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CNS Infections

Meningococcal Meningitis

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Opinion statement

Meningococcal meningitis (MM) is the most common presentation of meningococcal disease and an important cause of morbidity and mortality worldwide. When MM is associated with shock, early recognition and treatment of shock is essential. No investigation should delay starting antibiotics once the diagnosis is suspected. Corticosteroids can be started at the same time as the antibiotics or just before, but this is not a specific recommendation for MM. Low-dose steroids should be used in meningococcal disease with refractory shock. Altered blood flow, cerebral edema, and raised intracranial pressure are problems that should be considered in all patients with MM and decreased consciousness level. When mechanical ventilation is required, the target carbon dioxide level is 4.0 to 4.5 kPa, with avoidance of hypocapnia. Seizures, although not frequent, can occur in MM and require prompt treatment. Other treatments, such as mannitol and activated protein C, should be avoided. Potential new treatments requiring further investigation include neuroprotection with hypothermia or glycerol.

Introduction

Neisseria meningitidis infection is most frequently referred to as *meningococcal disease* (MD). It is a major health problem and a leading cause of morbidity and mortality around the world [1•,2]. All age groups are at risk of MD, but children are particularly vulnerable. The clinical presentation of MD varies: a few cases present as a mild illness, but meningitis and/or sepsis syndrome are the most severe presentation. Meningococcal meningitis (MM) is the most frequent clinical presentation of invasive MD and can present either as isolated meningitis (like other forms of meningitis) or as part of systemic disease in which the predominant feature is septic shock [3]. MM associated with septic shock has high mortality and therefore requires rapid identification and treatment. This article discusses both presentations of MD, with emphasis on the neurologic issues.

Neisseria meningitidis is carried in the nasopharynx of 8% to 25% of healthy individuals. It is spread through close contact with respiratory secretions or saliva. Meningococcal carriage is affected by a number of factors including age, social behavior (eg, bars, dormitories), and smoking [4]. The duration of carriage varies from days to many months. Damage to the upper respiratory tract by co-infection (eg, respiratory viral infections), smoking, very low humidity, and trauma induced by dust predisposes to carriage and MD [3].

Invasive meningococcal infection develops when the organism spreads from the nasopharyngeal mucosa and invades the bloodstream. Children from

6 months to 2 years of age are at higher risk of meningococcal infection because of the disappearance of protective maternal antibodies. Children with congenital or acquired antibody deficiencies are also at increased risk. In healthy individuals, genetic polymorphism in mannose-binding lectin and Toll-like receptor 4 are associated with susceptibility to disease [5]. The mechanism underlying *Neisseria meningitidis* invasion across the blood-brain barrier is poorly understood. Once in the subarachnoid space, where principal humoral and cellular host defense mechanisms are absent, *Neisseria meningitidis* proliferates [6]. Endotoxin release elicits activation of proinflammatory cytokines in the subarachnoid space, leading to increased blood-brain barrier permeability. The influx of neutrophils and subsequent release of neutrophil products contributes to the development of clinically overt meningitis [7].

Treatment

- MD is potentially lethal and should always be treated as a medical emergency. Admission to hospital is always recommended when MM is suspected. Prompt recognition and diagnosis of the disease and antibiotic therapy are the treatment cornerstones, which can prevent serious morbidity or death.

Recognition

Meningococcal meningitis

- Isolated MM has a clinical presentation similar to other forms of meningitis. In adults, fever, nausea, vomiting, photophobia, acute onset of headache, and neck stiffness are characteristic. The prevalence of the classic meningitis triad of fever, neck stiffness, and change in mental status is low (27%), but when rash is added to the triad, most patients (89%) present at least two of the four signs [8•].
- In young children, the clinical pattern is different, and the presentation is often more insidious. Irritability is a common feature and seizures (mostly of focal onset) typically occur in the first few days. Neck stiffness is often absent in children younger than 2 years of age. Systemic features may also be present, particularly purpuric rash and petechiae.

Meningococcal disease

- MM associated with septic shock is more common in children and progresses rapidly, with multiple organ failure and death occurring 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 disease. A classic, rapidly evolving purpuric rash associated with MD, along with neck pain or stiffness, usually develops after 12 h. Unfortunately, most cases with 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 [9].

Diagnosis

Meningococcal meningitis

- The diagnosis of MM relies on the recognition of clinical signs and symptoms; it is confirmed by lumbar puncture. The cerebrospinal fluid (CSF) opening pressure is frequently high, and CSF examination reveals pleocytosis, with high protein levels and low glucose levels [10]. A predominance of lymphocytes can be present in the CSF, but neutrophilia is more frequent. CSF gram staining can rapidly identify the organism, because patients with MM have high concentrations of meningococci in the CSF, despite low concentrations in plasma [11].
- Lumbar puncture can be hazardous, however, with risk of brain herniation in some cases. It is general practice to perform cranial imaging when raised intracranial pressure (ICP) is present or when there is a risk of transtentorial herniation, such as in patients with new-onset seizures, those who are immunocompromised, those with signs of space-occupying lesions, or those with moderate to severe impairment of consciousness [10]. Cranial imaging should not delay the use of antibiotics in suspected cases; therapy should be initiated before the patient is sent for neuroimaging [12, Class IV]. Lumbar puncture also should be avoided in patients with deranged clotting or shock.
- CSF culture is useful in identifying the causative organism and its sensitivity to antibiotics. Although culture results are positive in as many as 80% of patients with MM, the use of antibiotics before lumbar puncture can reduce the sensitivity of CSF culture.
- In developed countries, polymerase chain reaction (PCR) is frequently used for diagnosis of MM, with excellent results [13]. Latex agglutination testing also can provide rapid diagnosis where resources are limited [14].

Meningococcal disease

- In MM with septic shock, lumbar puncture is often not performed in the acute phase of illness, as the suspected clinical diagnosis of MD guides treatment choices. A CSF sample can be taken after the acute event, but culture results are often unreliable. PCR is recommended for diagnosis of these cases.

Antibiotic therapy

- Early and appropriate antibiotic treatment is essential (10, 12, Class III). Proliferation of *Neisseria meningitidis* is stopped immediately after antibiotic therapy begins, and the plasma endotoxin concentration is halved within 2 h. In the CSF, meningococci are killed within 3 h to 4 h of the administration of adequate intravenous antibiotics [3,11].
- Three factors influence the success of antibiotic therapy: when the antibiotics are given, their tissue penetration, and antibiotic resistance

[8•,9]. The use of prehospital antibiotics (oral, intravenous, or intramuscular) appears to be beneficial [15•], but its recommendation is still controversial [16].

- The choice of antibiotic should be based on local antibiotic resistance. Benzylpenicillin, cefotaxime, ceftriaxone, and chloramphenicol are the most common options. Although sensitivity of meningococci to benzylpenicillin has decreased in the past decade, the outcome of MD is currently linked to the bacterial serotype rather than to antibiotic resistance [17•]. In most places, an intravenous or intramuscular third-generation cephalosporin, such as ceftriaxone, and vancomycin should be used as the first choice of treatment for suspected meningitis until the causative agent is identified. If these antibiotics are not available, intravenous penicillin should be started. When antibiotic sensitivities become available, antibiotic therapy can be guided by these results, but careful consideration should be given to those antibiotics with adequate minimal inhibitory concentration. The recommended duration of antibiotic treatment is 7 days, but recent studies suggest that CSF sterilization may occur within 3 days to 4 days [18]. In our practice, we use ceftriaxone for treatment of MD and MM (Table 1).

Other therapies

- In the absence of shock or raised ICP, the treatment of MM is relatively simple, demanding only antibiotics and close monitoring. In patients with a more severe presentation, however, management is complex and the risk of complications is high. A wide variety of pathologic neurologic findings have been described in MD, but the most common are cerebral edema and focal hemorrhages [19]. Among survivors, 10% to 30% of patients have neurologic sequelae such as deafness, blindness, seizures, or cognitive impairment. Discussed below are other therapies that may be useful in treating MM.

Table 1. Recommended doses of antibiotics and corticosteroids in meningococcal meningitis and meningococcal disease in adults and children

Dosage	Meningococcal meningitis	Meningococcal disease
Antibiotics (duration)	Ceftriaxone[a,b] (5–7 days)	Ceftriaxone (5–7 days)
Adults	2 g (every 12 h)	2 g (every 12 h)
Children	80 mg/kg (every 24 h)	80 mg/kg (every 24 h)
Corticosteroids (duration)	Dexamethasone[c] (4 days)	Hydrocortisone[d] (until vasopressors are stopped)
Adults	10 mg (every 6 h)	100 mg (every 8 h)
Children	0.15 mg/kg (every 6 h)	100 mg/m^2 per day

[a]Addition of vancomycin is recommended in clinical meningitis until pathogen identification
[b]Penicillin can be used in patients with minimum inhibitory concentration <0.1 μg/mL
[c]Given before or at the time of initiation of antibiotics
[d]In patients with shock requiring catecholamine infusion

Treatment of shock

- In patients with MM and septic shock, treatment of shock takes priority. This presentation is frequent in children and requires early recognition because persistent shock has a time-dependent adverse impact on survival: each hour of delay in treating shock is associated with at least a twofold increase in mortality.
- Fluid resuscitation should be started with the first signs of shock, aiming to re-establish normal physiology for the patient's age (ie, heart rate, capillary refill time, urine output, blood pressure) [7,13,20], Class II]. In adults, targets are a central venous pressure from 8 mm to 12 mm Hg, mean arterial pressure higher than 65 mm Hg, urine output greater than 0.5 mL/kg per hour, and a central venous (or mixed venous) oxygen saturation of at least 65%. Initial emergency fluid resuscitation should include repeated boluses of 20 mL/kg (or 1,000 mL for adults) of isotonic crystalloid (eg, normal saline) until shock has resolved. If more than 60 mL/kg has been used in a child, that 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, since children with severe MD may require 100–200 mL/kg of fluid resuscitation. Such patients also need mechanical ventilation and vasoactive drugs.
- The predominant hemodynamic derangement in adults and children with MD is vasoplegia. Hence, noradrenaline is the first-line vasopressor, but it does need to be infused via a central vein. This requirement may be a problem for patients without such venous access or in whom jugular access should be avoided (eg, patients with suspected raised ICP). In these instances, dopamine infusion can be given through a peripheral vein while a central venous line is being sited. This option is not without risk, however, because prolonged dopamine infusion is associated with neuroendocrine dysfunction (eg, inhibition of prolactin secretion) in infants and children and increased mortality in adults. When cardiac dysfunction is present, inotropes are required. In adults, dobutamine is the drug of choice, but its chronotropic effect can lead to unacceptable tachycardia in children. Therefore, we use milrinone or adrenaline.
- Coagulopathy is frequent, but it has no specific treatment. The use of colloids and steroid supplementation may be beneficial; other new therapies such as insulin and activated protein C need further study. Rescue therapy with extracorporeal membrane oxygenation seems to have good results when it is used for severe acute respiratory distress syndrome but not for refractory shock [7,20].
- In patients with MM without shock, raised ICP can induce vasoconstriction that increases capillary refill time. This change should not be mistaken for poor peripheral circulation. Detailed examination and analysis of heart rate, blood pressure, and a blood gas can help to differentiate these two entities.

Corticosteroids

Dexamethasone for meningococcal meningitis

Dexamethasone is recommended for the treatment of meningitis in adults and children from developed countries [21••,22,23, Class I]. It should be given before antibiotics or at the time when they are started and should be continued for 4 days (Table 1). Patients who have already received antibiotics should not be given dexamethasone, as it is unlikely to improve outcome. Dexamethasone may reduce the inflammatory response in the subarachnoid space, and it could alleviate many of the consequences of MM, such as cerebral edema, cerebral vasculitis, changes in cerebral blood flow, and increased ICP.

In adults, dexamethasone reduces morbidity and mortality associated with meningitis. This reduction is observed mostly in *Streptococcus pneumoniae* meningitis, and isolated data for MM are inconclusive. In children from developed countries, dexamethasone prevents hearing loss in cases of *Haemophilus influenzae* type b meningitis, but its beneficial effects on hearing and other neurologic sequelae are not as clear in MM [24]. In developing countries, no significant clinical improvement has been associated with the use of dexamethasone in any type of meningitis.

Corticosteroids in meningococcal disease

In patients with MM and shock, use of corticosteroids is controversial. High-dose corticosteroids do not improve outcome in patients with shock, and they could even increase the risk of complications. However, these patients are at risk of developing critical illness-related corticosteroid insufficiency, so low-dose ("stress dose") corticosteroids may be beneficial. In children, little is known about critical illness-related corticosteroid insufficiency, but low-dose corticosteroids are considered a useful approach [20]. The hemodynamic effect of low-dose hydrocortisone in children with shock is being evaluated in a placebo-controlled study.

Although previously advocated, the adrenocorticotrophin hormone (ACTH) stimulation test is no longer needed before starting corticosteroid therapy in patients with MM and shock. All patients with fluid-refractory shock who have responded poorly to vasoactive agents should receive low-dose corticosteroids [25], Class II]. At present, hydrocortisone is often used in patients with shock in doses of 300 mg/day for adults and 100 mg/m^2 per day in children.

Another indication for corticosteroid therapy in MD is the development of bilateral adrenal gland hemorrhage (Waterhouse-Friderichsen syndrome). This entity is poorly recognized in patients with MD and is a frequent finding in post-mortem examination of patients with shock [19,26].

Treating altered cerebral blood flow and cerebral edema

- In general, patients with MM have preserved regional cerebral blood flow and slightly reduced cerebral metabolic rate of oxygen. How-

ever, these patients have impaired autoregulatory function [27,28], making them vulnerable to changes in blood pressure, carbon dioxide (CO_2), and ICP. Adequate blood pressure is the best control for ICP, so treatment of shock has priority. Specific measures to control ICP are discussed below. Ideally, an individualized approach should be used, with assessment of cerebral blood flow, because patients with MM vary widely in response to treatment [27]. Secondary cerebral ischemic lesions with altered cerebral blood flow are responsible for adverse short-term and long-term outcomes.

- Brain swelling in response to infection and inflammatory mediators may also lead to raised ICP. Intensive-care admission is required in patients with a Glasgow Coma Scale (GCS) score of 9 or less. Raised ICP may be indicated by hypertension associated with bradycardia; pupils that are unequal, dilated, or slow to react; focal neurologic signs or abnormal posturing; and seizures; or by papilledema. In patients with these signs, therapy should be aimed at providing adequate cerebral perfusion pressure. ICP monitoring is not standard, however, because two database analyses suggest that such monitoring does not reduce mortality in children with MM and may increase hospital stay and hospital costs [29,30].

Ventilation

- Mechanical ventilation is required in all patients with a low GCS to protect the patient's airway. This intervention allows control of CO_2 levels. Cerebral arterioles are indirectly sensitive to changes in blood CO_2 (through the mechanism of extracellular pH), and decreases in CO_2 lead to cerebral vasoconstriction, reduction in cerebral blood flow, and lower ICP.
- Despite the "protective" effect of hyperventilation in lowering ICP, hyperventilation causes significant reduction in cerebral blood flow and should be avoided in patients with MM. The current recommendation is to keep partial pressure of CO_2 in the arterial blood slightly below normal, ranging from 4.0 kPa to 4.5 kPa during the first 24 h of treatment or while ICP remains elevated. These recommendations are based on extrapolation of data from traumatic brain injury and animal studies, however, as there are no trials evaluating ventilation strategies in MM.

Mannitol

- Intravenous mannitol (0.25–0.5 g/kg) is an osmotic agent used to reduce acutely raised ICP until more definitive treatment can be applied. Besides its osmotic diuretic effect, mannitol has a rheologic effect that dilutes the blood and increases the deformability of erythrocytes, thereby decreasing blood viscosity and increasing cerebral blood flow. The sudden increase in cerebral blood flow causes autoregulatory vasoconstriction of cerebral arterioles, decreases the intracerebral blood volume, and lowers ICP.

- Mannitol is widely used as a therapeutic option for the treatment of raised ICP in patients with traumatic brain injury, but its clinical application in MM has never been evaluated in a formal trial. Laboratory studies suggest that it may be beneficial as a temporary measure to reduce ICP in patients with meningitis, but there are concerns about its safety when the blood-brain barrier is not intact because of the risk of disequilibrium induced by mannitol penetrating brain tissue. We use mannitol in MM only as a rescue therapy in patients with suspected supratentorial herniation due to raised ICP.

Treatment of seizures

- Seizures or status epilepticus may be the initial presentation of MM. Treatment begins with protecting the airway to ensure adequacy of breathing and maintaining the circulation. Serum electrolytes and blood glucose should be measured, and corrected if abnormal. Seizures should be treated with benzodiazepines, phenytoin, or phenobarbital. Lorazepam (0.1 mg/kg) is our usual first-line treatment, followed by phenytoin (20 mg/kg) if seizures do not resolve. If seizures are not stopped with this treatment, then other therapies such as continuous infusion of midazolam should be considered. Endotracheal intubation may be required, as sedatives may impair breathing. Prophylactic treatment with anticonvulsants is not recommended.

Activated protein C

- Activated protein C is an endogenous protein that promotes fibrinolysis and inhibits thrombosis and inflammation. Its use has been associated with improvement in coagulation screening and limb necrosis in case series of MD. In adults, it reduces mortality in patients with severe forms of septic shock and is associated with a low incidence of life-threatening bleeding and intracranial hemorrhage [31].
- Although activated protein C is potentially useful in patients with severe forms of MD, there are concerns about its use in patients with MM, because subgroup analysis of an activated protein C trial revealed a high incidence of intracranial bleeding in patients with meningitis [32]. In children, only one study has evaluated the effect of activated protein C, and that study was stopped because of lack of efficacy [33]. We do not recommend the use of activated protein C in MD [32,33], Class II].

Emerging therapies

Temperature control

Body temperature is directly associated with ICP. Hyperthermia during or after brain injury increases neuronal injury. Although no formal trial has evaluated this matter in MM, there is consensus that hyperthermia should be avoided. Hypothermia has been successfully used as a neuroprotective

strategy in adults who have suffered cardiac arrest [34,35] and in neonates after hypoxic-ischemic injuries [36]. Hypothermia engenders a number of mechanisms that may be neuroprotective, including prevention of cellular apoptosis and reduction of ICP, inflammatory changes, and cerebral edema. Although there are reasons for using hypothermia in MM, no clinical trials have yet evaluated its efficacy. Many complications are associated with hypothermia (eg, arrhythmias, hypotension, infection), so we should be cautious when considering this experimental therapy. We currently aim to maintain normothermia in all patients with severe MM by actively preventing hyperthermia.

Glycerol

Glycerol, an essential compound of the human cell membrane, is a naturally occurring trivalent alcohol that acts as a hyperosmolar agent and promotes osmotic diuresis. Its use in children with meningitis could, in theory, reduce cerebral edema by initiating a hyperosmolar euvolemic state [37]. A randomized controlled trial in Latin American children with bacterial meningitis suggested that glycerol can reduce neurologic sequelae either alone or in association with dexamethasone [38•, Class II]. Further trials are necessary before this therapy is recommended, but the safety, availability, and low cost of this treatment increase its potential usefulness in resource-limited settings.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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