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Meningitis caused by N. meningitidis: How to prevent this “younger generation killer”?

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Abstract:

Neisseria meningitidis is a gram-negative bacterium that inhabits the mucosal surface of the nasopharynx in approximately 10% of healthy persons. It stands out as a leading etiology of meningitis, particularly among children, adolescents, and young adults. Meningococcal infections account for an estimated 1.2 million cases annually worldwide, with a death toll exceeding 135,000. These infections are most prevalent in the “meningitis belt” of sub-Saharan Africa and have historically occurred in cyclic patterns in China. Chemoprophylaxis using antibiotics like rifampicin, ciprofloxacin, and ceftriaxone is effective in eliminating bacterial carriage and preventing disease spread. Vaccination represents another crucial preventive measure. This review provides an overview of meningococcal meningitis, emphasizing the importance of early diagnosis, chemoprophylaxis with antibiotics like ceftriaxone, and vaccination as key strategies to combat this deadly disease, particularly among vulnerable populations like infants, adolescents, and young adults.

Keywords:-*Neisseria meningitidis*, meningococcus, chemoprophylaxis, vaccination, combination therapy

1. Introduction

Meningitis is an infection that affects the meninges and the membranes surrounding the brain and spinal cord. Comprising the dura mater, arachnoid mater, and pia mater, the meninges line the vertebral canal and skull, protecting the brain. Typical symptoms of meningitis include fever, headache, and a stiff neck. Additionally, there may be other accompanying symptoms, such as nausea, vomiting, and photosensitivity. In the context of infancy, the identification of these prototypical symptoms poses a significant challenge, given that infants often manifest with non-indicative, generalized manifestations such as lassitude, diminished motor activity, or excessive fussiness, which may not immediately point to the underlying condition.[1]

Meningitis can result from both infectious and non-infectious processes. Among the infectious agents causing meningitis, bacteria, viruses, fungi, and, less frequently, parasites are all potential etiologic agents. Among the myriad infectious manifes-

tations, bacterial meningitis, stemming from a bacterial etiology, is esteemed as a more dire condition compared to viral meningitis or any alternate modalities of infection. The incidence of this particular meningitis demonstrates a nuanced pattern with respect to age demographics. Specifically, infants within the first two months of life are often afflicted by Group B *Streptococcus*, whereas across all other age brackets, barring individuals aged between 11 and 17, *Streptococcus pneumoniae* prevails as the preeminent culprit. In the latter age range, *Neisseria meningitidis* maintains its position as the primary cause.[2] Presently, *N. meningitidis* has emerged as the paramount factor underlying bacterial meningitis in pediatric and young adult populations, concurrently ranking second among the etiologies of community-acquired bacterial meningitis in adults.[3] This underscores the complexity and variability in the epidemiology of bacterial meningitis, necessitating age-specific considerations in preventive and therapeutic strategies.

N.meningitidis, also known as meningococcus (which will be used consistently hereafter), is a Gram-negative diplococcus bacterium that causes meningitis and meningococcal septicemia. Serving as a pivotal causative agent in bacterial meningitis and sepsis, it possesses the capability to elicit pneumonia and localized pathologies, further exacerbating its clinical significance. The intricacy in diagnosing meningococcal infections stems from the striking similarity of its symptoms to those manifested by diverse meningitis subtypes, thereby complicating the diagnostic trajectory. The conventional diagnostic strategy necessitates the meticulous collection of either blood specimens or cerebrospinal fluid (CSF, the vital fluid encircling the spinal cord), which are then subjected to rigorous analytical procedures for definitive diagnosis.

Approximately 1.2 million cases of meningococcal infections are annually estimated to occur worldwide, leading to an approximate global mortality of 135,000 individuals.[4] Infants and adolescents are particularly vulnerable to meningococcal disease, attributed to heightened nasopharyngeal colonization rates and the waning of maternal antibodies.[5] Geographically, the highest prevalence of this disease is concentrated within the expansive 'meningitis belt' region (Fig.1), spanning 26 countries in sub-Saharan Africa,[6] where seasonal outbreaks, typically during the dry season, are prevalent.

FIGURE 2. Sub-Saharan meningitis belt

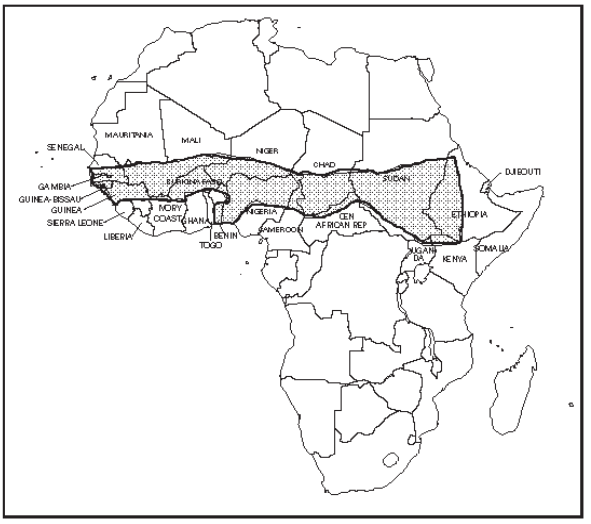

Fig.1 sub-Saharan meningitis belt [7]

In China, meningococcal disease exhibits a cyclical trend, recurring approximately every 8-10 years, with notable nationwide epidemics documented in 1959, 1967, 1977, and 1984. Then Figure 2 shows reported meningococcal meningitis and death cases in China during the period of 2002 to 2019. These periodic and seasonal epidemic patterns underscore the unpredictable nature of meningococcal disease outbreaks, emphasizing the need for ongoing vigilance and preparedness.[8]

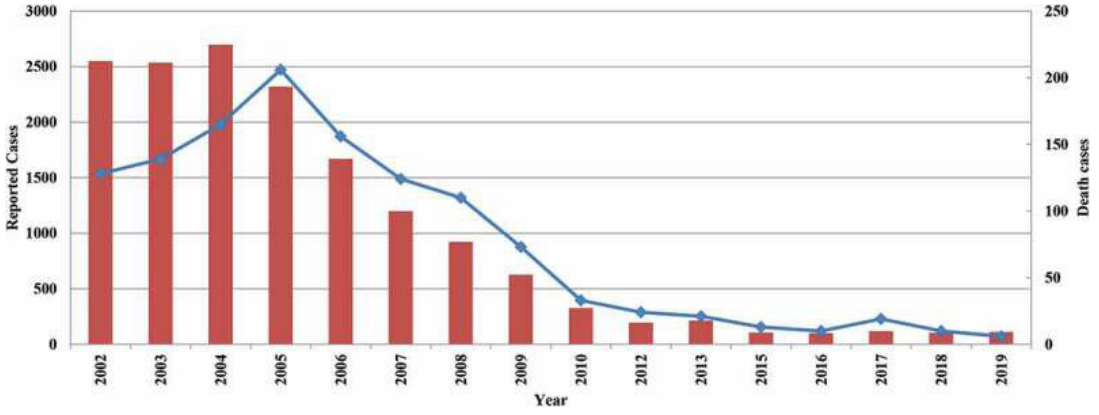

Fig.2 Reported meningococcal meningitis and death cases in China, 2002–2019 [9]

The remaining content will conduct a preliminary analysis of the causes of meningitis caused by this tricky bacteri-

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um. And provide a detailed introduction and comparison of two existing prevention methods, antibiotics and vaccines.

2. Pathology

The dissemination of meningococcus between individuals is facilitated through the inhalation of airborne droplets, which are expelled into the environment during coughing or sneezing episodes by an infected nearby individual. Frequently, these bacteria are transmitted by individuals who are asymptomatic carriers, harboring the meningococcus in their nasal and throat cavities without manifesting overt symptoms. The body's innate immune mechanisms generate antibodies against these bacteria, preventing their dissemination to other bodily regions. However, in rare cases, exposure to meningococcus can lead to the development of meningococcal disease, where the bacteria migrate to the bloodstream and brain, resulting in meningococcemia and/or meningococcal meningitis. This scenario may arise when the body has not had sufficient time to establish an antibody defense or in individuals with compromised immune systems.[10]

3. Antibiotics Used for Prevention

According to the official website of the CDC, empirical therapy for suspected meningococcal infection should encompass an extended-spectrum cephalosporin, such as cefotaxime or ceftriaxone. The use of penicillin or ampicillin necessitates susceptibility testing. Upon confirmation of the microbiological diagnosis, definitive treatment can proceed with an extended-spectrum cephalosporin. Both ceftriaxone and cefuroxime have undergone repeated assessments, consistently demonstrating their clinical efficacy as primary therapeutic options for bacterial meningitis in pediatric patients. Broadly speaking, these two cephalosporin-based drugs are viewed as interchangeable in the treatment of bacterial meningitis despite a paucity of direct comparative studies. A randomized controlled trial conducted in Switzerland, comparing ceftriaxone (administered to 53 pediatric patients) against cefuroxime (administered to an equal number of 53 patients), as the sole antibiotic therapy for bacterial meningitis in children, yielded results that demonstrate the superiority of ceftriaxone over cefuroxime for this particular clinical indication.[11] This finding underscores the efficacy of ceftriaxone in managing bacterial meningitis in the pediatric population. So, the subsequent content will utilize ceftriaxone as an example to elucidate antibiotic therapy.

Ceftriaxone ($C_{18}H_{18}N_8O_7S_3$), the structure shown in Figure 3, belonging to the third-generation cephalosporin class of antibiotics, exhibits a broad-spectrum bactericidal efficacy against both Gram-positive and Gram-negative bacterial strains. The rationale for opting for third-generation cephalosporins over their first and second-generation counterparts lies in the limited efficacy of the former against Gram-negative bacteria. Additionally, second-generation cephalosporins share comparable indications with their predecessors yet falter in terms of therapeutic efficacy, falling short of the potency demonstrated by third-generation cephalosporins, such as ceftriaxone.[12]

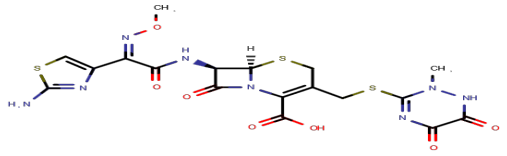

Fig.3 Ceftriaxone Structure [13]

As a third-generation cephalosporin, Ceftriaxone possesses the capability to traverse the blood-brain barrier (BBB), thereby attaining therapeutic concentrations within the confines of the central nervous system (CNS). Its potent bactericidal mechanism stems from its ability to inhibit cell wall synthesis by selectively binding to penicillin-binding proteins (PBPs), which are membrane-bound enzymes crucial for the terminal stages of bacterial cell wall construction and remodeling during cell division. By inactivating these PBPs, Ceftriaxone disrupts the crucial cross-linking of peptidoglycan chains, a fundamental component responsible for the structural integrity, strength, and rigidity of the bacterial cell wall. This leads to the weakening of the bacterial cell wall and ultimately causes cell lysis. By this mechanism, Ceftriaxone can effectively kill meningococcus.[14]

Ceftriaxone administration is exclusively facilitated via injection routes, namely intramuscularly or intravenously, due to its negligible oral bioavailability, estimated to be less than 1%.[15] In clinical trials, a single parenteral dose of ceftriaxone (125 mg intramuscularly for pediatric patients and 250 mg for adults) has demonstrated efficacy ranging from 97% to 100% in eliminating pharyngeal carriage of Neisseria meningitidis.[16] Notwithstanding their potent antibacterial properties, systemic cephalosporin administration poses a risk of severe adverse reactions,[17] necessitating the exploration of alternative, patient-compliant delivery methods to the brain. One promising avenue is the nose-to-brain pathway, which offers the potential to mitigate these risks. A pivotal advantage of this route lies in its ability to minimize plasma exposure,[18] thus alleviating peripheral side effects. Research indicates that formulations such as ceftriaxone-loaded gelatin nanospheres or tripalmitin-based solid lipid nanoparticles may

present a more viable and efficient nose-to-brain delivery system for the treatment of meningitis, outperforming comparable cefotaxime-based formulations.[19]

4. Vaccines Used for Prevention

It is universally acknowledged that the preponderance of meningococcal infections stems from six serogroups, namely A, B, C, X, Y, and W. And figure 4 shows predominant serogroups associated with meningococcal meningitis worldwide. Each of these six serogroups possesses the capability to initiate both endemic and epidemic outbreaks of the disease. Notably, the primary serogroups exhibit both geographical and temporal variations, contingent upon antigenic shifts or the influence of vaccination programs.[20][21] Two distinct categories of meningococcal vaccines are available now: (1) polysaccharide vaccines and (2) conjugated polysaccharide vaccines.[22]

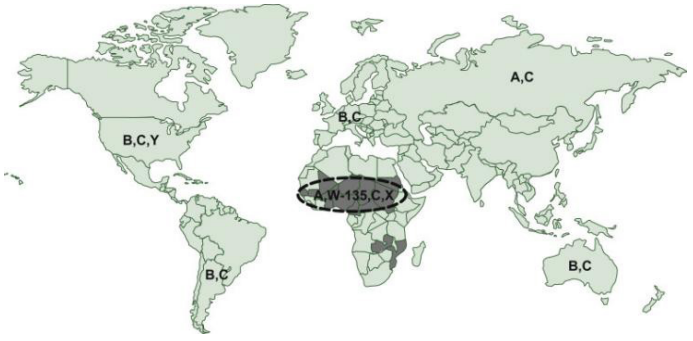

Fig.4 Predominant serogroups associated with meningococcal meningitis worldwide [23]

Initially, vaccines were solely comprised of polysaccharides, colloquially referred to as plain polysaccharide vaccines, and were available in diverse formulations: bivalent (targeting serogroups A and C), trivalent (encompassing A, C, and W), and quadrivalent (directed against A, C, Y, and W), all of which have been established as generally safe and well-tolerated entities.[24] In 1981, the United States licensed MPSV4, a quadrivalent vaccine containing 50 micrograms of each of four purified bacterial capsular polysaccharides, namely A, C, Y, and W-135.[25] This vaccine is indicated for the prevention of meningitis caused by these specific serogroups, with the exception of use in children under 2 years old, unless for providing temporary protection against serogroup A in infants older than 3 months.[25] Since the 1970s, unconjugated meningococcal vaccines containing purified capsular polysaccharides directed towards serogroups A, C, Y, and W have been accessible and continue to be administered to travelers and individuals at risk. Nevertheless, this particular type of meningococcal vaccine is no longer available for use in the United States,[26] underscoring the evolution of vaccination strategies over time.

Driven by the limitations of the initial vaccine type, which elicited a suboptimal immune response and offered a narrow range of pathogen protection, the quest for meningococcal vaccine advancements gained renewed impetus at the dawn of the 21st century, drawing inspiration from vaccines devised against other bacterial diseases. This culminated in the seminal development of Glycoconjugate vaccines.[27] The commercially viable conjugated vaccines are typically crafted by conjugating with a protein carrier, devoid of any additional adjuvants. Currently, three quadrivalent conjugated vaccines, each incorporating the prevalent polysaccharides (A, C, W, and Y), are globally available, yet they differentiate themselves based on their respective protein carriers: MenACWY-TT, tethered to tetanus toxoid; MenACWY-DT, fused with diphtheria toxoid; and MenACWY-CRM, linked to the non-toxic derivative of diphtheria toxin.[28] However, the efficacy and accessibility of these vaccines are hindered by multiple constraints, including the costly chemical conjugation process, the necessity for rigorous cold chain management (sustained refrigeration), and the intricate process of preparing individual doses. Collectively, these factors pose significant hurdles in the production and dissemination of conjugate vaccines,[29] necessitating ongoing research and innovation to address these limitations.

Until recently, the pharmaceutical landscape lacked an efficacious vaccine specifically targeting serogroup B meningococcal strains. To address this gap, the industry has devised vaccines incorporating outer membrane vesicles (OMV), offering diverse applications. However, the primary constraint lies in their inability to provide comprehensive protection against the vast global diversity and variability of serogroup B meningococcal strains.[30][31] Recent advancements in “reverse vaccinology” have yielded innovative formulations that offer comprehensive MenB protection, transcending prior constraints and potentially conferring immunity against select non-serogroup B meningococcal strains, albeit with the caveat

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of potentially neglecting certain serogroup B strains.[31] The fusion of vaccinology and nanotechnology has catalyzed the creation of pioneering meningococcal vaccine designs that mimic conjugation effects through the utilization of albumin-based nanoparticles encapsulated within spherical micro/nanoparticles, biologically mirroring N. meningitidis bacteria. This innovative approach prompts phagocytosis and elicits a respiratory burst, releasing reactive oxygen species (ROS), thereby augmenting oxidative killing and fostering adaptive immune responses.[29]

These nanoparticulate formulations demonstrate notably enhanced antigenicity in comparison to their solution-based counterparts, with their efficacy further bolstered when administered in conjunction with FDA-sanctioned adjuvants, such as alum or MF59. The slow-release antigens facilitated by nanotechnology possess the potential to amplify antigen presentation, evoke robust immune reactions, and surmount the shortcomings of conventional vaccines. Moreover, their cost-effectiveness, capacity for storage as dry powder without the necessity of a cold chain, and suitability for deployment in low-resource settings and during mass vaccination events like the annual Hajj, further emphasize their myriad advantages.[29]

As a means of preventing meningococcus, the official CDC website in the United States states that three varieties of meningococcal vaccines are currently accessible in USA: MenACWY vaccines, MenB vaccines, and the MenABCWY vaccine. It is a statutory requirement that individuals aged 11 to 12 years undergo MenACWY vaccination, with a subsequent booster administered at 16 years of age. Additionally, adolescents and young adults spanning the age bracket of 16 to 23 years have the option to receive the MenB vaccine. For those undergoing concurrent vaccination with both MenACWY and MenB during a single visit, the MenABCWY vaccine presents an alternative option. Furthermore, the Centers for Disease Control and Prevention (CDC) recommends meningococcal vaccination for children and adults who are identified as being at an elevated risk of developing meningococcal disease.

In the context of China's National Immunization Program, children under 24 months of age are deemed to have completed their MPSV-A vaccination regimen if they have received the prescribed dosage as outlined in the MPCV instructions, as per the "Childhood Immunization Procedures and Instructions (2021 Edition)" of the National Immunization Program Vaccine. Presently, non-mandatory vaccines that can serve as substitutes for MPSV-A include MPCV-AC, MPCV-AC Hib, and MPCV-ACYW. For 24-month-old children, vaccines incorporating components of Group A and Group C meningococcal vaccines can be utilized as alternatives to the corresponding MPSV-AC vaccination. Additionally, the list of non-mandatory vaccines capable of replacing MPSV-AC extends to include MPCV-AC, MPCV-AC Hib, MPCV-ACYW, and MPSV-ACYW.

A notable degree of control over meningococcal meningitis stemming from serogroup A has been attained across the "meningitis belt" in Africa, where comprehensive immunization campaigns employing meningococcal A conjugate vaccines (MenAfriVac) have been underway since 2010. Between 2010 and 2015, nine nations within this belt witnessed a remarkable 99% decrease in MenA disease incidence. Simultaneously, meningitis stemming from serogroups other than NmA constitutes a substantial health burden in sub-Saharan countries located within the meningitis belt. An epidemiological shift has manifested, transitioning from the predominance of a singular serogroup to a diverse array of causative agents for meningococcal meningitis and outbreaks. The strategic implementation of vaccines specifically targeting MenA, MenC, and more recently, MenB, has efficiently managed and mitigated meningococcal meningitis associated with these serogroups in European countries such as the United Kingdom, the Asia Pacific region, and the African meningitis belt. However, periodic and unforeseen surges in the prevalence of certain serogroups have been observed,[32] highlighting the need for continued vigilance and adaptability in vaccination strategies.

In China, serogroup A was predominantly responsible for over 95% of meningococcal meningitis cases from the 1960s to 1980s. Following the introduction of the MenA polysaccharide meningococcal vaccine in 1982, the incidence rate steadily declined. Conversely, the proportion of sporadic cases attributed to MenB significantly increased. Notably, from 2015 to 2017, 54.08% of clinical cases were due to MenB infections. This dynamic and unpredictable epidemiological landscape poses a unique challenge to meningococcal meningitis prevention efforts.

In conclusion, preventive measures, especially vaccination, have proven to be highly efficacious in containing the spread of meningococcal meningitis.[33] Ongoing epidemiological surveillance holds paramount importance, as it not only illuminates the temporal patterns of meningococcal meningitis but also serves as a cornerstone for data-driven vaccine development, policy formulation, and the assessment of the effectiveness of vaccination initiatives implemented.[32] This comprehensive approach ensures that strategies are tailored to the evolving epidemiology, maximizing the impact of prevention efforts.

5. Conclusion

The previous section have already discussed the use of the modalities available for post-exposure chemoprophylaxis and vaccination of meningococcal disease. As an antibiotic, ceftriaxone may be used in every age group, although the intramuscular route of administration makes it less convenient. But the nose-to-brain pathway's investigation as a potential route for delivery make its use more promising. Regarding vaccination, polysaccharide and conjugated polysaccharide vaccines are being used worldwide targeting serogroups A,C,Y, and W. Although by now no effective serogroup B vaccine was available, OMV vaccines and reverse vaccinology's development has pointed us the right direction. The new era of vaccinology and nanotechnology entered the field of meningococcal vaccines, which facilitate the development of novel meningococcal vaccine formulations that mimic conjugation effects by using albumin-based nanoparticles encapsulated into spherical shaped micro and nanoparticles that biologically mimics N.meningitis. There is a high potential for this novel vaccine formulation which can overcome the limitations of traditionally formulated vaccines. The emergence of novel vaccine technologies and with the combination of antibiotics offers promising avenues for broader protection against meningococcal infections. Of course, at the same time, we must always be vigilant about whether the current antibiotics have developed resistance and whether new strains and variants have emerged, in order to adjust treatment strategies in a timely manner. We believe that in the near future, people will definitely be able to overcome this "younger generation killer".

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