Meningococcal Disease

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ABSTRACT

Meningococcal disease occurs as both endemic and epidemic disease in most parts of the world with significant morbidity and mortality. Among the different serogroups of *Neisseria meningitidis*, serogroups A, B, C account for 90% of the disease. In the last few years there has been a change in the epidemiology of the disease with an increase in the prevalence of serogroup C in Europe and North America, serogroup Y in the United States of America and Sweden, and W135 in the Kingdom of Saudi Arabia. The emergence of *Neisseria meningitidis* serogroup W135 in the Kingdom of Saudi Arabia has lead to 2 major outbreaks mainly among Pilgrims during the Hajj season of 2000 and 2001. This has lead the health officials in the Kingdom of Saudi Arabia to change their vaccine requirements for the Umra and Hajj to include the quadrivalent meningococcal vaccine (A, C, Y, W135) instead of the bivalent one (A, C). Despite all the advances in prevention, diagnosis and treatment, the disease continues to have high mortality (5-10%). Prompt empirical treatment for suspected cases should include penicillin or a 3rd generation cephalosporin. A new conjugate vaccine against *Neisseria meningitidis* serogroup C has been recently licensed, while quadrivalent conjugate vaccine against serogroup A, C, Y and W135 is in early development. Meanwhile targeted vaccination with the available vaccines according to the epidemiology of the disease and rapid chemoprophylaxis for the close contacts of active cases are the most effective preventive strategies.

Keywords: Meningococcal disease, Hajj, prevention, vaccine, chemoprophylaxis.

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Epidemic cerebrospinal fever or spotted fever (meningococcal meningitis) was first described by Vieusseux in Geneva in 1805, but the organism was not described until 1884 by Marchiafara and Celli and isolated by Weichselbaum in 1887.[1] Infection with the organism diplococcus intracellularis meningitis later renamed *Neisseria meningitidis (N. meningitidis)* has been recognized for more than 300 years. During the 20th century, large outbreaks were reported during World War I and World War II, and from 1928 to 1941 significant worldwide epidemics occurred.[2] It was in 1947 that serum therapy for meningococcal disease was replaced with sulfonamides. This lead to a drastic reduction in the mortality from this disease. In 1963, resistance to sulfonamides became a recognized worldwide problem. It was then that efforts were reinvested in the development and discovery of effective vaccine against serogroup A and C meningococcal disease.[3] Today invasive meningococcal disease, both in endemic and epidemic forms are the cause of significant morbidity and mortality worldwide, and despite the major advances in prevention, diagnosis, and treatment, case fatality rate (CFR) for the septicemic form of the disease in developing countries is as high as 70% and in developed countries 5-10%.

Pathogenesis. *Neisseria meningitidis* is a gram-negative diplococcus, which only causes disease in humans by causing meningitis and septicemia The organism has a polysaccharide capsule, which is highly antigenic and important in classifying the organism into one of 13 serogroups. Strains are further divided into serotypes and subtypes by immunoreactivity of the outer membrane proteins.[4]

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The organism colonizes the nasopharynx of a substantial proportion of the population and spreads from person to person by aerosols. These aerosols are spread by coughing, sneezing, kissing and sharing drinks. A small proportion of the asymptomatic carriers go on to develop invasive disease. There are human factors and pathogen related factors that predispose progression to invasive disease. These include patient age, impairment of the host defense mechanism, such as functional or anatomic asplenia and complement deficiencies. Some meningococcal strains are more likely to cause disease than others. Serogroups A, B and C are responsible for approximately 90% of the causes of meningococcal disease. In contrast, isolates of asymptomatic nasopharyngeal carriers are non-groupable or express X, Z, or 29E capsule serogroup.

Clinical manisfestations. After an incubation period of 2 to 10 days, symptoms of meningitis start with flu like illness, intense headache, fever, stiff neck, irritability, photophobia, nausea, vomiting and skin rash. The disease could progress to fulminant sepsis, coma and shock. In 80% of the patient the presentation is meningitis while 20% present with pure septicemia without meningitis. Other less common syndromes include urethritis, arthritis, conjunctivitis, pneumonia and pericarditis. The mortality rate of the septicemia is 4 times that of meningitis in the developing countries 70-80%, while that of meningitis in developed countries is less than 5% but a similar proportion may suffer long-term neurological sequelae.

Microbiology and diagnosis. *Neisseria Meningitidis* is a gram-negative, oxidase-positive diplococcus which has a polysaccharide capsule. This capsule is an important virulence factor specifically acting as an attribute responsible for blood stream survival and dissemination. Based on the chemical composition of the capsule, the organism is classified into 13 serogroups: A, B, C, D, X, Y, Z, E,W-135, H, I, K , and L. Under the capsule is the outer membrane which contain proteins (OMPs). This is important in further classifying the organism into serotypes and subtype. Under the outer membrane lies the peptidoglycan cell wall. Isolates can be grown on selective media (for example, modified Thayer-Martin) or non-selective media such as chocolate agar in 2% or 5% CO_2 incubated at 35-37^{0}C. Biochemical testing will be needed to distinguish *N. meningitidis* from other Neisseria species. Acute meningococcal disease, especially the septicemic form, can be fatal in a matter of few hours. That is why early diagnosis and immediate institution of appropriate therapy is of paramount importance in improving the survival rate. Without a high level of suspicion the diagnosis of meningococcal disease could be very difficult. Definite diagnosis of the disease requires the isolation of *N. meningitidis* from a sterile body site usually the blood or cerebrospinal fluid (CSF). Prior administration of antibiotics will decrease the yield of positive cultures in the blood and CSF but it will not affect the retrieval rate of the organism from skin biopsy specimen.[5] Other methods not affected by prior antibiotic administration include antigen detection and polymerase chain reaction (PCR) of the blood or CSF. Latex agglutination tests on the CSF are of lower sensitivity than culture but maybe useful when cultures are negative. The yield of CSF culture in suspected meningococcal meningitis (without prior antibiotic therapy) could be as high as 99%, followed by blood culture, 50%.[6] The yield of gram stain and culture of peticheal skin lesion for *N. meningitidis* is approximately 70%. Newer technologies utilizing PCR on the CSF shown excellent results with reported sensitivity and specificity of 91%.[7] This area of molecular diagnostics will be of particular value in patients who already received antibiotics prior to presentation to the hospital. The new PCR technologies are also useful in rapid identification of the meningococcal serogroups and subtypes.[8]

Epidemiology. The epidemiology of meningococcal disease is influenced by multiple factors including geography, climate, serogroups, and human population. Of the 13 serogroups identified only serogroups A, B, C, and recently W135 are known to cause epidemics. Serogroup A is the most common cause of large epidemics.[9] These outbreaks can score up to 1,000 cases per 100,000 population annually. Resulting mortality remains high even with treatment at 5-10% in patients with meningitis.[10] The geographic distribution is peculiar for serogroup A involving the "meningitis belt" in Africa. This belt includes countries from East Africa starting in Ethiopia until Gambia in West Africa. Well-studied outbreaks in this region recur periodically every 8-12 years.[9] The onset correlates with dry seasons in January and ends abruptly with rain fall in May-June.[11] Sporadic disease stays in young children. When older children (5 to 10 years) are affected, an outbreak is impending. The largest epidemic occurred in 1996 in West Africa when 250,000 cases were estimated with 25,000 fatalities.[12] Serogroup A is not the predominant serogroup in developed countries. For unknown reasons, serogroup C is more prevalent in Europe, North America and some areas in Asia along with serogroup B. Serogroup C associated outbreaks in developed countries involve far smaller numbers of patients. Nevertheless, case fatality rates are 10-15% in spite of treatment and supportive care. These outbreaks are also occurring more frequently.[13] The Kingdom of Saudi Arabia (KSA) receives millions of visitors for Hajj and Umra every year. The crowding conditions constitute favorable circumstances to increase carrier rates. Such rates can be as high as 80% in crowded areas around the Holy Mosque in Makkah, KSA.[14] In 1987, *N. meningitidis* strains of serogroup A were

documented to have been brought from South East Asia to sub-Saharan Africa through pilgrims resulting in a series of outbreaks in many countries including Makkah, KSA for the subsequent years.[15-17] Bivalent meningococcal vaccine became a requirement for Hajj pilgrims after that.[18] Another Hajj-related outbreak developed in the year 2000 caused by serogroup W135. This was the first time that this serogroup was implicated in an outbreak setting.[19] During that season, more than 300 laboratory-confirmed serogroup W135 cases were reported from KSA and 9 other countries. Cases involved Hajj pilgrims and their contacts who did not travel to Makkah, KSA. During the subsequent year, and due to major shortage of quadrivalent vaccine worldwide, several hundred thousand pilgrims were given chemoprophylaxis. Still more cases of laboratory-confirmed W135 meningitis were detected from KSA and other countries following the Hajj season of 2001.[20] The increase in carrier rates correlates with higher chances of outbreaks. Invasive disease in individuals was independently related to tobacco smoking in case control studies. Meningococcal disease will remain to be a major public concern. Epidemiology of the disease continues to change faster than we can fully understand. Effective control efforts combined with reliable vaccines for major serogroups are important to reduce impact on communities all over the world.

Treatment. Most isolates of *N. meningitidis* remain sensitive to penicillin.[21] Strains resistant to penicillin have been reported as ß-lactamase producing and non-producing isolates.[22-25] In 1989, isolates from Spain were relatively resistant to penicillin minimum inhibitory concentratration (MIC) between 0.1 and 0.8 μg/mL in 20% of the time.[24] Successful treatment of relatively penicillin-resistant invasive *N. meningitidis* has been reported using regular penicillin doses.[25] However, these doses failed to prevent meningitis while a patient was receiving penicillin for a positive blood culture.[26] Although routine susceptibility testing for *N. meningitidis* is thought to be unnecessary,[27] increased resistance rates may be evolving unnoticed without such testing. If isolates are moderately resistant, penicillin alone may not be effective, especially in cases with meningitis. Some investigators believe that antibiotic concentration in CSF should be 10 times higher than the MIC to be effective.[28] As clinical presentation of meningococcal disease may be similar to other pathogens, empirical therapy need to consider these potential organisms. When meningococcal disease is strongly suspected by CSF stains or rapid antigen assays, or in an outbreak setting, penicillin alone may be adequate. Third-generation cephalosporins (ceftriaxone or cefotaxime) could be used as alternatives to ampicillin or penicillin. Chloramphenicol is a suitable substitute for penicillin-allergic patients. This agent can be used in an oily vehicle by intramuscular injection in outbreak settings in rural areas of developing countries. This formulation was comparable to intravenous ampicillin in Africa for patients with bacterial meningitis including *N. meningitidis*.[29] More important than the chosen agent, is the time of administration. Anti-meningococcal antibiotics should be administered as soon as disease is suspected. Therapy should not be delayed until lumbar puncture, computerized tomography (CT) scans, or transfers are arranged. Immediate administration of antibiotics for suspected invasive meningococcal disease in the general practitioners' office had improved mortality rates.[30-31] Due to severe complications of invasive meningococcal disease, adjuvant therapies were considered. The use of polyclonal or monoclonal antibodies remains investigational and of unproven benefit in fulminant meningococcemia.[32] The same applies to heparin in patients with disseminated intravacular coagulation (DIC) without active bleeding.[33-34] Corticosteroids have been beneficial in some forms of bacterial meningitis caused by *Hemophilus influenzae* type b but there is no evidence that it may be beneficial for *N. meningitidis* related disease. Use of corticosteroids remains controversial even for patients in shock. Other measures that have been used include plasmapheresis,[35] and extracorporeal membrane oxygenation.[36-37] Patients admitted to hospital with suspected or confirmed meningococcal meningitis should be placed in droplet precautions in private room until 24 hours after the start of treatment. Healthcare workers entering the room during the initial 24 hours should be wearing a mask.

Prevention. *Neisseria meningitidis* is exclusively a human pathogen. There is no non-human reservoir, intermediate host or a vector. The organism can be a nasopharyngeal colonizer producing an asymptomatic carrier state which may last up to 2 years,[38] or an invasive pathogen causing meningitis and blood stream infection for example. So prevention strategies are aimed at reducing carriers and preventing pathogen invasion. For the former chemoprophylaxis has been effective[39] and for the latter vaccination is utilized.

Chemoprophylaxis. Close personal contact is an important risk of acquiring meningococci and subsequent secondary cases. Antimicrobial chemoprophylaxis is considered the primary means of prevention in certain areas.[27] It should be given to household contacts, day-care center and school contacts, and close personal contacts where respiratory secretions may be transmitted. It should be given as soon as possible after an exposure or case identification. Potential recipients need not to be screened for carrier state by cultures. Sulfonamides were found efficacious as therapy. These agents were

Table 1 - Dosage and administration of chemoprophylaxis for meningococcal disease.

Agent and duration	Adults	Children younger than 15 years
Rifampin for 2 days	PO 600mg every 12 hours	PO 10mg/kg every 12 hours
Ceftriaxone for one dose	IM 250mg once only	IM 125mg once only
Ciprofloxacin for one dose	PO 500mg once only	Avoid
PO - oral, IM - intramuscular		

found to eliminate carrier state for prolonged periods.[40] However, rapid resistance evolution has rendered these agents unreliable. But the principle remains an essential part of prevention and control in outbreak settings. The ability of any agent to eradicate carrier state is not only dependant on its in vitro activity against meningococci, but also drug distribution and achieving bactericidal level in saliva.[41] Hence, agents such as erythromycin, cephalexin, and nalidixic acid failed to eradicate carrier state. Rifampin has been found as a suitable agent for carrier eradication. It needs to be taken for 2 days and break through infection was reported. Other active agents eliminating nasopharyngeal carriage include ciprofloxacin[42] and ceftriaxone.[43] **Table 1** summarizes doses and administration frequency of these agents. These agents are well tolerated.[44]

Immunoprophylaxis. Meningococcal vaccines are available for serogroups A, C, Y, and W135. Serogroup B has no licensed vaccine yet. Current vaccines are of high-molecular weight capsular polysaccharides. The first developed vaccines were A and C with proven efficacy and safety.[45,46] The Y and W135 vaccines were safe and immunogenic of bactericidal antibodies but lack field efficacy studies. The A and C vaccine have been used extensively in many parts of the world. However, Y and W135 were used less widely. They are part of a combination vaccine including all 4 types. Seven to 10 days are required after immunization to produce appreciable antibody levels. These vaccines provide an immunity lasting for 2 to 3 years.[47,48] The currently licensed meningococcal vaccines are of paramount importance in preventing disease in spite of several shortcomings. These include high cost especially for the quadrivalent vaccine, distribution and logistic difficulties, unpredictable and limited immunity duration, and poor immunogenicity in children younger than 2 years.[49] Meningococcal vaccine protects recipients only and no herd immunity has been demonstrated.[50] Adverse events are mild and limited to local erythema and irritability in children occurring in 4-6% of recipients. Given the recent outbreaks of W135 strain after Hajj,[19,51] only quadrivalent vaccine should be used. The Ministry of Health of KSA has recommended this vaccine for all Hajj and Umra participants, supporting staff, and neighbor residents of The Two Holy Mosques.[20] Attempts to improve meningococcal vaccines continue. To enhance immunogenicity in children, conjugation to carrier proteins was tried.[52-54] Serogroup C conjugate vaccine has an estimated efficacy of 92% in toddlers and 97% in teenagers in England.[55] This vaccine was added to the routine schedule of childhood immunization in late 1999 in the United Kingdom. For serogroup B, vaccine has been tried using OMP, H.8 antigen, IgA protease and others. Results remain mixed and more work is required.[56-58] Recently a hexavalent vaccine for the B serogroup was tried. Three doses in children were able to mount antibodies up to 2.5 years later.[59-60]

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