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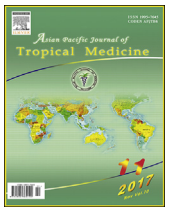

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Meningococcal disease, a clinical and epidemiological review

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ABSTRACT

Meningococcal disease is the acute infection caused by *Neisseria meningitidis*, which has humans as the only natural host. The disease is widespread around the globe and is known for its epidemical potential and high rates of lethality and morbidity. The highest number of cases of the disease is registered in the semi-arid regions of sub-Saharan Africa. In Brazil, it is endemic with occasional outbreaks, epidemics and sporadic cases occurring throughout the year, especially in the winter. The major epidemics of the disease occurred in Brazil in the 70's caused by serogroups A and C. Serogroups B, C and Y represent the majority of cases in Europe, the Americas and Australia. However, there has been a growing increase in serogroup W in some areas. The pathogen transmission happens for respiratory route (droplets) and clinically can lead to meningitis and sepsis (meningococcemia). The treatment is made with antimicrobial and supportive care. For successful prevention, we have some measures like vaccination, chemoprophylaxis and droplets' precautions. In this review, we have described and clarify clinical features of the disease caused by *N. meningitidis* regarding its relevance for healthcare professionals.

1. Introduction

Meningococcal disease (MD), known for more than 200 years, is recognized as a worldwide public health problem due to its cosmopolitan distribution, potential to cause outbreaks or epidemics, the greater impact on children and teenagers (especially during epidemics), high mortality rates and significant morbidity represented by complications of the disease, especially permanent neurologic damage [1–4]. Furthermore, MD is associated with high financial costs both in patient treatment and rehabilitation, thus, the investments in prevention of this disease through use of conjugated antimeningococcal vaccines appears to be a cost-effective public health measure [5–9].

Neisseria meningitidis (*N. meningitidis*) is a pathogen capable of causing extremely severe conditions in humans, especially meningococcal meningoencephalitis (MM) and meningococcemia [10]. With regards to meningitis, *N. meningitidis* was the primary etiology of acute bacterial meningitis (ABM) in Brazil during the period of 2010–2013 (Ministério da Saúde/SVS), and the second most common cause of community-acquired bacterial meningitis among adults in the United States [11]. With regards to meningococcemia, it is probably the infectious condition most rapidly fatal to a human being, with 92% of deaths reported within the first two days of hospitalization [1]. However less severe clinical conditions caused by meningococci can occur in less than 5% of cases [12].

The presence of fever and cutaneous alterations petechia or purpura in an acutely ill patient should mandatorily evoke in the physician, the hypothesis of MD [1]. Because it is an infectious

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emergency, on considering this diagnostic hypothesis the time between suspicion and institution of antimicrobial therapy should not be greater than half an hour [13–15]. Under no circumstances should therapeutic delays, for collection of exams or for transfer of the patient to larger healthcare units, be allowed [1,14].

In this article we present a review of the principal microbiological, epidemiological, pathophysiological, diagnostic, therapeutic, and preventive measures of MD.

2. Etiology

Microorganisms of the species *N. meningitidis* are gram-negative cocci grouped in pairs (diplococcus) with typical morphology (bean or kidney-shaped), with humans as their sole natural host. They neither form spores nor possess flagella, but have fimbria (pili) [1]. They are aerobic agents, catalase-positive, oxidizing glucose and maltose with acid production and without gas formation. They grow well in chocolate and blood agar at temperatures between 35 °C and 37 °C, requiring an atmosphere of 5%–10% carbon dioxide [16]. *N. meningitidis* is a frequent colonizer of the human naso- and oropharynx, but can be found in other areas of the body such as the anal mucosa, the conjunctiva and the urogenital tract [17].

The main virulence factors of *N. meningitidis* include:

(1) The polysaccharide capsule: a structure that protects the etiologic agent from complement-mediated phagocytosis and lysis [18], and is important for the differentiation of serogroups (total of 13) [10,12,17]. In human illness notable serogroups include A, B, C, W, X and Y [16,19];
(2) Lipopolysaccharide is an endotoxin (so-called because it presents in the bacterial wall), and very important to *N. meningitidis*, responsible for toxic shock, meningococcal adhesion and activation of the innate immune system [17]. *N. meningitidis* can be divided into 13 immunotypes (according to lipopolysaccharide structure) [16,18];
(3) Adherence factor: type IV pilus, that binds to CD46 receptors, is a complex protein structure, located on the external plasma membrane, which plays an important role in pathogen adherence to epithelial and endothelial cells of *Homo sapiens sapiens* and also in the "capture" of DNA molecules from the human host, diversifying and incrementing the meningococcal genome [6,18];
(4) External membrane proteins belonging to the porine class, believed to participate in adhesion and invasion of the host cell, which induces calcium influx and apoptosis of epithelial and phagocytic cells, in addition to activating Toll-like 2 receptors [16,12,46];
(5) Iron incorporation: when there is reduced iron in the extracellular medium, the bacteria express proteins present on its external membrane that capture iron from lactoferrin and transferrin in the medium and internalize it [16–18].

3. Epidemiology

Epidemics are historically common in sub-Saharan Africa (known as the African meningitis belt) since 1905, with periodicity every five to ten years [19]. The annual incidence of MD during these epidemics can reach 1 200 cases per 100 000 inhabitants [19–21]. In developed nations (North America, Europe and Australia), the disease tends to be endemic, with an estimated incidence ranging from 0.3 to above 3 cases per 100 000 inhabitants [20,21].

MD is also endemic in Brazil, with a periodic occurrence of epidemics in some cities [22]. In Brazil, there are records of four epidemic "waves" involving MD: a) 1920 to 1925 (serogroup A); b) 1945 to 1951 (serogroup A); c) 1971 to 1977 (serogroups C and A) and d) 1988 to 2002 (serogroups B and C). Of these, the epidemic that emerged in the 1970's was the most catastrophic in Brazil's history [23].

Serogroup A was the predominant MD etiology in Europe before and during the First and Second World Wars. While serogroup B was dominant in Europe in the 1970's and in South America in the 1980's, in the XXI century epidemics arose associated with serogroups W and Y. There was a deviation in the age range affected by MD with an increased incidence in the elderly, a fact associated with serogroup Y [24]. Additionally, there was a decline in MD cases caused by serogroup C in adolescents, due to implementation of routine vaccination against meningococci of this serogroup, leading to a reduction in the number of healthy carriers as well as the incidence of MD, with consequent emergence of collective immunity [24,25]. Recent epidemics caused by serogroup W occurred in some South American countries, but serogroups B and C are still responsible for most cases of MD on this continent [26]. The epidemiologic tendency of MD has remained relatively constant in Africa, with serogroup A the primary etiologic agent, although recently serogroups X and W were responsible for a large proportion of morbi-lethality of MD in that continent [24]. Serogroup A conjugate vaccine (MenAfriVac) began distribution to millions of 1–29 years old 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 [27]. Serogroup A carriage was eliminated in both vaccinated and unvaccinated populations for up to 13 mo after the mass vaccination campaign [28]. In Asia, large epidemics caused by serogroup A occurred historically in China, India, Nepal and Russia, more recently serogroups B and C were responsible for the majority of MD cases on this continent. Since the 1990's, serogroup W is the principal etiology of MD in Hajj pilgrims and their close contacts [16].

In Brazil, according to Sistema de Informação de Agravos de Notificação data, from 2010 to 2013, the number of confirmed MD cases varied between 2 083 and 3 003 and its incidence (per 100 000 inhabitants) varied between 1 and 1.5 (Ministério da Saúde/SVS). According to SIREVA II (conducted by the Pan-American Health Organization), in 2012 the distribution of MD cases in Brazil, by identified serogroups, was as follows: 71% from serogroup C, 19% from serogroup B, 6% from serogroup W and 4% from serogroup Y [29].

Lethality rates ranging from 10% to 20% were reported in recent years in several Latin American countries: Chile (14% in 2010), Argentina (7%–15%), Panama (13%), Mexico (18% between 2005 and 2008) and Uruguay (15%) [30]. However, a high lethality rate (21%–22% between 2010 and 2013) is still reported in Brazil (Ministério da Saúde/SVS), despite increased availability of intensive care units and improvements in healthcare [30]. During the recent MD epidemics, which were associated primarily with serogroup C, a very high lethality rate was reported (approximately 40%). Usually the MD associated lethality rate averages 10% (without important differences observed worldwide) that is lower than the rate

currently found in Latin American nations. Possible reasons that could explain why these high lethality rates in Brazil remain speculative, however the delay in care on the part of the healthcare system in some regions of this country could be included. Furthermore, since 2002, in Brazil there has been a significant increase in the number and proportion of MD cases attributed to serogroup C, associated with a new clonal complex, ST103, not commonly observed in other areas of the world [30]. Moreover comparative study of isolates from invasive disease and asymptomatic carriage demonstrated that some of these clonal complexes are more invasive than others: these are referred to as the 'hyper invasive lineages', and only a handful of these have caused the majority of reported disease globally in the last half of the 20th century [31].

N. meningitidis is a respiratory transmission bacterium (through droplets) that cannot survive in the environment, requiring close and prolonged contact, or direct physical contact (such as a kiss) for effective transmission [1]. The asymptomatic carrier, present among less than 2% of children under five years of age and 20%–25% of adolescents and young adults [32], is the primary element in the pathogen transmission pathway and its maintenance in nature, even during periods of epidemics [1]. From an epidemiological viewpoint, the patient is not important in *N. meningitidis* propagation, and is only responsible for bacterial transmission in exceptional situations, such as cardiopulmonary resuscitation maneuver, hospital bed occupation by more than one patient, and confinement conditions [1].

Over the last few years, there has been an expansion of the potential transmission pathways of *N. meningitidis*, such as vertical transmission and sexual (oral) transmission, creating new epidemiological challenges for MD [33].

The distribution of MD patients by gender shows a predominance of disease among men. However, in the population over 50 years of age, there is a clear predominance among women. In the context of an endemic, approximately 60% of MD cases occur in children under 10 years of age, while during epidemics there is a wider age range affected, with increased numbers of cases among adolescents and young adults [1].

The temporal distribution of MD cases shows a seasonal variation [34], with most cases occurring in winter [1]. Other factors influencing disease incidence and prevalence of meningococcal carriers are: small and poorly ventilated residences, agglomeration, precarious hygiene conditions, susceptibility of a given population to a given meningococcal serogroup, number of individuals per dormitory, tobacco use, climatic factors (air temperature and relative humidity), migrations and concomitant viral infections [1,34–36].

Complement deficiency (of both terminal and initial fractions) was associated with an increased susceptibility to the meningococci. Deficiency of factor C3 and properdin (a component of the alternative pathway) are also associated with inefficient defense against the bacteria. MD often affects patients with complement deficiency later in life (adolescents), and these patients tend to have a milder disease, with considerably lower lethality than patients who do not have this deficiency. MD in these patients can also recur and is associated with less common serogroups [1,37–39].

There is limited and conflicting data about a possible association between HIV and MD infection. Studies performed prior to the development of highly active antiretroviral therapy did not find an association between HIV and MD [40], though recent cohort studies performed in the highly active antiretroviral therapy era suggest that HIV-infected patients have a higher risk of developing MD [41–43].

4. Pathophysiology and pathogeny

The interaction between *H. sapiens sapiens* and *N. meningitidis* is quite complex. The process begins with the colonization of the upper respiratory tract, especially the nasopharynx, wherein the microorganism adheres to the epithelial cells. Subsequently, the bacterium is interiorized by these cells, and may traverse the cytoplasm, reaching the submucosal layer. From this point, *N. meningitidis* may access the bloodstream, evolving by one of two primary mechanisms: (1) rapid bacterial multiplication, associated with development of marked systemic inflammatory response, producing the typical clinical picture of meningococcemia; (2) slower reproduction of the agent, allowing for fixation and multiplication in the joints, the pericardium, and especially in the central nervous system, producing in the latter clinical picture of MM [17,44].

In meningococcemia, the pathogen multiplies very quickly, reaching high concentrations in the human bloodstream and profusely synthesizing molecules which are known as lipooligosaccharides (endotoxins). The lipooligosaccharides (endotoxins) play a central role in the pathogenesis of the morbid condition, stimulating cells of the immune system (such as macrophages, monocytes and neutrophils) to release a series of inflammatory mediators: interleukin (IL) 1, IL-6, IL-8, IL-10, interferon-gamma and tumor necrosis factor alpha. These cytokines play a critical role in activation of multiple pathways, including the coagulation cascade, the leukotriene and prostaglandin pathways and the complement pathway [17,18,44,45]. Thus, there is release of a large number of molecules within the blood vessels, leading to increased capillary permeability, "pathological" vasoconstriction and vasodilation, loss of "thrombus resistance" and disseminated intravascular coagulation and severe myocardial dysfunction. These events are directly responsible for the development of shock and multiple organ failure [45]. In disseminated intravascular coagulation, there is the emergence of disseminated cutaneous lesions (petechia, purpura and hemorrhagic suffusions), in addition to thrombotic lesions on the kidneys, choroid plexus, adrenals, limbs and occasionally the lungs [12].

With regards to the central nervous system, in terms of pathophysiology of MM, the primary aspect is the crossing by the bacteria of the blood–brain barrier [46]. Subsequently, it binds to endothelial cells of the cerebral microvasculature, and was found in the choroid plexus and capillaries of the encephalon at receptors. Once in the cerebrospinal fluid, the pathogens begin replication and trigger inflammatory process in the subarachnoid space, with pathophysiological consequences such as: (1) increased permeability of the blood–brain barrier; (2) cerebral edema; (3) intracranial hypertension; (4) reduced cerebral blood flow with cortical hypoxia; (5) cerebrospinal fluid alterations (acidosis, neutrophilic pleocytosis, hypoglycorrhachia, and elevation of proteinorachia). Worsening of the inflammatory reaction may originate as complications due to dramatic increase in intracranial pressure and consequent cerebral herniation, neurologic deficits (cranial or spinal nerves), seizures, encephalopathy, and more rarely, subdural suffusions [12,17,44,45].

5. Clinical aspects

A large part of MD patients present prodromal symptoms the week prior to hospital admission. These symptoms generally arise after an incubation period of 2 d–10 d (with an average of 3 d–4 d) and are suggestive of an upper respiratory tract infection, including sore throat, coryza, cough and otalgia. The presence of fever in this phase is described by few patients, and can be masked by the use of antipyretics. These prodromes may be caused by a viral respiratory infection that occasionally act as a predisposing factor [1].

History of sudden onset fever accompanied by sore throat, arthralgia or myalgia suggests diagnosis of MD. Other frequent symptoms are pain in the dorsal region and asthenia. History of otitis, sinusitis, mastoiditis or pneumonia are most often associates with meningitis caused by *Streptococcus pneumoniae* or *Haemophilus influenzae (H. influenzae)*, the latter observed predominantly among children not vaccinated for this pathogen [1].

The principal signs and symptoms of MD related at hospital admission, during an epidemic of the disease in the city of Rio de Janeiro, between 1993 and 1995, were fever, neck rigidity, vomiting, purpura, headache and reduced consciousness [1]. Additionally, roughly 10% of patients with MD had evident pulmonary infiltrates on chest radiograph [12].

Clinical aspects of MD associated with a worse prognosis include: occurrence at extreme ages, presence of multiple purpura lesions, primary meningococcal pneumonia, shock, hypotension, tachycardia, coma, convulsions, altered consciousness, absence of neck stiffness and clinical signs of hyperventilation [1,3,12,15,47]. Among laboratory and/or microbiological findings associated with a more somber prognosis are: leukopenia, thrombocytopenia, isolation of meningococcus from serogroups C or W, presence of isolated bacteremia, elevated and persistent endotoxemia, metabolic acidosis, lactate greater than 4 mmol/L, and global cell count in cerebrospinal fluid less than 100/mm^3 [1,12,15,47].

5.1. MM

This is the most common clinical presentation of MD (seen in 30%–60% of cases) [3]. The classical picture of MM (fever, intense headache and "projectile" vomiting) and stiff neck are not always present, but are more often observed in patients over the age of nine [1]. Special patient groups (such as neonates, infants and the immunosuppressed people) may develop MM without the classic findings of the nosological entity [3]. Exanthema may present in 26%–62% of meningitis cases and is often petechial [12]. Meningitis may be associated with purpura, in these cases, indicating the presence of concomitant meningococcemia (12% of cases), and the patient may progress to systemic arterial hypotension and shock [12]. The lethality of MM varies between 5% and 18% [10], and is principally a consequence of cerebral herniation secondary to intracranial hypertension [4].

Summarized below are the particularities of MM pictures in different circumstances:

(1) Newborns: in this age group fever (or hypothermia), general impairment (irritability, constant crying, food refusal, drowsiness, torpor, coma), vomiting and fontanelle bulging. In some circumstances, there is a picture of sepsis, without possibility of defining its origin in the central nervous system. Signs of meningeal irritation may be absent in this age group [1–3,46,48].

(2) Children over 9 years of age, adolescents, and adults: MM usually presents in these age groups with a picture of fever, intense headache, vomiting, changes in consciousness, hypotension or signs of intracranial hypertension (systemic arterial hypertension, bradycardia, headache, respiratory arrhythmia, and papilledema) [1,3,46]. Neck stiffness may present in 87%–90% of cases [1], while Kernig and Brudzinski signs are uncommon [3]. Convulsive crises, altered levels of consciousness and behavioral changes are part of the progression of meningoencephalitis [1]. Focal neurological deficits (paresthesia, cranial nerve alterations) are present in up to 20% of cases [3].

5.2. Meningococcemia

Occurs in 20%–30% of MD cases [3,12]. It is defined by the absence of meningitis (cerebrospinal fluid cell count less than or equal to 10/mm^3). Signs of meningeal irritation or encephalitis may present, even with initial normal cerebrospinal fluid analysis [1]. The lethality of this clinical presentation is approximately 35%, however when the meningococcemia is associate with meningitis, the lethality decreases to approximately 20% [3]. Meningococcemia often presents acute evolution, with sudden onset fever, generalized asthenia, cold extremities and skin pallor, leukocytosis or leukopenia, exanthema, headache, drowsiness and arterial hypotension [12]. The classic sign of meningococcemia is petechial purpuric exanthema, presents in 40%–80% of cases, but it can be difficult to spot at the early stage of the disease [2]. On the other hand, initially the exanthema of meningococcemia may be maculopapular or urticariform, later progressing to lesions with a petechial or purpuric aspect or remain unaltered as occurs in 13% of cases [2]. The petechial lesions my eventually affect the conjunctival or oral mucosa [12]. A total of 37%–65% of patients refer intense lower limb myalgia [14].

Evolution to shock may occur within a few hours (6 h–12 h) in some patients, and death may occur 12 h–24 h after onset of the clinical picture [1,48]. At this more advanced stage of disease, the patient is not responsive, peripheral vasoconstriction is present, characterized by the presence of cyanotic and poorly perfused extremities [12]. The petechia may increase in size with progression to purpura fulminans, upper gastrointestinal bleeding, bleeding of the gums and bleeding at venous puncture sites (reflections of the disseminated intravascular coagulation). There may also be development of renal or suprarenal insufficiency secondary to adrenal bleeding (Waterhouse–Friderichsen syndrome), respiratory insufficiency and cardiac insufficiency, which may culminate in multiple organ failure [12,45,46].

A mild or transitory form of meningococcemia may occur in less than 5% of cases. It is characterized by an initial clinical picture suggestive of a respiratory or exanthematic virus or by the presence of fever alone. Clinical recovery occurs within 2 d–5 d, often without the use of specific antibiotics, with collected cultures showing unexpected growth of *N. meningitidis*. In these patients, bacteremia levels are usually low [12].

5.3. Other clinical presentations of MD

Primary pneumonia: presents in 5%–10% of MD patients, more common in adults, especially in those over 50 years of age. Of the serogroups isolated, serogroup Y was the most frequently associated with this clinical presentation. The prognosis of this presentation is poor in the elderly, with a 16% lethality rate in this population [12].

Septic arthritis: corresponds to 2% of clinical presentations of MD. It is generally monoarticular, affecting mainly the knee and the hip. Adolescents and younger adults have a greater propensity to develop this clinical presentation. It is associated with serogroups C and W [12].

Chronic meningococcemia: is an unusual presentation of MD, and can last from weeks to months. It is characterized by the presence of intermittent low fever, maculopapular exanthema and arthralgia or arthritis. It may evolve to meningitis and death [4].

Primary pericarditis (purulent): is described primarily in adolescents and adults, and in some cases, it may evolve with voluminous pericardial effusion and cardiac tamponade. It is associated with serogroups C and W [12,49–52].

Other unusual clinical presentations of MD include: conjunctivitis, peritonitis, panophthalmitis, epiglottitis, sinusitis, otitis, orbital cellulitis, osteomyelitis, endocarditis, salpingitis, urethritis and proctitis [1,12,33,53,54].

5.4. Complications and sequelae

Inflammatory syndromes may arise in 6%–15% of MD patients [3], due to deposits of antigen–antibody complex, composed mainly of capsular polysaccharides, specific immunoglobulins and complement fraction C3 [12]. These reactions generally occur 4 d–12 d after disease onset and include arthritis, mostly monoarticular (7%–14% of patients), cutaneous vasculitis, iritis, episcleritis, pleuritis and pericarditis [3]. Simultaneously, reappearance of fever, leukocytosis and increased serum C-reactive protein may occur. These inflammatory complications are more frequent in patients with severe MD, associated with meningococci of serogroup C and in adults and adolescents [2].

Other complications that can occur in MD patients include: activation of herpes simplex infection, symmetrical distal necrosis, extensive ulcerations on vasculitis topographies, digestive bleeding, subdural effusion, myocarditis, rhabdomyolysis, adult respiratory distress syndrome, acid–base and hydroelectrolyte disorders, cerebral infarction and intracranial suppuration [1,45,52,54–56].

Sequelae may occur in MD survivors. The risk of neurological sequelae occurrence is 7%–12% (a smaller rate than that of pneumococcal meningitis), primarily occurs in infants [1,4,57]. Hearing loss (persistent or transitory) is the most common complication, occurs in approximately 4% of cases [2]. Other sequelae includes: visual deficits, hydrocephaly, ataxia, dysphasia, motor deficits, developmental delays, arthritis, spasticity, convulsions, renal failure, osteonecrosis, atrophic scarring, loss of parts of the extremities, learning disabilities and behavioral disorders among others [1,2,12,45,58,59].

6. Diagnosis

Given the hypothesis of MM, the most important conduct in diagnostic terms is cerebral spinal fluid (CSF) analysis [60]. CSF collection is performed via rachicentesis, a procedure contraindicated in cases of intracranial hypertension (respiratory arrhythmia, papilledema, anisocoria, systemic arterial hypertension and bradycardia), recent onset seizure, lowered consciousness level (Glasgow coma scale less than 10), septic shock, presence of focal neurological deficit, thrombocytopenia (less than 50 000/mm^3) and cutaneous infection at the puncture site [15,60–63]. However, a study performed in Sweden demonstrated that exclusion of reduced consciousness level as a contraindication to the spinal tap and the performance of a spinal tap without previous cranial tomography were significantly associated with an earlier treatment and a more favorable clinical outcome [64]. The incidence of cerebral herniation after the spinal tap procedure in patients with suspected ABM is less than 1% [63]. Initiation of antimicrobial treatment should never be postponed in a patient with suspected meningitis, with the justification of awaiting rachicentesis. In these cases, the antimicrobial should be started, and the procedure performed posteriorly [60].

Imaging exams (cranial computerized tomography and nuclear magnetic resonance) may be useful in the evaluation of patients, especially in the following circumstances: (1) MM with the presence of focal signs; (2) diagnostic doubt (for instance, with cerebral abscess and/or intracranial suppuration is suspected); (3) patients with a history of chronic, recurring otitis media, due to the possibility of a picture of intracranial suppuration; (4) persistence of coma or seizures, after 72 h of adequate therapy; (5) patients with recurring meningoencephalitis; (6) infants with increased head circumference (if the fontanelle is open, preferentially perform transfontanelle ultrasonography); (7) association (suspected or confirmed) with congenital malformation; (8) patients with acquired immunodeficiency syndrome and other immunodeficiencies [1,60,63].

In MM, the CSF presents greatly increased cellularity (greater than 1 000 cells/mm^3, usually with a predominance of polymorphonuclear cells), low glycorrhachia (less than 40 mg/dL or less than 40% of blood glucose measured simultaneously with the spinal tap) and elevated proteinorrhacia (greater than 50 mg/dL) [57,63,65]. Nevertheless, one or more of these findings typical of ABM may be absent [65]. A Gram-stained bacterioscopy should also be performed, in which gram-negative diplococci are observed, presents a mean sensitivity of 75% (varying between 30% and 89%, depending on previous antibiotic use) [66] and specificity greater than 95% [67]. The sensitivity of the test for bacterial antigens in the CSF using the latex technique is widely variable (22%–93%), that drastically decreases with previous use of antibiotics (from 60% to 9%) [57], whereas CSF culture sensitivity varies from 80% to 94% (prior to antibiotic use) [14,66].

All patients with suspected MD should have blood drawn for hemocultures, immediately prior to initiation of specific antibiotic treatment. Its sensitivity varies from 50% to 93% [14,57], but can decrease to approximately 20% in patients who have previously used antibiotics [66]. The gold standard for the diagnosis of MD is isolation of *N. meningitidis* through culture of sterile body fluid such as blood or CSF, or less frequently the synovial, pericardial or pleural fluid. Isolation of the meningococcus through culture is important, not only for etiological diagnosis, but also to perform antimicrobial susceptibility tests (antibiogram), given the emergence of penicillin-resistant strains [12].

Polymerase chain reaction (PCR), on detecting small quantities of meningococcal DNA, is very useful in the diagnosis of MD

when Gram staining, culture, and/or latex are negative [3]. It is a laboratory test that can establish etiologic diagnosis more rapidly than culture, and whose sensitivity is unaffected by previous antibiotic use, and it can be performed even with inviable bacteria. PCR of the CSF in the diagnosis of MM presents sensitivity of 89%–100% and specificity of 95%–100% [66,68]. Another advantage of this laboratory test is its capacity to simultaneously test for *N. meningitidis*, *S. pneumoniae* and *H. influenzae* through multiplex PCR [3]. However, there are some disadvantages to this exam: a) PCR does not replace traditional culture methods since the antibiogram cannot be performed from PCR; b) it is not routinely available in many hospitals; c) false negative results may occur in meningococcal strains possessing genetic polymorphisms [10,14,69].

Biopsy of cutaneous lesions may be useful in the diagnosis of MD. Despite the relatively low sensitivity of skin sample culture (34%–47%), the culture can remain positive for up to 13 h after antibiotic administration, and Gram staining of the skin sample may identify *N. meningitidis* up to 45 h after antibiotic treatment [14]. Furthermore, a study reported a 56% sensitivity and a 100% specificity, when culture and Gram staining of the skin sample were simultaneously performed in cutaneous biopsies of patients with MD [70]. It is important to point out that the absence of growth in the skin sample culture does not exclude MD diagnosis [14].

7. Differential diagnosis

In the case of MM, must be made differentiation from other types of meningoencephalitis bacterial (*S. pneumoniae*, *H. influenzae* and *Listeria monocytogenes*), meningoencephalitis viral, intracranial suppuration, sepsis, sinusitis, tetanus, rabies, medications (such as metoclopramide) and strokes (with associated subarachnoid hemorrhage). The principal differential diagnoses of meningococcemia are: sepsis, disseminated gonococcemia, infectious endocarditis, Rocky Mountain spotted fever, typhus (endemic or epidemic), leukocytoclastic vasculitis, "hemorrhagic" dengue and other exanthematous viruses (enteroviruses, infectious mononucleosis, rubella, measles), ehrlichiosis, anaplasmosis, borreliosis (Lyme disease), Brazilian purpura fever, thrombotic thrombocytopenic purpura and idiopathic thrombocytopenic purpura, among others [1,12].

8. Treatment

Effective antibiotics can immediately interrupt *N. meningitidis* proliferation. The meningococci in the CSF are killed within 3–4 h of intravenous infusion of an adequate dose of an effective antibiotic. Plasmatic endotoxin concentrations were observed to decline by 50% 2 h after a dose of antimicrobial, and no emergence of an exacerbated inflammatory response was observed following a dose of the antibiotic (Herxheimer reaction) [12].

In 2012, SIREVA II tested 410 clinical specimens from Brazil, and found that 56% of these samples were sensitive to penicillin (MIC of penicillin to meningococcus less than 0.1 mcg/mL) and 44% presented intermediate sensitivity (MIC of penicillin to meningococcus of 0.1 mcg/mL to 1 mcg/mL). All tested samples were sensitive to chloramphenicol [29]. This intermediate sensitivity of the meningococcus to penicillin is secondary to the reduced affinity of penicillin binding proteins and the presence of gene *penA* polymorphisms in the meningococcus. The clinical significance of this intermediate sensitivity is not yet clear [12].

As a consequence of the results presented above and the extreme gravity represented by MD, it is essential that initial empiric treatment in a suspected MD case be a third generation cephalosporin (ceftriaxone or cefotaxime) [3,15]. The recommended dose of ceftriaxone in MD is 50 mg/kg every 12 h (maximum dose of 4 g/d) administered preferentially by intravenous route. Cefotaxime should be administered intravenously, at the dose of 50 mg/kg every 4 or 6 h (maximum dose of 12 mg/d) [60]. The choice between the two cephalosporins is based on patient age: use of cefotaxime is recommended for patients under 3 mo of age, due to immaturity of hepatic enzyme actions that occur in the neonatal period. The use of ceftriaxone may lead to an increase in serum indirect bilirubin levels in infants, which may in extreme cases lead to kernicterus [71].

If the culture results show sensitivity of the meningococcus to penicillin, substitution of third generation cephalosporin for crystalline penicillin G or ampicillin may be used [60] (both administered by intravenous route) due to their low cost and narrow action spectrum [10,72,73]. The recommended dose of crystalline penicillin G is 300 000 U.I./kg to 500 000 U.I./kg [1,60], in 4 h intervals (maximum dose of 24 million units/d) [60]. The recommended dose of ampicillin is 300 mg/kg/d to 400 mg/kg/d [1,60] in 4 h intervals (maximum dose of 12 g/d) [60].

In an exceptional situation of temporary in-hospital unavailability of third generation cephalosporins and the patient doesn't present penicillin allergy, a treatment option for intermediate sensitivity meningococcus is meropenem [12], administered intravenously, at the dose of 40 mg/kg every 8 h (adults: two grams every 8 h) [12].

In patients with severe allergy to beta-lactams, the treatment of choice is chloramphenicol [1,3,12,15], at the dose of 25 mg/kg every 6 h (maximum dose of 4 g/d), since this agent possesses bactericidal action against the meningococcus, adequately penetrates the blood–brain barrier, and is active against meningococcus that has an intermediate sensitivity to penicillin [12]. If chloramphenicol is unavailable, options that can be used in patients severely allergic to beta-lactams are: aztreonam at the dose of 50 mg/kg every 6 h or 8 h depending on severity (in adults it is possible to use 2 g every 6 h, at the maximum dose of 8 g/d) [60] or a fluoroquinolone such as moxifloxacin (400 mg by intravenous route in a single daily dose) [12,60]. Use of the latter treatment is currently restricted in the United States to the treatment of MD, due to recent reports of meningococcal serogroup B resistance to the quinolones in some American states [15], and also due to lack of controlled clinical studies using this antibiotic in the treatment of MD [74].

Despite speculation in the medical literature about the ideal duration of MD treatment [10,15], antimicrobial treatment is usually maintained for 7 d [14,60], although this duration can be individualized according to the clinical response of each patient [60].

Dehydrated or hypotense patients should be initially hydrated with rapid intravenous infusion of crystalloids (as recommended in sepsis and septic shock in general), which should be carefully monitored to avoid a possible water overload [48]. If hypotension persists or evolves to shock, initiate sympathomimetic amines [75]. In patients with MM or milder cases of meningococcemia, fluid restriction should be avoided, unless there is hyponatremia

(laboratorial manifestation of syndrome of inappropriate antidiuretic hormone secretion) or a clinical picture suggestive of intracranial hypertension [12].

The use of steroids in meningococcemia, especially in patients with concomitant purpura fulminans or Waterhouse–Friderichsen syndrome is controversial [12,45,48]. However, some authors recommend the use of low dose steroids (hydrocortisone 200 mg/d by intravenous route) in adults with septic shock who do not respond adequately to intravenous fluid replacement and the use of vasoactive amines [75].

Dexamethasone is indicated as an adjuvant treatment in pneumococcal meningitis (suspected or confirmed) in adults and in meningitis caused by *H. influenzae* type B in children. In these cases, dexamethasone at the dose of 0.15 mg/kg intravenously every 6 h during the first two to four days should be initiated 10 min–20 min or concomitantly with the first dose of antibiotic [60]. Accordingly, dexamethasone is usually administered to adults and children with ABM while awaiting culture (blood and/or CSF) results [14]. Dexamethasone was not shown to be beneficial in patients with MM, and should thus be suspended as soon as this microbiological diagnosis is confirmed [15,48,76,77].

The inflammatory complications associated with MD are treated with acetylsalicylic acid or another non-steroidal anti-inflammatory agent and in most cases complete resolution of the clinical picture is achieved within 14 d of treatment initiation, usually without associated sequelae [2].

Although its efficacy is controversial [12,15], mannitol (at the initial dose of 0.5 g/kg to 1 g/kg, followed by maintenance doses of 0.25 g/kg to 0.30 g/kg every 4 h) may be used in the treatment of intracranial hypertension [48,78]. Other measures that may be useful in reducing intracranial pressure are elevating the headrest to 30° and correct positioning of the patient in the hospital bed: avoid head turning to either side and not allowing the neck to hyperextend [1].

Orotracheal intubation may be needed to protect the airways of patients with Glasgow coma scale less than or equal to seven and/or for those who require hyperventilation, in cases of intracranial hypertension [48,78,79].

Proposed treatment of disseminated intravascular coagulation and/or purpura fulminans, which may present in MD and in other severe sepsis cases (recombinant activated protein C and unfractionated heparin) were investigated, but none showed clinical benefits in the investigated endpoints. A randomized clinical trial that included children with suspected MD did not show increased survival in the more severe cases among subjects who received an endotoxin neutralizing protein or recombinant bactericidal or permeability-increasing protein ($rBPI_{21}$) [14]. Furthermore, there are no controlled studies that currently endorse the use of other supportive treatments (plasmapheresis, induced hypothermia, paracetamol and polyclonal immunoglobulin) in MD [13,14,45,80].

9. Prevention

9.1. Chemoprophylaxis for N. meningitidis

Indicated for close contacts with a case of MD: intradomicile contacts, daycares, orphanages, barracks, shelters, pre-primary classes, kindergarten, nursery, play groups and individuals who have been in daily contact for at least 4 h in the 7 d preceding patient hospitalization, or individuals who have had more than eight consecutive hours of contact during at least one of the 7 d preceding patient hospitalization. These close contacts carry a risk of developing MD up to 1 000 times greater than the general population. It should be clarified to the group of close contacts that there is risk of falling ill, even receiving chemoprophylaxis and that this risk may persist over the subsequent months [1].

Healthcare professionals who have been exposed to patients with MD should also receive chemoprophylaxis, in the following situations: mouth-to-mouth resuscitation, orotracheal intubation, aspiration of respiratory and fundoscopy exam secretions (procedures performed without the use of surgical masks) [15].

The recommended antibiotics for MD chemoprophylaxis are: a) rifampicin 20 mg/kg/d (in children) or 600 mg/d (in adults), by oral route (PO), every 12 h for 2 d; b) ceftriaxone 250 mg (for children under 15 years old, the dose is 125 mg), in a single intramuscular dose (preferred option for pregnant women); c) ciprofloxacin 500 mg, PO, in a single dose (not recommended routinely for those under 18 years old, pregnant and nursing women) [15,81,82] and d) azithromycin 10 mg/kg (maximum dose of 500 mg), PO, in a single dose [83]. The risk of MD in the domiciliary contacts of the index patient can be reduced by roughly 89%, if the above-mentioned antibiotics are administered [84].

Due to the risk of secondary cases during the first few days after exposure in a case of MD, chemoprophylaxis should be initiated as soon as possible, preferably within the first 24 h of identification of the index patient. Chemoprophylaxis should not be administered after 14 d of the last contact with the index patient, since the benefit of the chemoprophylaxis in this situation is likely small or null [46,81].

Furthermore, patients treated with penicillin or chloramphenicol should receive chemoprophylaxis, because these antibiotics are not capable of decolonizing the nasopharynx, and thus a nasopharynx colonization with a virulent strain of *N. meningitidis* persists, [15,84] unlike cases treated with ceftriaxone in which decolonization occurred by the employed antibiotic [15].

9.2. N. meningitidis vaccines

Conjugated antimeningococcal vaccines can be administered to young infants, as with other conjugated vaccines [25]. Their efficacy is greater than 95%, and the studies published with conjugate vaccine C in England and Holland indicated a protective effect on the unvaccinated when high vaccine coverages are reached in the population (collective immunity) [85–87]. Early in 2013, the European Commission approved the four-component meningococcal serogroup B (4CMenB) vaccine, Bexsero [88]. The 4CMenB is a novel vaccine composed of three recombinant proteins: factor H-binding protein, Neisserial heparin-binding antigen, and Neisserial adhesin A, the outer membrane vesicles from the New Zealand outbreak strain (NZ98/254), which incorporates the immunodominant Porin A P1.4 protein [89]. This and the bivalent recombinant lipoprotein (rLP2086, lipoprotein responsible for dysregulation of the complement pathway) vaccine, Trumenba, have subsequently been used prior to licensure in the United States, under investigational new drug applications, to respond to outbreaks of serogroup B disease among university students [88].

Different countries with different epidemiology of MD have of that reason various recommendations for meningococcal vaccination:

a) United States

There are three conjugated vaccines available: quadrivalent polysaccharide and diphtheria toxoid conjugate vaccine, quadrivalent polysaccharide and mutant diphtheria toxin conjugate vaccine, and the bivalent meningococcal conjugate vaccine and *H. influenzae* type b conjugate vaccine [25]. The Advisory Committee on Immunization Practices recommends routine vaccination with one quadrivalent conjugated anti-meningococcal vaccine (MenACWY) for all individuals between the ages of 11 and 18 years (initial dose at 11 or 12 years, and booster dose at 16 years) [81,90], and also for some individuals between the ages of 2 and 10 and 19 and 55 years who present an increased risk for developing MD: individuals with persistent complement component deficiencies; individuals with functional or anatomic asplenia; microbiologists routinely exposed to *N. meningitidis*; individuals identified as at risk due to an outbreak of MD caused by serogroups A, C, W, or Y; military recruits; university freshmen residing in collective housing, and people to travel to or reside in areas where MD is hyperendemic or epidemic [81,82]. Routine use of quadrivalent conjugated antimeningococcal vaccine is not recommended in the US, for healthy adults between the ages of 19 and 55 years, since incidence of MD in this age group is low, and is not altered by routine immunization. For adults 56 years old and elders who require anti-meningococcal vaccination but that will likely only use one dose of this vaccine, the quadrivalent polysaccharide meningococcal vaccine (MPSV4) is preferred, since it is immunogenic in older adults. For individuals 56 years old and elders who require more than one anti-meningococcal vaccine, the choice is the quadrivalent conjugated meningococcal vaccine [81].

A meningococcal serogroup B (MenB) vaccine is indicated for individuals 10 years and elders who present an increased risk of developing MD: patients with persistent deficiency of complement components; those with anatomical or functional asplenia; microbiologists routinely exposed to *N. meningitidis* and those identified as being at high risk due to an outbreak of MD caused by serogroup B [90,91]. MenB vaccines are not licensed for children less than 10 years of age and are currently not recommended for children between the ages of 2 mo and 9 years who have increased risk for MD caused by serogroup B. The MenB vaccines are not recommended for individuals who travel to or reside in locations where MD is hyperendemic or epidemic, because most cases of MD in these countries are not caused by serogroup B. The vaccines are also not routinely recommended for university freshmen living in group housing and military recruits. MenB vaccines can be administered to adolescents and young adults between the ages of 16 and 23 years to generate short-term protection against most serogroup B meningococcal strains, and its preferred use is in the age group between 16 and 18 years [91,92].

b) United Kingdom (UK)

Since 1999, all infants should receive the meningococcal conjugate C vaccine [7]. As an emergency response to a national outbreak of group W meningococcal disease, 13–18 years old and new university entrants have been offered the quadrivalent MenACWY conjugate vaccine since August, 2015 [93]. Posteriorly, Campbell *et al.* found a major reduction (69%) in observed serogroup W meningococcal cases compared with predicted serogroup W meningococcal cases among the first cohort in England to be offered MenACWY conjugate vaccine after the first year of an emergency vaccination program for teenagers, even with a small number of cases. This decrease occurred despite national vaccine coverage of only 37% for this cohort [94].

The 4CMenB vaccine is immunogenic in young infants and older children. The vaccine has been estimated to provide coverage against 88% of circulating serogroup B strains in England and Wales [95]. In September, 2015, the UK Department of Health incorporated it into their childhood immunization schedule: the vaccine was offered to all infants born since July 1, 2015, at 2 mo, 4 mo and 12 mo [89]. Studies in adolescents and adults demonstrated that 4CMenB was highly immunogenic after two doses [88]. Moreover a national observational cohort study conducted in England demonstrated that two-dose 4CMenB priming schedule (at 2 mo and 4 mo of age) was highly effective in preventing MenB disease in infants. By the end of June, 2016, MenB cases in vaccine-eligible infants had halved, irrespective of the infants' vaccination status or expected vaccine strain coverage [89].

Serum samples from children immunized with a meningococcal serogroup B vaccine demonstrated potent serum bactericidal antibody activity against the hypervirulent *N. meningitidis* serogroup W strain circulating in England. However, the effectiveness of 4CMenB against meningococcal carriage, and therefore, its ability to provide herd protection, which is a major objective of an adolescent programme, is less certain than with conjugate vaccines. These observations support the recent implementation of both the adolescent MenACWY conjugate and infant serogroup B meningococcal immunization programmes in the UK [96].

c) Brazil

The meningococcal conjugate C vaccine has been used in the *Centros de Referência de Imunobiológicos Especiais* for special subgroups since 2003 and was included in the immunization schedule for children as of 2010, and is recommended starting at 2 mo of age [97].

MD vaccination is recommended, 2 wk prior to departure, for individuals traveling to countries where MD is hyperendemic or epidemic, especially if there is to be prolonged contact with the local population. Hyperendemic regions of MD include the African meningitis belt, during the months of December to June [81,98]. For those traveling to Mecca for the Hajj, proof of vaccination against *N. meningitidis* (preferably the quadrivalent conjugated antimeningococcal vaccine) is required in the preceeding 3 years. Children between the ages of 9 mo and 23 mo can receive the second dose of tetravalent conjugated meningococcal vaccine 8 wk after the first dose, prior to traveling [81].

Meningococcal vaccination is contraindicated for individuals with known severe allergic reaction to any component of the vaccine, includes the diphtheria or tetanic toxoid. History of Guillain Barré syndrome is not considered a contraindication or precaution for meningococcal vaccination. Despite the absence

of randomized clinical studies of the MPSV4 or MenACWY vaccines performed exclusively on pregnant or nursing women, pregnancy does not justify a delay in meningococcal vaccination, if there is precise use of this vaccine [81].

9.3. Other measures

In addition to chemoprophylaxis and vaccination, there are other important epidemiological measures in MD: (i) mandatory notification within the first 24 h of hospitalization; (ii) respiratory droplet precautions, previously known as "respiratory isolation", which should be maintained for a period of 24 h following the first dose of antibiotic; (iii) patient hospitalization preferably in an individual room until the respiratory droplet precaution has passed; if this is not possible, maintain a divisor and a distance between hospital beds of at least 1.5 m [1,15].

Conflict of interest statement

We declare that we have no conflict of interest.

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