Epidemiology and Prevention of Bacterial Meningitis and Meningococcal Serogroup B Infection

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Abstract

Acute bacterial meningitis (ABM) continues to be associated with high mortality and morbidity, despite advances in antimicrobial therapy. The causative organism varies with age, immune function, immunization status, and geographic region, and empiric therapy for meningitis is based on these factors. *Haemophilus influenzae* type b (*Hib*), *Streptococcus pneumoniae*, and *Neisseria meningitidis* cause the majority of cases of ABM. Disease epidemiology is changing rapidly due to immunization practices and changing bacterial resistance patterns. Hib was the leading cause of meningitis in children prior to the introduction of an effective vaccination. In those countries where Hib vaccine is a part of the routine infant immunization schedule, Hib has now been virtually eradicated as a cause of childhood meningitis. Vaccines have also been introduced for pneumococcal and meningococcal diseases, which have significantly changed the disease profile. Where routine pneumococcal immunization has been introduced, there has been a reported increase in invasive pneumococcal disease due to non-vaccine serotypes. In those parts of the world that have introduced conjugate meningococcal vaccines, there has been a significant change in the epidemiology of meningococcal meningitis. Antibiotic resistance is an increasing problem, and early diagnosis and prevention of ABM are important. In infants, 60% of cases are caused by serogroup B in the United States and Europe. Asymptomatic colonization of the upper respiratory tract provides the source from which the organism is spread. It has been demonstrated that conjugate meningococcal B vaccine is immunogenic in infants. *(J Pediatr Inf 2014; 8: 33-9)*

Keywords: Bacterial meningitis, meningococcal B infection, vaccine, prevention, childhood

Introduction

Acute bacterial meningitis (ABM) is still a health risk due to high mortality and morbidity despite the advances in vaccination and antibiotic treatment. Since the immune system is not fully developed in childhood, there is a high sensitivity for polysaccharide capsule bacteria causing ABM (1). It is estimated that more than 75% of the ABM cases in the world are children under 5 years old. The World Health Organization has reported that 170000 deaths occur annually and the case-mortality rate is as high as 50% in those who do not receive any treatment (2, 3). The estimated median sequellae is reported to be 19.9% (12, 3-35, 3%) (4). The age of sequellae patients with meningitis varies depending on the active microorganisms and the country of inhabitance.

Haemophilus influenzae type b *(Hib)* was the most common pathogen in the childhood bacterial meningitis before the onset of conjugated vaccines. Invasive Hib infection is frequently seen in children between 6-18 months. In unvaccinated children under 4 years of age, there is a high risk of invasive Hib. The patients of sickle-cell anemia, asplenia, immunodeficiency, infection of human immune deficiency virus (HIV) and malignity are the predisposing for the Hib infection. After the Hib conjugated vaccination in the USA, the invasive Hib infection in children under 5 years of age decreased 99% (5). Hib conjugated vaccine was improved by the addition of capsular polysaccharide (poliribosilribotol phosphate) and carriage protein. Diphtheria, tetanus, aselluler pertussis and the combination of inactive polio and Hib (DTaP-IPV/Hib) or the forms combined with hepatitis B and Hib obtained license. DTaP-IPV/Hib are administered in the months of 2, 4, 6 and 15-18. Pentavalent vaccine has been available on the national vaccina-

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tion schema since 2006. Unvaccinated children under 4 years of age with household contact have a great risk of infection. Rifampicin prophylaxis of 20 mg/kg/day is recommended for 4 days and it prevents nasopharyngeal carriage status in the rate of 95% (5).

Streptococcus pneumoniae is one of the most important causes of invasive bacterial infections in childhood. In patients with sickle cell anemia, asplenia, immunodeficiency, HIV infection, cochlear implantation and cerebrospinal fluid leakage, the frequency of pneumococcal infection has increased. With the introduce of seven-valent pneumococcal conjugated vaccine (PVC 7) in 2000, it was reported that there was 99% decrease in the frequency of vaccine serotypes -associated invasive pneumococcal infections. The thirteen-valent pneumococcal conjugate vaccine (PCV13) obtained license to be administered to 6 week-71 month children after the PCV 7 (6). In addition to the serotypes of PCV13, PCV7 (4, 6B, 9V, 14, 18C, 19F and 23F), it also includes 6 serotypes (1, 3, 5, 6A, 7F and 19A) has been conjugated with non-toxic diphtheria toxin carriage protein (CRM_{197}). 23-valent pneumococcal polysaccharide vaccine (PPSV-23) obtained license in order to be administered to children older than 2 years of age and adults. PCV13 vaccine is recommended to be administered in the months of 2, 4, 6 and 12-15 in the routine vaccine schedule. Prophylaxis is not recommended in pneumococcal infections after contact. In cases with splenectomy, oral penicillin V prophylaxis, independent of vaccination is recommended (6). Meningococcal infections are one of the main severe diseases that are vaccine preventable. Meningococcus is the most important pathogen of meningitis in children after routine administration of the Hib and PCV13 vaccine. Every year 500.000 invasive meningococcal disease are seen in the world, and 50.000 mortalities are reported (7). Meningococcus (*Neisseria meningitis*) cause the epidemics. 13 serogroups of meningococcus have been defined and five of them (A,B,C, W135 and Y) frequently cause diseases. Meningococcal infections may be seen all over the world. While sporadic cases are frequently seen in developed countries, it is reported that group A and W135-related epidemics are reported in the African meningitis zone (all the way from Ethiopia from the east to Senegal in the west) (8-10). Meningococcus C-associated epidemics were seen in schools and university dormitories in North America and in England (10). W135 epidemics were seen during the pilgrimage in Saudi Arabia in 2000 and 2001 (10). While serogroup A is the most common meningococcal meningitis agent in Africa, serogroup B and C are the most common types in Europe and America continents (11, 12). In a study carried out in Turkey, it was reported that after the inclusion of Hib and pneumococcal vaccinations into the routine vaccine schedule, *N. meningitidis* was the most prevalent pathogen of meningitis in children (13). The last epidemic of meningococcal infections was reported in the USA in 2010-2012. Meningococcal infection was developed in male homosexual cases (14). 52 cases were reported in 2011 and 88 cases in Chili. The most prevalent one was serogroup W135 with 42.5%. As a result of this, the Ministry of Health in Chili made a decision to administer a vaccination campaign with the ACYW conjugated vaccine and administered it to children aged 9 month to 4 years old as of 2013. A multi-centered meningitis surveillance study was initiated in Turkey by Ceyhan et al. (8) in 2005 and has still been underway. It was found in the first two years of the study that 56.5% of *N.meningitidis*, 22.5% *S. peumoniae* and 20.5% Hib were present in bacterial meningitis. It was also found that W135 was 42.7% and serogroup B 31.1% in meningococcal serogroups. Majority of the cases were under the age of 1, the second peak mostly seen in adolescents in Europe was not observed in our country. It is reported that W135 serogroup is associated with the pilgrimage travel. While W135 serogroup declined in the 2007-2008 period of surveillance, serogroup B (35.1%) turned out to be the most prevalent pathogen. While W135 began to rise (56.1%) again in the 2009-2010 period of surveillance, the total meningococcal infection rate approached almost the double of *S.pneumoniae* (31.8%), while Hib went down to 6.1%. This result had an impact over the fact that Hib in 2006 and pneumococcal vaccines in 2009 were included into the national vaccination schedule and administered over 90% in Turkey.

Meningococcal colonizes in the nasopharynx of people and is colonized in 10% of adults. Colonization is lower in children. In a meta-analysis study, it was found that while meningococcal carriage in infants was 4.5%, it was 23.7% at the age of 19 (15). Metastasis occurs from human to human through droplets. Infection is seen in children below 2 years of age in developing countries and children above 10 years of age in developed countries (8). In their study, Greenfield *et al*. (16) reported that the 88% of strains detected in carriages were grouped and majority of them were comprised of serogroup B. While the most frequent group was found to be serogroup B (47.5%) in a carriage study done in Turkey Ankara in 1996, it also turned out that W135 was 10%, Y 7.5% and C 3.3% (17). In a study done in Manisa in 2001-2001, serogroup B was 35.2%, A 28.1% and W135 11.2% (18). The most important predisposing factor in meningococcal disease is nasopharyngeal carriage. The other factors are living in a crowded environment, exposure to smoking, previous viral respiratory tract infection and phagocytosis disorder.

Despite invasive meningococcal disease is seen in every age, it has a greater risk for especially children under 2 and adolescents aged 15-19, freshman at univer-

sity living in university dormitories, or adolescent military recruits, adolescents and young adult (19-25). Those with a deficiency of complement, anatomical or functional asplenia, deficiency of congenial and acquired immunoglobulin have a greater risk of invasive meningococcal disease (19).

Meningococcus serogroup B

Group B meningococcus is effective in majority of the endemic diseases in develop countries. This bacterium responsible 80% of meningococcal infections in some European countries and 30-40% in the USA (10). It accounts for the epidemics in developed countries and attack rate is reported to be 5-50/100,000 (26). Two serogroup B epidemics were reported to the Centers for Disease Control and Prevention (CDC) in 2010 (27). After conjugated meningococcus C vaccination in the United Kingdom, a change was observed in the meningococcus epidemiology. In recent studies, serogroup W125 and B have been the most frequent serogroups (28). In the multicentered meningitis surveillance study done by Ceyhan *et al.* (8) in Turkey, meningococcus B turned out to be the most prevalent one. While 13 meningococcal diseases were observed in 2008-2010 in the USA, 10 of these were serogroup B (29). 8 serogroup B meningococcal infections were detected in New Jersey in 2013 (30). In another study in Belgium, 420 meningococcal isolates were investigated and it was demonstrated that epidemic serogroup B meningococcus strains spread from Holland to Belgium (31). Developing a vaccine against meningococcal serogroup B infection differs from other polysaccharide-protein conjugated vaccines. The study concluded that the four-component meningococcal vaccine demonstrated more powerful immunogenicity in infant, childhood and adolescence periods (32).

Meningococcal vaccines

In case of epidemic, together with chemoprophylaxis, a strain-specific meningococcal vaccine is recommended. Routine meningococcal vaccines are not recommended to health children (9 months-10 years of age) (19). Besides, meningococcal vaccine is also recommended to those who travel to the regions where the disease is hyperendemic (19).

Meningococcal polysaccharide vaccines

First tetravalent polysaccharide meningococcal vaccines (MPSV4) proving protection against the diseases formed by the meningococcal A, C, Y and W135 serogroups were developed early 1980s (22). The MPSV4 vaccine obtained license in the USA in 1981 to be used subcutaneously. Polysaccharide vaccines were used as monovalent, bivalent and trivalent (20, 24, 33, 34). Polysaccharides were antigens independent of T cells and therefore, memory B cells do not develop. The immune response induced by polysaccharide vaccines in children under 2 years of age is weak and does not provide sufficient protection against the disease; therefore, polysaccharide vaccines cannot be administered to the children under 2 years of age (20-23, 33, 35). Polysaccharide vaccines do not reduce the nasopharyngeal carriage of *N. meningitidis* and do not induce herd immunity (20, 21, 35).

Conjugated meningococcal vaccines

The first conjugated meningococcal vaccine is serogroup C conjugated vaccine (35). It went into use in 1999 in the United Kingdom (33). Later tetravalent (A, C, W135, Y) vaccine and bivalent conjugated C and Y vaccines were developed (33). Hib conjugated meningococcal serogroup C and Y vaccine obtained license in the USA to be used for high risk group 6-week-18-month children (20, 36). As a carriage for meningococcal A, C, W135 and Y polysaccharides, a non-toxic purified protein obtained from *Corynebacterium diphtheria* and known as 197 (CRM 197) is used (37)." One dose of Menveo in adolescents and adults aged 11-55 was approved by the American Food and Drug Administration in February 2010 (38-40). Since it was demonstrated that it was immunogenic and reliable for the infancy period in August 2013, Menveo was licensed for use. Menveo is currently indicated in the USA to be used intramuscularly for those aged 2 months-55 years of age for the prevention of invasive meningococcal disease (39-41). Nimenrix is a meningococcal vaccine that obtained license to be used as one dose as of 12 months. Nimenrix is quadrivalent meningococcal conjugated vaccine inclusive of serogroup A, C, W135 and Y, and carriage protein tetanus toxoide (TT). In a randomized multi-centered study, it was demonstrated that the use of one dose constituted a powerful response against 4 serogroups in healthy 12-23-month infants, 2-17 aged children and adolescents and adults aged 18-55 (42).

In the USA, recommendations in tetravalent conjugated meningococcal vaccine (MCV4) are as in the following: MCV4 is recommended routinely for adolescent aged 11-18 and for those (For Menactra, those aged 9 months-55 years old) aged 2-55 who have greater risk of meningococcal disease (8, 43). The Advisory Committee on Immunization Practices (ACIP) in the USA has recommended the administration of MCV4 to adolescents since 2005 (36, 44). The adolescents who were administrated

MCV4 before the age of sixteen are recommended 1 booster dose (19). In the USA, one routine dose of MCV4 is recommended to those aged 11-12 and a booster dose is recommended at 16 (19, 45). As vaccines, Menactra or Menveo can be administered. ACIP recommends the administration of MCV4 to those unvaccinated at 11-12 at the age of 13-18 (19). A booster dose is recommended at the age of 16-18 after the first MCV4 dose administered to adolescents of 13-15 (19, 45). A booster dose is not recommended to the adolescents aged 16 and above after their conjugated meningococcal vaccine as there is no risk factor. MCV4 is not recommended as a routine vaccine to those aged 19-21. However, it can be given as an interception vaccine to those who were not administered one dose after 16th birthday (19). One dose of MCV4 is recommended to the unvaccinated freshmen (aged 11-18) who will be living in university dormitory (19). Those with a great risk of invasive meningococcal disease are recommended the MVC4 vaccination as of 9 month (19). Those with a great risk are as follows:

- 9 month-old or older children and adolescents with a deficiency of persistent complement component (C5-C9, properdin, factor H or factor D) (19, 20). If children with a deficiency of persistent complement component are vaccinated as of 9-23 months old, two doses of primer series need to be administered at least with 8-week interval (19).
- It is recommended to those 24 month-old or older children with anatomic or functional asplenia and adolescents. Since invasive pneumococcal disease is high in children with anatomic or functional asplenia, MCV4-D should not be administrated to children before 2 years of age in order for it not to break the immune response against conjugated pneumococcal vaccine series (19). If MCV4-D is to be used as conjugated meningococcal vaccine, it is recommended to be administered at least 4 weeks after the completion of all the conjugated pneumococcal vaccine doses (19).
- Those travelling to the regions where the disease is hyperendemic or epidemic (19, 20). 9-23 month-old infants travelling or wishing to reside in those regions where meningococcal disease is hyperendemic or epidemic should be administered 2-dose primary vaccine series ideally with 3-month interval (at least 8 weeks) (19). 2-10 year-old children travelling or wishing to reside in those regions where meningococcal disease is hyperendemic or epidemic should be administered one dose of the vaccine (19). If the high risk continues in 9-month-6 year-old primary dose-administered children, a booster dose is to be administered after 3 years (19). If the high risk still continues, one booster dose should be repeated every 5-year (19). The most risky travels in respect of meningococcal infection is to go to Saudi Arabia for pilgrimage or umrah, and travel to Sub-Saharan Africa (meningitis zone) (20). The vaccine recommended to those who will go on a risky travel in respect of invasive meningococcal disease is tetravalent conjugated meningococcal vaccine (20).
- Military men and military personnel are recommended the vaccine.
- Since those infected with HIV have a greater risk of meningococcal disease, they may be vaccinated with MCV4 (19). Those who 2 years-old or older infected with HIV should be administered two-dose primary series with at least 8 weeks interval (19).
- In order to control the meningococcal epidemics caused by vaccine-preventable serogroups (A, C, Y or W135), those aged 9-month-55-year old are recommended the MCV4 vaccine (19). In case of an epidemic, MPSV4 should be administered to those over 55 years of age (19).
- If three years have passed since the administration of MPSV4 in previously MPSV4-vaccinated children, immunization with MCV4 is recommended (19).

Serogroup B meningococcal vaccines

Since polysaccharide capsule of serogroup B is composed of polycyclic acid also available in some human glycoproteins and polycyclic acid is similar to the carbohydrates present in fetal brain tissue, human beings have a natural immune tolerance against serogroup B polysaccharides, and as a result serogroup B capsule is weak immunogen (20, 21). If the glucose structure of polysaccharide is modified in order to make the vaccine more immunogenic, there is a fear that antibodies to be generated by the vaccine will go into cross-reaction with the tissue antigens and will trigger the autoimmune disease (20-22). Due to the difficulties regarding the development of capsule vaccine against serogroup B, based on the non-capsular structures such as meningococcal outer-membrane vesicles and/or outer-membrane proteins with antigenic features (for instance, porin A), vaccines against serogroup B may be developed (21, 33).

Outer-membrane vesicles vaccines

Outer-membrane vesicles vaccines (OMV) have been developed in order to control serogroup B clonal epidemics (20-22, 33). Cuba, Norway, France, Brazil, Chili and New Zealand were used in order to control the epidemics and different protection rates were found (57.2-94%) (20-22, 33). The limitation of OMV vaccines is that they can

generate strain-specific immune responses and that they fail to generate cross-protection against other strains especially in babies (20, 22).

Four-component serogroup B vaccine (4CMenB vaccine)

Since the immunogenecity of serogroup B capsule is low, trials have been carried out for the last 40 years in order to develop serogroup B vaccine by determining bactericidal antibody generation potential of serogroup B and the protected proteins expressed on the bacteria surface (21, 22). These trials ended up with the development (Bexsero, Novartis) of serogroup B meningococcal vaccine (4CMenB vaccine) with four major immunogenic components (three sub-capsular meningococcal B protein antigen and outer-membrane vesicles with major immunogenic antigen Por A) through reverse vaccinology method. All these antigens induce bactericidal antibodies against themselves (22). In the studies carried out, the vaccine was administered to 2 month old or older infants, children, adolescents and young adults (20, 22). It was demonstrated that the vaccine in infants was immunogenic and well-tolerated (22, 46). 4CMenB vaccine obtained license to be used in 2 month or older infants in order to be protected against meningococus B in February 2013 in the European Union by European Medicines Agency (EMEA).

Table 1. Chemoprophylaxis after contact with meningococcal disease

Antibiotic	Dose	Duration
Rifampicin		2 day
Infants <1 month	5 mg/kg, once in 12 hours, orally	(4 dose)
Children >1 month	10 mg/kg, once in 12 hours, orally	
Adults	600 mg, once in 12 hours, orally	
Ceftriaxone		
Children <15 year-old	125 mg, intramuscular	1 dose
Children >15 year-old	250 mg, intramuscular	1 dose
Ciprofloxacin		
Adults >18 year-old	500 mg, orally	1 dose

Table 2. Increased risk groups who had contact with meningococcal disease

• Those with household contact
• Those in childcare and preschool contact
• Those at a school and university during an epidemic
• Those who had a contact with oral secretions (kissing, sharing the same water bottle, mouth to mouth resuscitation at the hospital, those who perform intubation)

Chemoprophylaxis in meningococcal infection

There is an increased risk of infection in those with close contact with meningococcal patients. The attack rate for household contacts is 500-800 times the rate for the general population. Together with the child who had the meningococcal infection, everyone had a contact with patients at home, childcare and preschool within the seven days before the onset of the disease and those who had contact with the oral secretion of the child should be given antibiotic prophylaxis. The doctors who give mouth to mouth resuscitation or perform endotracheal intubation at the hospital are recommended prophylaxis (19). Prophylaxis should be administered within the first 24 hours. Since prophylaxis is not ultimate protector, those who have had a contact with a patient should be followed up at least for 10 days (47-49). While rifampicin is used in children in chemoprophylaxis, one dose of ceftriaxone, rifampicin and ciprofloxacin can be given to the adults (19). Rifampicin eradicate carriage very quickly and the effect of this therapy lasts for as far as 6-10 days. The eradication rate is about 80-85%. Since rifampicin requires 4 doses, it is a disadvantage against the single-dose drugs. When ceftriaxone intramuscular is administered as one dose, it gives over 97% carriage eradication. After a one dose, ciprofloxacin and ofloxacin effectively eradicates meningococcal carriage. However, the use of quinolone is not approved in pregnancy and children. Quinolone-resistant meningococcal strains have been reported (47-49). It has also been reported that one dose of azithromycin is as effective as rifampicin in asymptomatic carriage (50). Chemoprophylaxis diagram is given in Table 1. Table 2 illustrates increased risk groups who have had a contact with a meningococcal patient. If the indexed case has been treated with penicillin or ampicillin, rifampicin prophylaxis is recommended in order to eradicate carriage. Carriage is eradicated in those treated with ceftriaxone (19).

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