

MENINGOCOCCAL DISEASE IN CHILDREN

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Case History 1

A three-year-old girl presents to her doctor with fever, lethargy and a rash. The rash is initially petechial but spreads rapidly. He makes a presumptive diagnosis of meningococcal disease and gives her intramuscular penicillin and refers her to hospital by ambulance. On arrival, she is confused, shocked and has widespread purpura. She receives appropriate resuscitation and emergency treatment in the emergency department and is transferred to the Intensive Care Unit. Meningococci are seen on microscopy of a skin scraping of a purpuric area. She develops multiple organ failure and requires inotropes and ventilation. Three fingers on her left hand become necrotic and require amputation, however after 5 days she has recovered and leaves ICU.

Case History 2

A fifteen-year-old boy presents to hospital with fever, vomiting and lethargy. He has no neck-stiffness, photophobia or rash and is admitted with a diagnosis of a viral infection. Over the next few hours he becomes irritable and drowsy and he is started on ceftriaxone and intravenous fluids, after a blood culture is taken. His level of consciousness continues to decline and he has a seizure on the ward. He is admitted to Intensive Care where he is ventilated but he later dies from raised intracranial pressure.

These two cases represent the opposite ends of the spectrum of meningococcal disease. The first case is an example of meningococcal septicaemia whilst case 2 is an example of meningococcal meningitis. A mixed picture is also very common. It is vital that all doctors that may treat sick children have a good understanding of how to diagnose and treat this condition, as it occurs worldwide and is currently the leading infective cause of death in children in the developed world.

This article will discuss the microbiology, epidemiology, pathophysiology, clinical features and treatment of this potentially devastating disease.

Microbiology

Neisseria Meningitidis (meningococcus) is a capsulated gram-negative diplococcus. There are more than ten serogroups based on the polysaccharide that makes up their capsule. The commonest serogroups are A,

B, C, Y and W-135. They can be further serotyped and subtyped based on proteins in the outer membrane of the bacterium. More complex techniques of enzyme electrophoresis and DNA typing allow the accurate identification of individual strains of individual meningococci to be determined. This is important public health information.

Epidemiology

The disease occurs worldwide but the incidence varies greatly. In the UK, the incidence is about 5 cases/100 000 population/year but in sub-Saharan Africa (the 'meningitis belt') epidemics occur every 5-10 years with rates of 500 cases/100 000 population/year. In the UK serogroups B and C, and worldwide serogroups A, B and C, are responsible for the majority of cases. Serogroup W-135 has been particularly associated with pilgrims attending the Haj religious festival in Saudi Arabia. The disease is characterised by local clusters or outbreaks and there is a winter predominance in the UK. Nasopharyngeal carriage of the organism occurs in about 10% of the population. Most of these strains are non-pathogenic and the factors associated with pathogenicity are not well understood at present. Age (< 1 year of age), overcrowding, poverty, smoking and complement deficiency are all risk factors for the disease. Although the relative risk of developing meningococcal disease following exposure to a case is high (500-1000 times the background rate in the population) only about 1 in 200 contacts will develop the disease.

The epidemiology of this disease may change due to **vaccines** being developed. Purified polysaccharide vaccines have been developed against serogroups A, C, Y and W-135 but they are poorly immunogenic in young children and the immunity is short-lived. This is because the immunological response is T-cell independent. These vaccines may be useful for controlling outbreaks and epidemics, but are not suitable for use as part of a primary vaccination program. A conjugated group C vaccine has been developed where the polysaccharide antigen is conjugated to a carrier protein. The immunological response to this is T-cell dependent, which overcomes the problems associated with the purified vaccines and makes it suitable for primary immunisation. In the UK all children receive conjugated meningococcal C vaccine at 2, 3 and 4 months of age. A conjugated group A vaccine has been developed but it has not yet been licensed due to problems with long-term immunity found in a study in the Gambia. Group B polysaccharide appears not to be immunogenic.

Pathophysiology

The development of disease involves colonisation of the nasopharynx, invasion and multiplication. Both innate and acquired immune mechanisms are responsible for host protection. The resultant disease process may be focal infection (normally meningitis), septicaemia or both. About 60% of cases in Europe have evidence of meningitis and septicaemia while about 20% have meningitis only and 20% septicaemia only. Endotoxin and other bacterial factors cause a host response that results in much of the damage. This pattern of events is shown in Figure 1. In meningococcal septicaemic shock the endothelial changes cause capillary leak (leakage of fluid into the interstitial space and hypovolaemia) and pathological vasospasm and vasodilatation. Intravascular thrombosis causes organ ischaemia and consumptive coagulopathy. Generalised endothelial injury activates procoagulant pathways while anticoagulant pathways (protein-C and fibrinolytic) are down-regulated. Multiple organ failure is caused by cytokine production and ischaemia due to intravascular thrombosis and shock. Cardiac dysfunction is often an important feature of septic shock due to meningococci.

Clinical Features

Patients who present early may have very non-specific symptoms and signs. The disease may progress very rapidly however, and a high index of suspicion needs to be maintained if the diagnosis is to be made early enough for treatment to be effective. The classical feature of the disease is a petechial or purpuric **rash** (purple rash, which does not fade on pressure) but up to 20% of cases may have no rash or an atypical maculopapular rash. Other infections can rarely produce a similar rash and septicaemia. Symptoms of **meningitis** include headache, fever, vomiting, photophobia and lethargy or confusion. Some

patients may present with seizures. Neck stiffness, neurological signs and signs of raised intracranial pressure should be sought on examination. In infants, particularly, the features can be very non-specific and they frequently present with only irritability, refusal to eat, drowsiness or fever. Death is usually caused by refractory raised intracranial pressure.

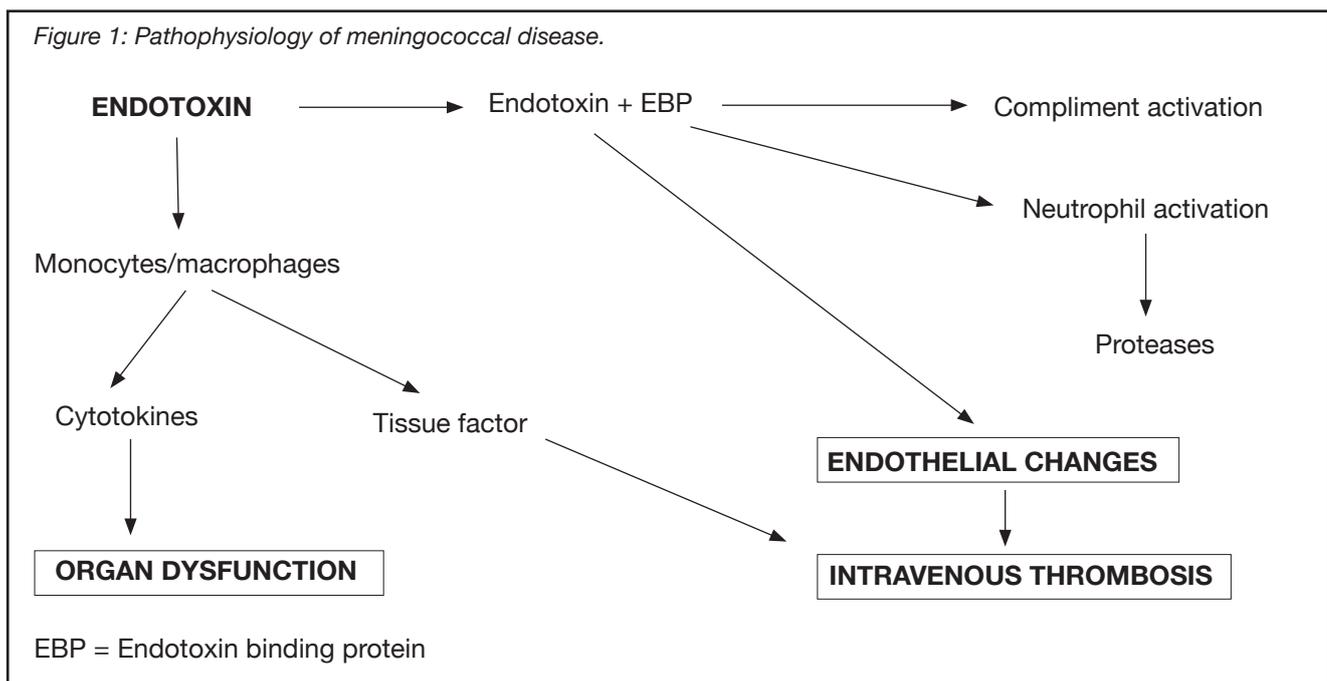
Septicaemia is characterised by fever, rash, vomiting, headache, myalgia, abdominal pain, tachycardia, cool peripheries and hypotension. Typically the rash spreads rapidly and can lead to widespread necrosis and gangrene of skin and underlying tissues. The rash is a visible manifestation of the endothelial changes and coagulopathy, which is occurring throughout the body. Death due to septic shock will ensue rapidly if these patients are not resuscitated promptly.

Diagnosis

Because of the need for immediate treatment when the disease is suspected, laboratory results are not of use in making the initial diagnosis. If relied on, they may also offer false reassurance since in fulminant infections the white cell count, C-reactive protein and lumbar puncture may all be normal early in the disease. The **initial diagnosis is based on clinical history and examination** and, following the institution of treatment, the diagnosis can be confirmed later by microbiological culture (blood, CSF or skin), antigen detection (PCR, latex agglutination test) or serology. Blood cultures and CSF cultures are more likely to be positive if taken before antibiotics are given.

Following a number of reports suggesting that major morbidity (particularly death following cerebral herniation) was caused by performing lumbar punctures (LP) in patients with meningitis, and because cephalosporins are effective in treating all the common causes of bacterial meningitis, there

Figure 1: Pathophysiology of meningococcal disease.



has been a trend not to perform LP on these patients. While it is vital to be aware of the contra-indications to lumbar puncture (GCS <13, focal neurological signs, raised intracranial pressure, recent or prolonged seizures, cardiorespiratory compromise, coagulopathy, infection at the site) some experts believe that too few lumbar punctures are done and this remains a controversial area.¹

If a positive microbiological diagnosis can be made from a skin scraping, LP is unnecessary. However LP may be useful for the following reasons: first, a gram stain is frequently diagnostic and thus allows a definite diagnosis to be made early, second, it will detect resistance (in some areas pneumococci are resistant to penicillin and cephalosporins) and third, LP will identify unusual pathogens and allow a positive diagnosis of viral meningitis to be made (enteroviral meningitis can be diagnosed on PCR allowing hospital discharge on no antibiotics). LP also allows public health monitoring of the aetiology of meningitis, allows appropriate prophylaxis to be given to contacts and makes it possible to investigate vaccine failures. As a result, unless a contra-indication exists, patients with suspected meningitis should have a lumbar puncture, but it should be done promptly and should not delay giving the antibiotics by more than thirty minutes.

CT scanning is of no benefit in making the diagnosis of meningitis or in determining whether the intracranial pressure is raised in patients with known meningitis. It should only be used to exclude other causes for focal neurological signs or to investigate complications of meningitis.

Treatment - Initial Assessment and Resuscitation:
Early recognition and prompt treatment is vital. If the diagnosis is suspected in the primary care setting the patient should be given intramuscular penicillin or a cephalosporin, if available, and referred immediately to hospital. In hospital, **assessment and resuscitation of vital functions should occur together**, with problems treated as they are found. Initial efforts should therefore be directed at maintaining a patent **airway** and supporting **ventilation** as necessary. All patients should receive a high concentration of inspired oxygen. Patients with a decreased level of consciousness due to meningitis or shock may need assistance in maintaining their airway. Ventilatory drive may be impaired due to raised intracranial pressure and hypoxia is common due to the capillary leak associated with shock (acute lung injury). Intubation and ventilation may be required soon after the patient reaches hospital because of these problems.

The next priority is the **circulation**. Shock is recognised by the presence of an increased heart and respiratory rate for age, a prolonged capillary refill time and cool skin and peripheries. Reduced end organ perfusion will cause a metabolic acidosis (Kussmaul breathing), oliguria (not a sign that can be elicited immediately)

and a decreased level of consciousness. Note that hypotension is often a very late clinical sign. The treatment of shock requires stabilisation of the airway and breathing, intravenous or intraosseous access and replacement of circulating blood volume. This should be achieved by giving 20ml/kg boluses of resuscitation fluid (crystalloid or colloid) and assessing the response to this treatment. As soon as intravenous access is obtained, blood should be taken for culture and biochemical (including glucose) and haematological tests and antibiotics given (see later). Large volumes of fluid may be required with 60ml/kg frequently required in the first hour. The increased vascular permeability that is associated with septic shock means that fluid will continue to extravasate and these patients may become very oedematous. If more than 40ml/kg of resuscitation fluid is required initially consider intubation and ventilation since pulmonary oedema is likely to develop. Use a tidal volume of 6-7ml/kg and add positive end-expiratory pressure (PEEP).

After the circulation has been assessed and resuscitation commenced, the next priority is to determine whether major neurological compromise exists. A rapid assessment of level of consciousness ('AVPU' - alert, responds to voice, responds only to pain or unresponsive), examination of the pupils, and observation for seizures or abnormal posturing should be done at this stage. Patients with meningitis rather than septicaemia may develop raised intracranial pressure and present with a fluctuating or decreasing level of consciousness, unequal, dilated or poorly-reacting pupils, focal neurological signs, abnormal posturing, seizures and hypertension accompanied by tachycardia or bradycardia. Papilloedema is sometimes seen. It may be difficult to distinguish the central nervous system effects of shock (caused by decreased cerebral perfusion) from those of raised intracranial pressure, especially since raised intracranial pressure, can sometimes be associated with abnormal vasoconstriction. Patients with raised intracranial pressure require treatment to optimise cerebral perfusion. They should have their airway protected by intubation and their breathing controlled by mechanical ventilation to a normal PaCO₂. Shock, if present, should be treated aggressively. Patients with isolated meningitis (i.e. no shock) should receive dexamethasone (0.4 mg/kg bd for 2 days) either with or before the first dose of antibiotic (see later).² Mannitol and frusemide may be useful if the intracranial pressure is raised. The patient should be examined for the typical rash but this may not always be present.

Antibiotic Therapy

A **third generation cephalosporin** is the drug of choice for suspected meningococcal disease and should be given intravenously for 7 days. Cefotaxime 100mg/kg initially and then 200mg/kg/day in 3 divided

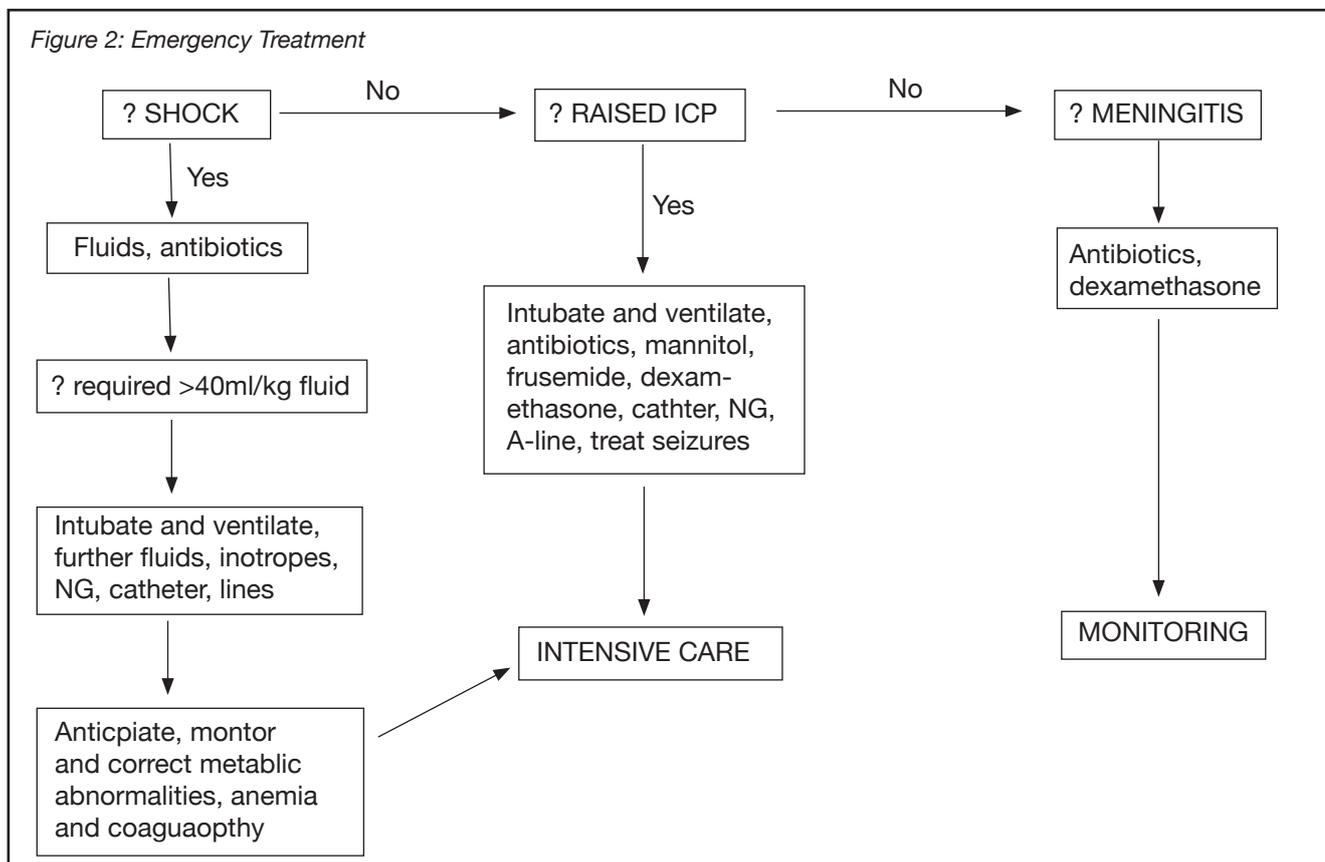
doses or ceftriaxone 80mg/kg/day as a single daily dose are appropriate. The advantage of these agents over penicillin is their broader spectrum (covering the other common causes of bacterial meningitis), their activity against meningococci that are less sensitive to penicillin (due to a different penicillin binding protein) or resistant to penicillin (rarely meningococci can produce β -lactamases), better CSF penetration and less CNS toxicity (especially important if renal failure). Cephalosporins also eliminate carriage of the organism which penicillin does not do.³

Ongoing Treatment and Intensive Care

The initial priority of management is the identification and treatment of immediately life threatening problems. These problems (e.g. airway obstruction or shock) should be treated as they are detected, even if the cause for them is not immediately obvious. After the resuscitation has commenced, a focussed **medical history, fuller examination** and the results of **special investigations** will either confirm the initial diagnosis of meningococcal disease, or allow a differential diagnosis to be made which will determine what further treatment is required. Other complications that may need treatment include hypoglycaemia, hypokalaemia, hypomagnesaemia, hypocalcaemia, anaemia and coagulopathy. **Hypoglycaemia** is particularly common, causes major morbidity if unrecognised, and is easy to treat. The blood glucose should be determined at the time that intravenous access is first obtained.

Many of these patients will require ongoing **intensive care**. Patients who remain hypotensive following intravenous fluid resuscitation need vasoactive drug administration to counter ventricular dysfunction and vasodilation. A central venous line should be inserted as a route for **inotropic/vasopressor** agents although their use as a guide fluid therapy is limited. In very young children a femoral line may be inserted as it is associated with less morbidity than jugular or subclavian lines. Where available an arterial line will be required for cardiovascular monitoring and to facilitate blood sampling. Ventilated patients should have a nasogastric tube and urinary catheter inserted.

The use of inotropes/vasopressors should be guided by clinical assessment and markers of 'global metabolic status' such as clinical signs, arterial blood pH, blood lactate, base deficit and mixed venous oxygen saturation.⁴ Choice of vasoactive drug should be guided by the clinical picture (warm shock and low BP, cold shock with low BP or cold shock with a normal BP) and titrated to achieve an acceptable cardiac output and systemic vascular resistance. The haemodynamic picture can change frequently during the first 48 hours and high doses of drugs may need to be given due to receptor down-regulation. Dopamine, dobutamine, epinephrine, norepinephrine, vasopressin and various vasodilators may all have a place in managing the haemodynamic changes associated with this condition. Because children with septic shock and particularly those with



meningococcal disease often die with a high systemic vascular resistance and low cardiac output (compared to adults that tend to have a low systemic vascular resistance that is refractory to therapy) the American Task Force on Paediatric Sepsis still recommends dopamine or dobutamine as the first line agents but high dose epinephrine or norepinephrine are usually required in severe cases.

The **skin and limb involvement** in meningococcal septicaemia distinguishes it from most other causes of sepsis and can be responsible for major morbidity. Widespread thrombosis and haemorrhagic necrosis of the skin and underlying tissues is called “**purpura fulminans**” and, when the thrombosis involves large vessels, infarction and gangrene of the limbs occurs. The combination of ischemia, necrosis and oedema can cause a compartment syndrome. The management of these problems is difficult but it has been suggested that fasciotomies are only indicated in the first 24 hours after the onset of purpura fulminans and only for compartment syndrome of the lower limb and where there is no major bleeding diathesis. A combination of clinical assessment, doppler flow studies and compartment pressures should be used to guide the decision to perform a fasciotomy. Gangrenous limbs should also be left to demarcate if possible and amputation should be done as an elective procedure.⁵

There is now evidence from randomised controlled trials of adults with septic shock that low dose hydrocortisone treatment (1mg/kg 6 hrly) in those patients with **relative adrenal insufficiency** (as shown by an ACTH challenge test) decreases mortality and the duration of shock⁶. In paediatric septic shock adrenal insufficiency has been shown to be associated with an increased vasopressor requirement and duration of shock. Also, in paediatric meningococcal septicaemia a low serum cortisol and a high ACTH has been shown to be associated with severe disease or death. As a result, many paediatric intensivists give hydrocortisone in a replacement dose (1 mg/kg 6 hrly) to patients with meningococcal septicaemia either on the basis of an ACTH stimulation test or to all those that have shock requiring high dose inotropic support. If the patient is already receiving dexamethasone, further steroid supplementation is not required.

Coagulopathy

Deranged clotting is commonly seen as a part of the septic process and blood products are often required to correct this.

Protein C

Protein C (an important natural anticoagulant and anti-inflammatory) activation is known to be impaired

in sepsis and low levels are associated with a risk of death. Following the PROWESS study⁷ **activated protein C** has now been licensed for use in adults with severe sepsis and a randomised controlled trial of its use in paediatric patients is in progress. It is very expensive and at present in UK it is only used in paediatric patients as part of a trial.

Outcome

The mortality of all patients admitted to hospital is about 5-10%, but the mortality of those admitted to intensive care varies from 5-35%. The mortality is greater in those patients who have septicaemia. Approximately 10% of patients will have long-term morbidity due to neurological complications (especially deafness) or amputations. Long-term problems related to renal or myocardial function are less common.

Secondary Prevention

Patients remain infectious for 24 hours after receiving a cephalosporin and should be isolated during this period. Household contacts and carers exposed to oropharyngeal secretions should receive chemoprophylaxis: either rifampicin twice daily for 2 days (< 1 year 5mg/kg/dose and >1 year 10mg/kg/dose up to 600mg) or a single IM injection of ceftriaxone (<12 years 125mg and > 12 years 250mg) or adults can take a single oral dose of ciprofloxacin 500mg. If the infection is due to serogroup C, contacts should also receive the conjugated group C vaccine.

Further information on meningitis and meningococcal disease is available at www.meningitis.org.

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