Meningococcal Disease: A Review

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Invasive meningococcal disease continues to cause significant morbidity and mortality, particularly in the developing world. This review focuses on the epidemiology, clinical syndromes, therapy, and prevention of meningococcal disease. Future progress will depend on an improved understanding of the epidemiology of both endemic and epidemic disease. Prevention will be enhanced by the development of effective, long-lasting vaccines against all the major meningococcal serogroups, particularly serogroup B.

Since Vieuxseux's first description of epidemic meningitis almost 200 years ago, substantial progress has been made in defining the clinical syndromes, treatment, and prevention of meningococcal disease. Despite these advances, disease due to Neisseria meningitidis continues to cause significant morbidity and mortality, particularly in developing countries. Though host risk factors, such as complement component deficiencies, play a role in sporadic disease, risk factors for epidemic disease are poorly understood. This review will focus on the epidemiology, clinical syndromes, therapy, and prevention of meningococcal disease. The pathophysiology of bacterial meningitis has been recently reviewed and will not be covered.

The Organism and Nomenclature
First isolated from cerebrospinal fluid (CSF) by Weichselbaum in 1887, N. meningitidis is a Gram-negative diplococcus distinguished from N. gonorrhoeae by its ability to ferment both maltose and glucose; the gonococcus ferments only glucose. The meningococcus is classified on the basis of its capsular polysaccharides, outer membrane proteins (OMP), and lipopolysaccharides (LPS).

Currently, there are 12 capsular polysaccharide serogroups: A, B, C, X, Y, Z, W135, 29E, H, I, K, and L. Antigenic differences in the class 2 and 3 outer membrane porin proteins define different serotypes, while differences in the class 1 outer membrane protein determine subtypes.

Epidemiology
While endemic meningococcal disease incidence rates in developed countries are 1–3/100,000 persons, endemic rates in many developing countries range from 10–25/100,000 persons. Periodically, epidemic attack rates approach 500/100,000. In 1988, over 56,000 cases of meningococcal disease were reported from the African continent; in 1989, the number of cases increased to over 70,000 (World Health Organization, unpublished data). Given the lack of reporting from many countries, and incomplete reporting from others, this figure likely represents an underestimation of the actual number of cases.

Epidemics have occurred with great regularity in countries forming the ‘meningitis belt’ of sub-Saharan Africa. In some countries, notably Burkina Faso, epidemics appear to recur regularly.
every 8–12 years.\(^8\) Consistent cyclical patterns, however, are difficult to detect in most countries. The incidence of sporadic disease is highest in the young. During the 1986 active surveillance project for meningitis in the USA, 53% of cases of invasive meningococcal disease occurred in children under 5 years of age (Centers for Control, unpublished data). In contrast, during epidemics, the average age of the patients increases. During two epidemic years in Finland, the ratio of cases in persons over 4 years of age compared with those under the age of 4 years increased over three-fold when pre- and post-epidemic years were evaluated.\(^9\) The reason for this age shift is unclear.

Intercontinental spread has been documented for an epidemic strain of serogroup A meningococcus, the III-1 clonal group. First noted in Nepal in 1983, this clonal complex appeared in Saudi Arabia in 1987 and spread into Chad in 1988.\(^10\) The 1987 epidemic in Saudi Arabia was associated with the Hajj, the annual Muslim pilgrimage to Makkah. Carriage of the epidemic strain was found in 11% of Hajjis returning on flights from Makkah to the USA, illustrating how widespread dissemination of an epidemic strain can occur.\(^11\)

Clinical Syndromes

Infection with the meningococcus can result in one of four major clinical syndromes. The most common form of infection is asymptomatic nasopharyngeal carriage, which was first described by Dopter in 1915. Humans are the only known carriers of the meningococcus and serve as reservoirs for continued transmission. The organism spreads from person to person by intimate contact with oral secretions and exposure to respiratory droplets. Baseline carriage prevalence rates in the USA range from 5% to 11%, and the median duration of carriage is 9.6 months.\(^12\) Factors shown to increase the carriage rate include crowded conditions such as those existing in military barracks,\(^13\) coincident viral infections,\(^14\) and cigarette smoking.\(^15\) Natural immunity develops as the result of asymptomatic carriage, typically 2 weeks after nasopharyngeal infection begins.\(^16\)

Meningococci are occasionally grown from blood cultures in the absence of the classic findings of meningococcaemia. This ‘benign bacteraemia’ is discovered when blood cultures are obtained as part of the routine evaluation of fever; frequently no antibiotic therapy has been initiated and the patient has improved by the time the positive cultures are found.

Meningitis, the most common pathologic presentation, manifests with the classic findings of fever, headache, and stiff neck. Meningeal infection is the result of haematogenous dissemination of the organism. Laboratory evaluation of the CSF shows an elevated number of white blood cells (predominantly polymorphonuclear leukocytes), usually in the hundreds or even thousands per ml. The CSF glucose concentration is decreased (less than 50 mg/dl) and the protein level elevated. Mortality under the best conditions of antimicrobial treatment and supportive care remains about 10–15%.

Meningococcaemia is the most severe form of infection: patients may present with a petechial or purpuric rash, hypotension, disseminated intra-vascular coagulation (DIC), and multi-organ failure. The condition is often fulminant, with death occurring 12–48 hours after presentation. The case-fatality rate ranges from 15 to 30%. Poor prognostic findings include shock, coma, acidosis, seizures, DIC, and thrombocytopenia.\(^17\)

Other forms of meningococcal disease such as purulent arthritis, pericarditis, and endophthalmitis\(^18\) are less common and are the result of metastatic infection during the bacteraemic phase.

Therapy

Historically, serum therapy was the first successful treatment of meningococcal disease. In 1913, Flexner\(^19\) published a report of 1294 cases treated with direct subdural injections of serum. Mortality, compared with that in historical controls, decreased from 70–90% to 31%. The discovery in the 1930s of sulphonamides and their successful application in meningococcal disease represented a major advance and replaced serum therapy as the treatment of choice. With the development of sulphonamide resistance in the 1950s, penicillin emerged and remains the antibiotic of choice for invasive meningococcal disease.

Disconcerting reports from Spain\(^20\) and England\(^21\) have documented the emergence of meningococci which are relatively resistant to penicillin (MIC 0.1–1.28 μg/ml). Penicillin resistance remains rare among most clinical isolates. None of the 2124 meningococcal isolates tested at CDC over the past 10 years has been penicillin-resistant (Carolyn Baker, CDC, personal communication). The relatively resistant isolates from Spain have remained sensitive to ceftriaxone.\(^22\) Ceftriaxone and other third-generation cephalosporins such as cefotaxime, and cefazadime are highly active against Gram-negative bacteria and are capable of achieving high CSF concentrations. Although these antimicrobial agents have increased the number of therapeutic choices, cost prohibits their extensive use.

Chloramphenicol has been widely used as an alternative antimicrobial agent for meningococcal meningitis. Though usually considered a bacteriostatic agent, chloramphenicol achieves high concentrations in CSF and is bactericidal against the meningococcus.\(^23\) Early uncontrolled studies in Africa\(^24\)–\(^26\) showed that a single injection of
chloramphenicol in oil successfully treated 75–92% of the patients with meningococcal meningitis. A controlled trial by Wali et al. showed that a single injection of chloramphenicol in oil was as effective as a 5-day course of crystalline and procaine penicillin, providing an acceptable treatment option in areas where access to medical care is limited. Because chloramphenicol in oil is not effective in the treatment of pneumococcal meningitis, great care should be used in the empiric application of this drug. This regimen should be reserved for treatment of diagnostically confirmed cases or treatment of cases in a documented meningococcal epidemic.

The importance of adequate supportive care for patients with meningococcal meningitis and meningococcaemia cannot be understated. Careful attention to intravascular volume, urinary output, and cardiopulmonary function is critical.

Immunity

In the late 1960s, Goldschnieder et al. showed that the incidence of meningococcal disease correlates inversely with the level of serum bactericidal activity against the meningococcus. In military recruits studied prospectively, they showed that serum samples from 51 of 54 persons with meningococcal disease lacked bactericidal antibody to the disease-producing strain of meningococcus. The lack of bactericidal activity of these sera could be corrected by the addition of purified gamma globulin but was not enhanced by exogenous complement.

Natural immunity follows both nasopharyngeal carriage and disease. Carriage of the meningococcus results in increased bactericidal antibody to the carriage isolate in 92%, and to heterologous strains in 87% of carriers. Increases in titers of IgG, IgM, and IgA antimeningococcal antibodies usually occur within 2 weeks of the onset of carriage. Although immunity in neonates is the result of transplacental transfer of maternal IgG, carriage of non-pathogenic Neisseria species, such as Neisseria lactamica, is thought to produce protective antibody in young children. Carriage of N. lactamica increases steadily from birth to 18 months of age, when the point prevalence in one study reached 21%. Protective levels of antimeningococcal antibody have not been established. Finnish investigators suggested that meningococcal-specific antibody levels in excess of 2 μg/ml were protective.

Prevention: Vaccines

Since the late 1960s polysaccharide vaccines for the prevention of meningococcal disease have been developed for a number of N. meningitidis serogroups. Despite the availability of these vaccines, success in controlling endemic and epidemic disease has been limited for several reasons. First, current meningococcal polysaccharide vaccines produce only marginally protective antibody responses in young children. Second, duration of immunity is age dependent and diminishes rapidly in children vaccinated at less than 4 years of age. Third, while group B meningococcus continues to cause most of the sporadic disease in the USA and epidemic disease in Brazil and Chile, no effective group B polysaccharide vaccine has been found. The recent development and testing of conjugate (protein-polysaccharide) vaccines for Haemophilus influenzae type b show great promise for inducing an antibody response in children under 1 year of age. These vaccines may serve as a model for the development of similar conjugate vaccines against the meningococcus. Incorporation of meningococcal vaccines which are immunogenic and provide a durable antibody response into routine childhood immunization programmes would greatly enhance control efforts, particularly in young children.

Efforts to develop a successful vaccine against the meningococcus began in the early 1990s, field trials of these early vaccines yielded mixed, but generally poor, results. Failure of the early vaccines may have been due to degradation of the immunogen. For example, the size of the polysaccharide correlates with immunogenicity; to be consistently antigenic, polysaccharides must be greater than 100 000 mol wt. In addition, endotoxin contamination of vaccine preparations led to severe pyrogenic reactions, limiting the amount of vaccine which could be administered.

Laboratory advances led to the development of purified component vaccines. Based on a novel technique to purify large molecular weight polysaccharides from meningococcal culture supernatants, Gotschlich et al. developed the first consistently immunogenic vaccines for the groups A and C meningococci in the late 1960s. Field trials of the group C polysaccharide vaccine in military recruits showed an 87% reduction in meningococcal disease; protection was limited to serogroup C.

Successful efficacy trials for the group A meningococcal polysaccharide vaccine took place in Finland and Egypt in the mid-70s. Several aspects of these studies deserve comment. First, the vaccine was well tolerated with less than 2% of the group experiencing serious side-effects. Second, the investigators theorized, but could not prove, that vaccination of 40% of the population appeared to decrease the incidence rate of disease in the entire population. They speculated that this population immunity may be due to a decrease in transmission from cases and to a decrease in carriage. The effect of the vaccine on nasopharyngeal
carriage is controversial. Although one study showed that group C vaccine reduced carriage of the meningococcus, subsequent investigators have been unable to show a lasting effect of vaccine on carriage rates. (CDC, unpublished data). Unfortunately, carriage rates in the Finnish studies were too low to assess the impact of the vaccine. Finally, although the group A polysaccharide vaccine appeared to be protective when the population of infants and young children was examined as a group, the numbers of infants or young children in each age stratum were not specified, precluding estimates of age-specific vaccine efficacy.

Meningococcal serogroups Y and W135 polysaccharide vaccine are both safe and immunogenic; no efficacy studies exist for these two serogroup vaccines.

A number of factors such as age, coexistent malaria infection, and lymphoid malignancies affect antibody response to the polysaccharide vaccine. Of these, age is the most critical. Maturation of the humoral immune response to polysaccharide antigens is progressive and is considered complete at 60 months. Heterogeneous antibody responses to different polysaccharide antigens are seen depending on the age of the child. For example, the H. influenzae type b polysaccharide antigen (polyribosyl-ribide-phosphate) has limited immunogenicity in children less than 16 months of age; polysaccharides from pneumococcal serotypes 3 and 8 are highly immunogenic from the age of 6 months, yet pneumococcal serotypes 6A, 14, 19F, and 23F, the most common in the pediatric age group, are poorly immunogenic in children less than 5 years of age.

Antibody response to the meningococcal serogroup A polysaccharide is limited in children less than 1 year of age; a second dose given 3 months after the primary vaccination induces antibody levels similar to a single dose in that age group. The group C polysaccharide induces a weak antibody response in children less than 1 year of age; no booster effect is demonstrated. Additionally, efficacy studies of the group C polysaccharide vaccine in Brazil showed no protection in children less than 2 years of age. The limited response to the meningococcal polysaccharide antigens in the very young precludes incorporation of these vaccines into routine childhood immunization programs.

Malaria infection transiently impairs the humoral immune response to a number of vaccines. The response to the group C meningococcal vaccine, however, remains depressed up to 1 month after malaria infection in children. The effect of chronic malaria infection on the development of natural immunity to the meningococcus in parts of the world where both diseases are highly endemic is unclear.

Individual host factors may limit antibody response to the meningococcal polysaccharide vaccines. Individuals with asplenia due to trauma, immune thrombocytopenic purpura, and non-lymphoid tumours respond to a bivalent A/C vaccine almost as well as do controls, whereas those with associated lymphoid tumours respond poorly. Ambrosino et al. have described an immunodeficiency syndrome characterized by recurrent sinopulmonary infections and the absence of an IgG response to any polysaccharide vaccines. They speculate that a defect in a subpopulation of B or T cells is critical to the recognition of polysaccharides. The absence of similar cell populations during infancy and their gradual appearance during early childhood may account for the observed maturation of the immune response to polysaccharide antigens.

No data are available on the immunogenicity of meningococcal vaccine in persons infected with human immunodeficiency virus (HIV). Antibody response to the pneumococcal polysaccharide vaccine is decreased both in individuals with acquired immunodeficiency syndrome (AIDS) and those with asymptomatic HIV infection compared with non-infected controls. Although blunted, the response may still be protective.

Early studies of the group A and C polysaccharide vaccine showed a persistent antibody response measured by indirect haemagglutination and fluorescent antibody up to 18 months after immunization in a group of laboratory workers. Duration of immunity, however, is also a function of age. Children vaccinated at 4 years of age and older have sustained protection against the group A meningococcus for 3 years; those vaccinated before the age of 4 show a rapid decrease in vaccine efficacy in the next 3 years. No long-term studies of vaccine efficacy exist, and current recommendations are that high-risk individuals be revaccinated every 3–5 years.

Except for military personnel, meningococcal vaccine is not routinely recommended in the USA for two reasons. First, more than 50% of meningococcal disease is due to serogroup B, for which an effective vaccine does not exist. Second, more than half of cases are in children under the age of 4 years (CDC, unpublished data), an age group in which vaccine displays a limited duration of protection. Vaccine should be targeted at specific groups with an increased risk of meningococcal disease; for instance, vaccine has been successfully used by the US military to prevent outbreaks of meningococcal disease in recruits, and Saudi Arabia has required meningococcal vaccination for all Hajjis since the 1987 outbreak. These policies have
substantially reduced the number of cases in both of these populations. National ongoing surveillance programs are crucial for establishing baseline sporadic disease incidence data and for promptly detecting the onset of epidemics. In addition, surveillance is useful for assessing the age distribution of disease and the meningococcal serogroups responsible for cases. National vaccination policies should be formulated on the basis of these data.

Chemoprophylaxis

Although nasopharyngeal carriage in the population is common, invasive disease is rare. Chemoprophylaxis is not appropriate for epidemic control. During the 1987 Hajj epidemic, carriage rates for pilgrims returning to the USA were similar in those who did and did not report using rifampin prophylaxis (14% vs 10%). Furthermore, a study of chemoprophylaxis during the same outbreak showed substantial acquisition of carriage in the control population, suggesting that a few of the prophylaxis failures were due to recolonization with the epidemic strain. The role of antibiotics in eliminating carriage is limited to those persons with an increased risk of developing invasive disease. Household contacts exposed to a case of meningococcal disease have a 500–800 to 3000–4000-fold increased risk of developing invasive disease. Current recommendations by the Immunization Practices Advisory Committee are that household members, day-care centre contacts, and persons exposed to the oral secretions of the patient should receive prophylaxis. Unless the organism is known to be sensitive to sulphadiazine, the antibiotic of choice rifampin (600 mg every 12 h for adults, 10 mg/kg every 12 h for children aged 1 month and older and 5 mg/kg every 12 h for 2 days for children less than 1 month old). Minocycline 100 mg orally twice daily for 3 days or ceftriaxone 250 mg intramuscularly are acceptable alternative agents. Because it is a teratogenic drug, rifampin should not be used in pregnant women. Minocycline, in addition to causing vestibular toxicity, discolors teeth and should not be used in pregnant women or children.

Control of meningococcal disease will be contingent on a better understanding of its epidemiology, in particular those factors which lead to epidemic disease. The development of an effective group B vaccine remains an important priority. Additional progress will depend on the development of vaccines that will be immunogenic and effective in children less than 1 year of age, and will provide long-term protection in all age groups.

References


