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Meningococcal disease in children

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Summary

Both meningitis and meningococcal septicaemia can present with non-specific initial signs and symptoms but progress rapidly. Prompt diagnosis and treatment are vital. Mortality of those reaching hospital remains 5-10% with a further 10% long term morbidity.

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. The doctor 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. After 5 days she has recovered sufficiently to leave 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. After a blood culture is taken, he is started on ceftriaxone and intravenous fluids. 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.

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. 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 Saudia 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. The factors associated with pathogenicity are not well understood at present. Risk factors include:

- Age (<1 year of age)
- Overcrowding
- Poverty
- Smoking
- Complement deficiency.

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.

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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 3, 4 and 12 months of age. A conjugated group A vaccine has recently been developed and was introduced into African countries in December 2010, with the aim of introducing it into all 25 countries in the African belt by 2016. It as already led to a decrease in the number of confirmed cases in these countries. Group B polysaccharide appears not to be immunogenic.

PATHOPHYSIOLOGY

Development of the disease involves:

- Colonisation of the nasopharynx
- Invasion
- 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,

- 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.
- Anticoagulant pathways (protein-C and fibrinolytic) are down-regulated.
- Multiple organ failure is caused by cytokine production and by ischaemia due to intravascular thrombosis and shock.
- Cardiac dysfunction is often an important feature of septic shock due to meningococci.

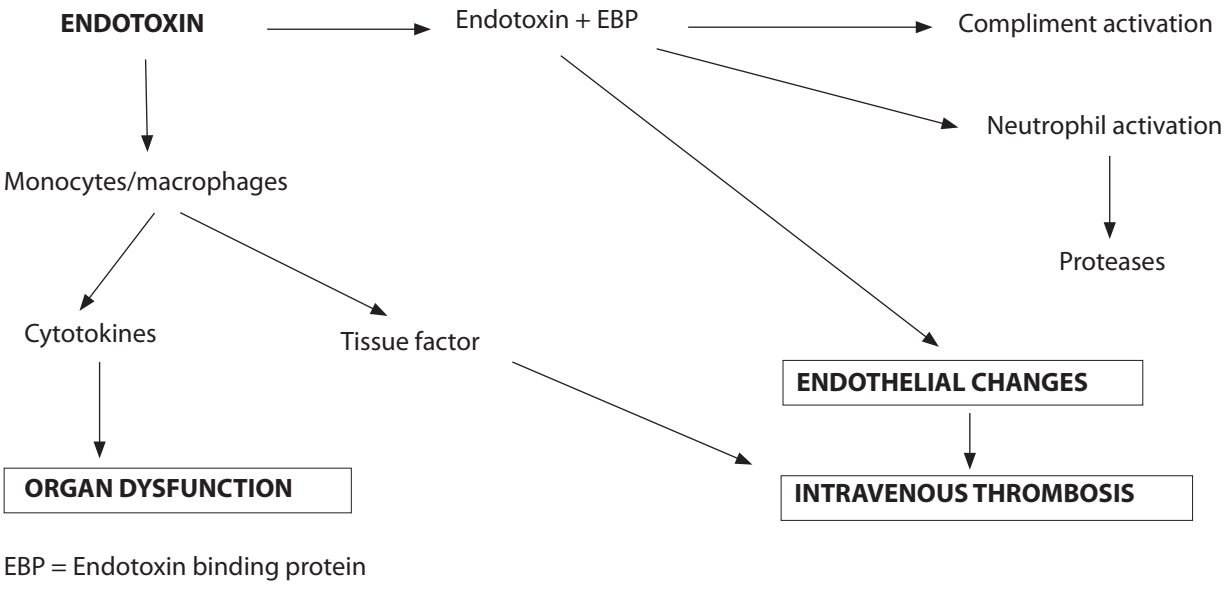
CLINICAL FEATURES

Patients who present early may have very non-specific symptoms and signs. The disease may progress very rapidly, so 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 rarely can produce a similar rash and septicaemia.

Symptoms of **meningitis** include:

- Headache
- Fever
- Vomiting
- Photophobia
- Lethargy or confusion

Figure 1. *Pathophysiology of meningococcal disease*



EBP = Endotoxin binding protein

- Some patients 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; they frequently present with only:

- Irritability
- Refusal to eat
- Drowsiness
- Fever.

Death is usually caused by refractory raised intracranial pressure.

Septicaemia is characterised by:

- Fever
- Rash
- Vomiting
- Headache
- Myalgia (muscle pains)
- Abdominal pain
- Tachycardia
- Cool peripheries
- Hypotension.

Typically the rash spreads rapidly and can lead to widespread necrosis and gangrene of skin and underlying tissues. The rash is a visible sign 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 once the disease is suspected, laboratory tests are not of use in making the initial diagnosis. 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**. 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.

There have been a number of reports suggesting that major morbidity (particularly death following cerebral herniation) was caused by performing lumbar punctures (LP) in patients with meningitis. Cephalosporins are effective in treating all the common causes of bacterial meningitis. There has thus been a trend not to perform LP in these patients. Some experts believe that too few lumbar punctures are done and this remains a controversial area.[1] Contra-indications to lumbar puncture are:

- GCS <13
- Focal neurological signs
- Raised intracranial pressure
- Recent or prolonged seizures
- Cardiorespiratory compromise
- Coagulopathy
- Infection at the site.

If a positive microbiological diagnosis can be made from a skin scraping, LP is unnecessary. However LP may be useful for the following reasons:

- Gram stain is frequently diagnostic and thus allows a definite diagnosis to be made early.
- It will detect resistance - in some areas pneumococci are resistant to penicillin and cephalosporins.
- 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).
- Allows public health monitoring of the aetiology of meningitis.
- Allows appropriate prophylaxis to be given to contacts.
- Makes it possible to investigate vaccine failures.

Unless 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 receive intramuscular penicillin or a cephalosporin, if available, and be referred immediately to hospital. In hospital, **assessment and resuscitation of vital functions should occur together,** with problems treated as they are found. Priorities are:

1. Maintaining a patent **airway**. Patients with a decreased level of consciousness due to meningitis or shock may need assistance in maintaining their airway.
2. Supporting **ventilation** as necessary.
    - All patients should receive a high concentration of inspired oxygen Ventilatory drive may be impaired due to raised intracranial pressure.

- 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.

3. **Circulation**
   - Shock is recognised by the presence of an increased heart rate 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
   - Hypotension is often a very late clinical sign

Treatment of shock requires:

- Stabilisation of the airway and breathing.
- Intravenous or intraosseous access.
- Replacement of circulating blood volume. Give 20ml.kg^{-1} boluses of resuscitation fluid (crystalloid or colloid) and assess the response. As soon as intravenous access is obtained, take blood for culture, biochemical (including glucose) and haematological tests, and give antibiotics (see later).
- Large volumes of fluid may be required, frequently 60ml.kg^{-1} 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^{-1} 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^{-1} and add positive end-expiratory pressure (PEEP).

4. Determine whether major neurological compromise exists:
   - Rapid assessment of level of consciousness (AVPU - alert, responds to voice, responds only to pain or unresponsive).
   - Examination of the pupils.
   - Observation for seizures or abnormal posturing.

Patients with meningitis rather than septicaemia may develop raised intracranial pressure. Look for:

- Fluctuating or decreasing level of consciousness
- Unequal, dilated or poorly reacting pupils
- Focal neurological signs
- Abnormal posturing
- Seizures
- 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. Protect their airway by intubation and control their breathing by mechanical ventilation to a normal $PaCO_2$. Treat shock aggressively if present.

Patients with isolated meningitis (i.e. no shock) should receive dexamethasone (0.4mg.kg^{-1} BD for 2 days) either with or before the first dose of antibiotic (see later).[2] Mannitol and frusemide may be used 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 50mg.kg^{-1} 4 times a day or ceftriaxone 80mg.kg^{-1} as a single daily dose are appropriate. Advantages of these agents over penicillin are:

- Broader spectrum (covering the other common causes of bacterial meningitis)
- Activity against meningococci that are less sensitive to penicillin (due to a different penicillin binding protein) or resistant to penicillin (rarely meningococci can produce B-lactamases)
- Better CSF penetration
- Less CNS toxicity (especially important if renal failure is present)
- They 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. This is particularly common, causes major morbidity if unrecognised, and is easy to treat. Determine the blood glucose when intravenous access is first obtained
- Hypokalaemia
- Hypomagnesaemia
- Hypocalcaemia
- Anaemia
- Coagulopathy.

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 for 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':

- Clinical signs
- Arterial blood pH
- Blood lactate
- Base deficit
- 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 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, epinephrine, norepinephrine, vasopressin and various vasodilators may all have a place in managing the haemodynamic changes associated with this condition. Children with septic shock, 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). This makes dopamine an appropriate first line agent. 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". When the thrombosis involves large vessels, infarction and gangrene of the limbs occurs. The combination of ischaemia, necrosis and oedema can cause compartment syndrome. The management of these problems is difficult. It has been suggested that fasciotomies are only indicated in the first 24 hours after 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 as a guide to the decision to perform a fasciotomy. Leave gangrenous limbs to demarcate if possible; amputation should be an elective procedure.[5]

There is now evidence from randomised controlled trials of adults and children with septic shock that low dose hydrocortisone treatment (1mg.kg^{-1} 6 hourly IV) decreases 28 day mortality.[6] 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 (1mg.kg^{-1} 6 hourly) 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 part of the septic process and blood products are often required to correct this.

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:

- Ciprofloxacin as a single oral dose (>12 years 500mg, 5-12 years 250mg, <5 years 30mg.kg^{-1} up to 125mg); or
- Rifampicin twice daily for 2 days (> 12 years 600mg, 1-12 years 10mg.kg^{-1}, < 12 months 5mg.kg^{-1}); or
- A single IM injection of ceftriaxone (<12 years 125mg and >12 years 250mg)
- If the infection is due to serogroup C, contacts should also receive the conjugated group C vaccine
- If infection is due to serogroup A, W-135 or Y, contacts should also receive the quadrivalent conjugate vaccine.

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

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