Review Article

Meningococcal Disease - Outbreak in Delhi

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Meningococcal disease occurs both endemically and epidemically across the world. In India also meningococcal disease occurs sporadically with epidemics occurring at regular intervals. Epidemics of meningo-coccal disease have occurred in Delhi in the year 1935, then in the year 1966 which lasted for a year and again in 1985-86. The last epidemic took a great toll with case fatality rate nearly 13%. This year also there has been an outbreak of meningococcal disease with nearly 400 cases and case fatality rates of about 10%; majority are males between the age group of 21-30 years and from the inner crowded areas of the city.

Meningococcal disease is caused by the gram-negative bacterium *Neisseria meningitidis*, also known as meningococcus(1). Infection occurs both endemically and epidemically, in developed and developing countries(1,2). The impact of the disease persists due to the lack of effective control measures necessary to significantly decrease the number of asymptomatic carriers(3). For every case of meningococcal disease there are hundreds of persons in normal conditions with upper respiratory tract colonization. Humans are the only reservoir in nature(3,4).

Why a particular individual colonized by the microorganism develops infection while others who are equally colonized develop immunity to infection is not known (5). There are two main forms of clinical manifestation of the disease meningococcal meningitis, which has a good prognosis if it is adequately treated(1,4) and meningococcemia or *Meningococcal septicemia*, which is less frequent and highly lethal even when treated. It is characterized by positive blood cultures and an exaggerated systemic inflammatory response, associated with endotoxemia(1,6). Cases of simultaneous meningitis and bacteremia are generally considered as cases of meningitis. *Meningococcal septicemia* is considered a medical emergency and can result in death rapidly(2,7).

Worldwide Epidemiology of Meningococcal Disease

Early detection is necessary for the control of *Meningococcal meningitis* epidemics.

- A weekly incidence of 15 cases per 1,00,000 inhabitants averaged over 2 consecutive weeks is recommended by the World Health Organization (WHO) for the detection of meningitis epidemic in Africa. A stage of "epidemic" would be signaled when the following thresholds are reached:
- An attack rate of 10 cases per 100,000 inhabitants per week or 5 cases per

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100,000 cases per week for 2 consecutive weeks or doubling of cases over a 3 week period.

- In special situations *e.g.*, refugee camps, two laboratory confirmed cases of meningococcal disease in one week would be considered synonymous to an epidemic.

A stage of an "alert" would be signaled if:

- In areas with population between 30,000 and 100,000: an attack rate of 5 cases per 100,000 inhabitants per week.
- Areas having population less than 30,000 inhabitants: 2 cases in a week or an increase in the number of cases compared to the previous non-epidemic years.

In the Sub-Saharan "meningitis belt"(1) the epidemics typically start during the dry season (Jan-March) and at the onset of the rainy season (May-June). In some areas the outbreaks seem to have been kindled by Muslims' religious pilgrimages to Mecca in Saudi Arabia(2,8). During the later half of the twentieth century, serogroup A has been the predominating variant, although other serogroups (B, C, Y, W-135, and X) have been present in the past few years. The factors associated with these outbreaks are overcrowding, population mobility, climatic factors, and virulence of circulating strains.

Since 1970, the incidence of disease has increased in some American, Asian, and European countries. A number of outbreaks have occurred between 1973 and 1974 in Finland, Mongolia, and the Soviet Union. Finally, some outbreaks have occurred in Brazil since 1971 (1,2,4).

Most cases around the world are caused by Serogroups A, B, and C. Serogroups A and C are common in Asia and Africa(1). The countries where serogroup Y has increased in the past decade are the United States, Sweden, and Israel(9). During the 1980's meningococcal disease caused several outbreaks throughout India, Nepal, and Africa(2). Outbreaks caused by serogroup B occurred between 1982 and 1984 in Cuba and between 1986 and 1993 in Chile(9). The most frequent in the United States has been serogroup C. However, some outbreaks in 2000 were associated with serogroup W-135 in pilgrims returning from Saudi Arabia (8-10). Sporadic disease is still associated with serogroups B and C(1,9,10-14). The latest outbreak that affected the American continent occurred in Uruguay in 2001, caused by serogroups B and C(15).

In Delhi the outbreaks have occurred at regular intervals in 1935, 1966-67 and in1985-86. In 1966, 616 cases were recorded with peaks - May and December. In 1985, 1731 cases with 569 deaths and in 1986, 6133 cases of meningitis with 799 deaths were documented. Overall case fatality rate was 13%. In Delhi during the past three years (2002-2004) the number of cases, have been 971 with 118 deaths. Agewise breakup of 258 cases reported till middle of May this year is 27, 61, 71, 79, 12, 12, 8 and 4 in the age group 0-5, 6-12, 13 to 20, 21- 30, 31-40, 41-50, 50-75 and >75 respectively. It is obvious that the majority of the cases are adolescents and young adults. Most of the cases were from crowded inner city areas. (Personal Communication Dr. J.N. Banvaliker,)

Transmission mechanisms

Transmission results from person-to-person contact or from inhalation of respiratory droplets containing meningococci(1,16). It does not survive in the environment or in animals, is vulnerable to temperature changes and desiccation. Coughing and sneezing contribute to the transmission mechanism (1,2). The coloniza-

tion rate is greater than 50% during periods associated with an increase in viral infections and upper respiratory tract infections(5,17).

The carrier rate is low during childhood and high in adolescents and young adults. Transmission is relatively slow in open populations and is greater in isolated populations and is aggravated by smoking or respiratory infections.

Health workers may contract the disease only when directly exposed to the patient's secretions(2). It has been determined that the risk of the sibling of a child for being infected is 2 to 3% and the attack rate for persons living in the same household is 2 to 4 per 1000 subjects(2,5). In outbreaks, colonization may be subsequent or simultaneous by the same or different serogroups(5).

When cases occur in schools, a student's risk of becoming infected ranges between 0.04% and 2.5%, with a higher risk in middle schools than in elementary schools. The variation in the attack rate is representative of the variation in the established control measures, but it also depends on factors related to the bacterium, the environment, and the host (1,2,4,5,18). The distance between student's seats has proved a risk factor for colonization. Similar situations are found in prisons. Outbreaks due to type C serogroup have been identified in these institutions and associated with 40% overpopulation(3,19).

Microbiological characteristics and pathogenesis

N. meningitidis is a gram negative, aerobic, immobile, non-sporulated bacterium; it is usually encapsulated and has pilli. It is classified in serogroups according to the immune reactivity of its capsular polysaccharide, which is the basis of the polysaccharide vaccines currently available (1,2). Serogroup B contains a polysaccharide of low immunogenicity, probably due to its polysialic acid content. This acid is also present in human fetal neurons (1). Meningococcus can change from serogroup B to C or vice versa. The pathogenic process of *N. meningitidis* begins when the bacterium adheres to the surface of the microvilli of the cylindrical non-ciliated epithelium of the nasopharynx, where it reproduces.

Most subjects colonized by *N. meningitidis* remain asymptomatic. However, a lower percentage of meningococci enters the mucosa and the circulatory system, causing systemic disease(1,17). An increase in the incidence of meningococcal disease in a given population reflects the introduction, transmission, and acquisition of a virulent strain of a clonal group previously inexistent in a susceptible population. These bacterial strains produce a protective capsule that aids in evading the host's immune response, particularly the activation of complement-mediated and antibody-dependent lysis(1,2). Individuals with a deficiency of complement mediated antibody-dependent bactericidal system are susceptible to meningococcal infection(1). Predisposed individuals include people who have been splenectomized, or with functional asplenia, properdine deficiency, or deficiency of the terminal component of the complement’s cascade. However, although these predisposed individuals have an increased risk of meningococcal disease, they represent only a small proportion of total cases (1,2,4,5). It is thought that AIDS patients may also have an increased risk for infection, although not as high as compared with other encapsulated organisms. Other genetic characteristics have been associated with an increased risk of the disease, including polymorphisms in the genes for lectin, associated to mannose, and in the genes for tumor necrosis factor alpha.

Active or passive exposure to cigarette smoke, viral infections of upper respiratory tract, damage of the respiratory mucosa is fundamental for meningococcal invasiveness (5).

Clinical manifestations

A great obstacle in diagnosing meningococcal disease is that clinical manifestations are hard to tell apart from other, less serious upper respiratory tract infections. Acute purulent meningitis is the usual manifestation of meningococcal disease(1,2). It is believed that meningeal infection is the result of hematogenous dissemination of the bacterium. This is observed in 50% of patients and is similar in its initial manifestations to other types of bacterial meningitis. The symptoms start with sudden cephalea, fever, stiff neck, nausea, vomiting, photophobia, and neurological alterations that may include stupor, delirium, comma, and convulsions. In infants, meningitis may be more difficult to identify, with atypical symptoms of a stiff neck, but a swollen fontanel may be present(1,2,5). Also, the child may be irritable, cry inconsolably, vomit, have seizures, refuse to eat, and be hypotonic.

Blood cultures are positive in 75% of *Meningococcal meningitis* patients. Meningococcemia is difficult to identify in isolated cases, as opposed to outbreaks. However, it is characterized by sudden fever, purpuric or petechial exanthema, which may progress to purpura or fulminant septicemia, associated with hypotension, acute adrenal hemorrhage (Waterhouse-Friderichsen syndrome) and multiple organic failure(1). Sometimes the exanthema associated with meningococcal disease may be maculopapular, similar to a viral exanthema, non-pruritic and transient, lasting approximately two days. Serogroups A and C are most commonly associated with meningitis out-breaks. However, they can also be present as meningococcemia(2).

N. meningitidis may affect the respiratory tract causing pneumonia, epiglotitis, and otitis media. Pneumonia occurs in 5 to 15% of invasive meningococcal disease cases, particularly when serogroups Y and W-135 are involved(9,11). Diagnosis of meningococcal pneumonia is difficult because isolation of the bacterium from sputum cannot differentiate asymptomatic carriers from diseased individuals. Some focal infections also occur in the form of septic arthritis, urethritis, pericarditis and conjunctivitis.

The latter type of infection may become complicated in 18% of cases, progressing from a localized infection of the conjunctiva to meningococcemia or bacterial meningitis(11). Chronic meningococcemia is rather un-common and is characterized by intermittent fever, exanthema, arthralgia, and cephalea (1,2,4).

Standard case definition of meningococal meningitis and meningococcemia

- *Suspected case of acute meningitis:* Sudden Onset of fever (>38.5ºC rectal or 38ºC axillary) with stiff neck. In patients under one year of age, a suspected case of meningitis occurs when fever is accompanied by a bulging fontanelle.
- *Probable case of bacterial meningitis:* Suspected case of acute meningitis as defined above, with turbid CSF.
- *Probable case of meningococcal meningitis:* Suspected case of either acute or bacterial meningitis as defined above, with Gram stain showing Gram negative diplococcus, or ongoing epidemic, or petechial or purpural rash.
- *Confirmed case:* Suspected or probable case as defined above, with either positive

CSF antigen detection for *N. meningitides*, or positive culture of CSF or blood with identification of N. meningitides

- This case definition allows the detection of cases of meningococcal septicemia

Often the only diagnosis can be made in the dispensaries (peripheral level of health care)

Diagnose in health center where Lumbar Puncture and CSF examination are feasible (intermediate level)

Standard case definition of meningococcemia

Probable: Sudden onset of fever (.38.50C rectal or 380C axillary) with or without shock and one of the following: (*i*) Petechial rash; (*ii*) Gram staining showing Gram negative diplococci.

Confirmed: Probable case and demonstration of *N. meningitidis* or antigen in blood and/or CSF

Diagnosis

Diagnosis of meningococcal meningitis is based upon analysis of cerebrospinal fluid (*Table I*). The adequate medium is Mueller-Hinton or GC enriched with supplement, which have replaced agar chocolate medium. Gram stain of the cerebrospinal fluid is an important test for prompt and accurate identification of *N. meningitidis*(1,2). Commercial kits are available to detect the polysaccharide antigen in cerebrospinal fluid are also very useful for preliminary diagnosis of meningococcal disease, including sero-group identification. False negative results may occur, particularly when serogroup B is involved. Currently, testing is performed with the polymerase chain reaction (PCR) in cerebrospinal samples, to identify the sero-group, with the advantage of not requiring live organisms to perform the test with a sensitivity and specificity greater than 90%. In addition to cerebrospinal fluid abnormalities, one may find high white cell counts with an increased number of polymorphonuclear cells. When severe purpura occurs, it is usually associated with systemic intravascular co-agulation. Blood cultures are frequently positive. When purpuric lesions occur, direct microscopic observation and culture of tissue specimens or pus may provide the diagnosis (1,2).

TABLE I– *Cerebrospinal Fluid Characteristics in Meningococcal meningitis*

Macroscopic characteristics: murky or purulent.	
WBC count:	>1000 cells/mm^3 with over 80% polymorphonuclears.
Proteins:	>80 g/L
Glucose:	<0.4 g/L
Gram stain:	Gram negative intracellular diplococci in 80% of untreated cases.

Differential diagnosis of meningococcal disease mainly has to exclude other bacterial meningitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* (20). Meningococcemia is hard to tell apart from other acute febrile illnesses, particularly in the absence of purpuric exanthema. However, the presence of fever, purpura, and shock strongly suggests a diagnosis of meningococcal disease.

Treatment

At the beginning of the 20th century, mortality from meningococcal disease was 70%. The introduction of IV fluid therapy and sulfas caused a reduction in the case-fatality rates of this disease. However, even with the use of adequate supportive care and antibiotics, case fatality rates of between 9 and 12% have remained stable in the past 20 years. The case fatality rate of meningococcemia is as high of 50(1,2). The patient must be admitted

to a hospital or clinic for diagnosis and treatment. Infectivity of patients is moderate and fades away soon after antimicrobial therapy; thus, isolation of the patient is not considered necessary after the initial 24-48 h. Antibiotics, include penicillin G, beta lactamic derivatives, ampicillin sulbactam combinations, amoxicillin, clavulanic acid, and cephalosporines like cefotaxime, ceftriaxone, cefuroxime and cefepime (*Table II*).

Third generation cephalosporines like ceftriaxone and cefotaxime are excellent but costly alternatives. Nevertheless, ceftriaxone frequently becomes the ideal alternative, since it can be administered once a day for periods as short as two days. The high morbidity and mortality rates associated with meningococcal disease, even in patients who are given appropriate antimicrobial therapy, suggest that some anti-inflammatory therapies may help to improve clinical prognosis. It has been estimated that 11 to 19% of meningococcal disease survivors are left with sequel like deafness, neurological abnormalities, and loss of a limb in cases of meningococcemia. Some studies have suggested that routine utilization of corticosteroids like dexamethasone may be useful prior to antimicrobial therapy to diminish meningeal inflammation caused by bacterial death; however, its use has not been established as standard therapy. Traditionally, two clinical situations are acknowledged to require the use of steroids to prevent sequel and probably to improve survival of patients; one is neurological damage resulting from meningeal inflammation identified at the moment of diagnosis, the other is the presence of a Gram stain positive for *N. meningitidis* (20-22).

TABLE II–*Antibiotics for Treating Meningococcal Disease*

Antibiotics	Dose*
Penicillin G	400,000 u/kg
Ampi/Amoxicillin	250 mg/kg
Chloramphenicol	100 mg/kg
Cefotaxime	250 mg/kg
Ceftriaxone	100 mg/kg

* Intravenously for 7 days

Treatment is recommended for seven days in most countries. Intensive care by properly trained personnel is recommended for patients with severe disease, septic shock, fulminant purpura, meningitis, and coma(2).

Control and prevention measures

Meningococcal disease is potentially preventable by vaccination and chemoprophylaxis under specific circumstances. In some countries with high endemic rates of meningococcal disease vaccines against it are included within universal vaccination programs. Available vaccines should be used to control outbreaks in different regions of the world(23-30,16,31-33). It has been estimated that control of transmission with vaccine immunoprophylaxis to protect the population against virulent strains of N. meningitidis clonal groups would eliminate about 75% of endemic disease and the majority of epidemic outbreaks(5).

Chemoprophylaxis

The purpose of chemoprophylaxis is to prevent the occurrence of secondary cases by eliminating carriers with *Neisseria meningitidis*. Chemoprophylaxis is an important control measure; however, it has limited effectiveness and its use should be restricted to special circumstances. These circumstances include close contacts of cases, such as institutionalized subjects, those who share quarters (households, schools, military stations, jails, and nurseries), as well as subjects who have been in contact with oral

fluids of patients, either by kissing or by sharing food or beverages. Patients with meningococcal infection treated in a hospital or clinic, who has received an antibiotic, which does not eliminate the carrier state (penicillins or chloramphenicol), should receive chemo-prophylaxis with an effective antibiotic (ciprofloxacin, rifampicin, or ceftriaxone) upon hospital discharge. Massive chemo-prophylaxis is not recommended by any health authority during outbreaks(1,2).

Since the risk of secondary cases among close contacts of the index case is very high during the first day of infection, chemoprophylaxis should be started early, preferably within 24 hours from initial contact (*Table III*). Secondary cases usually occur within 10 days after exposure. Close observation of this group of subjects is recommended for at least 10 days to ensure administration of appropriate and timely therapy of secondary cases, which may occur even in the presence of adequate chemo-prophylaxis(1,5). Chemoprophylaxis is effective only when administered together with systemic antibiotic therapy. Among potentially useful antibiotics, the most fre-quently used is rifampicin(1,2). Nevertheless, utilization of oral ciprofloxacin as a single dose is a useful alternative, since in addition to easier adherence it is as effective as rifampicin. Rifampicin use has some disadvantages; it is the main drug for tuberculosis control and its excessive utilization may result in un-acceptably high rates of microbial resistance. Utilization of ciprofloxacin in childhood, particularly when given as a single dose, has not been associated with toxicity. This makes it suitable for chemoprophylaxis in children (33). Also, ceftriaxone given intramuscularly is a third alternative that has great effectiveness, but at a high cost (2).

TABLE III–*Chemoprophylaxis Schemes Against Meningococcal Disease*

Drug	Age group	Dose
Ciprofloxacin	Children	20 mg/kg, single dose
	Adult	500 mg single dose
Rifampicin	< 1month	5 mg/kg, twice a day for 2 days
	> 1 month	10 mg/kg, twice a day for 2 days
	Adults	600 mg single dose
Ceftriaxone	< 15 years	125 mg, single dose, intramuscularly
	> 15 years	250 mg, single dose, intramuscularly

Vaccination

Serogroup specific polysaccharides, with the exception of serogroup B, are the basis for development of vaccines against meningo-coccal infection(16,23-29). Capsular poly-saccharide vaccines against serogroups A, C, Y and W-135 have shown 75 to 90% efficacy in adults and school age children, and lower efficacy in children aged under two years. Development of vaccines against meningo-coccal infection, stimulation of herd immunity by reducing the proportion of carriers, and the acquisition of virulent meningococcal strains among adolescents and adults have been considered basic strategies to control this devastating disease(1,2).

Several studies show that protective antibody levels may not persist in the majority of children immunized with vaccine C beyond two years, while the concentration of anti-C antibodies in adults persists for longer. Repeated immunization with vaccine C before 18 months of age in children who were vaccinated at three months of age showed greater efficacy(16).

The main culprits of meningococcal disease in the world are serogroups B, A, C, Y

and W135. Several vaccine trials have been conducted against the serogroup B. Polysaccharide B also has a weak immunogenicity in natural infections; frequently, it is not possible to show the presence of anti-B antibodies during or after meningococcal disease or in nasopharyngeal carriers of meningococcus B(1). To increase the immunogenicity, modifications of polysaccharide B, by covalent bonding with tetanic toxoid, iron-binding protein vaccines, and pilli and IgA protease vaccines. The only vaccine currently approved is the Cuban anti-meningococcal BC vaccine, which has an efficacy of 83%, as shown by a phase II placebo vaccine study conducted in Cuba, eight years after the epidemic(32,33).

The use of conjugate vaccines that induce cellular immunologic memory is probably the best option for immunoprophylaxis, since it provides adequate levels of protection The only conjugate vaccine available is that against serogroup C (Wyeth), widely used in the United Kingdom(23).

Vaccination need during outbreak/ epidemic

In India routine immunization with meningococcal vaccine is not recommended. It is routinely recommended for high risk children *e.g.*, anatomic or functional asplenia, immunodeficiency states, sickle cell disease *etc.* However, in an outbreak/epidemic situation if the primary attack rate of *Meningococcal meningitis*/meningococcemia exceeds 10 cases per 100,000 population, then mass vaccination to the age specific population group is targeted. In such situation, meningococcal A vaccine can be given as early as 3 months of age. If the polysaccharide vaccine is administered before the age of 2 years than 2 doses at 3 months interval is recommended during an outbreak.

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