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Review article

Treatment of Meningococcal Disease

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A B S T R A C T

Meningococcal disease is a life-threatening infection that may progress rapidly, even after appropriate treatment has commenced. Early suspicion of the diagnosis is vital so that parenteral antibiotic treatment can be administered as soon as possible to reduce the complications of infection. The outcome of meningococcal disease is critically dependent on prompt recognition of two important complications: shock and raised intracranial pressure. Rapid recognition of disease and of these complications, together with appropriate management is crucial to the outcome of affected patients. This article summarizes the clinical features of invasive meningococcal disease, diagnostic tools, treatment modalities, and common post-infection sequelae.

Infection with the bacterial pathogen *Neisseria meningitidis* is the predominant cause of meningitis and septicemia globally [1,2]. Humans are the only reservoir for the bacterium, which resides primarily in the nasopharynx; colonization occurs in approximately 10% of adults and can increase to 24% during adolescence [3–5].

Prompt recognition of meningococcal infection and aggressive early treatment are of paramount importance in reducing mortality, which occurs in approximately 10% of those with invasive meningococcal disease (IMD), even with treatment, and can reach as high as 50% in those left untreated [6].

The rapid recognition of IMD is of critical importance to patient survival and outcomes. Understanding the signs of infection is particularly important in industrialized countries, such as the United States and United Kingdom, where disease rates are low and physicians will likely see few cases over the course of their practice. Prompt administration of effective parenteral antimicrobial therapy and early recognition and management of the complications of IMD, including shock and raised intracranial pressure (ICP), are critical to improving patient outcomes. This manuscript will review the clinical features of IMD, methodologies for identification of the bacterium, current treatment modalities, and post-infection sequelae.

Clinical Features of Invasive Meningococcal Disease

The initial onset of IMD follows the clinical course of a classic bacterial infection which may pose a challenge for the attending physician. Typically, a nonspecific febrile illness with chills, muscle aches, nausea, and vomiting may precede the development of more specific features of meningococcal infection, such as classic features of meningitis (e.g., headache, neck stiffness, photophobia, and altered mental state); however, less than a third of patients will present with this traditional "typical" diagnostic combination [5,7]. In approximately 40%–70% of patients with meningococcal disease, the nonspecific features will progress to sepsis due to meningococcal septicemia, with signs of circulatory insufficiency, shock, and the pathognomonic petechial/purpuric rash [8].

Meningitis and septicemia are the most common clinical features of IMD and each can occur independently or in

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combination [9]. The presence of a nonblanching hemorrhagic rash is pathognomonic of IMD and reflects coagulopathy. Coagulopathy is universal in severe sepsis regardless of the etiology, but the pathognomonic hemorrhagic rash is a distinguishing feature of IMD. The petechiae and purpura may occur anywhere on the body, so their presence with fever and signs of sepsis should automatically suggest IMD and prompt the initiation of immediate parenteral antimicrobial therapy. It should be noted that the classic rash may not be present until the disease is well advanced and may be atypical or absent in a significant proportion of IMD cases [9].

Shock is a consistent feature of meningococcal septicemia and is multifactorial in origin due to the consequence of several pathophysiologic processes, including endothelial cell dysfunction, myocardial dysfunction, altered vasomotor tone, and impaired cellular metabolism [10]. Shock occurs because perfusion of vital organs, such as the brain and heart, is maintained at the expense of perfusion of less vital organs (e.g., skin, kidneys, and gut). In the early phase of shock, vasoconstriction reduces blood flow to skin, peripheries, and certain organs, particularly the kidneys and gut, and patients usually present with cool peripheries, prolonged capillary refill time, and oliguria. It should be noted that children may have normal blood pressure until shock is advanced. In severe cases, focal ischemia of the skin or even whole limbs may occur as well as renal failure. Despite the presence of shock, brain perfusion and function is often relatively well preserved until the disease is far advanced, which can lead to an underestimation of the degree of cardiovascular collapse by less-experienced clinicians. Eventually, a decreased level of consciousness indicates loss of cerebral vascular autoregulation and reduced brain perfusion.

Septic shock can lead to and is the consequence of impaired myocardial function, the origin of which is multifactorial: hypovolemia leads to decreased cardiac filling; metabolic derangements (including hypoxia, acidosis, hypokalemia, hypocalcemia, hypophosphatemia, hypomagnesemia, and hypoglycemia) lead to impaired myocardial contractility. In addition, bacterial products and inflammatory cytokines directly suppress myocardial contractility. Plasma interleukin-6 has been identified as a specific myocardial depressant factor in meningococcal septicemia [11]. Myocardial contractility may improve with volume resuscitation and correction of metabolic derangements, but patients with signs of ongoing shock despite adequate volume resuscitation require inotropic support to improve myocardial function.

The onset of hypotension signifies a failure of homeostatic mechanisms. It should be remembered that diagnosis of shock in children does not rely on the presence of systemic hypotension. Children may have normal blood pressure until shock is advanced.

Raised ICP occurs as a result of inflammation of the meninges and capillary leak in the brain, leading to cerebral edema. Most patients with meningococcal meningitis have mildly raised ICP, but significantly raised ICP is uncommon. Although most critically ill children with meningococcal infection have shock as their primary clinical problem, some present with meningitis and raised ICP as their predominant clinical manifestation. Signs of raised ICP include declining level of consciousness, focal neurologic signs (including unequal, dilated, or poorly responsive pupils; relative hypertension; and bradycardia), and papilledema (a late finding in acutely raised ICP).

Identification of Meningitis: Lumbar Puncture and Computed Tomographic Imaging

Lumbar puncture (LP) is a definitive diagnostic tool that can yield rapid microbiological confirmation of meningococcal meningitis and can exclude other causes of meningeal infection. In the absence of antibiotic treatment before assessment, LP detects meningococcus in 90% of meningitis-positive patients while blood cultures detect 40%–75% of cases [12]. It should be noted that antibiotic treatment before LP reduces the efficacy of bacterial detection by multiple methods (e.g., cerebrospinal fluid culture, polymerase chain reaction, latex agglutination) [13]. Although microbiological confirmation is important for establishing disease etiology, LP may be dangerous in the presence of raised ICP or shock because it may cause cerebral herniation or further cardiovascular compromise; consequently, this procedure should be avoided in the initial assessment of patients with clinically apparent meningococcal disease. Contraindications to LP include cardiorespiratory insufficiency, raised ICP (evidence for which includes fluctuating or deteriorating levels of consciousness [Glasgow Coma Score $\leq$ 8]; normal or high blood pressure in the presence of a slow or normal heart rate; unequal, dilated, or poorly reacting pupils; focal neurologic signs or abnormal posturing; seizures; and papilledema) and coagulopathy [14]. When LP is contraindicated, blood culture, polymerase chain reaction, urine antigen detection, skin biopsy, and serum inflammatory markers can be used to establish a diagnosis [13].

Computed tomographic brain imaging is frequently used in patients with a depressed level of consciousness and is particularly recommended where there is a broader differential diagnosis. However, cranial computed tomographic scanning is not a sensitive way of assessing ICP and cannot help in making the decision to perform an LP, which must be made on the basis of clinical assessment [14].

Treatment of Invasive Meningococcal Disease

Treatment guidelines have been developed over many years. These are regularly updated and are useful reminders of the management principles for infants, children, and young adults with meningococcal septicemia and meningitis, leading to substantial improvements in mortality (Figures 1–3). Recognition and management of shock and/or raised ICP is the priority in effective treatment of IMD. Early and aggressive fluid resuscitation is associated with improved survival in pediatric septic shock [15]. In the absence of shock, ICP can be treated with osmotherapy to reduce cerebral edema and improve brain perfusion.

In the newly diagnosed patient, parenteral antimicrobial therapy is a top priority and should be given as quickly as possible and certainly within 1 hour of recognition of IMD as recommended in the most recent national and international guidelines (Table 1) [14,16]. It should be noted that patients with IMD can transmit meningococci within the first 24 hours of antibiotic therapy, therefore, measures such as droplet precautions should be taken to minimize exposure to health care workers [17]. Antibiotic therapy rapidly reduces circulating plasma endotoxin levels in patients with IMD; increased endotoxin levels have been associated with severity of illness, including the presence of septic shock, multiple organ failure, and death in patients with IMD [18]. Even with antibiotic