Meningococcemia in Adults: A Review of the Literature

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Abstract

We mainly refer to the acute setting of meningococcemia. Meningococcemia is an infection caused by Neisseria meningitidis, which has 13 clinically significant serogroups that are distinguishable by the structure of their capsular polysaccharides. N. meningitidis, also called meningococcus, is a Gram-negative, aerobic, diplococcus bacterium. The various consequences of severe meningococcal sepsis include hypotension, disseminated intravascular coagulation (DIC), multiple organ failure, and osteonecrosis due to DIC. The gold standard for the identification of meningococcal infection is the bacteriologic isolation of N. meningitidis from body fluids such as blood, cerebrospinal fluid (CSF), synovial fluid, and pleural fluid. Blood, CSF, and skin biopsy cultures are used for diagnosis. Meningococcal infection is a medical emergency that requires antibiotic therapy and intensive supportive care. Management of the systemic circulation, respiration, and intracranial pressure is vital for improving the prognosis, which has dramatically improved since the wide availability of antibiotics. This review of the literature provides an overview of current concepts on meningococcemia due to N. meningitidis infection.

Key words: meningococcemia, Neisseria meningitidis, meningococcus, meningitis, meningococcal infection

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Introduction

Meningococcemia, a meningococcal infection caused by Neisseria meningitidis, can have devastating clinical consequences in infected individuals. It also causes epidemics in developed and developing countries, with incidence rates varying from 1-1,000 cases per 100,000 population (1, 2). N. meningitidis infection was first reported by Viesseux in 1805, who described the quintessential clinical picture of meningococcemia as ‘fièvre cérébrale maligne non contagieuse’ (noncontagious malignant cerebral fever) (3). N. meningitidis was first isolated approximately 80 years later, in 1887 (4). N. meningitidis, which belongs to the family Neisseriaceae, has 13 clinically significant serogroups distinguished by the structure of their capsular polysaccharides. Of the 13 serogroups, the following 6 can cause fatal disease: A, B, C, W135, X and Y (5). These serogroups differ in their geographic distribution and lethality (6). The manifestations include pharyngitis, fever, renal failure, disseminated intravascular coagulation (DIC), and meningococcemia with or without meningitis (7-10).

Epidemiology

Meningococcal disease remains a devastating cause of epidemic meningitis and sepsis worldwide, especially among children and young adults (11-13). Each of the 13 serogroups of N. meningitidis has a specific geographic distribution and attack age (Figure) (6, 11, 14, 15). Serogroups A, B, and C are the major serogroups. A and C are reported in Asia and Africa while B and C are reported in the US and Europe (11, 14). In developing countries, most meningococcal diseases are caused by serogroup A (16). Organisms of this serogroup cause pandemics once in every 10 years in the African meningitis belt, which is distributed along the Sahelian and sub-Sahelian areas of Africa (17-19). The African meningitis belt is well known as an epidemic area, but
the reason for this is poorly understood (20). Molecular surve-

surveillance has revealed a shift of the clonal complex of sero-
group A organisms from the sequence type 5 (ST-5) com-
pex to the ST-7 complex in all countries in this area over
the last 2 decades (21). Serogroup B rarely causes out-
breaks; however, it spreads easily once an outbreak
starts (22). Serogroup C epidemics have occurred among
adolescents and young adults in the US (23). Serogroup
W135 has caused epidemic and endemic infections associ-
ated with high mortality rates in the African meningitis
belt (24-26). Outbreaks of this strain occurred during the
Hajj pilgrimages to Mecca in 2000 and 2001 (25). Sero-
group Y infections have increased in the US and Is-
rael (23, 27). Serogroup X epidemics have occurred in sub-
Saharan Africa (17, 28). Endemic infection with serogroup
B occurs in infants (<1 year old) and that with serogroup C
occurs in adolescents (5-22 years old). Endemic infection
with serogroups B and Y occurs in the elderly. The inci-
dence rates of infection with serogroups C, B, and Y in their
respective populations are 35%, 32%, and 26%, respectively,
in the US (11, 23, 29). The immune system plays an impor-
tant role in protecting the host from meningococcal dis-

Microbiology

N. meningitidis, also called meningococcus, is a Gram-
negative, aerobic, diplococcus bacterium and a member of
the family Neisseriaceae of the β subclass of the Proteobac-
teria class (4, 10). The organism is approximately 0.6-1 μm
in diameter and has flattened adjacent sides. Growth condi-
tions suitable for meningococci are provided by a moist en-
vironment with 3-10% carbon dioxide saturation and tem-
peratures in the range of 35-37°C. The organism grows well
on various medium bases, including blood agar base, tryp-
ticase soy agar, supplemented chocolate agar, and Mueller-
Hinton agar (36). The bacterium produces an oxidase and
shows a positive reaction to an oxidase test (37). N. menin-
gitidis has various virulence factors, including pili, opacity-
associated proteins, lipooligosaccharides, capsular polysac-
charides, and outer membrane proteins (4, 38). Differences
in the structure of the capsular polysaccharides determine
the serogroup, lipooligosaccharides, which are major components of the outer membrane. They differ in structure from endotoxins and are significant components of the inflammatory signaling by the Toll-like receptor 4 pathway (39). These lipooligosaccharides are important scaffolds for bacterial adherence and colonization. They therefore play an important role in the development of fulminant sepsis and meningitis. Meningococci change their cytoskeletal structures when they come into contact with cells (40). The α-chain structure of meningococcal lipooligosaccharides mimics that of human polysaccharides; this is an example of the application of molecular mimesis as a means of escaping a host’s immune mechanisms (41). Colonization of the nasopharynx can cause systemic infection (11), whereas bacterial load in the circulation is associated with the activation of the complement and coagulation systems (42).

**Clinical Manifestations**

Meningococcal disease occurs within 2 weeks of exposure. Up to 20% cases of meningococcal disease present with meningococcal septicemia, which is known as meningococcemia (45). Clinical manifestations of meningococcemia, including the acute onset of fever, hypotension, DIC, multiple organ failure, and in severe cases, osteonecrosis due to DIC, reflect the systemic symptoms of the infection (43). Petechial, purpuric, or maculopapular rash and arthritis are also reported as systemic signs (31, 44, 45). While these skin rashes are often observed all over the body, including in the mucous membranes, they occur predominantly on the extremities (11). The form of meningococcemia associated with skin rashes and adrenal hemorrhage is known as Waterhouse-Friderichsen syndrome (46). Adrenal hemorrhage is a manifestation of fulminant meningococcemia, which also causes thrombotic lesions in the skin, kidneys, choroid plexus, lungs, and extremities (47, 48). Meningococci are sometimes observed in biopsy samples of the dermis, which can be cultured for up to 12 hours after the initiation of antibiotic therapy (49-51). Local symptoms of meningococcal infection include rhinorrhea, cough, sore throat, abdominal pain, and cutaneous vasculitis. However, there is little evidence regarding the association of these symptoms with meningococcemia (8, 31, 52).

**Diagnosis**

The gold standard for the identification of meningococcal infection is the bacteriologic isolation of *N. meningitidis* from sterile body fluids such as blood, cerebrospinal fluid (CSF), synovial fluid, pleural fluid, and pericardial fluid or skin biopsy. According to several retrospective reports, the sensitivity of blood culture is 50-60%; this is lower than that of CSF culture (80-90%) (53). In a prospective study, the sensitivities of blood, CSF, and skin biopsy cultures were 56%, 50%, and 36%, respectively. When culture and Gram staining were combined, the sensitivities were 56%, 64%, and 56% (54). Gram staining and a skin biopsy culture analysis can improve the sensitivity of blood culture analysis. However, negative results do not exclude the diagnosis of meningococcal infection. An investigation is currently underway to determine the diagnostic properties of a polymerase chain reaction (PCR) assay. In the UK, a fair amount of meningococcal disease has been diagnosed by PCR alone (55). A PCR has advantages over a culture analysis because it enables faster diagnosis; furthermore, its sensitivity (reportedly 96%) is not affected by the prior administration of antibiotics (56). The sensitivity of a PCR is higher than the sensitivities of CSF or blood culture analyses (56). In addition, the PCR of skin biopsy cultures (100%) has been shown to be more sensitive than the PCR of blood cultures (58.8%) (44, 57). These findings indicate that although PCR assays are very effective in diagnosing meningococcemia, bacterial culture is still necessary for the testing of antibiotic susceptibility. The antibodies to meningococcal capsular antigens are available for use in the body fluids (except blood). These testing kits are capable of detecting agglutination of five capsular types: A, B, C, Y, and W135. The sensitivity for serogroup B is low.

**Treatment**

In the absence of prompt and appropriate treatment, meningococcemia remains a life-threatening condition (42). Meningococcal infection is a medical emergency and the prompt provision of antibiotic therapy and intensive supportive care, including the management of septic shock and intracranial pressure, is required to improve the prognosis in infected patients (see Prognosis). Antibiotic therapy should be initiated as soon as possible in an intensive care unit in order to prepare for aggressive systemic treatment. The primary treatment goal is to stabilize blood pressure because vascular collapse and septic shock often result from meningococcal endotoxins and lipooligosaccharides (58-60). The WHO has recommended four antibiotics for the empirical treatment of meningococcal infection: penicillin G, third-generation cephalosporins, namely ceftriaxone and cefotaxime, and chloramphenicol (61). Penicillin G is safe and effective at the usual recommended dose of 300,000 units/kg/day, and almost all strains are susceptible to this drug. A few penicillin-resistant strains have recently been reported. These strains form as a result of a decreased binding affinity to penicillin-binding protein 2 (62-64). However, penicillin resistance is very rare and is not related to mortality (65). Third-generation cephalosporins such as ceftriaxone and cefotaxime are reasonable alternatives to penicillin, especially when acute bacterial meningitis is suspected in nonendemic areas (66). Chloramphenicol is not suitable for use in empirical therapy in nonendemic areas because a high level of chloramphenicol resistance was reported in the late 1990s (67). The single intramuscular administration of long-acting chloramphenicol is used as the empirical therapy in
endemic areas (11). For the definitive therapy, Penicillin G or a third-generation cephalosporin is recommended. The standard duration of therapy for meningococcal infection is 7 days. A shorter regimen is useful in developing countries, and several researchers have shown that 3 days of intravenous treatment with Penicillin G is effective (68). Treatment with single doses of both ceftriaxone and chloramphenicol resulted in a good outcome in a meningococcal meningitis epidemic in Niger, with a mortality of approximately 5% (69). Rifampin and ciprofloxacin showed significant efficacy in the eradication of N. meningitides, however, they are seldom used in current treatments - rather, they are used for chemoprophylaxis. During 2000 and 2006 in the African meningitis belt, susceptibilities to beta-lactam antibiotics remained high, whereas other classes of antibiotics displayed a decreased affinity (70). The use of dexamethasone reduces morbidity in adult pneumococcal meningitis patients; however, there are no data concerning its effects in patients with meningococcal meningitis (71).

Prognosis

The mortality of meningococcal infection currently ranges from 10-14%, which is much lower than the 70-90% reported during the era before antibiotics became available (72, 73). Although additional supportive care, including intensive systemic care and the use of glucocorticoids, has recently come into focus, the marginal benefit that such treatments confer to mortality has not changed since the late 1960s (74, 75). The largest prospective population-based study of clinically independent prognostic factors for mortality in cases of meningococcal infection revealed that hemorrhagic diathesis (OR, 101; 95% CI, 30-333), focal neurologic signs (OR, 25; 95% CI, 7-83), and age ≥60 years (OR, 10; 95% CI, 3-34) were poor prognostic factors that were associated death (76). On the other hand, the administration of an appropriate antibiotic therapy for suspected meningococcal infection was found to be a more favorable prognostic factor (OR, 0.09; 95% CI, 0.02-0.4).

Antibiotic chemoprophylaxis

Effective chemoprophylaxis to control secondary cases of meningococcal infection is indicated for individuals who have been in prolonged (>8 hours) close proximity (<3 feet) with a patient or who have been directly exposed to the patient’s oral secretions. These include household members, roommates, intimate contacts, individuals at child-care centers, young adults living in dormitories, and military recruits in training centers, who have had prolonged exposure to an infected patient for at least 1 week before the onset of the patient’s symptoms or until 24 hours after the initiation of appropriate antibiotic therapy (72, 77). The Centers for Disease Control and Prevention recommend the administration of rifampin (600 mg orally every 12 hours for 2 days), ciprofloxacin (a single oral dose of 500 mg), and ceftriaxone (a single intramuscular dose of 250 mg, recommended for pregnant women) as treatment regimens for antimicrobial prophylaxis (72). These should be administered as early as possible (ideally within 24 hours) because the rate of secondary disease development in contacts is the highest immediately after the onset of symptoms (72). However, resistance to rifampicin can develop rapidly, and quinolone resistance in meningococci has also been reported (78). In addition, droplet precautions should continue to be maintained for 24 hours after the administration of effective antibiotics (77).

Vaccination

Two quadrivalent polysaccharide-protein conjugate vaccines are currently available: the meningococcal polysaccharide vaccine (MPSV4) and the meningococcal conjugate vaccine (MCV4). These A, C, Y, W-135 quadrivalent meningococcal polysaccharide vaccines have been used in the United States and many other industrialized countries. In the United Kingdom and European Union, the serogroup C meningococcal conjugate vaccine has been administered since 1999.

Adults who require either the MPSV4 vaccine or the MCV4 vaccine include college freshmen living in a dormitory, military recruits, people with a damaged spleen or without a spleen, people with terminal complement deficiency, microbiologists who are routinely exposed to N. meningitidis, and travelers or residents in a country in which the disease is common (hyperendemic or epidemic). Previously vaccinated travelers and travelers to and residents of the meningitis belt of Africa should be revaccinated. Adults <55 years of age who were previously vaccinated with MPSV4 should receive an additional dose 5 years after their previous dose and every 5 years thereafter for as long as the risk continues. Travelers >55 years of age should be revaccinated with MPSV4 if they have not been revaccinated for >5 years. Prior to travel, unvaccinated travelers with HIV, functional or anatomic asplenia, or complement component deficiency (C3, properdin, factor D, or late component) should receive a 2-dose primary series of conjugate vaccines at an interval of 2 months if they are <56 years of age or a single dose of polysaccharide vaccine if they are >56 years of age (72, 79, 80).

Conclusion

Meningococcemia remains a life-threatening condition if prompt and appropriate treatment is not administered. The prompt initiation of proper treatment, including systemic care and antibiotic therapy, dramatically decreases the incidence of meningococcal infection. On the other hand, rifampicin and quinolone resistance have been reported, which suggests a need for caution in the proper usage of antibiotics to prevent the emergence of drug-resistant strains. In addition, further epidemiologic studies are in needed in order
to provide insights into the environmental and host factors affecting the development of meningococcal infection, especially in Africa and other developing areas, where the infection poses the greatest persistent threat (11).

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References


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