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Chapter

# Meningococcal Meningitis

*Trond Flægstad*

## Abstract

Meningococcal disease may present as meningitis, septicemia, or a combination of the two. Generally, meningitis has a gradual onset, with fever, headache, and neck stiffness as the most frequent clinical symptoms. By contrast, fulminant septicemia may develop within hours, and is characterized by petechial bleedings and shock. It is of vital importance to diagnose and treat meningococcal disease rapidly. The diagnosis is based on the culture of Neisseria meningitides from blood or cerebrospinal fluid, or on the polymerase chain reaction (PCR) of spinal fluid. Cefotaxime or ceftriaxone are usually recommended as antibacterial treatment. There is a vaccine effective against disease with serogroups A, C, Y, and W.

**Keywords:** meningococci, meningitis, Neisseria, vaccine

## 1. Clinical features of meningococcal disease

Meningococcal disease is one of the most devastating infections in an individual or community, and is caused by the bacterium *Neisseria meningitidis* with diseases most often in the forms of meningitis, septicemia, or a combination of meningitis and septicemia [1–4]. The onset can be nonspecific, but is usually abrupt with symptoms as fever, malaise, and myalgia, and a rash that initially may be urticarial, maculopapular, or petechial (purpuric). Fulminant meningococcal septicemia is usually characterized by the rapid development of hypotension, ecchymosis, and disseminated intravascular coagulation (DIC).

**Meningitis** is characterized by gradual onset of fever, headache, neck-stiffness, backache, and nausea.

In meningococcal meningitis, drowsiness, reduced cognitive function, stiff neck, and positive Kernig and Brudzinski's signs, all manifestations of meningeal inflammation, are usually present along with fever. Neurological findings may be cranial nerve dysfunction, seizures, focal cerebral signs, and reduced consciousness. The symptoms and signs of meningococcal meningitis are indistinguishable from those associated with acute meningitis caused by *Haemophilus influenzae* type b bacteria, *Streptococcus pneumoniae*, and other bacteria. However, the presence of petechiae strongly implicates *N. meningitidis.*

## 2. Typing systems and classification of *Neisseria meningitidis*

*N. meningitidis* is a Gram-negative diplococcus. Several methods for typing and classification of *N. meningitidis* exist. The system currently used most widely is based on antigenic differences of different bacterial surface structures and on susceptibility to sulfonamides. According to this scheme, meningococci are classified by:

(a) serogroup (capsular polysaccharides) (A, B, C, X, Y, W are most common in invasive disease); (b) serotype (the class 2 or 3 outer-membrane proteins); and (c) subtype (the class 1 outer-membrane protein). The phenotype of a meningococcus is written: serogroup:serotype:subtype. According to this, the epidemic strain in North Norway (serogroup B, serotype 15, subtype P1.7.16) is designated: B:15:P1.7.16 [5].

## 3. Epidemiology of meningococcal meningitis

*N. meningitidis* only infects humans; there is no animal reservoir. The bacteria can be carried in the throat and sometimes, for reasons not fully understood, can overwhelm the body's defenses allowing infection to spread through the bloodstream to the brain. It is believed that 1–10% of the population carries *N. meningitidis* in their throat at any given time. However, the carriage rate may be higher in epidemic situations [6].

The bacteria are transmitted from person to person through droplets of respiratory or throat secretions from carriers. Close and prolonged contact—such as kissing, sneezing or coughing on someone, or living in close quarters (such as a dormitory, sharing eating or drinking utensils) with an infected person facilitates the spread of the disease. The average incubation period is 4 days, but can range between 2 and 10 days.

Meningococcal disease occurs in almost every country in the world regardless of climate and economic development. Serogroup A disease has been most often associated with widespread epidemics in Africa where epidemics of serogroup A meningococcal disease tends to occur every 7–10 years in sub-Saharan Africa (**Figure 1**).

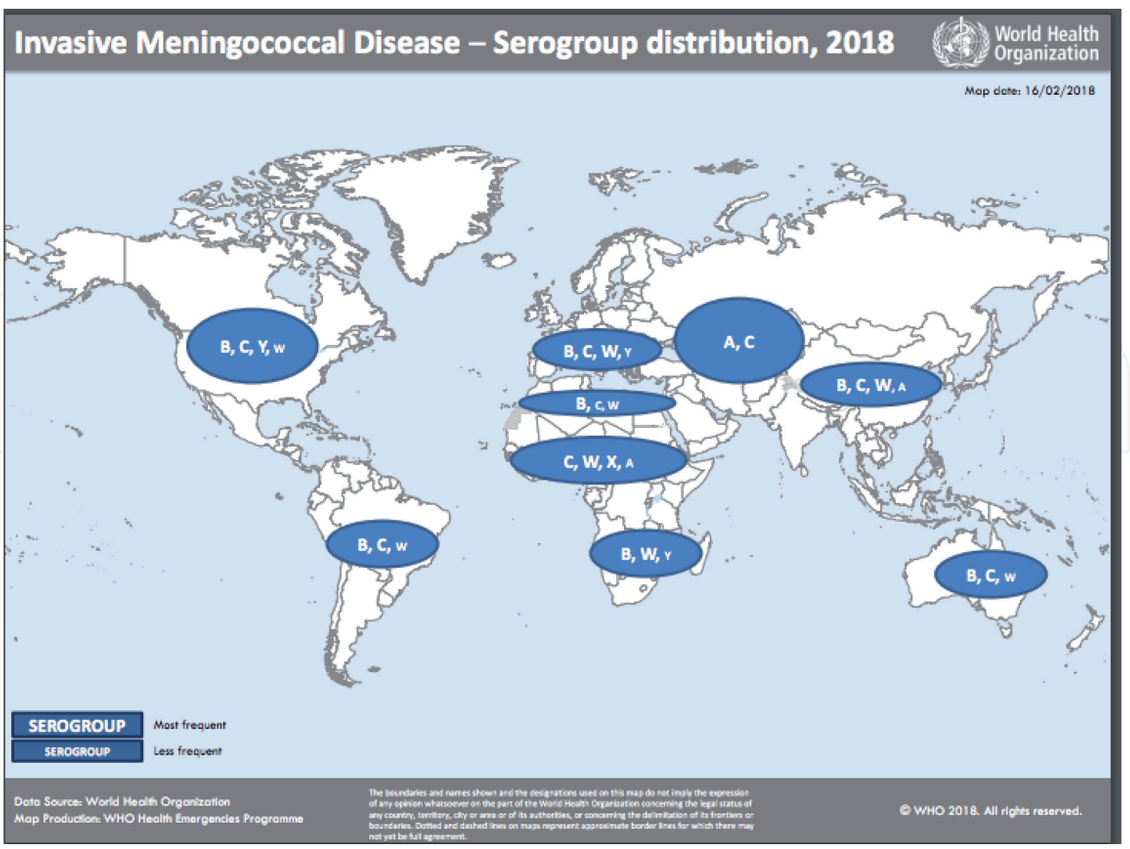


**Figure 1.**
*Serogroup distribution of invasive meningococcal disease, 2018. Source: http://www.who.int/emergencies/diseases/meningitis/serogroup-distribution-2018.pdf.*

The highest rate of meningococcal disease occurs in children below 4 years of age, but all age groups may be affected [5–7].

The overall mortality rate for invasive meningococcal disease is 10–15%, while about 15% of the survivors suffer from permanent sequelae like hearing impairment, neurological disability, and digit or limb amputation [3].

In 2015, there were 379,000 deaths caused by meningitis worldwide, of those 73,000 by *N. meningitis*; most of these deaths were in children less than 5 years of age [6, 8].

## 4. Laboratory diagnosis of meningococcal meningitis

Initially, the diagnosis of meningococcal disease rests on clinical signs and symptoms. On admission, appropriate specimens should be immediately collected to ensure correct diagnosis.

### 4.1 Collection of appropriate specimens for bacteriological analysis

Antibacterial treatment of suspected meningococcal meningitis must be started as soon as possible and is often initiated before admission. To ensure correct diagnosis, it is important to collect bacteriological specimens before therapy is started. At the hospital, blood culture should always be collected. Cerebrospinal fluid (CSF) is collected for microscopy, culture, and detection of meningococci by antigen testing or by polymerase chain reaction (PCR). One drop of CSF is collected on microscope slide and dried in air for microscopy. One or two drops of CSF are tapped on a swab and placed in a tube of Amies or Stuart transport medium for culture. When placed in a transport medium, the bacteria will stay alive for a longer period of time than in liquid.

CSF can also be collected in a liquid culture medium, like a blood culture medium. Some laboratories supply clinical departments with agar culture media so that CSF can be collected directly on them before being sent to the laboratory. Finally, 1 ml of liquid CSF is collected in a sterile container for bacterial culture and polymerase chain reaction (PCR).

Because meningococci survive longer in the throat than in the CSF and blood after antibacterial treatment has started, a throat sample is highly recommended. The specimens should be sent to the laboratory and processed immediately. If the specimens have to be stored before transport, they should preferably be kept at 8–10°C or at room temperature. Petechial skin lesions also represent a potential diagnostic specimen. Meningococci are often present in the petechiae, and Gram-stain smears and culture of needle aspirates or punch biopsies from skin lesions are positive in up to 60% of cases [9]. This can be particularly useful when antibiotic treatment was started before cultures were obtained.

PCR can detect small quantities of bacterial DNA and is useful, because of results may be obtained after a few hours, and sensitivity is not affected by previous antibiotic treatment [10].

### 4.2 Microbiological diagnosis of meningococcal meningitis

#### *4.2.1 Culture*

Conventionally, culture is the standard method for making a diagnosis of meningococcal disease. If the specimens have to be stored before transport, they should preferably be kept at 4°C for CSF in order to be analyzed by PCR or at room

temperature (suitable for the strains in Amies medium, or cultures on chocolate agar medium) in order to be analyzed.

In the microbiology laboratory, CSF from patients with suspected meningococcal meningitis is cultured on blood agar and chocolate agar overnight at 36.5–37.0°C in 10% $CO_2$. In some laboratories, CSF is also cultured in blood-culture bottles or in another liquid medium. Throat specimens are cultured on agar media selecting growth of meningococci. Blood is cultured in commercially available bottles containing a rich culture medium supporting the growth of a wide range of bacteria.

*4.2.2 Microscopy and agglutination methods*

A Gram-stained preparat of CSF is most often analyzed. Meningococci typically are seen as Gram-negative [red] coffee bean-like diplococci. A fluorescent staining method using acridine-orange which stains bacteria orange-red and human cells pale yellow has also proved valuable. Agglutination method, directly from sediment coming from CSF, after centrifugation, can be used to determine meningococcal serogroup, except for serogroup B.

*4.2.3 Genetic methods*

Microbial nucleic acids are stable and can be detected in body fluids and tissues even though the microbes are dead and are in very small quantities. Real-time PCR can give results in approximately 2 h, much easier by comparing with conventional PCR, and can give species and serogroup identification.

### 4.3 Nonbacterial tests

In meningococcal meningitis, the number of leukocytes and levels of acute phase proteins such as procalcitonin and C-reactive protein in the blood are normally elevated. The number of leukocytes in CSF usually exceeds 800 cells/$mm^3$, and there is a relative increase in the number of granulocytes. The concentration of protein is increased and that of sugar decreased. In early stages of meningococcal meningitis, leukocytes may be absent from the CSF, although the culture later may grow meningococci. The absence of leucocytes does therefore not exclude bacterial meningitis.

## 5. Treatment of meningococcal meningitis

### 5.1 General principles

National and international guidelines for treatment of meningococcal disease exist, and our recommendations are based generally on these guidelines [3, 11]. In addition to prompt use of antimicrobial agents, the immediate treatment of increased intracranial pressure, seizures, and shock if present, must be started, and normal hydration and electrolyte balance must be restored. Because shock is a very early event and can often be life threatening, its management should take precedence over fluid restrictions aimed at preventing the inappropriate secretion of antidiuretic hormone. Infants with vomiting may show relative hypovolemia.

There is no report supporting the use of prophylactic glucocorticoid therapy in meningococcal meningitis. The majority of patients enrolled in trials with adjunctive dexamethasone therapy are children with *H. influenzae* meningitis. The benefits

of glucocorticoid therapy may not extend to children with other pathogens, and the benefit in adults is even less clear.

### 5.2 Principles of antimicrobial treatment

Bacterial meningitis is an infection in an area of impaired host resistance. Specific antibodies and complement are frequently absent from the cerebrospinal fluid in patients with meningococcal meningitis, resulting in inefficient phagocytosis and subsequent rapid bacterial multiplication. It is therefore necessary to treat meningitis with antimicrobial agents that are bactericidal, penetrate to the CSF easily, and rapidly reach bactericidal concentrations. The increased permeability of the blood-brain barrier during meningeal infection enhances the penetration of most antibiotics into CSF.

In experimental meningitis, it has been found that maximal bactericidal activity of an antibacterial agent occurs at a concentration 10–30 times greater than the minimal in vitro bactericidal concentration. Cranial imaging is required before spinal puncture in patients who are in coma, have papilledema, or have focal neurological symptoms. Before imaging, adequate clinical specimens must be collected and empirical therapy started. Empirical therapy must be selected on the basis of the age of the patient, symptoms, and the local frequency of etiological bacterial pathogens.

In cases of suspected bacterial meningitis (or meningococcal sepsis), patients should be treated empirically to cover the most likely pathogens while awaiting culture results. Cefotaxime or ceftriaxone is usually recommended [3]. This might be changed to penicillin G when the diagnosis is bacteriologically confirmed. For patients with a life-threatening penicillin allergy characterized by anaphylaxis, chloramphenicol is recommended.

The duration of therapy is normally 7 days. Rare isolates of beta-lactamase producing meningococcal strains with high-level resistance have been described, as have clinical isolates with altered penicillin-binding proteins and intermediate resistance to penicillin [MIC, 0.1–1.0 g/l]. Since many of these patients were successfully treated with benzylpenicillin, the importance of in vitro penicillin insensitivity in meningococci is unclear.

## 6. Prevention of meningococcal meningitis

### 6.1 Primary prevention of meningococcal disease

Vaccines against meningococcal disease exist, but protection is only against meningococcal disease of the same capsular polysaccharide present in the vaccine. A present, there are vaccines against serogroups A, C, Y, and W; commonly combined in a quadrivalent conjugated vaccine (A, C, Y, W).

Recommended immunization with this vaccine is for children and adults with complement deficiency, asplenia, who are at risk during a community outbreak attributable to a vaccine serogroup, are residents or will travel to endemic areas, or are HIV positive [3]. The conjugate vaccines confer long-lasting immunity (5 years or more), prevent carriage, and induce herd immunity.

Polysaccharide vaccines are used during a response to outbreaks, mainly in Africa. They are either bivalent (A, C); trivalent (A, C, W); or tetravalent (A, C, Y, W) [6]. They are not effective before 2 years of age, offer a 3-year protection but do not induce herd immunity.

At present, there is no long-lasting protective vaccine against the serogroup B meningococcus, but it is used in outbreak response [6].

### 6.2 Secondary prevention of meningococcal disease

Following a case of meningococcal disease, contacts should be vaccinated if the causative strain belongs to a serogroup against which a protective vaccine exists (A, C, Y, and W). However, it takes 2–3 weeks to produce protective antibodies, during which period secondary disease may develop. The use of chemoprophylaxis to eradicate the disease-causing strain from close contact, thereby stopping the spread of the infection, is therefore recommended. Household members of a patient with meningococcal disease have a much higher risk of contracting the disease than the general population. Household members of the patient and kissing contacts are most likely to carry the disease-causing strain and need chemoprophylaxis. Other close contacts to whom chemoprophylaxis may be considered are babysitters including grandparents or other family members, and kindergarten employees. Rifampicin, ceftriaxone, or ciprofloxacin are the recommended drugs [3].

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