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Invasive Meningococcal Disease in the 21st Century—An Update for the Clinician

Rachel Dwilow · Sergio Fanella

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Abstract *Neisseria meningitidis* is a gram-negative diplococcus, for which humans are the only reservoir. While colonization is common, invasive meningococcal disease in the form of meningitis or bacteremia can be devastating and potentially fatal. Certain populations are at higher risk for disease including infants, adolescents, those with asplenia or complement deficiencies, and potentially those with human immunodeficiency virus (HIV) infection. Use of conjugate meningococcal vaccines has impacted disease epidemiology in both high- and low-income countries. Outbreaks of serogroup B disease at university campuses have drawn further attention to the recent development of a novel serogroup B vaccine now approved in many countries. 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.

Keywords *Neisseria meningitidis* · Invasive meningococcal disease · Reverse vaccinology · Outbreaks · Conjugate immunizations

Introduction

The first description of the clinical presentation of invasive meningococcal disease (IMD) occurred over 200 years ago and still is of concern in the twenty-first century. Of all *N. meningitidis* serogroups identified, five cause the majority of IMD (A, B, C, Y, W135); however, epidemiology can vary by region and over time. This review will cover an overview of IMD issues relevant to clinicians, but will also focus on the newest developments in the area of disease epidemiology, including outbreaks at major universities in the United States, as well as major developments in the long-awaited goal of an effective serogroup B meningococcal vaccine.

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R. Dwilow · S. Fanella (✉)
Department of Pediatrics and Child Health, College of Medicine, University of Manitoba, Room 530B, Basic Medical Sciences Building, 745 Bannatyne Avenue, Winnipeg, MB, Canada R3E 0J9
e-mail: Sergio.Fanella@med.umanitoba.ca

R. Dwilow
e-mail: rdwilow@exchange.hsc.mb.ca

Epidemiology

Invasive meningococcal disease can occur as endemic disease with sporadic cases, or epidemics of IMD with outbreaks of varying size and duration. The two main peaks of IMD incidence occur in infants under 1 year of age, and again in teenagers and young adults. Lack of bactericidal antibodies following waning of maternal levels is the main factor for infants, while adolescents have high rates of nasopharyngeal colonization [1]. Rates of IMD can increase in older age groups during outbreaks and epidemics, and can be associated with groups and settings where crowding and close contact are seen, such as schools, university dormitories, and barracks [1]. Other individuals at higher risk for IMD include those with certain deficiencies in the complement system or asplenia.

The incidence of endemic IMD in developed regions such as North America, Europe, and Australia has been historically low, with overall rates ranging from 0.3 to above 3.0 cases per 100,000 population, with a predominance of serogroups C and B [2, 3]. The annual incidence rate in Canada is roughly 1.0 per 100,000 population [4]. An active surveillance program (IMPACT), which spans 12 tertiary care centers and covering over half of the Canadian population, recently examined the IMD burden following implementation of universal meningococcal serogroup C immunization programs [5]. The

incidence was highest with serogroup B (0.20 per 100,000 in 2009), with the greatest age-specific incidence in children under 1 year of age (6.16 per 100,000 in 2009). Adolescents had the next highest incidence rate. This mirrors closely the experience in the United States, as demonstrated in a review of changes of IMD following implementation of quadrivalent conjugate immunization programs [6]. The Active Bacterial Core surveillance (ABC) network captures approximately 13 % of the US population. From 1998 to 2007, the average annual incidence rate was 0.55 cases per 100,000 population, but a 64.1 % drop in the annual incidence of meningococcal disease occurred, with a rate of 0.33 cases per 100,000 population reported by 2007. By age group, the highest rates were in infants <1 year old (5.38 per 100,000), children 1–4 years old (1.4 per 100,000), and in adolescents 15–24 years old (0.78 per 100,000). Overall, 39 % of isolates were serogroup B, followed by Y (30 %) and C (25 %).

There is a stark contrast in incidence in developing countries. The "*meningitis belt*" made up of several sub-Saharan nations has the highest reported rates of endemic disease, along with epidemics that occur every 5–12 years, generally during the dry season [7, 8]. While endemic disease rates are several fold greater than in developed areas, rates that occur during epidemics can approach and exceed 1 % (1000 per 100,000 population). Low nighttime temperatures, humidity, dust, and wind are thought to play role [9]. Most IMD in sub-Saharan Africa has been serogroup A, but within the last few decades, large epidemics of serogroup W135 have occurred across the belt, associated with pilgrims from the Hajj [10, 11]. A large outbreak of W135 in The Gambia identified an incidence of 1312 cases per 100,000 population in children <1 year old, and associated risk factors of male gender, contact with meningitis cases, and concurrent respiratory illness [12]. This followed regional introduction of a serogroup A conjugate vaccine program in 2010.

Increased risk for IMD among university students has received recent attention with outbreaks of serogroup B disease at several, large institutions. A prolonged outbreak at a university in Ohio spanned three academic years, with 10 of 13 cases caused by serogroup B [13••]. Risk factors for IMD included Greek Society membership, >1 kissing partner, and bar attendance. While chemoprophylaxis was used, a serogroup B-specific immunization was not available.

More recently, two separate serogroup B outbreaks demonstrated the potential impact of meningococcal B immunization on individual serogroup B outbreak epidemiology. In the spring of 2013, an outbreak of serotype ST409 associated with the Princeton University identified nine cases of IMD, with at least one fatality [14]. As part of the response from the CDC and public health, the Food and Drug Administration allowed the use of meningococcal serogroup B vaccine for all undergraduates through an Investigational New Drug (IND) application, with initial immunization clinics in December 2013 with second doses 2 months later [15]. No additional cases were identified after the program began. A separate, distinct outbreak of serogroup B occurred at the University of California, Santa Barbara in November 2013, with four cases of IMD due to serotype ST32 [16]. In addition to chemoprophylaxis and cancelling of some group events, meningococcal B vaccine was offered to all undergraduate students through another IND application, with initial clinics in February 2014.

Microbiology and Pathogenesis

Neisseria meningitidis appears as a gram-negative coccus, generally oriented in pairs (diplococcus). The two primary members of the genus *Neisseria* implicated in significant human diseases are *N. meningitidis* and *Neisseria gonorrhea* [17, 18]. Many species of *Neisseria* inhabit the nasopharynx as commensals, including *N. meningitidis*.

N. meningitidis has outer and inner membranes surrounding a layer of peptidoglycan. The outer membrane contains important virulence factors including lipopolysaccharide (LPS) and outer membrane proteins (OMPs), which function as porins. Other OMPs enhance adherence and invasion [19]. Pili are also present on meningococci and play a key role in the process of adherence, colonization, and subsequent invasion. Recent in vitro work has identified a host cell surface receptor critical in the adhesion of pathogenic meningococci to endothelial cells [20]. One of the most important virulence factors for invasive meningococcal isolates is the presence of an outer polysaccharide capsule. The capsule contributes to the fitness of invasive isolates through inhibition of phagocytosis, but also in mitigating meningococcus' susceptibility to drying. Differences exist between capsular polysaccharides for the basis for determining serogroup status of IMD isolates. Thirteen different serogroups have been identified based on capsular typing, with a handful responsible for the bulk of cases of IMD (A, B, C, Y, W135, and X) [21]. Variations in porins and other OMPs can also be used to further delineate meningococcal isolates into serotypes for epidemiologic purposes, as specific antibody responses can be identified [22, 23]. Having paved the way for the development of novel meningococcal B vaccines, the complete genomes of some meningococcal isolates have been sequenced, and this approach will likely provide additional epidemiologic information in the future [24–26].

Specific mechanisms responsible for the process of invasion and subsequent disease are not fully understood. Similar to other invasive bacterial diseases, a minimum sequence of events must occur. An initial exposure to *N. meningitidis* must occur in the form of respiratory droplet contact or direct contact (e.g., sharing cigarettes). The only naturally occurring reservoir for meningococci is the human nasopharynx; however, the vast majority of isolates will be non-pathogenic

strains [27]. Exposure and subsequent colonization is enhanced in crowded settings, such as university dormitories, military barracks, and other institutional settings with some carriage rates exceeding 50 % of individuals [28, 29]. This is in contrast to carriage rates of ~10 % across the general population [30]. Individuals can have stable carriage, often of a single clone, for many months [28]. Damage to local epithelial cells and effects on local immunity from tobacco smoke or viral infections enhance colonization risk [31]. With an appropriate humoral immune response, invasive disease is prevented. However, if antibody is suboptimal, invasion and spread will occur, with penetration of the mucosal epithelium through phagocytotic vacuoles and subsequent bacteremia [32]. Once in the circulation, meningococci utilize a spectrum of virulence factors to evade host immune responses, including the capsule, IgA proteases, transferrin binding proteins, and surface blebs containing LPS which function as an endotoxin [33]. Release of endotoxin promotes a cascade of pro-inflammatory cytokines, especially TNF-α, IL-1, IL-6, and Il-8. These mediators lead to the downstream effects of endothelial damage, capillary leak, a procoagulant state, and microthrombi formation.

Clinical Presentation

Meningococcal infection may present in a number of ways, ranging from a non-localized febrile illness to fulminant meningitis and/or septicemia [18, 34, 35]. The most common and severe manifestations of IMD are meningitis and septicemia (meningococcemia). Some patients can have a mixed clinical picture of meningitis and meningococcemia.

Studies examining the prevalence of occult bacteremia in febrile, non-toxic children have found evidence of *N. meningitidis* bacteremia presenting with no apparent focus of infection [36, 37]. No unique characteristics or laboratory parameters are able to distinguish those with unsuspected, blood culture positive meningococcal disease from controls. A small proportion of children with unsuspected meningococcal disease spontaneously clear the bacteremia; however, a larger proportion develop complications without antibiotics [37].

The most widely recognized feature of IMD is the rapidly progressive, purpuric rash, often starting on the lower extremities. Most patients have very non-specific symptoms during the evolution of meningococcal meningitis or sepsis [38, 39]. Generally, younger children have a more rapid progression to symptoms associated with sepsis or meningitis than older children by several hours.

Meningococcal meningitis shares similar features as other causes of acute bacterial meningitis [34, 38–40]. Typically, young infants will have non-specific signs such as irritability or lethargy. Older children, teens, and adults are more likely to develop the typical signs and symptoms associated with bacterial meningitis such as vomiting, headache, photophobia, agitation, decreased level of consciousness, and meningismus. Unlike meningitis secondary to *Streptococcus pneumoniae* or *Haemophilus influenzae*, meningococcal meningitis is less likely to present with focal neurological signs and/or seizures [35]. Reported rates of neurologic sequelae vary but are generally lower than in pneumococcal meningitis. Neurologic sequelae commonly reported in survivors of meningococcal meningitis include sensorineural hearing loss, spasticity, seizures, attention disturbances, and intellectual disability [33]. Meningococcal meningitis results in lower rates of morbidity and mortality than meningococcemia [40, 41]. Mortality rates vary from 5 to 18 % [38].

The classic hemorrhagic rash associated with meningococcemia generally occurs following non-specific symptoms. A variety of skin lesions have been reported in patients with meningococcemia including macules, maculopapules, urticaria, petechiae, purpura, or ecchymoses [18, 34, 42]. They are prominent on the extremities but are also seen on the mucous membranes and sclera. A significant proportion of patients with meningococcemia will not have any rash. Meningococcemia is characterized by severe and persistent shock, leading to circulatory collapse and severe coagulopathy. Multi-organ dysfunction and failure may develop. Reported mortality rates vary, but can range from 20 to 80 % [33]. Complications resulting from this clinical syndrome include skin necrosis, ischemia, and infarction of digits or limbs requiring amputation [35, 42].

Chronic meningococcemia is another recognized clinical syndrome and described as recurrent attacks of fever with arthralgia/arthritis and rash (purpura, petechiae, or maculopapular) [43, 44]. The definitive diagnosis is made by isolating *N. meningitidis* by blood culture during a febrile episode, but multiple blood cultures may be required to isolate the organism. This clinical syndrome is rarely seen, but about 90 % of reported cases occur in adults. The prognosis is more favorable than other forms of IMD.

Diagnosis

The traditional method of confirming IMD is by direct detection of either gram-negative diplococci on gram stain or isolation of *N. meningitidis* from sterile body fluids, such as cerebral spinal fluid (CSF) or blood [35, 43]. In patients who have not received antibiotics prior to sampling, blood cultures have only been reported to be positive in 40–75 % of cases suspicious for meningococcemia. Spinal fluid cultures are positive in up to 90 % of cases later diagnosed as meningitis [18]. When antibiotics are administered prior to sampling, blood cultures sterilize rapidly, in as little as 6 h [45]. Prior

administration of antibiotics before lumbar puncture reduces the rate of positive CSF culture to 50 % [18].

To overcome the limitations of traditional culture techniques as well as rapid sterilization of cultures with antibiotics prior to sampling, several additional methods have been used. Latex agglutination testing to identify meningococcal antigen from sterile fluids was more widely used in the past. Limitations of this test include poor overall sensitivity and specificity, poor sensitivity for certain serogroups, and inability to identify certain serogroups prohibiting its usefulness as a routine test [46]. The advent of polymerase chain reaction (PCR) methods to detect meningococcal DNA in body fluids has resulted in the confirmation of more cases of IMD as well as overcoming some of the problems seen with latex agglutination testing [43]. In comparison to traditional culture methods, real-time PCR has a higher sensitivity, specificity, negative predictive value, and positive predictive value. It is useful in situations where antibiotics have been given prior to testing. It can also determine subtypes that were previously untypeable [45]. However, this method may not be available at all centers, and it may be more costly, prohibiting its routine use.

For whole blood, real-time PCR testing is supported by some experts when initial testing is sent on presentation (if it is available). Due to the lack of high-quality evidence supporting routine use of CSF PCR for meningococcus, it has been suggested that this testing be reserved for when microscopy and culture have failed to identify an organism. Testing of skin lesions for meningococcus is of low yield. Throat swabs should not be used to diagnose IMD as a significant proportion will have asymptomatic colonization of the nasopharynx with nonpathogenic strains that do not reflect the etiology of a case of IMD [47].

Treatment

Management in many countries includes administration of pre-hospital antibiotics in an attempt to reduce mortality secondary to the rapid proliferation of bacteria and endotoxin production [35, 48].

A third-generation cephalosporin, specifically cefotaxime or ceftriaxone, should be used. Once *N. meningitidis* has been isolated from a sterile fluid, appropriate treatment regimens include intravenous penicillin G, ceftriaxone, or cefotaxime. The duration of therapy that is generally recommended is 7 days, although shorter courses of therapy have been found to be effective and are in routine use in some areas [49, 50].

Penicillin is still widely recommended once *N. meningitidis* is confirmed because of its low cost and narrow spectrum. Penicillin-resistant strains have emerged in Africa, the UK, Spain, Argentina, and North America. Rates remain low in the United States (around 3 %), with the highest prevalence of resistant strains reported in Spain, exceeding 40 % [18, 51].

Adjunctive treatment with corticosteroids has been studied in acute bacterial meningitis in an attempt to reduce mortality and neurological sequelae. Benefits have been seen with meningitis caused by *H. influenzae* and *S. pneumoniae*. The same findings have not demonstrated with meningococcal meningitis [52•].

Prevention

Prevention of IMD incorporates elements of both chemoprophylaxis and the use of immunization. In settings of both endemic and outbreak-associated cases, close contacts of index cases of IMD have a substantially increased secondary attack rate, nearly 1000 times the general population [53]. Given spread via droplets or from secretions, current recommendations for chemoprophylaxis include household contacts, child care contacts, healthcare workers with unprotected contact to the index patient's secretions, or others who have close or intimate contact with respiratory secretions within the 7 days preceding clinical illness of the index patient, although length of communicability is not well established [21]. Agents for eradication include third-generation cephalosporins, ciprofloxacin, and rifampin [54]. Selection depends on individual patient characteristics and local resistance. In adults, single-dose ceftriaxone or 48 h of oral rifampin can be used. Single-dose ciprofloxacin is an option provided there is no evidence of fluroquinolone-resistant *N. meningitidis* locally. Rifampin and ciprofloxacin should not be used in pregnancy, and ciprofloxacin is not recommended for those <18 years old. Single-dose azithromycin is an option, although it should not be a first-line, routine choice as data on successful eradication is limited to only one study [55].

Similar to other vaccines against prominent bacterial pathogens, available formulations against IMD include both polysaccharide and conjugate protein-based formulations. There are key immunologic differences to consider between these vaccines. In contrast to other diseases, IMD has a very short period of incubation, thus the view that sufficient levels of antibodies are constantly needed, rather than reliance on generation of a memory response [56•].

There are currently seven meningococcal vaccines approved for use in Canada (two quadrivalent conjugate, three monovalent serogroup C conjugate, one quadrivalent polysaccharide, and one multicomponent serogroup B) and four in the United States, reflective of different serogroup trends between countries [56•, 57]. After several serogroup C outbreaks in the late 1990s, all Canadian provinces and territories instituted routine infant serogroup C immunization programs by 2007 [58]. This has resulted in a substantial drop in serogroup C disease incidence, including in populations who were under-immunized. American guidelines only recommend routine immunization of adolescents and those at high risk, and

licensed formulations have all included serogroup Y [56•]. Individuals considered at high risk for IMD include university students living in dormitories, military recruits, laboratory workers routinely exposed to *N.* meningitis, travelers to hyperendemic or epidemic areas of *N. meningitidis*, individuals with asplenia, congenital complement, properdin, factor D or primary antibody deficiency, or acquired complement deficiency [59, 60]. Immunization should also be considered for HIV-positive patients. The UK was the first country to use conjugate serogroup C vaccine and instituted a mass vaccination campaign to children 1–17 years of age in 1999, with ≥85 % coverage in targeted groups [61]. This demonstrated the influence of age on the estimated duration of protection. The cohort immunized in the routine campaign (<5 months of age) had a vaccine effectiveness of 66 %, compared to cohorts which were part of the catch-up programs (>80 %). The program also underlined the impact conjugate vaccines have on carriage and herd immunity. After 24 months, nasopharyngeal carriage rates of serogroup C in adolescents fell by 67 %, and disease rates in declined by 52 and 35 % in unvaccinated children and adults >26 years of age, respectively [62]. Following US recommendations in 2005 for routine use in adolescents, the initial effectiveness of $MenACYW_D$ was estimated between 80 and 85 % [63]. A recently published placebo-controlled trial using meningococcal quadrivalent conjugate vaccine (MenACWY-CRM) in young adults in the UK demonstrated a significant effect on the carriage of vaccine serogroups [64••]. No difference in carriage was noted 1 month after series completion. However, at any point after 2 months, a significant reduction in carriage rate of against serogroups CWY were noted (36.2 %). The impact of quadrivalent conjugate meningococcal vaccine reduction in carriage on population herd protection will likely become evident after national vaccination programs have been implemented.

A serogroup A conjugate vaccine began distribution to millions of 1–29-year-olds in Mali, Niger, and Burkina Faso. Benefits were immediate, with a drop in incidence rate of meningococcal A meningitis of 99% in Burkina Faso within the first year [65]. Serogroup A carriage was eliminated in both vaccinated and unvaccinated populations for up to 13 months after the mass vaccination campaign [66•].

A safe and effective vaccine against serogroup B has been a long-time goal given trends in epidemiology and incidence in infants. Using a similar design approach of a conjugated capsular polysaccharide would have been both futile and potentially unsafe, given that serogroup B polysaccharide is highly similar to human neural cell glycopeptide [67]. Some regional successes have occurred using outer-membrane vesicle-based (OMV) vaccines for local outbreak control [68]. These OMVs can be extracted and generate a very good immune response to antigens expressed on their surface, such as PorA. Due to the antigenic diversity of PorA between serogroup B strains, this design approach would not be feasible for a vaccine that would work against endemic disease in other countries. To circumvent these issues, "reverse vaccinology" was utilized. The genome of *N. meningitidis* was searched for genes that encoded potential targets on the bacterial cell surface and would thus be possible targets for an immune response. This approach was used in the design of the first multicomponent serogroup B vaccine, 4CMenB (Bexsero®; Novartis Vaccines), which was licensed in the European Union in early 2013 and in Canada in December 2013 [69]. The four components include factor H binding protein (fHbp), neisserial adhesion A (NadA), neisserial heparin binding antigen (NHBA), and OMV containing PorA [67, 70–72].

Several clinical trials studied the immunogenicity of 4CMenB across a variety of age ranges and schedules in children [73–75]. However, these trials cannot provide data on vaccine efficacy because IMD is overall a rare event and would require routine use in a large birth cohort to establish. As a surrogate marker, the serum bactericidal activity assay (hSBA) was used, essentially measuring the amount of complement-mediated activity against specific meningococcal antigens by recipient antibodies [67]. Protective titers of at least 1:4 were seen in almost 100 % of recipients, with slightly lower rates for responses to PorA and NHBA. In studies using an infant primary series of three doses, titers did wane by 1 year of age but a booster dose after 1 year of age resulted in >95 % of children having protective titers against all 4CMenB antigens [74]. A limitation of the hSBA testing is that information on the relative proportion of each antigen to the immune response is lacking. A novel typing system was created, Meningococcal Antigen Typing System (MATS), which uses an enzyme-linked immunosorbent assay (ELISA) to quantify if the amount of antigen on a serogroup B isolate's cell surface is above a cut-off to predict an appropriate response [76]. Current use of MATS would suggest that strain coverage varies by region. Approximately two thirds of Canadian serogroup B isolates over the last decade would demonstrate susceptibility to 4CMenB [77]. In contrast, over 80 % of recent isolates from across several European countries would have predicted susceptibility to 4CMenb [78].

In addition to uncertainty regarding efficacy, the cost-effectiveness of 4CMenB has been an area of attention. In the UK, an initial policy recommended against the use of 4CMenB due to lack of cost-effectiveness data, even if the cost of vaccine was zero [79]. This view was subsequently updated to await additional cost-effectiveness before a final decision [67]. A recent cost-utility analysis from Ontario also included estimated effects from 4CMenB use over the lifetime of a birth cohort [80]. Including considerations for schedule, coverage, quality of life loss estimates, and effect on herd immunity, the authors concluded that a 4CMenB program would exceed cost-effectiveness thresholds in an area such as Ontario with an overall low rate of IMD. Given the complex interplay of many factors in IMD epidemiology,

immunology, and surveillance, real-world implementation will be required to fully inform cost-effectiveness calculations, especially effect on carriage. This point is emphasized by a phase 3 trial in young adults who were immunized with either 4CMenB, MenACWY-CRM, or a Japanese encephalitis vaccine (placebo) to study the impact on nasopharyngeal carriage [64••]. While no differences in carriage were noted after 30 days, 3 months after series completion 4CMenB showed a broad effect, significantly lowering carriage rates almost 30 % against serogroups B, C, W, and Y, relative to placebo. If 4CMenB immunizations programs were to demonstrate an effect on carriage and herd immunity after widespread implementation, this would impact cost-effectiveness calculations.

Outcomes

Following an episode of IMD, survivors may develop a spectrum of neurologic, physical, and psychiatric sequelae. A matched-cohort study of adolescent survivors of IMD from the UK revealed that 57 % had major physical sequelae, including mobility, speech, and hearing problems [81]. Symptoms of depression, fatigue, reduction in quality of life, and lower educational attainment were all greater compared to controls. These sequelae were greater in survivors of serogroup C disease compared to B. Lack of continuity of care was common, with 48% reporting no follow-up care after discharge.

Recent data from the UK suggests that most younger children survive serogroup B IMD with major side effects [82]. Patients diagnosed from 1 month to 13 years of age and followed through the UK National Meningococcal Registry were matched in a case–control study. About 1 in 10 were diagnosed with major disabling deficits at follow-up; however, over a third had at least one deficit in areas of physical, physiological, or cognitive function. They were also more likely to have deficits in memory and executive function compared to controls.

Meningococcal Disease and HIV

Variability in immunization recommendations for patients with HIV/AIDS reflects the evolving knowledge of the relationship between IMD and HIV [56•, 59]. Surveillance in Atlanta prior to implementation of any conjugate vaccination programs revealed a 24-fold increased risk for IMD in adults 25–49 years old with HIV and an estimated average annual incidence of 11.2/100,000 adults [83]. South Africa, an area with high incidence of HIV, demonstrated similar risks [84]. From a 5-year surveillance study, the incidence of IMD in HIV-infected individuals was 11-fold greater compared to uninfected controls. The case-fatality rate was 20 % in HIV-infected versus 11 % in uninfected cases, and HIV infection was associated with increased odds of bacteremia.

A population-based cohort study from New York estimated the mortality risk from IMD in HIV-infected patients, and the relative contribution of CD4 counts and viral loads on outcomes [85]. The mean annual incidence of IMD overall was 0.39 cases/100,000 population. However, in those with HIV/AIDS, the mean rate was 3.4 cases/100,000. The relative risk of IMD in HIV-infected patients was 10.0 and was highest in those 25–44 years old. The potential for prevention was noted, with 87 % of IMD cases in those with HIV being due to vaccine serogroups. In addition, HIV+ patients with IMD were 5.3 times as likely compared to controls to have CD4 counts <200. Having "unsuppressed" HIV viral loads (>400 copies/mL) resulted in a 4.5-fold risk to have IMD compared to suppressed HIV patients. Canadian and US guidelines both include HIV+ patients (children >2 years old, adolescents, and adults) for targeted immunization with two doses of quadrivalent conjugate meningococcal vaccine at least 8 weeks apart [21, 56•, 59]. Booster doses should also be given every 3–5 years, depending on the age of primary immunization. Although not authorized for use in patients >55 years old, evidence and opinion to date would suggest benefit in those who remain at high risk of infection.

Conclusion

Invasive meningococcal disease continues to be a disease that strikes fear in the minds of both clinicians and patients, despite the advance in medical care. Cornerstones of care remain a high index of suspicion, cultures of sterile fluids, and rapid initiation of antibiotics when needed. With increasing use of conjugate meningococcal immunizations, both endemic and epidemic disease epidemiology has changed over time, as highlighted by the incidence of serogroup B IMD. The full benefit of serogroup B meningococcal vaccines will likely not be realized until their widespread use and large studies on herd immunity are completed.

Compliance with Ethics Guidelines

Conflict of Interest Rachel Dwilow and Sergio Fanella declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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