

## Meningococcal disease and meningitis

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### Abstract

**Objective:** To review the literature relevant to diagnosis and management of meningococcal disease (MD).

**Sources:** Non-systematic review of medical literature through the MEDLINE database using the terms meningococcal, septic shock, diagnosis, and treatment. Articles were selected according to their relevance to the objective of the study and according to the authors' opinion.

**Summary of the findings:** MD is a leading cause of death due to infection in children. It progresses rapidly and a high level of suspicion is necessary for early diagnosis. Early intervention with aggressive fluid resuscitation and antibiotic therapy can significantly improve outcome. In the pediatric intensive care unit, a large amount of fluids may be required during the first few days and vasoactive drug infusions are often needed. Coagulopathy is frequent, but it has no specific treatment. The use of colloids and steroids may be beneficial, but other new therapies such as insulin and activated protein C still need further assessment. Rescue therapy with extracorporeal membrane oxygenation may be appropriate in cases complicated by severe acute respiratory distress syndrome, but not for refractory shock. Meningitis is often not diagnosed in MD because of the severity of illness and the inability to perform a lumbar puncture safely in a patient with coagulopathy, coma, or hemodynamic instability. When present, cerebral edema and altered cerebral blood flow are the main concerns. The use of osmolar solution may be necessary, but the main therapeutic intervention is to ensure adequate blood pressure for adequate cerebral perfusion. Seizures and hyponatremia should be aggressively treated. Steroids do not appear to affect outcome in meningococcal meningitis.

**Conclusions:** MD is a life-threatening infection that requires early recognition and treatment. Time sensitive fluid resuscitation and antibiotic therapy are the most effective therapies for MD. Other therapies such as steroids may have a place in MD treatment but more definitive studies are necessary.

*J Pediatr (Rio J). 2007;83(2 Suppl):S46-53: Meningococcal disease, sepsis, meningitis, critical care, pediatrics, purpura.*

### Meningococcal disease

Meningococcal disease (MD) is a leading cause of death due to infection in children. Mortality in developed countries is close to 10% and in developing countries it is as high as 50%. In Brazil, MD has a mortality rate close to 20%.<sup>1</sup>

*Neisseria meningitidis*, the casual agent of MD, is carried in the nasopharynx of normal individuals. Meningococcal infection develops when the organism spreads from the

nasopharyngeal mucosa and invades the bloodstream. Genetic polymorphism of molecules such as mannose-binding lectin is greatly associated with individual susceptibility to disease.<sup>2</sup> Clinical presentations of MD vary, with a few cases presenting as a mild illness, but sepsis syndrome and/or meningitis is the main presentation. In this article we will focus the discussion on the most severe forms of the disease that often require pediatric intensive care unit (PICU) admission.

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**Suggested citation:** Branco RG, Amoretti CF, Tasker RC. Meningococcal disease and meningitis. *J Pediatr (Rio J)*. 2007;83(2 Suppl):S46-53.

doi 10.2223/JPED.1612

## Critical points in MD

### Early recognition

Severe MD progresses rapidly with shock, multiple organ failure and death within 24 h if no emergency treatment is given. Nonspecific symptoms such as fever, drowsiness, nausea and vomiting, irritability and poor feeding, are present within 4-6 h from the onset of the disease. Nonspecific signs of sepsis (e.g., leg pain, cold hands and feet, and abnormal color) are also found within 12 h of disease onset. The classical, rapidly evolving purpuric rash associated with MD and neck pain, or stiffness, usually develops after 12 h. Unfortunately, most cases of MD are diagnosed after the appearance of these late signs and it is not infrequent for children who are admitted to hospital to have been initially misdiagnosed.<sup>3</sup>

In primary care, there should therefore be high level of suspicion of MD in children with early, nonspecific signs. Public health has an essential role in such early diagnosis of MD and educational campaigns that lead to early recognition should decrease mortality.<sup>4</sup>

### Early recognition of shock

The early recognition of shock is crucial. Early recognition leads to early intervention and improved outcome.<sup>5</sup> Shock is the failure of the circulatory system to provide adequate tissue perfusion; therefore, signs of hypoperfusion such as poor peripheral perfusion, impaired level of consciousness, and reduced urine output should be evident. However, the body can compensate for the loss of up to 25-40% of blood volume without developing hypotension. Tachycardia may be the only early sign that is present and hypotension usually means that the child has little hemodynamic reserve. In daily practice, if a child is suspected of having MD, fluid resuscitation should be initiated early.

### Early intervention

#### Fluid resuscitation

Fluid resuscitation should be started at the first signs of shock. The aim is to re-establish normal physiology for age (i.e., heart rate, capillary refill time, urine output, blood pressure). Initial emergency fluid resuscitation should include repeated boluses of 20 mL/kg of isotonic crystalloid (e.g., normal saline) or colloids (e.g., albumin) until shock has resolved. If more than 60 mL/kg has been used, the child should be referred to a tertiary center. Elective endotracheal intubation and treatment with vasoactive drugs should be considered. Fluid resuscitation should not be stopped at 60 mL/kg, and children with severe MD may require 100-200 mL/kg of fluid resuscitation, but such patients will need ventilatory support.

Experimental and clinical studies of septic shock support the concept that persistent shock has an adverse impact on survival in a time-dependent manner. Each hour delay in treating shock is associated with at least a two-fold increase in mortality. Adequate treatment of shock by community physicians improves the outcome in children. There is a 94% rate of survival when shock is reversed within 75 minutes of presentation.<sup>5</sup> In the UK, implementation of a community, hospital-based education and resuscitation program with specialized PICU transport was associated with a tenfold decrease in mortality from MD.<sup>6</sup> In adults, early goal-directed therapy - aimed at achieving adequate central venous pressure, mean arterial pressure, urine output and central venous oxygenation - within 6 hours of presentation with severe sepsis / septic shock, also improved outcome.<sup>7</sup>

Fluid resuscitation, however, should be given more carefully if a child presents with signs of shock and hepatosplenomegaly or rales, because myocardial dysfunction may be present.

#### Antibiotics

Antibiotics are essential for the treatment of MD. They should be initiated early, following clinical diagnosis of MD. Antibiotic therapy should not be delayed because of clinical investigation. Polymerase chain reaction (PCR) tests are able to identify bacterial causes of sepsis without being affected by previous use of antibiotics. If the PCR test is not available, antibiotics should still be started early because the effect on outcome far outweighs the need for microbiological diagnosis.<sup>8,9</sup> The choice of which antibiotic to use should be based on local antibiotic resistance and availability. In most places, intravenous or intramuscular third-generation cephalosporin, such as ceftriaxone, should be used as the first choice. If these are not available, intravenous penicillin should be started.

#### Tips for intubation of children with meningococcal disease

Provide adequate fluid load and have good intravenous access. Sedation for intubation can cause vasodilatation and reduce cardiac performance, worsening shock. Always have a fluid bolus ready and be prepared to use vasopressors.

Use a sedation algorithm that you are confident with. If no signs of raised intracranial pressure (ICP), use ketamine because of its minor hemodynamic effects compared with other agents. Do not use etomidate as it inhibits cortisol release and worsens outcome.<sup>10</sup>

Use atropine. Reflex bradycardia (or inhibition of tachycardia) will worsen shock.

Intubation should be performed by a professional with good experience in pediatric airway management (e.g., pediatric emergency room specialist, intensivist or anesthetist).

## **Critical care issues in meningococcal disease**

### ***Fluid resuscitation and maintenance***

During the early stages of MD, large amounts of fluids are required to re-establish optimal circulatory volume. Even after initial resuscitation and establishment of adequate intravascular status, ongoing capillary leak and further vasodilatation may necessitate additional fluid resuscitation.<sup>11</sup> In the PICU, adequate monitoring of heart rate and invasive blood pressure, as well as clinical (e.g., capillary refill time and pulse pressure amplitude) and laboratory (e.g., lactate, mixed venous saturation) parameters helps to judge the necessity for further fluid resuscitation. In general, tachycardia is associated with the requirement of more fluid, but also consider other factors that may be responsible, such as fever and certain drugs. The development of rales in lungs and hepatomegaly are associated with an adequate intravascular status and sometimes with cardiac dysfunction. Central venous pressure measurement is not a reliable guide to cardiac filling pressure or preload.

The amount of maintenance fluid has been debated. Most authors suggest using 2/3 of the child's expected daily fluid requirement with careful assessment of intravascular status. Excessive fluids can impair tissue perfusion by increasing venous pressure. Whenever signs of decreased intravascular status are evident, further fluid resuscitation is used.

### ***Types of fluid***

The decision on the type of fluid that should be used for resuscitation is controversial. The lack of randomized controlled studies in children with shock, in particular with MD, makes it impossible to provide definitive recommendations. In 2004, the Saline versus Albumin Fluid Evaluation (SAFE) study compared 4% albumin with normal saline as the initial fluid for resuscitation in 7,000 critically ill adults.<sup>12</sup> This trial heavily influenced all recent meta-analyses on this subject. The trial found no difference in outcome after 28 days. However, a post-hoc analysis of a subgroup of patients with severe sepsis showed that the use of albumin had a relative risk of 0.87 (95%CI 0.74-1.02;  $p = 0.09$ ), suggesting a beneficial effect of albumin in septic patients.<sup>12</sup> A second post-hoc subgroup analysis, looking at patients with baseline serum albumin < 25 g/L, showed that the use of albumin was associated with a trend towards lower mortality [odds ratio of 0.87 (95%CI 0.73-1.05;  $p = 0.14$ )].<sup>13</sup> Children with MD are known to present with severe sepsis and lower serum albumin, therefore, they may be in the subgroups benefiting from 5% albumin. In the UK a number of pediatric intensivists advocate the use of colloids (4.5% albumin) in MD.<sup>14</sup> Over the last 15 years, mortality from MD has decreased to 2%.<sup>6</sup> The cause of this reduction in mortality is clearly multifactorial, but the routine use of albumin may play a part.<sup>14</sup>

Given the lack of direct evidence on the use of colloids in MD, it is difficult to make recommendations. As a guide, the non-evidence-based recommendation of 20 mL/kg of colloid for each 40 mL/kg of normal saline may be useful in the management of MD.

### ***Choice of antibiotic***

Antibiotic therapy is the cornerstone of treatment. In MD, three factors influence the success of antibiotic therapy. First, the timing of when antibiotics are given (as previously discussed). Second, the antibiotic tissue penetration. Third, antibiotic resistance. Early initiation of antibiotics reduces mortality in meningococemia,<sup>8,9</sup> however, inadequate coverage also increases mortality. Therefore, treatment with a broad-spectrum antibiotic that provides good penetration into the cerebrospinal fluid (e.g., ceftriaxone, cefotaxime) should be given as early as possible. If antibiotics with a narrower microbiological spectrum have already been started, they should be replaced with a broad-spectrum antibiotic until antibiotic sensitivities are known. When sensitivity results become available, antibiotic therapy can be guided by these results, but careful consideration should be given to those antibiotics with adequate minimal inhibitory concentration (e.g., ceftriaxone < 0.12 mg/L; penicillin < 0.06 mg/L).<sup>15</sup>

### ***Hemodynamic support***

In MD, several factors lead to hemodynamic instability, e.g., vasodilatation, capillary leak, myocardial dysfunction, and microthrombosis. Restoration of effective tissue perfusion is the ultimate therapeutic target of shock treatment. Normalization of blood pressure will not necessarily normalize tissue perfusion because there may be microvascular failure due to microthrombosis and endothelial damage.

Fluid therapy is the first-line treatment of hemodynamic disorders in MD. If adequate fluid resuscitation has been given and the child remains hemodynamically unstable, then vasoactive drugs should be started. Noradrenaline is the first-line vasopressor for the treatment of hypotension and needs to be infused into a central vein. In children with suspected raised intracranial pressure, the jugular vein should be avoided. Dopamine can be given via a peripheral vein while a central venous line is being sited. Dopamine infusion is associated with neuroendocrine dysfunction, such as inhibition of prolactin,<sup>16</sup> and has recently been associated with increased mortality in adults.<sup>17</sup> We do not recommend prolonged use of dopamine infusion. High doses of noradrenaline are often required in severe cases of MD and, in some cases, other vasopressors (e.g., vasopressin) can be used in children with very low vascular resistance. Excessive vasopressor therapy can lead to increased systemic vascular resistance, microvascular failure, and impaired peripheral

perfusion. Children with MD may have myocardial dysfunction<sup>18</sup> and may require inotropic support. Milrinone improves myocardial performance and reduces cardiac afterload. However, hypotension and low diastolic pressure may complicate treatment and be associated with worsening clinical status. Dobutamine has inotropic and chronotropic effects, thereby increasing myocardial performance. It improves microcirculatory flow in situations where systemic vascular resistance is increased and cardiac output is low. However, in children with MD and severe tachycardia (possibly requiring further fluid resuscitation) the chronotropic effect of dobutamine can lead to unacceptable tachycardia and further hemodynamic instability. The article "Pharmacologic Support of Infants and Children in Septic Shock" in this issue of *Jornal de Pediatria* provides further information about these and other vasoactive drugs used to treat shock.

### **Use of steroids**

The use of steroids in MD is controversial. In adults with sepsis, relative adrenal dysfunction is a frequent finding and the use of hydrocortisone in patients who fail to respond to an adrenocorticotropic hormone (ACTH) stimulation test improves outcome.<sup>19</sup> There are no such studies in children. However, indirect evidence supports the use of hydrocortisone in meningococcal shock.

First, the coagulation disorder that accompanies MD is associated with microvascular thrombosis, endothelial damage, and increased risk of bleeding. The adrenal gland vasculature seems to be particularly susceptible to these changes and bilateral adrenal hemorrhage (Waterhouse-Friderichsen syndrome) is well described.<sup>20</sup> It is important to note that an initially elevated cortisol level does not rule out significant adrenal hemorrhage. Such hemorrhage can occur at any time during MD and the decrease in cortisol level may be delayed.<sup>21</sup> Children with evidence of adrenal hemorrhage should receive stress-replacement dose of hydrocortisone.

Second, the association between cortisol level and outcome in children with MD differs significantly from adults. Adults who die of septic shock have higher baseline cortisol levels than survivors.<sup>22</sup> Children who die from MD have lower baseline cortisol levels compared with children who survive.<sup>23</sup> Children who die of MD also present with higher ACTH levels (i.e., lower cortisol:ACTH ratio), which denotes an inappropriate cortisol production.<sup>23,24</sup> Furthermore, when children with MD are grouped according to the intensity of treatment required, children with a moderate requirement have higher baseline cortisol levels compared with children with mild and extensive treatment requirements. However, after a low-dose ACTH test, children in the mild and moderate groups have higher cortisol levels than children requiring more extensive management.<sup>24,25</sup> This finding suggests that

adrenal dysfunction is present in severe MD. Finally, reduced levels of cortisol-binding protein (CBP) are found in adults (which could invalidate total cortisol measurements), but not in children with MD.<sup>23</sup>

In children with sepsis, there are a growing number of studies describing the importance of ACTH stimulation tests. In children with MD, there is not enough evidence to support or refute the use of ACTH stimulation tests. The different adrenal responses of adult sepsis and pediatric MD makes extrapolation unreliable. It is our practice to use hydrocortisone empirically in a stress-replacement dose in children with severe presentations of MD. Since plasma cortisol levels in MD survivors can increase 5 to 10 times their baseline level, we suggest that the stress replacement dose of hydrocortisone should be 5 to 10 times the physiological replacement or 5 to 10 mg/kg/day (divided into three doses; maximum dose of 300 mg/day).

Use of dexamethasone for meningococcal meningitis will be discussed later (see Meningitis).

### **Glycemic control**

Hyperglycemia is a common finding in critical illness and this physiological response has been tolerated in the PICU for quite long. It is known to be a part of the normal response to stress, being associated with peripheral resistance to insulin, and allied to anabolism. In critically ill children, recent studies show that the intensity and duration of hyperglycemia are associated with outcome.<sup>26</sup> We have described the influence of glucose levels in children with septic shock, reporting a 2.6-fold rise in mortality when glucose levels exceed a peak level of 178 mg/dL.<sup>27</sup>

In adults, Van den Berghe et al. described the use of insulin to treat hyperglycemia and to normalize blood glucose levels. This intervention was associated with a 42% relative reduction in mortality in a surgical ICU.<sup>28</sup> Reduction of bloodstream infection (46%), acute renal failure (41%), red-cell transfusion (50%), and critical illness polyneuropathy (44%) were also reported.<sup>28</sup> In adult medical intensive care, however, the results were not as impressive. Mortality was decreased only in patients who stayed in the ICU for more than 3 days (31.2% vs. 38.1%).<sup>29</sup> Among patients who stayed less than 3 days, insulin therapy was associated with an increase in mortality (26.8% vs. 18.7%).

In children with MD, a small cohort study showed an association between hyperglycemia and severity of the disease. However, hyperglycemia was associated with low insulin levels, thereby revealing a significant difference between the pathophysiology of stress in adults and children.<sup>23</sup> No studies have evaluated the use of insulin therapy in critically ill children. Despite the positive results in critically adults, differences between adults and children

requiring ICU treatment make it difficult to recommend the routine use of insulin. Other factors also raise concern. First, hypoglycemia is frequent in children requiring PICU admission and is associated with increased mortality.<sup>30</sup> Therefore, hypoglycemia associated with insulin therapy could be detrimental. Implementation of tight glycemic control in children may be associated with a high incidence of hypoglycemia and a significant increase in nursing workload (unpublished observation). Finally, given the adult medical ICU experience, the most severe cases of MD are unlikely to benefit from glycemic control since the most severe cases die within 3 days of admission.

We are currently evaluating the endocrine response to insulin in critically ill children. In our experience, normoglycemia is difficult to be achieved safely with insulin; mild hyperglycemia is more easily managed, but still requires great vigilance to avoid hypoglycemia. We do not recommend the routine use of insulin in children with MD outside the scope of medical trials. Severe hyperglycemia (glucose > 200 mg/dL or evidence of glycosuria) should be treated.

### **Coagulation in MD**

Coagulopathy associated with MD is frequent and often multifactorial. The usual balance between coagulation and fibrinolysis is disturbed, therefore, although formal coagulation tests may be markedly prolonged, there is a tendency towards intravascular thrombosis. The non-blanching purpuric rash associated with MD is a result of endotoxin-induced endothelial damage and of vasculitis. Presence of shock induces a vicious cycle, where vasculitis and associated microvascular thrombosis lead to hypoperfusion. Shock induces endothelial damage, vasculitis, and disseminated intravascular coagulation.

The presence of meningococcal endotoxin in the blood induces a severe acute proinflammatory response. Cytokines stimulate the release of tissue factors leading to the formation of thrombin and fibrin clot. Both cytokines and thrombin inhibit tissue plasminogen activator through the release of plasminogen-activator inhibitor 1, impairing the endogenous fibrinolytic pathway. Thrombin formation stimulates inflammatory pathways and further suppresses the endogenous fibrinolytic system by activating the thrombin-activatable fibrinolysis inhibitor. Endotoxin complement activation (mainly through alternative and mannose-binding pathways) leads to the accumulation of C3a and C5a, which induce endothelial damage. Microthrombosis and endothelial dysfunction associated with the proinflammatory response reduce the endothelial expression of thrombomodulin and endothelial protein C receptors, and impair activation of protein C, further inactivating fibrinolysis. The procoagulant and proinflammatory state associated with these changes lead to

endovascular injury, microvascular thrombosis, organ ischemia, and multi-organ dysfunction.<sup>31</sup>

There are no effective therapies for the coagulation disorder associated with MD. Mild clotting derangements are tolerated. Treatment with fresh frozen plasma is recommended if clotting is severely deranged or if clotting is moderately deranged and there is evidence of bleeding. Currently, the best treatment for MD-related coagulopathy is the optimal management of shock. Correction of shock will break the vicious cycle described above.

Replacement of activated protein C is an exciting therapeutic option, but currently there is no evidence to support its routine use in MD. It has been associated with improvement in coagulation screening and limb necrosis in case-series of meningococcal purpura,<sup>32</sup> however, the RESOLVE (randomized controlled trial of activated protein C in children with severe sepsis) trial has recently been stopped because of failure to meet the primary endpoint.<sup>33</sup>

### **Skin/limb perfusion**

In severe MD, microthrombosis and hypoperfusion can lead to extensive purpura (mainly in limbs or skin) that can become necrotic. Extensive necrotic areas can consume clotting factors, worsen any coagulopathy, and serve as reservoir for bacteria, leading to prolonged bacteremia. Necrotic areas in the extremities should be carefully monitored since surgical debridement may be required.

### **Other therapies**

#### *Mechanical support*

Despite the reduction in mortality associated with the early recognition and treatment of MD, severe cases of *purpura fulminans* have a high mortality rate. Several rescue therapies have been used in these cases. Continuous renal replacement therapy and extracorporeal membrane oxygenation (ECMO) are among the most studied interventions. In both cases, not enough evidence exists to support their routine use, but they deserve consideration in extreme cases. Continuous renal replacement therapy remains an important therapy for the support of renal dysfunction and fluid overload. In children with meningococcal sepsis-induced renal failure, it should be considered early.<sup>34</sup> In practice, initiating continuous renal replacement therapy in a hemodynamically unstable child is challenging, often requiring a large amount of fluid resuscitation and/or temporary increase in vasoactive drugs.

ECMO is an accepted therapy for children with intractable cardiorespiratory failure. Only small series have been published with somewhat contradictory results. In general, mortality associated with ECMO in MD is less than 50%, in a population with expected mortality close to 90%. Apparently, excellent outcome occurs when the indication for ECMO is



severe ARDS. However, when the indication is refractory shock, mortalities are much higher (60% to 84%).<sup>35,36</sup> The main concern about ECMO is the need for anticoagulation in children with clotting disorders, which could increase the risk of intracranial bleeding.

#### *Transfusion*

Children with MD frequently require blood transfusion. Packed red cells should be considered when the hemoglobin level is below 7.0 g/dL.<sup>37</sup> Platelets are often consumed in MD because of microvascular thrombosis and disseminated intravascular coagulopathy. Platelet transfusion should be used to maintain a platelet count above 20-50,000/mm<sup>3</sup> if no bleeding is evident, or above 50-100,000/mm<sup>3</sup> if there is bleeding.

#### *Electrolyte correction*

Electrolyte derangement is frequent in children with MD. The large amount of fluid resuscitation and transfusion required frequently lead to hypokalemia, hyperchloremia, hypocalcemia and hypomagnesemia. Potassium, calcium and magnesium should be corrected.

### **Meningococcal meningitis**

Meningitis is the infection of the cerebral meninges, not affecting the cerebral parenchyma. The symptoms of bacterial meningitis vary with age, but consist mainly of fever, headache, photophobia, vomiting, depressed consciousness, seizures, purpuric rash and petechiae. Neck stiffness may be present in children older than 2 years. Impaired consciousness and prolonged seizures often compromise airway protection.

The diagnosis of meningitis will depend on whether the patient is in shock. An initial septic screening (e.g., full blood count, electrolytes, CRP, and cultures) should be performed when meningitis is suspected. Whenever possible, a lumbar puncture should be performed and cerebrospinal fluid (CSF) should be sent for analysis (i.e., glucose, protein, and cell count with differential) and culture. However, in an obtunded child, or in a child with a coagulation disorder, or shock, CSF sampling may be dangerous. In MD with shock, we are often left without knowing whether meningitis is present or not. A cerebrospinal fluid sample can be taken after the acute event.

#### **Critical care issues**

The key critical care issues in meningococcal meningitis are now discussed.

#### *Altered cerebral blood flow*

Alteration in cerebral blood flow may be due to hypotension or raised ICP. Treatment of shock should take precedence. An adequate blood pressure is the best therapy for the control of ICP. Secondary cerebral ischemic lesions in

face of altered cerebral blood flow are responsible for adverse short- and long-term outcomes.

#### *Cerebral edema*

Brain swelling in response to infection and inflammatory mediators may lead to severely raised ICP. Cranial computed tomography is not sensitive to rule out the presence of raised ICP and even if the scan appears normal if the patient is unconscious a lumbar puncture should not be performed, and neuroprotective therapies should be started.

PICU admission is required in children with a Glasgow coma scale score  $\leq 9$ . Hypertension associated with bradycardia, unequal, dilated or slow-reacting pupils, focal neurological signs, abnormal posturing, seizures or papilledema provide good clues to the possibility of raised ICP.<sup>14</sup> In these cases therapy should be directed to providing adequate cerebral perfusion pressure. If the patient is not shocked, hyperosmolar solutions and diuretics (e.g., mannitol and furosemide) may be started.<sup>38</sup> Mechanical ventilation should be aimed at normocapnia (pCO<sub>2</sub> 30 to 35 mmHg).

#### *Seizures*

Seizures or *status epilepticus* may be the initial presentation of meningitis. Treatment begins with airway protection, ensuring adequacy of breathing and circulation. Serum electrolytes and blood glucose should be measured. The seizures should be treated with benzodiazepines and phenytoin or phenobarbitone. If the seizures are not stopped with this treatment, then other therapies such as continuous midazolam or thiopentone infusion should be considered.<sup>38</sup> Endotracheal intubation may be required as sedatives may impair breathing.

#### *Hyponatremia*

Hyponatremia may occur at any stage of the disease and the main differential diagnoses are inappropriate antidiuretic hormone secretion (SIADH), cerebral salt-wasting syndrome (CSWS) and adrenal insufficiency due to Waterhouse-Friderichsen syndrome. All of these conditions require investigation and treatment.

#### *Steroids*

Dexamethasone is recommended by some authors for the treatment of meningitis. Adjunctive dexamethasone may reduce the inflammatory response in the subarachnoid space. It could therefore alleviate many of the pathologic consequences of bacterial meningitis (e.g., cerebral edema, cerebral vasculitis, change in cerebral blood flow, and increase in ICP). In children, dexamethasone prevents hearing loss in cases of *Haemophilus influenzae* type B meningitis.<sup>39</sup> There are no data about children with meningococcal meningitis. A subgroup analysis of adult studies suggests that dexamethasone does not affect

outcome in patients with meningococcal meningitis.<sup>40</sup> Patients who have already received antimicrobial therapy should not be given dexamethasone, as it is unlikely to improve their outcome. Since antibiotic therapy is likely to have been given in all cases of MD, we do not use dexamethasone as part of our treatment of such cases.

### Conclusion

Meningococcal disease (MD) is a leading cause of death due to infection in children. Its progress can be very fast and a high level of suspicion is necessary for early diagnosis. (Early) intervention with aggressive fluid resuscitation and antibiotic therapy can significantly improve outcome. In the PICU, large amounts of fluids may be required during the first days and vasoactive drug infusions are often needed. Coagulopathy is frequent, but it has no specific treatment. The use of colloids and steroids may be beneficial, but other new therapies such as insulin and activated protein C still need to be further studied. Rescue therapy with ECMO seems to have good results when it is used for severe ARDS, but not for refractory shock. Meningitis is often not diagnosed in meningococcal disease because of the severity of the clinical presentation. When present, cerebral edema and altered cerebral blood flow are the main concerns. The use of osmolar solutions may be necessary, but the main therapeutic intervention is to ensure adequate blood pressure for adequate cerebral perfusion. Seizures and hyponatremia should be aggressively treated. Steroids do not seem to affect outcome in meningococcal meningitis.

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