



Outbreak of Meningococcal Meningitis

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ARTICLE INFO

Article history:

Received: 23 May 2015;

Received in revised form:

17 July 2016;

Accepted: 22 July 2016;

Keywords

Meningococcal meningitis,

Neisseria meningitidis,

Epidemiology,

Etiology,

Vaccines.

ABSTRACT

Meningococcal disease is a severe illness with high case fatality (5-10%) and frequent sequelae. Meningococcal meningitis is a major cause of morbidity and mortality in the meningitis belt. Meningococcal disease is a major public health challenge in countries of sub-Saharan Africa lying in the meningitis belt. Human infections caused by meningococcal (*Neisseria meningitidis*) remain a serious health problem, infecting 500,000 to 1.2 million people and killing between 50,000 and 135,000 per year worldwide. The causative agent, *Neisseria meningitidis* normally lives in a commensal relationship with humans, colonizing the nasopharynx, and is transmitted between healthy persons by close contact. The most common symptoms are a stiff neck, high fever, sensitivity to light, confusion, headaches and vomiting. Low meningitis thresholds improve timely detection of epidemics. The diagnosis of meningococcal meningitis is confirmed by cerebrospinal fluid pleocytosis, Gram stain, polymerase chain reaction, culture of cerebrospinal fluid. Meningococcal disease can be treated with a number of effective antibiotics. It is important that treatment be started as soon as possible. If meningococcal disease is suspected, antibiotics are given right away. Antibiotics effective for this purpose include rifampicin, ciprofloxacin, ceftriaxone or azithromycin. Currently available meningococcal vaccines include polysaccharide vaccines against serogroups A, C, W135 & Y and newer protein polysaccharide conjugate vaccines against serogroup C. This review covers key aspects of the pathogenesis and management of meningococcal disease, as well as the very recent developments in disease epidemiology, outbreaks, and the evolution of meningococcal immunizations.

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Introduction

Meningococcal disease is a severe illness with high case fatality (5-10%) and frequent sequelae (10-20%) that require lifelong medical attention^[1]. Meningococcal meningitis is a major cause of morbidity and mortality in the meningitis belt of sub-Saharan Africa where it occurs in epidemics every 8-12 years^[2]. Meningococcal meningitis is a bacterial form of meningitis, a serious infection of the meninges that affects the brain and spinal cord. It can cause severe brain damage and is fatal in 50% of cases if untreated^[3]. Human infections caused by meningococcal (*Neisseria meningitidis*) remain a serious health problem, infecting 500,000 to 1.2 million people and killing between 50,000 and 135,000 per year worldwide^[4]. Meningococcal disease is a relatively new disease that was first observed in 1805 in Europe, 1806 in North America, and 1905 in Africa^[5]. From 1 January to 12 May 2015, Niger's Ministry of Public Health notified WHO of 6179 suspected cases of meningococcal meningitis, including 423 deaths. This is a rapidly growing outbreak with some unprecedented features^[6]. Meningococcal disease, also referred to as cerebrospinal meningitis is a contagious bacterial disease caused by the meningococcus (*Neisseria meningitidis*). It is spread by person to person contact through respiratory droplets of infected people^[7]. There are 3 main clinical forms of the disease: the meningial syndrome, the septic form and pneumonia^[8]. The onset of symptoms is sudden and death can follow within hours. In as many as 10-15% of survivors, there are persistent neurological defects, including hearing loss, speech disorders, loss of limbs, mental retardation and paralysis^[9]. Meningococcal meningitis

and septicaemia tends to be more common during winter and early spring^[3]. Most cases occur below age 5 years and particularly during the first year of life. There is also a smaller peak at age 14-19 years. However, about one third of the cases of meningococcal disease occur in adults^[10]. There has been a shift in the age groups affected by invasive meningococcal disease with an increase among the elderly due to serogroup Y and a decrease in adolescents due to serogroup C^[5]. The extended meningitis belt of sub-Saharan Africa, stretching from Senegal in the west to Ethiopia in the east (26 countries), has the highest rates of the disease^[11]. This experiences epidemics during the hot, dry, and windy months from December through April. Because of a lack of affordable conjugate vaccines, African countries in the meningitis belt have adopted a strategy of reactive immunization^[12]. As of January 2015, over 217 million persons have received meningococcal A conjugate vaccine in 15 countries of the African belt^[13]. Between 1 January and 25 April 2015, the Ministry of Public Health of Niger notified WHO of 1543 suspected cases of meningococcal disease, including 147 deaths^[14].

Epidemiology

Many countries suffer from endemic meningococcal disease at an annual attack rate of around 1 to 3 per 100,000 of the population. Some of these countries, mostly in the developing world, suffer from repeated epidemics of meningococcal disease^[15, 16]. In temperate regions the number of cases increases in winter and spring^[3]. Serogroups B and C together account for a large majority of cases in Europe and the Americas. Several local outbreaks due to *Neisseria meningitidis* sero group C have

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been reported in Canada and the United States (1992-93) and in Spain (1995-97) [17]. Major African epidemics are associated with *Neisseria meningitidis* serogroup A [18], which is usually the cause of meningococcal disease in Asia [19]. *N. meningitidis* serogroup A and C outbreaks are occasionally reported to the World Health Organization (WHO) Regional Office in Asia, or to national authorities [20]. Between 1988 and 1997, 704,000 cases and more than 100,000 deaths were reported in Africa, some 20,000 occurring in 1996, the largest epidemic year ever recorded. Between 1998 and 2002, African countries within the meningitis belt reported more than 224,000 new cases of meningococcal disease [17]. In Africa, major epidemics have been occurring over the past 100 years [5]. Most of them have been attributed to sero group A and occurred in the African "meningitis belt", a large area that spans sub Saharan Africa from Senegal in the west to Ethiopia in the east [21, 22]. In 1996 to 1997, the largest epidemic in history swept across the belt, causing over 250 000 cases, an estimated 25 000 deaths, and disability in 50 000 people. Large epidemics recur in the meningitis belt on a regular basis [23]. In Togo, the 1997 meningitis epidemic spread rapidly. Overall annual incidence was 652 cases/ 100000 inhabitants [24]. 48 198 cases reported in 174 districts in Benin, Burkina Faso, the Gambia, Ghana, Mali, Niger, and Togo. These cases were 80.3% of those reported from Africa to WHO during the 1997 epidemic period [25]. Serogroup X meningococcus outbreak in Kenya, An age- and location-matched case-control study for risk factors was done. From December 2005 to April 2006, 82 suspect cases of meningitis were reported [26]. During the 2006–2007 epidemic season, 53 438 suspected cases and 3816 deaths were reported to WHO from 15 African countries [27]. In 2012, an outbreak of *Neisseria meningitidis* serogroup W135 occurred in The Gambia. The attack rate was highest among young children. During Feb. 1 to June 25, 2012, a total of 469 suspected cases were identified, and 114 were confirmed to be serogroup W135. Most (67%) suspected case patients were <5 years of age, and 56% of cases occurred in male patients. The overall case fatality rate was 8% [28]. In Nigeria, all of the 856 and 333 clinically suspected meningitis cases were treated in 2013 and 2014, respectively. Overall attack (AR) and case fatality (CFR) rates were 673/100,000 population and 6.8% in 2013, and 165/100,000 and 10.5% in 2014 [29]. Limited data available on the epidemiology of meningococcal infection in India reveal a low background incidence of disease. There are occasional large epidemics mostly distributed in the drier Northern states [30]. During the 2014 epidemic season, 19 African countries implementing enhanced surveillance reported 11 908 suspected cases including 1146 deaths [13]. From 1 January to 12 May 2015, Niger's Ministry of Public Health notified WHO of 6179 suspected cases of meningococcal meningitis, including 423 deaths. This is a rapidly growing outbreak with some unprecedented features [6].

Etiology

Several different bacteria can cause meningitis. *Neisseria meningitidis* is the one with the potential to cause large epidemics [31]. Twelve serogroups of *Neisseria meningitidis* have been identified [32, 33], Six of which (A, B, C, W135, X and Y) can cause epidemics. Geographic distribution and epidemic capabilities differ according to the serogroup [34]. *Neisseria meningitidis* was first identified as the causative agent of bacterial meningitis by Weichselbaum in 1887 [35]. Meningococcal serogroups A, B, C and Y cause the majority of cases of invasive disease in the US and throughout the world, with epidemics usually caused by serogroups A and C [36]. Serogroup

W causes a small portion of disease, and serogroup A causes disease in developing countries and the meningitis belt of sub-Saharan Africa [37]. Meningococcal disease is caused by the bacterium *Neisseria meningitidis*, also called meningococcus. About 10% of people have this type of bacteria in the back of their nose and throat with no signs or symptoms of disease, called being 'a carrier'. But sometimes *Neisseria meningitidis* bacteria can invade the body causing certain illnesses, which are known as meningococcal disease [15].

Pathogenesis & Transmission

The first step in the pathogenesis of meningococcal disease is attachment of the organism through surface pili to non-ciliated columnar epithelial cells of the nasopharynx [38]. Meningococci can pass through the epithelial cells and enter the blood stream, where they occasionally survive and multiply intravascularly. Progression to severe meningococcal disease can occur very rapidly [39]. This pathogen may also translocate across the blood-meningeal barrier to infect the meninges and cause meningitis. In the blood, meningococci produce a strong inflammatory response with activation of the complement and coagulation cascades [40, 41]. Bacteria are transmitted from person to person through droplets of respiratory or throat secretions [42].

Risk Factors

Certain groups of people are at increased risk for meningococcal disease. For some of these groups, there are recommended vaccines that prevent two of the three major serogroups ("strains") of *Neisseria meningitidis* bacteria [43]. Vaccination is the best way to protect against meningococcal disease. Some risk factors include:

Age: Meningococcal disease is more commonly diagnosed among infants, adolescents and young adults [44]. A vaccine is available and recommended for all 11 through 18 year olds. A vaccine is also available for infants and children 6 weeks through 10 years of age, but it is only routinely recommended for those with certain medical conditions or who are traveling to specific countries [45,46].

Community setting: Infectious diseases tend to spread quickly wherever large groups of people gather together. As a result, first-year college students living in residence halls are at slightly increased risk compared with other persons of the same age. A vaccine is available and recommended for all first-year college students living in a residence hall. However, any college student can receive the vaccine to decrease their chances of getting meningococcal disease [2, 44].

Certain medical conditions: There are certain diseases, medications and surgical procedures that put people at increased risk of meningococcal disease, such as not having a spleen. A vaccine is available and recommended for those with these conditions. Learn more about those with certain medical conditions being at risk [47].

Travel: Travelers to the meningitis belt in sub-Saharan Africa may be at risk for meningococcal disease, particularly during the dry season [2].

Signs & Symptoms

A common outcome of meningococcal infection is meningitis. When caused by *Neisseria meningitidis* bacteria it is known as meningococcal meningitis. When someone has meningococcal meningitis, the protective membranes covering their brain and spinal cord, known as the meninges, become infected and swell [48]. The most common symptoms are a stiff neck, high fever, sensitivity to light, confusion, headaches and vomiting [4, 45]. The symptoms of meningococcal meningitis can appear quickly or over several days. Typically they develop within 3-7 days after exposure [49]. In newborns and infants, the

classic symptoms of fever, headache, and neck stiffness may be absent or difficult to notice. The infant may appear to be slow or inactive, irritable, vomiting or feeding poorly. In young children, doctors may also look at the child's reflexes, which can also be a sign of meningitis^[50]. Meningococcal meningitis is very serious and can be fatal. In fatal cases, deaths can occur in as little as a few hours. In non-fatal cases, permanent disabilities can include hearing loss and brain damage^[51].

Diagnosis

The diagnosis of meningococcal meningitis is confirmed by cerebrospinal fluid pleocytosis, Gram stain, polymerase chain reaction, culture of cerebrospinal fluid, or cultures of blood or skin lesions^[4, 45]. Early diagnosis and treatment are very important^[25]. If meningococcal disease is suspected, samples of blood or cerebrospinal fluid are collected and sent to the laboratory for testing^[42]. It is important to know if it is meningococcal disease because the severity of illness and the treatment will change depending on the cause. In the case of meningococcal disease, antibiotics can help prevent severe illness and reduce the chances a close contact will also develop disease^[15]. If *Neisseria meningitidis* bacteria are present, they can be grown (cultured). Growing the bacteria in the laboratory is important for confirming the presence of bacteria, identifying the specific type of bacteria that is causing the infection, and deciding which antibiotic will work best. Other tests can sometimes detect and identify the bacteria if the cultures do not^[52]. Methods based on rapid polymerase chain reaction (PCR) can complement standard laboratory procedures as they are less affected by prior antibiotic therapy and these methods are being used increasingly^[53, 54]. Evaluate dipstick rapid diagnostic tests (RDTs) for meningococcal meningitis in basic health facilities^[55]. Diagnosis of bacterial meningitis is based on identification of the pathogen in the cerebrospinal fluid (CSF), obtained by lumbar puncture, using a combination of macroscopic, microscopic and culture or PCR techniques^[56]. For a macroscopic examination, samples are checked for clarity, cloudiness and the presence of blood. Microscopy includes white blood cell (WBC) count and Gram stain. Intracellular Gram-negative diplococci on Gram stain indicate the presence of meningococci, but this technique cannot confirm the serogroup(s) involved. In addition, PCR is often performed to enhance confirmatory results^[57].

Treatment

Meningococcal disease can be treated with a number of effective antibiotics. It is important that treatment be started as soon as possible. If meningococcal disease is suspected, antibiotics are given right away. Antibiotics effective for this purpose include rifampicin, ciprofloxacin, ceftriaxone or azithromycin^[58]. Once the diagnosis is confirmed^[59], treatment can be changed to intravenous penicillin G. Alternatively, ceftriaxone may be used for the entire duration of therapy owing to ease of dosing and reports of decreased susceptibility to penicillin in several countries^[60, 61]. A single dose of long-acting chloramphenicol or ceftriaxone is used for the treatment of epidemic meningococcal meningitis in sub-Saharan Africa^[62].

Vaccination

There is a vaccine for the bacteria that cause meningococcal disease. However, available vaccines do not cover all serogroups ("strains") of *Neisseria meningitidis* bacteria. Like with any vaccine, meningococcal vaccines are not 100% effective. This means that even if you have been vaccinated, there is still a chance you can develop a meningococcal infection^[63-65]. MenAfriVac, a safe, immunogenic and affordable conjugate vaccine was developed especially to eliminate NmA epidemics in the

meningitis belt^[7]. The PsA-TT vaccine elicited a stronger response to group A antibody than the PsACWY vaccine^[66]. Currently available meningococcal vaccines include polysaccharide vaccines against serogroups A, C, W135 & Y and newer protein polysaccharide conjugate vaccines against serogroup C^[1, 67]. Several types of vaccine are available: polysaccharide vaccines-available in either bivalent (groups A and C), trivalent (groups A, C and W135), or tetravalent (groups A, C, W135 and Y) forms; and conjugate vaccines against group A and group C and tetravalent vaccines against groups A, C, W135 and Y^[68, 69]. The 4CMenB vaccine, invented through the process of reverse vaccinology, and studied extensively for its immunogenicity and safety in infants, adolescents and adults, holds the potential to help decrease further the global burden of IMD (invasive meningococcal disease)^[70]. Meningococcal vaccines routinely used in the United States protect against most types of meningococcal disease, but they do not prevent all cases. There are two kinds of vaccines against *Neisseria meningitidis* bacteria available in the United States: meningococcal polysaccharide vaccine (Menomune®) and meningococcal conjugate vaccine (Menactra®, Menveo® and MenHibrix®)^[71, 72].

Conclusion

Meningococcal meningitis is a major cause of morbidity and mortality in the meningitis belt of sub-Saharan Africa where it occurs in epidemics every 8-12 years. Meningococcal disease is spread by person to person contact through respiratory droplets of infected people. Meningococcal meningitis and septicaemia tends to be more common during winter and early spring. Most cases occur below age 5 years and particularly during the first year of life. In newborns and infants, the classic symptoms of fever, headache, and neck stiffness may be absent or difficult to notice. Several different bacteria can cause meningitis. *Neisseria meningitidis* is the one with the potential to cause large epidemics. Diagnosis of bacterial meningitis is based on identification of the pathogen in the cerebrospinal fluid (CSF), obtained by lumbar puncture, using a combination of macroscopic, microscopic and culture or PCR techniques. Early diagnosis and treatment are very important. Meningococcal disease can be treated with a number of effective antibiotics. Vaccination is the best way to protect against meningococcal disease.

Acknowledgements

The authors reported no conflict of interest. The authors alone are responsible for the content and writing of the paper and no funding has been received on this work. Ethical Approval was not required.

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