puncture, which must be made on a basis of clinical assessment (Heyderman et al., 1992; Nadel et al., 1999).

**Antibiotic therapy**

Cefotaxime (80 mg kg\(^{-1}\) t.d.s.) or ceftriaxone (50–80 mg kg\(^{-1}\) o.d.) is preferred as the *initial* therapy in patients with a clinical diagnosis of meningococcal disease. Penicillin resistance is rare amongst clinical isolates of *N. meningitidis* in the UK and therefore benzylpenicillin is the logical choice when the microbiological diagnosis has been made. However, until a positive identification is available, there remains the possibility of both penicillin resistance or alternative bacterial diagnoses that might not be adequately treated by penicillin therapy. Other rare bacterial causes of purpura fulminans include *Streptococcus pneumoniae*, *Staphylococcus aureus* and other Gram-negative bacteria.

The duration of antibiotic therapy for meningococcal disease does not need to be prolonged and most centres use a 5–7 day course for both meningococcal meningitis and septicaemia. Indeed, the efficacy of a daily dose of ceftriaxone for 4 days in the treatment of meningococcal meningitis is now well established and is probably effective because this drug has a long half-life in blood, and its CSF concentrations remain above the minimal inhibitory concentration of most organisms for 24–48 h after a dose (Roine et al., 2000). Recent studies from sub-Saharan Africa indicated that in this resource-poor setting, a single intramuscular dose of ceftriaxone was as effective as standard therapy with oily chloramphenicol (Nathan et al., 2005).

**Adjunctive therapies**

Steroids given with the first dose of antibiotics appear to reduce the incidence of neurological sequelae in both *Haemophilus influenzae* type b and pneumococcal meningitis (McIntyre et al., 1997), and there is a trend to improved outcome in meningococcal meningitis (van de Beek et al., 2004). In our opinion, based on data from other causes of
bacterial meningitis and an extrapolation of those results, systemic high-dose dexamethasone should be given in cases of suspected bacterial meningitis with, or shortly before, the first dose of antibiotics. A dose of 0.15 mg kg\(^{-1}\) b.d. for 4 days has been recommended, but 0.4 mg kg\(^{-1}\) b.d. for 2 days is equally effective (Feigin & Pearlman, 1998). However, there is some debate about the routine use of steroids in meningococcal meningitis (Grandgirard & Leib, 2006).

High dose steroid use is contraindicated in meningococcal shock in the absence of meningitis, as this has been shown to worsen the outcome of adults with septic shock (Lefering & Neugebauer, 1995).

There is some evidence that refractory septic shock may be more common in children with impaired adrenal gland responsiveness in the acute phase (Hatherill et al., 1999). In adults with septic shock and documented adrenal hyporesponsiveness, low-dose, replacement steroid supplementation may improve their chances of survival (Annane et al., 2002).

There have only been two properly conducted randomized controlled studies of other adjunctive therapies in meningococcal disease: an antiendotoxin antibody, HA-1A, was investigated in a randomized controlled trial as a treatment for children with meningococcal septicemia. This study showed that there was no significant reduction in mortality in the children treated with HA-1A when compared with placebo (Derks et al., 1999). Subsequent studies in adults with Gram-negative septicemia also showed no benefit of adjunctive therapy with HA-1A (McCloskey et al., 1994).

Recombinant bactericidal permeability increasing protein (rBPI21), which binds to and neutralizes endotoxin and blocks the inflammatory cascade, has been evaluated for use in meningococcal disease. In a large placebo-controlled randomized multicentre trial, there was evidence of improvement in outcome in a variety of parameters. Unfortunately the study was not sufficiently powerful to be able to detect a reduction in mortality (Levin et al., 2000). However, the patients treated with rBPI21 suffered fewer amputations, fewer blood product transfusions and improved functional outcome compared to those treated with placebo. In addition, fewer children died who had received a full 24-h infusion of rBPI21 (2% rBPI21 vs. 6% placebo, \(P = 0.07\)), compared to those who had not received the full infusion. This suggests that rBPI21 used earlier may be beneficial in children with meningococcal disease. However, the only published data at present would not support its routine use.

A randomized controlled trial of APC has been carried out in children with septic shock, with its primary endpoint being the reduction in time to resolve respiratory, cardiovascular and renal organ failure, as a surrogate indicator of mortality (Giroir et al., 2006). The study was terminated early as it was felt that it would be unlikely to reach its primary endpoint, with suggestions of an unfavourable risk/benefit profile.

Low dose replacement steroid therapy may be beneficial in patients with refractory shock. One clinical trial of replacement steroid therapy in adults with septic shock and adrenal insufficiency found that 53% died in the steroid-treated group compared with 63% in the placebo group (\(P = 0.04\)) (Annane et al., 2002). Few of the patients in this trial had meningococcal disease, and there have been no comparable studies in children.

It has been suggested that recombinant tissue plasminogen activator may reduce peripheral necrosis and minimize the risk of amputation. However, its use in patients with meningococcal Purpura fulminans has been associated with an unacceptably high risk of intracranial haemorrhage and its use in this scenario cannot currently be recommended (Zenz et al., 2004).

### Transfer to intensive care or treatment on the general ward?

Different countries will have differing referral pathways for patients felt to be seriously ill with meningococcal disease. Much of the discussion below relates to the situation in the UK. However, in some countries, children with meningococcal disease will initially be managed in an ICU setting.

Most patients with meningococcal disease will not require intensive care. However, those with persistent shock or signs of raised ICP should be managed in a specialist high dependency or intensive care unit.

For those who do not immediately require transfer to an intensive care unit, management on the general ward should be undertaken, with careful monitoring of vital signs (pulse, blood pressure, transcutaneous oxygen saturation, respiratory rate, urine output and conscious level) for the first 24–48 h. This is likely to be better facilitated by initial management in a high dependency unit. The failure to recognize deterioration following hospital admission is associated with increased mortality. A large case-control study of healthcare delivery in children with meningococcal disease in the UK has demonstrated that suboptimal emergency care significantly increased the likelihood of death in children with meningococcal disease (Ninis et al., 2005). In 143 children with meningococcal disease who died, there were significantly more departures from optimal (per protocol) management compared with controls (children with meningococcal disease who survived). In this study, a multivariate analysis identified three factors independently associated with an increased risk of death: the failure of patients under the age of 16 years to be looked after by a paediatrician; inadequate supervision of junior medical staff; and failure to administer adequate inotrope doses. In addition, failure to recognize complications of the disease was a
significant risk factor for death, although not independent of the absence of paediatric care. The odds ratio for death was 8.7 (95% confidence interval 2.3–33) with two failures in management, increasing with multiple failures in management. The authors concluded that suboptimal healthcare delivery significantly reduced the likelihood of survival in children with meningococcal disease and that improved training of medical and nursing staff, adherence to published protocols, and increased supervision of junior staff by consultants may improve the outcome for these children as well as those with other life threatening illnesses.

The decision to transfer critically ill or unstable patients to a more specialized unit can be difficult. A prolonged period of resuscitation may be necessary in the Emergency Department before a child with severe shock is stable enough to move. Transporting children before they are adequately resuscitated is hazardous and the child should be fully stabilized, with monitoring equipment securely in place, before transfer to the PICU is undertaken. Stabilization includes provision of a secure airway, controlled mechanical ventilation, central venous, arterial and urinary catheterization, and cardio-respiratory monitoring. Transport-related morbidity and mortality can be reduced by the use of a specialist paediatric intensive care transfer team (Britto et al., 1995).

The benefits of transferring patients to specialized units for ongoing intensive care management has been borne out by a significant reduction in mortality of children with severe meningococcal infection (Booy et al., 2001; Thorburn et al., 2001). It is likely that centralisation in the care of critically ill children with meningococcal sepsis into units with a large experience of dealing with such patients, has had a significant impact in reducing their mortality. The organization of paediatric intensive care in the UK has necessitated the development of paediatric critical care transport teams, with a network of outreach education to district general hospitals. This should improve the initial resuscitation and stabilization of all critically ill children. The model of specialized tertiary centres giving telephone advice to district hospitals where the child presents has also been shown to improve outcome in meningococcal disease. Whether health services can be organized in this way for adults as well as children with meningococcal infection presenting to their local hospital is a challenge for health service planners, but efforts to promote this should be made to improve the outcome of all patients with life-threatening infection.

**Conclusion**

The outcome of meningococcal disease has improved in recent years due to enhancements in the recognition, resuscitation, stabilization, transfer and ongoing care of individuals with the disease. However, despite these advances, meningococcal infection remains a major cause of morbidity and mortality throughout the world. Introduction of serogroup C conjugated meningococcal vaccine has been an impressive success, but the challenge remains to develop effective vaccines against all the disease-causing serogroups for use throughout the world for the prevention of this devastating disease. Until that time, a restructuring of health services to allow patients with meningococcal infection to gain access to units with a large experience in treating this fulminant disease should be made a priority.

**References**


Management of meningococcal disease


