

Clinical and Epidemiological Implications of Meningococcal Disease

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Abstract

Meningococcal disease is caused by *Neisseria meningitidis* and is an infection which rapidly progresses to multiorgan failure. It was a major killer in the epidemics of the 1980's in the United States. With the advent of *Haemophilus influenzae* type b (Hib) vaccine in the 1990s, *Streptococcus pneumoniae* and *Neisseria meningitidis* have become the most common causes of bacterial meningitis in the United States. This article provides a review of the meningococcal illness and attempts to update current information regarding the same. ©

INTRODUCTION

As New Delhi goes through the meningococcal epidemic, we are reminded of the devastating force of this disease. Though meningococcal disease is not unheard of in India, this ensuing epidemic is a first in recent years. The last outbreak hit India in 1985 with 6133 cases and 799 (13%) deaths. With the advent of *Haemophilus influenzae* type b (Hib) vaccine in the 1990s, *Streptococcus pneumoniae* and *Neisseria meningitidis* have become the most common causes of bacterial meningitis in the United States. The mortality of meningococcal meningitis in spite of appropriate antibiotic therapy is about 10-15%. It causes both endemic and epidemic disease and peaks in late winter to early spring.^{1,2}

Neisseria meningitidis (the meningococcus) causes disease septicemia (*meningococemia*) or meningitis, which occurs alone or concomitantly with meningococemia. The bacteria are transmitted by respiratory or oral secretions via a nasopharyngeal carrier. The disease is spread from person-to-person and has no known animal reservoir besides humans. The disease is not contracted with casual contact.^{1,2} Populations at increased risk for contracting the disease are discussed later. A current of review of literature is hereby presented.

Epidemiology

N. meningitidis is the only bacterium that causes epidemic bacterial meningitis. The worldwide distribution of meningococcal disease has an incidence

of 0.5-5 per 100,000. African countries have experienced the largest epidemics. A stretch of sub-Saharan Africa, termed the "meningitis belt" sees an inordinate number of meningococcal cases each year. For the last 10 years, epidemic meningococcal disease has caused over 700,000 cases, with a mortality rate of 10%. This area spans from West Africa in Senegal to the east in Ethiopia and encompasses part or all of 15 countries. The cases peak in the dry months, which occur from December to June, and drop off as soon as the rainy season begins. In the 2005 season alone, there have already been outbreaks in Sudan and Chad involving primarily serogroups W-135 and A, respectively. The Philippines have also seen an outbreak starting in October with 98 cases and 23 deaths to date. Serogroup A has been responsible for the majority of epidemic cases, but in recent years there has been an emergence of W-135 as a cause of epidemic disease. Saudi Arabia saw the first outbreak of W-135 in 2000 and 2001 when several hundred pilgrims attending the Hajj in Mecca were affected. In 2002, the first large scale epidemic of W-135 occurred in Burkina Faso, with over 13,000 cases and 1400 deaths, of which W-135 was responsible for 84% of the cases.^{1,2}

Infants and young children are at an increased risk for endemic disease. Other populations at risk include those subjected to overcrowding (e.g. refugees), military recruits, college freshman that reside in dormitories, laboratory workers that handle *N. meningitidis* in solution that may become aerosolized, those exposed to active or passive tobacco smoke, and persons with concomitant respiratory infections. It is estimated that 5-10% of the general population may be asymptomatic carriers though it may be as high as 50% in military recruits and 95% during serogroup A epidemics. The bacteria reside in the mucosal membrane of the nasopharynx among the normal oral flora, which usually

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causes no harm. Most cases of meningococcal disease are acquired from an exposure to asymptomatic carrier. Meningococcal disease relies on the asymptomatic carriers for dissemination. Epidemics occur in favorable conditions, such as waning immunity of a particular subtype within a population, overcrowding, and certain climatic conditions, such as dry seasons, prolonged drought, and dust storms.^{1,2}

There are certain criteria used to assess the level of confidence in suspected meningococcal cases. *Confirmed* cases are those in which *N. meningitidis* has been isolated from typically sterile body fluid, such as blood or cerebral spinal fluid (CSF). *Presumptive* cases are made on the basis of visualization of Gram-negative diplococci in sterile body fluid. *Probable* cases are those with clinical illness that is characteristic of meningococcal infections plus a positive antigen test without a positive culture.²¹ Criteria for a community-based outbreak include an attack rate of at least 10 per 100,000, three or more confirmed or probable case, with less than 3 months between the cases. The cases are also not close contacts and have only a common affiliation.¹

Microbiology

N. meningitidis is a Gram-negative coccus or diplococcus, capsular organism. The species is further subtyped into 12 subgroups, but only A, B, C, W-135, and Y are clinically relevant at the present time. In the U.S., serogroup B accounts for 46% and serogroup C accounts for 45% for invasive meningococcal cases, with the rest caused by W-135, Y, and non-typeable serogroups. Serogroup A is rare in the U.S., whereas it is the main serogroup responsible for meningococcal disease in African and Asian countries. The outbreak in India in 1985 was caused by subgroup A. Though all groups may cause epidemics, serogroups A and C are most closely associated with epidemic meningococcal disease. According to the National Institute of Communicable Diseases (NICD), *N. meningitidis* serogroup A has been confirmed with isolation from cerebrospinal fluid (CSF) in five cases thus far.^{1,2}

Clinical Features

Invasive meningococcal disease often begins with symptoms that are commonly mistaken for common illness, such as influenza. The hallmark of the disease, however, is the abrupt onset of the disease. A history of wellness in the preceding day in a patient that now presents with sudden-onset flu-like symptoms should prompt the practitioner to consider meningococcal disease. This warrants observation and further work-up. The most striking and potentially dangerous aspect of the disease is its rapid progression to death, which can follow in a matter of hours. Most deaths from meningococcal disease occur within 24-48 hours of the onset of symptoms. The average incubation period is four days, with a range of two to 10 days. Meningitis and sepsis are the most common clinical manifestations

of meningococcal disease. In rare cases, *N. meningitidis* can cause urethritis, conjunctivitis, pericarditis, epiglottitis, pneumonia, or arthritis.¹⁻⁴

Meningitis caused by the meningococcus occurs as a result of hematogenous seeding. Classic meningeal symptoms include high fever, headache, stiff neck, and mental status changes. Other associated symptoms are nausea, vomiting, photophobia, confusion, and sleepiness. Infants often present with a less specific clinical picture, thus meningitis is always considered as part of the differential diagnosis in any infant presenting with fever. Neck stiffness, the classic symptom of meningitis, is usually absent in infants. Signs and symptoms in infants with meningitis include fever, slowness, inactivity, irritability, vomiting, and poor feeding. As the disease progresses, seizures may occur.¹⁻⁴ Meningococcal meningitis is indistinguishable from meningitis caused by *H. influenzae* or *S. pneumoniae* based on signs and symptoms alone. The classic triad of fever, neck stiffness, and mental status change is less likely to occur in meningococcal meningitis than pneumococcal meningitis (27% vs. 58%).⁵ Meningococcus usually causes a purulent spinal fluid seen on lumbar puncture (LP).

Meningococemia is somewhat less common than the meningeal infection, but is more fatal. Even with aggressive management, the mortality rate of meningococemia alone is 20%.⁶ The disease involves septicemia, hemorrhagic rash, and rapid circulatory collapse. The purpuric rash—the cardinal feature of meningococemia—is often a late finding with acute nonblanching petechiae (usually greater than 2mm) and purpura. There is a 10-15% chance of serious sequelae following meningococemia, including permanent hearing loss, mental retardation, and loss of a limb. Meningococemia is a medical emergency and should be managed aggressively as it progresses rapidly from purpura fulminans to shock and death.^{3,4}

The dreaded complication, **fulminant meningococemia**, is an end-result of severe perturbation of the coagulation system. The release of endotoxin, a component of lipopolysaccharide (LPS), which is found in Gram-negative cell walls, sets off a cascade of inflammatory reactions that release a multitude of cytokines. The endotoxemia generates coagulation within the intravascular space, causing thrombosis of small vessels and hemorrhagic infarction. The tissue damage often results in necrosis of skin, digits, and distal limbs. Amputations and skin grafting are usually needed once the patient recovers from this catastrophic illness.^{7,8}

Neisserial (meningococcal and gonococcal) infections are more common in patients with component deficiencies in the terminal common complement pathway (C3, C5-C9) and tend to recur. It is recommended that after the first episode of systemic

meningococcal or gonococcal infection, all patients should be screened for total hemolytic complement function (CH50 assay). This would allow for patients with terminal complement deficiencies to undergo prompt evaluation of febrile illnesses, receive the meningococcal vaccine and boosters, and undergo genetic counseling.⁹ Due to the capsule, persons with functional or anatomic asplenia are less able to clear the bacteria and are therefore at increased risk. Immunosuppression secondary to HIV was not shown to have a substantial increased risk for contracting the epidemic serogroup A strain.¹⁰ However, HIV did pose an increased risk for sporadic meningococcal disease.¹¹

Immunoprophylaxis

The polysaccharide vaccines for meningococcal disease have been available for over 30 years. The vaccine covers serogroups A, C, Y, and W-135 in a variety of combinations. The quadrivalent vaccine in the U.S. has had limited recommendations for routine use. Its main indications for use are in the cases of controlling outbreaks, college freshman living in dormitories, patients with terminal complement deficiencies, functional or anatomic asplenia, and laboratory personnel that routinely become exposed to potentially aerosolized *N. meningitidis*. In the U.S., all military recruits receive the quadrivalent A, C, Y, W-135 meningococcal vaccine. Only recently, since the production of a conjugate quadrivalent vaccine, has the U.S. started to recommend routine vaccination of all children 11-12 years old. The conjugate vaccine is only indicated for use in 11-55 years old at this time. Those not meeting the age requirement receive the polysaccharide preparation when indicated. The polysaccharide vaccine is not recommended for children younger than two years—the age group that is at highest risk for endemic disease—because it does not provoke substantial immunity to the vaccine. Though its use is generally restricted to children two years and older, the vaccine may be given as young as 3 months if necessary to elicit protection against serogroup A meningococcal disease over a short time.^{1,2} For children three to 18 months, two doses should be administered three months apart. If children less than four years old are vaccinated, they will need to be re-vaccinated after two to three years if the indication still persists.¹² The main benefit of the vaccine in civilians has been for controlling serogroup C meningococcal outbreaks.

Overseas travelers that may be visiting areas with periodic epidemics or areas that are hyperendemic (e.g. African Meningitis Belt) are recommended to receive the vaccine at least 10 days prior to departure. The Saudi Arabian government now requires proof of vaccination with the tetravalent vaccine against A, C, Y, W-135 at least 10 days prior to departure for all travelers during the annual pilgrimage to the Hajj or Umrah. Proof of vaccine must be less than three years old. The vaccine

does not prevent colonization or transmission of *N. meningitidis*, therefore, it is still possible for travelers returning from areas of epidemic disease to pass on the infection to close contacts.^{1,2}

The polysaccharide vaccine used in adults and children is given as a single 0.5mL dose. After seven to 10 days, protective levels of serum antibodies are observed. The injection may be given at the same time as other vaccinations, but at different sites (i.e. deltoid and buttock). Revaccination after 3-5 years is recommended if the indication persists. Adverse effects are low, with the most common being pain and redness at the site of the injection, which only lasts one to two days. Some patients may experience a transient fever. Contraindications to the vaccine are previous serious reactions (i.e. life-threatening anaphylactic reaction) to the vaccine or a vaccine component. Also, patients with a moderate to severe illness should not be vaccinated. The Centers for Disease Control and Prevention (CDC) does not advise altering the recommendations of meningococcal vaccinations in cases of pregnancy. The vaccine has been found to be safe and efficacious in pregnant women, with antibody level in the baby falling after birth within the first few months.^{1,2}

The limited duration, poor immunogenicity in young children, and high cost of meningococcal conjugate vaccines has challenged the use of vaccine in Africa to control epidemic disease. In 2001, the World Health Organization (WHO) and the Program for Appropriate Technology in Health (PATH) established the Meningitis Vaccine Project with the financial support from the Bill and Melinda Gates Foundation. This 10-year joint venture aims to develop a conjugate meningococcal vaccine that can be instrumental in improving the public health problem in the African meningitis belt.²

When countries are facing meningococcal outbreaks that approach epidemic proportions, they can make a request to the International Coordinating Group (ICG) on Vaccine Provision Epidemic Meningitis Control. The ICG is composed of members from the United Nations, WHO, non-governmental organizations, and the private sector. The ICG was established to ensure that the vaccines were used prudently and without wastage and to coordinate rapid and equal distribution of this potentially limited resource. The ICG also coordinates dispersal of injection materials and oily chloramphenicol to affected areas in need of assistance. The WHO recommends mass vaccination for outbreak control in all districts in an epidemic phase and adjacent districts in an alert phase. When mass inoculation is swiftly implemented, 70% of the cases can be avoided.²

A vaccine against serogroup B has been difficult to produce because of its poor immunogenicity. This is probably because of the likeness serogroup B antigens share with fetal neurocrest cells. A vaccine for serogroup B is estimated to be a least five years away.¹³

Chemoprophylaxis

Antimicrobial chemoprophylaxis for meningococcal disease is the principal method of preventing disease among close contacts in the U.S.. Antimicrobial chemoprophylaxis aims at the eradication of nasopharyngeal carriage of *N. meningitidis*, thus agents used must penetrate nasopharyngeal secretions to be effective. Persons who qualify as being at increased risk for contracting *N. meningitidis* from an index case should receive chemoprophylaxis and patient education. People in the same household, those in direct contact with oral secretions (kissing, mouth-to-mouth resuscitation, endotracheal tube intubation and management, sharing fomites), and day-care center contacts are the only contacts for which chemoprophylaxis is recommended. Chemoprophylaxis should be initiated as soon as possible, preferably within 24 hours of identification of the index case. Prophylactic treatment beyond 14 days after the case is identified is of little or no value. Nasopharyngeal cultures are not useful in determining who should receive prophylaxis and only delays preventative therapy for a potentially deadly disease. It is currently unknown whether previously vaccinated close contacts will benefit from chemoprophylaxis.¹⁻⁴

The drug of choice for meningococcal chemoprophylaxis is rifampin and has been shown to eradicate nasopharyngeal carriage of *N. meningitidis*.¹⁴ For adults, the recommended dose is 600 mg of rifampin given twice a day for two days. For children older than one month old, the recommended dosage is 10mg/kg (max 600mg) given every 12 hours for two days. For infants less than one month old, the recommended dose is 5mg/kg given every 12 hours for two days. Rifampin is contraindicated in pregnancy as it has been shown to have teratogenic effects in pregnancy. A major side effect of rifampin is that it turns body fluids, including urine, sweat, and tears, a reddish-orange color. As such, it may permanently stain contact lenses. Rifampin is also a well-known inducer of the cytochrome p450 enzyme system, subtype 3A. Its effects increase the metabolism of certain medications and hormones. Drugs that are affected by rifampin include coumadin, digoxin, glucocorticoids, seizure medication, and oral contraceptives.^{4,15} Reasonable alternate choices to multi-dose rifampin chemoprophylaxis is the use of single-dose ciprofloxacin or ceftriaxone. Ciprofloxacin can be given as a single oral dose of 500mg. Ciprofloxacin is contraindicated in children less than 18 years old and pregnant or lactating mothers because of the increased risk of cartilage damage. However, an international consensus report has deemed that ciprofloxacin is acceptable for use in children as chemoprophylaxis when no other alternate therapy is available.¹⁶ Ceftriaxone can be administered as a single parenteral dose and offers acceptable efficacy of greater than 97% for eradication of the *N. meningitidis* carrier state.¹⁷ It is given as an

intramuscular injection at 125mg for children less than 12 years old and at 250mg for adults and children older than 12 years old. For children older than 1 year old and adults, ceftriaxone can be mixed with 1% lidocaine to reduce pain since a major side-effect of ceftriaxone is pain. Ceftriaxone also has the benefit of adherence to compliance, since the shot is a highly effective one-time dose. The WHO states that minocycline and spiramycin are also acceptable alternatives for chemoprophylaxis. If meningococcal patients are treated with penicillin or other non-mucosal-penetrating antibiotics, then they too should be treated for nasopharyngeal carriage of *N. meningitidis*.¹⁸ Patients treated with antibiotics for chemoprophylaxis need to be educated about warnings signs of meningococcal infection. Since they are close contacts, they stand at considerable risk over the general population for contracting invasive meningococcal disease and are therefore treated accordingly. However, no prophylactic is completely efficacious and patients should be instructed to receive immediate medical attention with the onset of a febrile illness.

Management

Management of meningococcal disease begins with rapid clinical assessment and differential diagnosis. A lumbar puncture, blood cultures, and a complete blood count (CBC) are routinely performed in the work-up for invasive meningococcal disease. In the setting of a hemodynamically unstable patient or with evidence of increased intracranial pressure it is best to forego the diagnostic LP. An LP is not critical for determining appropriate therapy. If possible, blood for a complete blood count (CBC) and blood culture should be drawn prior to beginning empiric antibiotic therapy in patients with fever and petechiae.³ In emergent settings, urine latex agglutination testing for *N. meningitidis* has been used. This test, however, has is associated with low sensitivity and specificity in serogroup B infections, which cause roughly a third to half of all meningococcal infections in the U.S.¹⁹ A diagnostic study should not prohibit appropriate therapy. Moreover, antibiotics take at least one hour to reach the subarachnoid space, allowing sufficient time for a diagnostic LP. Laboratory values that may aid in diagnosing disseminated intravascular coagulation(DIC) include a prolonged prothrombin time (PT), prolonged activated partial thromboplastin time (aPTT), low fibrinogen, and increased D-dimer.²³

When meningococcal disease is suspected, empiric therapy should be started by the initial physician. Empiric therapy for meningitis consists of a combination of ceftriaxone (which covers most causative agents such as *H. influenzae*, *N. meningitidis*, and *S. pneumoniae*) and vancomycin (which covers the drug-resistant *S. pneumoniae* strains). The use of corticosteroids has been an on-going controversy. Though it has been shown to be beneficial in other causes of meningitis, corticosteroid

use in meningitis caused by *N. meningitidis* has not been proven to change outcomes.²⁰

As stated before, meningococemia is a rapidly progressive and potentially deadly disease that requires expeditious treatment. These patients may often present to outpatient clinics and must be managed appropriately. Once meningococemia is recognized or suspected, prompt transfer to a tertiary care center is essential. Intensive care unit (ICU) management of meningococemia gives the patient an optimal chance for recovery from meningococemia.²¹

Airway, breathing, and circulation should always be part of the initial assessment. Airway and breathing are assisted with supplemental oxygen. Elective intubation with mechanical ventilation may be warranted.²¹

The management of shock is initiated at the first sign of deterioration. Signs of imminent shock include tachycardia, hypotension, poor perfusion, and oliguria. Treatment with normal saline or lactated Ringer's at 20 mL/kg for children and one liter over 20 minutes empirically for larger children and adults is the standard of care. Central venous access is preferred. Fluid overload, a major concern with these patients, may cause cerebral edema. Volume expansion is not always sufficient to maintain adequate blood pressure and perfusion, thus requiring the use of vasopressors, such as dobutamine.^{3,4}

Complications

Purpura fulminans is a consequence of disseminated intravascular coagulation (DIC) where the hemorrhagic purpura become confluent. Though the treatment of DIC is often a source of contention, it is usually treated with fresh frozen plasma, blood, and sometimes platelets.⁴ All blood products contribute to the total volume used in resuscitation. Rapid progression of the purpuric rash, hypotension, shock, coma, and seizures all indicate poor prognostic indicators. Laboratory values that also herald poor outcomes are a white blood cell (WBC) count less than 10,000 per mm³, a CSF WBC less than 100 per mm³, an erythrocyte sedimentation rate (ESR) less than 20 mm/hour, metabolic acidosis (pH less than 7.3), and positive blood cultures.^{3,4} Progression of purpura fulminans leads to Waterhouse-Friderichsen syndrome. This state is characterized by rapid deterioration and vasomotor collapse. Shock occurs from a decrease in intravascular volume and congestive heart failure. Progression of DIC causes hemorrhagic thrombi and arterial embolization, leading to acute renal failure, coma, and acute hemorrhagic necrosis of the adrenal glands.²³

Antibiotic therapy

Most strains of *N. meningitidis* are sensitive to Penicillin G. The recommended dose is Penicillin G 250,000 IU intravenously every six hours for seven days. Cefotaxime, ceftriaxone, and ampicillin are reasonable choices for treating meningococcal disease especially

early in the disease when empiric therapy is used. Under epidemic conditions with limited healthcare facilities, chloramphenicol is the drug of choice. This is long-acting formula given as a single dose has been shown to be effective. The WHO does not recommend isolation; however, most institutions implement respiratory precautions for the first 24 hours after the start of antimicrobial therapy.^{2,4}

Current Research

New treatment modalities for management of sepsis are currently being investigated. The only adjuvant therapy to sepsis licensed in the U.S. is recombinant human activated protein C (rhAPC). This vitamin K-dependent protein displays anticoagulant, fibrinolytic, and anti-inflammatory properties making it attractive for use in sepsis. The therapy was borne from observations from sepsis patients where lower levels of APC corresponded with worse outcomes. The most notable adverse effect, however low, is an increased risk of bleeding, which included intracranial hemorrhage. Randomized control trials are currently ongoing.⁸

CONCLUSION

The vaccine provides no protection for at least 10 days after administration. There is no effective vaccine for *N. meningitidis* serogroup B, which accounts for a significant portion of meningococcal cases. Chemoprophylaxis with antibiotics, such as rifampin, is critical to controlling the extent of outbreaks. Practitioners should have a high index of suspicion, especially during times of epidemic disease, for illnesses with abrupt onset and non-specific symptoms characteristic of early meningococcal infection. Meningococcal disease requires urgent antibiotic therapy and aggressive management of patient deterioration, which is best handled at a tertiary care center.

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Book Review

Practical Approach to Respiratory Diseases with CD ROM

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Clinical and epidemiological features of chronic liver disease among Nov 22, 2014 - disease among the East Kazakhstan residents exposed to 2International School of Public Health, Northern State Medical UniversityÂ Meningococcal disease requires urgent antibiotic therapy and aggressive management of patient deterioration, which is best handled at a tertiary care center. REFERENCES 1. Centers for Disease Control and Prevention (CDC).