Treating meningococcal infections in children

Steven B Welch, Simon Nadel

Aggressive early treatment of meningococcal disease in children can reduce mortality. This relies on prompt recognition of septicaemia and meningitis, and treatment of the complications of shock and raised intracranial pressure.

Meningococcal infection remains an important health problem in children, with a significant mortality and morbidity. In 2001, 2256 cases of meningococcal disease in children aged less than 15 years were notified to the Public Health Laboratory Service in England and Wales (Public Health Laboratory Service, 2001). While the long-term aim is prevention of infection by immunization, there is at present no effective vaccine against serogroup B infection, which is responsible for the majority of cases in the UK. Prompt recognition and aggressive early treatment are the only effective measures. This requires immediate administration of antibiotic therapy, and recognition and treatment of severe cases who may have shock, raised intracranial pressure (ICP) or both (Nadel et al, 1998; Pollard et al, 1999). Encouragingly, there is evidence that aggressive treatment has been effective in reducing mortality (Booy et al, 2001).

RECOGNITION

The key to improvement in outcome is early recognition. The most common features of meningococcal disease are a non-blanching rash, meningitis and septicaemia (Steven and Wood, 1995).

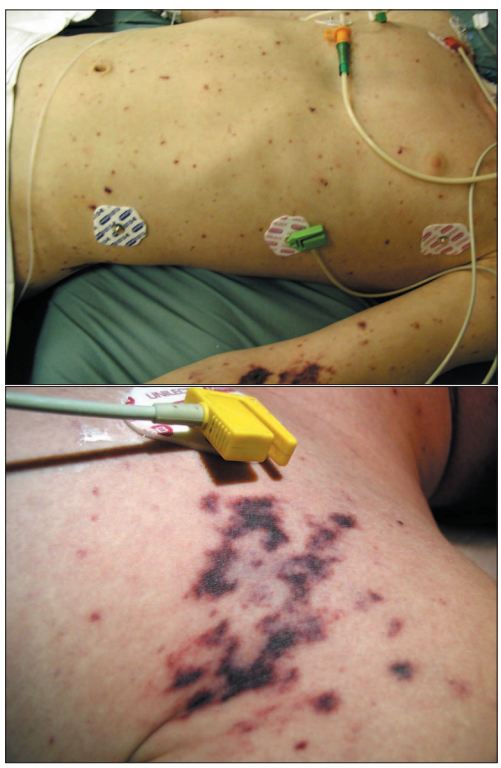
Any child with fever and a non-blanching rash should be suspected of having meningococcal disease until proven otherwise. However, 1 in 5 cases do not have a typical rash, so patients without a rash or with a maculopapular rash may still have meningococcal disease (Marzouk et al, 1991) (*Figure 1*).

Meningitis alone is present in about half the cases of meningococcal disease; septicaemia alone is present in about 10%, and 40% have a mixed picture (Kirsch et al, 1996).

Symptoms of meningitis include headache, fever, vomiting, photophobia, lethargy and neck stiffness. Over 50% of cases have a rash, and up to 20% may have fits at presentation. Clinical signs of neck stiffness, photophobia and a positive Kernig's sign may be absent, particularly in infants and young children.

Septicaemia is characterized by fever, rash, vomiting, headache, myalgia (especially leg pain), abdominal pain, tachycardia, hypotension and cool hands and feet. Early in the disease, symptoms may be indistinguishable from a viral illness and may be confused with influenza, particularly when myalgia is promi-

Figure 1. Characteristic purpuric rash of meningococcal septicaemia.



Dr Steven B Welch is Children Nationwide Clinical Research Fellow in Paediatric Infectious Diseases and **Dr Simon Nadel** is Consultant in Paediatric Intensive Care, Department of Paediatrics, Faculty of Medicine, Imperial College, St Mary's Hospital, London W2 1NY

Correspondence to: Dr SB Welch s.welch@ic.ac.uk

nent. The progression of the disease may take only a few hours. Parents of children who appear well and are sent home with viral symptoms should always be told for which new symptoms to look out and be encouraged to seek further medical attention if there is any change or deterioration in their child's condition.

Because of the need for immediate institution of treatment in suspected cases, laboratory results are not usually available rapidly enough to help in the initial clinical diagnosis.

PRE-HOSPITAL MANAGEMENT

Children suspected of having meningococcal disease should be given intravenous or intramuscular antibiotics (*Table 1*) and sent to hospital immediately.

INITIAL ASSESSMENT AND MANAGEMENT IN HOSPITAL

Immediate assessment

Children with meningococcal disease may develop shock and/or raised ICP, which may evolve and progress very rapidly. The responsible consultant should be involved in their management from the outset, and paediatric intensive care advice should be sought early. When the diagnosis is suspected, an immediate evaluation of airway, breathing and circulation should be made, high-flow oxygen should be given and resuscitation shoulde be instituted as indicated.

Intravenous access should be obtained, and antibiotics need to be given promptly (*Table 2*).

Evidence of shock (predominant in septicaemia) and raised ICP (predominant in meningitis) should be sought urgently.

Diagnostic samples

Blood culture should ideally be taken at the time of intravenous line insertion, immediately before giving antibiotics. However, on no account should treatment be delayed to allow cultures to be taken, and children may in any case have had antibiotics before coming to hospital. Other useful samples for diagnosis are blood for polymerase chain reaction (PCR) for meningococcal DNA, latex agglutination test and acute serology (later paired with a convalescent sample), and cultures of throat swabs or skin scrapings from affected areas (Carrol et al, 2000).

Throat swabs from household members may grow meningococci circulating among contacts, but it may not be desirable to label individuals as responsible for transmitting the case.

Lumbar puncture is not indicated during the acute stage of the illness in children who are unwell (Nadel, 2001). It may be dangerous in the presence of shock, raised ICP or coagulopathy, and it is unlikely to alter initial management. It is only really helpful in cases where the diagnosis is in doubt, or who are in a high-risk group for meningitis with an unusual organism (neonates, immune-compromised, ventriculoperitoneal shunt, head trauma or cerebrospinal anatomical defect).

Recognition of shock

The main cause of shock in meningococcal septicaemia is decreased circulating volume as a result of increased vascular permeability, together with myocardial dysfunction, altered vasomotor tone and impaired cellular metabolism (Mercier et al, 1988; Nadel et al, 1995). Shock may be life threatening and needs to be recognized and treated immediately.

Children may not develop hypotension until they have lost 25–40% of their blood volume, and even children with shock may have a normal blood pressure. Shock is therefore recognized by measuring increased heart and respiratory rate for age. There may be prolonged capillary refill and cool skin and peripheries. Hypoxia, metabolic acidosis, reduced urine output and confusion or drowsiness result from reduced end-organ perfusion. Shock should be suspected in the presence of any of these signs, even if the child appears relatively alert (*Tables 3* and *4*).

TABLE 1.
Drug doses for pre-hospital treatment of suspected meningococcal disease

Benzyl penicillin (intravenous or intramuscular)	Less than 1 year: 300 mg
	1–9 years: 600 mg
	10 years and over: 1.2 g
or	
Chloramphenicol (penicillin allergic, intravenous)	Less than 12 years: 25 mg/kg
	Adult: 1.2 g

TABLE 2.
Drug doses for hospital treatment of suspected meningococcal disease

Ceftriaxone (intravenous)	80 mg/kg once daily
or	
Cefotaxime (intravenous)	80 mg/kg three times daily

Estimated body weight (kg) = (age in years + 4) x 2. From Advanced Life Support Group (2000)

Treatment of shock

Treatment requires adequate stabilization of the airway and breathing, intravenous access and replacement of circulating volume. Initially, a bolus of 4.5% human albumin 10–20 ml/kg should be given over 5 minutes. This should improve objective measures of circulation, such as heart rate and urine output. It should be followed by immediate reassessment and administration of further boluses of fluid if there is still evidence of shock. Large volumes may be required, as ongoing capillary leak means that fluid administered for resuscitation will continue to extravasate. This problem may be exacerbated if crystalloid is used instead of albumin (Nadel et al, 1998).

If evidence of shock persists after administration of albumin 40 ml/kg, there is a high chance of pulmonary oedema developing. Further fluid administration is unavoidable with ongoing shock, and early elective endotracheal intubation and ventilation are required to maintain adequate oxygenation. Anaesthetic support should be sought for intubation, and transfer to intensive care will be required. An inotrope, such as dopamine or dobutamine, should be started peripherally to support the circulation; epinephrine (adrenaline) may be started following intubation once central venous access has been established.

Further complications may arise requiring attention before transfer to intensive care. These include hypoglycaemia, acidosis, hypokalaemia, hypomagnesaemia, hypocalcaemia, anaemia, thrombocytopenia, coagulopathy and raised ICP (Khilnani, 1992) (*Table 5*).

TABLE 3.
Signs of shock in children

Tachycardia
Metabolic acidosis (base deficit >5 mmol/litre)
Poor urine output (<0.5 ml/kg/hr)
Tachypnoea
Oxygen saturation <95% in room air on pulse oximetry
Hypoxia on arterial blood gas
Confusion or drowsiness
Increased capillary refill time (>4 seconds)
Cool peripheries or pallor
Hypotension (late sign)

From Pollard et al (1999)

TABLE 4.
Age-specific normal values in childhood

Age (years)	Heart rate (beats per minute)	Respiratory rate (breaths per minute)	Systolic blood pressure (mm Hg)
<1	110–160	30–40	70–90
2–5	95–140	25–30	80–100
5–12	80–120	20–25	90–110
>12	60–100	15–20	100–120

From Advanced Life Support Group (2000)

TABLE 5.
Common early complications in shocked patients

Complication	Management
Hypoglycaemia (<3 mmol/litre)	10% dextrose intravenously 5 ml/kg
Metabolic acidosis (pH <7.2)	Sodium hydrogen carbonate intravenously 1 mmol/kg over 20 minutes (= 8.4% sodium hydrogen carbonate 1 ml/kg, 4.2% sodium hydrogen carbonate 2ml/kg in neonates)
Hypokalaemia (K^+ <3.5 mmol/litre)	Potassium chloride 0.25 mmol/kg intravenously over 20 minutes, monitor electrocardiogram
	Caution if anuric
Hypomagnesaemia (Mg^{2+}<0.75 mmol/litre)	50% magnesium sulphate 0.2 ml/kg (max 10 ml) intravenously over 30 minutes
Hypocalcaemia (Ca^{2+} <2 mmol/litre or ionized Ca^{2+} <1 mmol/litre)	10% calcium chloride 0.1 ml/kg (max 10 ml) intravenously over 30 minutes or 10% calcium gluconate 0.3 ml/kg (max 20 ml) intravenously over 30 minutes
Anaemia	Red cell transfusion 10–15 ml/kg
Thrombocytopaenia	Platelets 10 ml/kg
Coagulopathy	Fresh frozen plasma 10 ml/kg
Raised intracranial pressure	See *Table 7*

From Pollard et al (1999)

Recognition of raised ICP

Patients with meningitis rather than septicaemia may develop raised ICP.

Evidence includes fluctuating or deteriorating level of consciousness; hypertension and bradycardia; unequal, dilated or poorly reacting pupils; focal neurological signs; abnormal posturing or seizures; and papilloedema (*Table 6*). A decreased level of consciousness may occur in shocked patients because of cerebral hypoperfusion or hypoglycaemia. Care should be taken not to confuse shock with raised ICP. If relative bradycardia, normal or high blood pressure and other neurological signs are present, it should be assumed that abnormal neurology is the result of raised ICP.

Treatment of raised ICP

Patients with evidence of raised ICP require neurointensive care to maximize cerebral perfusion. They should be intubated and ventilated, and treated with mannitol and frusemide. Cautious fluid restriction may be useful, but fluid balance requires careful monitoring, and any coexisting shock should be treated aggressively. Intubation, ventilation for neurointensive care and transfer

to an intensive care unit are required (Sarnaik and Lieh-Lai, 1993) (*Table 7*).

Any seizures should be treated according to standard protocols (Advanced Life Support Group, 2000). Lumbar puncture is contraindicated in patients in whom raised ICP is suspected.

TREATMENT ON GENERAL WARD

Patients who have had no evidence of shock or raised ICP, or who have responded immediately to initial treatment of these, may be treated on a general paediatric ward. They require very close monitoring and observation, particularly in the first 24–48 hours, as shock or raised ICP may develop later or may deteriorate again following initial improvement. Children with evidence of meningitis should be treated with steroids (dexamethasone 0.4 mg/kg twice daily for 2 days) (Odio et al, 1991).

ONGOING WARD MANAGEMENT AND MEDIUM-TERM COMPLICATIONS

Children with uncomplicated disease require 7 days treatment with intravenous antibiotics. Those treated with third generation cephalosporins require no further treatment; those given only penicillin also require oral rifampicin to eliminate nasopharyngeal carriage. The index case remains infectious, requiring isolation for 24 hours after receiving intravenous ceftriaxone or cefotaxime, or until oral rifampicin is given. Public health should be notified, and close contacts should receive antibiotic prophylaxis (*Table 8*).

Most children who have not required intensive care will be well enough to go home after a few days and, depending on community nursing arrangements, many can complete their intravenous antibiotic course at home.

Medium-term complications that may be encountered before discharge include neurological sequelae, lack of resolution of fever, secondary fever, secondary rash, arthralgia and antibiotic side effects. Fever should always prompt a search for ongoing or secondary sepsis. Neurological signs or seizures following meningitis need careful evaluation and imaging. Rash and arthralgia may be caused by immune complex deposition and may respond symptomatically to non-steroidal anti-inflammatory agents.

TRANSFER TO PAEDIATRIC INTENSIVE CARE UNIT

Patients requiring intensive care following initial resuscitation first require stabilization and transfer. This is particularly important, as children may need to be transferred between hospitals. This requires a secure airway, the ability to ventilate during transfer and adequate vascular access to maintain blood pressure, sedate the patient and allow monitoring. Owing to the unstable nature of these children, transport should only be carried out by specialized and experienced personnel.

ONGOING MANAGEMENT ON THE PAEDIATRIC INTENSIVE CARE UNIT

The principles of management in intensive care are the same as those during initial resuscitation (Nadel et al, 1995), and attention to maintaining the airway, breathing and circulation are most

TABLE 6.
Signs of raised intracranial pressure

Decreasing or fluctuating level of consciousness
Hypertension with relative bradycardia
Unequal, dilated or poorly reacting pupils
Focal neurological signs
Abnormal posturing or seizures
Papilloedema

From Sarnaik and Lieh-Lai (1993); Pollard et al (1999)

TABLE 7.
Neurointensive care for raised intracranial pressure

Intubation and ventilation with normal arterial carbon dioxide levels ($PaCO_2$ 4–4.5 kPa)
Avoid internal jugular lines
Repeat mannitol and frusemide if required
Sedation
Cautious fluid resuscitation (but treat shock if present)
Minimal handling
Monitor pupillary size

From Sarnaik and Lieh-Lai (1993)

TABLE 8.
Drug doses for prophylaxis of contacts of meningococcal disease

Drug	Dose	Comment
Rifampicin (twice daily for 2 days)	Less than 1 year: 5 mg/kg per dose	Advise of colouring of body fluids and interference with oral contraceptive pill. Do not give in pregnant women
	1–12 years: 10 mg/kg per dose	
	Over 12 years: 600 mg per dose	
Ceftriaxone (single intramuscular injection)	Less than 12 years: 125 mg	Drug of choice in pregnant women
	Over 12 years: 250mg	
Ciprofloxacin	Adults: 500 mg as a single dose	Do not use for prophylaxis in children

important. Shock and raised ICP remain the main dangers. The effects of extravasation of large volumes of resuscitation fluid become apparent in addition to the ongoing disease process, and each organ system requires careful attention.

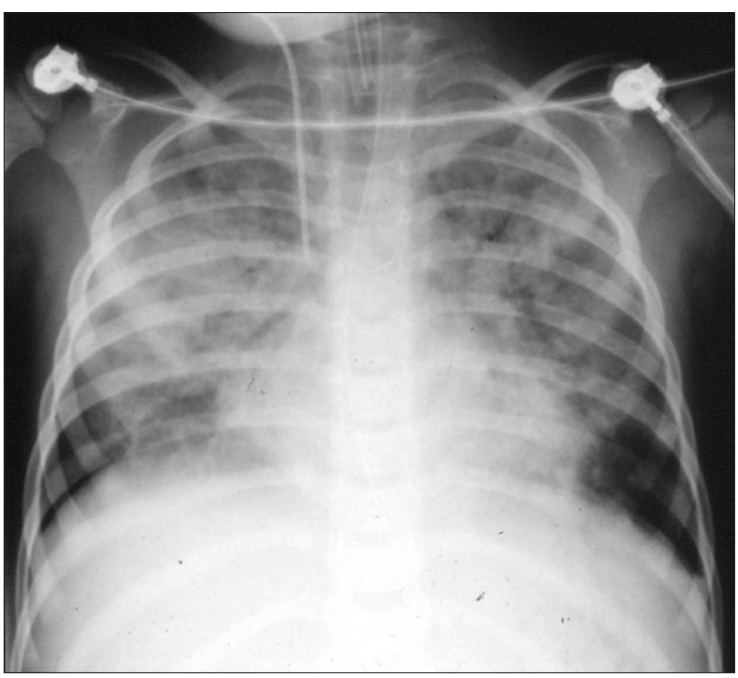
Airway
Maintenance of a secure and appropriately sized airway remains paramount. Reintubation may be made more difficult by facial oedema and hazardous by pulmonary oedema and coagulopathy.

Breathing
Extravasation into the lungs and myocardial dysfunction may cause pulmonary oedema (*Figure 2*), leading to acute respiratory distress syndrome. This requires ventilation with high positive end-expiratory pressure (PEEP) to maintain adequate oxygenation. Breathing may be further compromised by pleural effusion or splinting of the diaphragm by ascites. Either of these may be relieved by drainage.

Circulation
Further fluid boluses may be required as capillary leak continues. In addition, myocardial dysfunction is very common, and high-dose inotrope infusions may be required, usually with epinephrine (adrenaline) or norepinephrine (noradrenaline).

Neurological
Patients who have raised ICP require neurointensive care as described above; other patients require continued vigilance for the development of raised ICP. Seizures or focal neurological signs should be sought, which means that muscle relaxants need to be used with caution. Long-term neurological effects of meningitis, such as hemiplegia, ongoing seizures or developmental regression, may become apparent while on intensive care.

Figure 2. Chest radiograph showing pulmonary oedema in a patient with meningococcal septicaemia.



Metabolic
Hypoglycaemia or hyperglycaemia, acidosis, hypokalaemia, hypomagnesaemia and hypocalcaemia may all need treatment as during the acute presentation (Khilnani, 1992).

Renal
Acute renal failure may occur, usually because of hypoperfusion of the kidneys. This requires treatment to restore circulation – adequate fluid resuscitation, inotropes and drainage of ascites. If these do not work, or in the presence of severe intractable pulmonary oedema, massive fluid requirements or severe metabolic derangements, then renal replacement therapy with peritoneal dialysis or haemofiltration may be required. Very rarely, long-term renal replacement therapy may be required.

Coagulation and haematology
Anaemia, thrombocytopaenia and coagulopathy are common, and transfusions of red cells, platelets and fresh frozen plasma are frequently required.

Limbs
Limbs or areas of skin with extensive purpura fulminans may become necrotic. In addition, hypoperfused areas of skin are vulnerable to pressure damage. Compartment syndrome may threaten the blood supply of underlying muscle. Input from orthopaedic and plastic surgeons may be needed for limb care and possible fasciotomy. Amputation should be delayed until demarcation is defined and only performed following extensive multidisciplinary discussion (Davies et al, 2000).

Gastrointestinal
Maintenance of enteral feeding is desirable wherever possible, but the combination of gut ischaemia, ascites and intestinal oedema may make this impossible, and parenteral nutrition may be required.

Medium-term complications on intensive care
In addition to complications encountered on the general ward, patients in intensive care are more vulnerable to nosocomial infection and iatrogenic complications. Children ventilated for

long periods of time may require tracheostomy, and families require psychological support in dealing with prolonged hospitalization.

NEW TREATMENTS

Antibiotics and supportive intensive care, with early recognition and treatment of shock and raised ICP, are still the mainstays of treatment for meningococcal disease. There is a long history of seeking adjunctive treatments that may actually moderate the inflammatory process and further improve outcome. The most promising treatments which have been or are being evaluated include bactericidal permeability-increasing protein, activated protein C and high-volume haemofiltration, but none is yet part of routine clinical practice (Giroir, 2000; Levin et al, 2000).

FOLLOW UP AND LONG-TERM COMPLICATIONS

Most patients who survive meningococcal disease make an excellent recovery. However, about 5% have severe neurological sequelae, and all patients should have a hearing test (Fellick et al, 2001). Rarely, there may be long-term renal or myocardial dysfunction. Children who have had limb amputations require long-term multidisciplinary rehabilitation.

Most patients with meningococcal disease have no underlying immune deficiency. Defects in the terminal or alternative complement pathways are known to predispose to meningococcal disease and may be tested for in convalescence, but such defects are rare (Hoare et al, 2002). HM

Conflict of interest: none.

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Further information

A flowchart summary of the early management of meningococcal disease can be found at the website of the charity and patient support organization Meningitis Research Foundation at www.meningitis.org

Further information can also be obtained from the National Meningitis Trust at www.meningitis-trust.org.uk and the Public Health Laboratory Service at www.phls.co.uk

KEY POINTS

- Early recognition of meningococcal disease allows prompt administration of antibiotics.
- Pay attention to airway, breathing and circulation.
- Assess for shock and raised intracranial pressure and treat these early.
- Senior doctors and members of the paediatric intensive care unit should be involved from the beginning.
- Avoid lumbar puncture during acute management.
- Steroids may be useful in patients with meningitis.
- Remember to notify public health and arrange prophylaxis of contacts.
- New adjunctive treatments are under investigation.
- All children who have had possible or suspected meningitis should have a hearing test.