EDUCATIONAL COMMENTARY – MENINGOCOCCAL MENINGITIS: NEISSERIA MENINGITIDIS SEROGROUPS

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Learning Outcomes

Upon completion of this exercise the participant should be able to

- recognize and understand the causes of meningococcal meningitis
- describe the microbial behavior of Neisseria meningitidis in humans
- understand how Neisseria meningitidis infection is treated and prevented
- determine what laboratory testing should be used to confirm the presence of Neisseria meningitidis
- understand what a serogroup is, and which serogroups are primarily responsible for meningococcal meningitis infections

Background

Meningococcal meningitis is a serious, contagious disease that can have a fatal outcome when not treated promptly or can leave a patient with serious lifelong complications. Neisseria meningitidis is considered a normal bacterium in the nasopharynx of many healthy individuals. Transmission occurs when an individual comes in contact with the saliva of a person who is contagious. In certain circumstances, the organism can enter into the central nervous system and cause meningitis. Meningitis is defined as inflammation of the thin lining of the brain and/or spinal cavity. In addition to meningococcal meningitis, N. meningitidis causes other meningococcal disease such as septicemia which is a bacterial infection in the blood, pneumonia, urethritis, conjunctivitis, septic arthritis, and pericarditis.

In the United States, meningitis is most commonly caused by a viral infection. The second most common cause is a bacterial infection, and in rare circumstances it can be caused by a fungal infection. Viral infections are commonly caused by non-polio enteroviruses. Bacterial meningitis is normally caused by a few bacteria: Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, Group B Streptococcus, or Listeria monocytogenes. Fungal infections are typically seen in individuals with weakened immune systems. There are several risk factors for bacterial meningitis, which include age (infants are more likely to contract the infection due to their immature immune system). Community settings such as college campuses, military quarters, or communal living quarters can contribute to the spread of bacteria. Asplenic patients or those with weakened immune systems are also at increased risk of meningococcal infection. Those who have undergone certain surgical procedures, those working in the medical field who are exposed to infected patients or infected patient specimens, and those who travel to
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certain parts of Africa during dry seasons or to Mecca are also at risk.\textsuperscript{4,5,6} The prognosis for viral meningitis is more promising than bacterial meningitis, as bacterial meningitis has a fast onset and must be treated with antibiotics without delay to ensure patient survival. Despite antibiotic availability, 5-10\% of patients die from meningitis and 10-20\% are left with permanent damage.\textsuperscript{5}

**Neisseria meningitidis** Infection

As stated, bacterial meningitis onset can occur quickly, in as little as a few days to a few hours. Common symptoms include sudden onset of fever, stiff neck, vomiting, confusion, headache, skin rash, and sensitivity to light. Bacterial meningitis is serious in nature and it is crucial to begin antibiotic treatment immediately to avoid death and permanent neurological impacts to vision, speech and cognitive skills.\textsuperscript{4,5,6}

*Neisseria meningitidis* is a Gram-negative diplococci only found naturally in humans.\textsuperscript{1} In 2014 in sub-Saharan Africa, 11,908 suspected cases of meningococcal meningitis were reported, with 1,146 deaths.\textsuperscript{5} In the U.S., there were 4,100 cases of all forms of bacterial meningitis each year between 2003 and 2007, with 500 deaths each year.\textsuperscript{4} One in four adolescents is an asymptomatic carrier of *N. meningitidis*, and most infected individuals experience a period as an asymptomatic carrier.\textsuperscript{4,5,7,8}

*Neisseria meningitidis* can exist as an encapsulated or unencapsulated bacterium, though most invasive organisms are encapsulated which means they are surrounded by a polysaccharide capsule. This capsular polysaccharide is used to classify an isolate by one of twelve known serogroups.\textsuperscript{9} A serogroup is a group of bacteria containing a common antigen, used in the classification of certain genera of bacteria.\textsuperscript{10} The 12 *N. meningitidis* serogroups are identified as follows: A, B, C, H, I, K, L, W, X, Y, Z, and 29E (Z'). At one point there were 13 serogroups identified, but in recent years serogroup D is no longer recognized.\textsuperscript{11} Of the twelve known serogroups, most bacterial meningitis is caused by six of the twelve. These six serogroups are groups A, B, C, W, X and Y.\textsuperscript{5,9,12} In the U.S., 40\% of all meningococcal disease is caused by serogroup B.\textsuperscript{13}

Treatment of bacterial meningitis caused by *N. meningitidis* is not serogroup dependent. It is recommended that antibiotic treatment should be started immediately, even before laboratory testing results report the presence of *N. meningitidis*. However, to confirm the diagnosis it is best to obtain a lumbar puncture for cerebrospinal fluid (CSF) culture before antibiotic treatment begins, as antibiotics can impact growth of the culture and cause a false negative. Many antibiotics can be used to treat *N. meningitidis*, including penicillin, ampicillin, chloramphenicol and ceftriaxone. Treatment should be guided by antimicrobial susceptibility testing. Penicillin should not be used for empiric therapy as the organism could be resistant. Empiric therapy recommendations are currently cefotaxime or ceftriaxone.
(third-generation cephalosporins) until the antimicrobial susceptibility report is available. If the organism is susceptible to penicillin, penicillin G may be used with dosing correlating to the MIC result. According to the World Health Organization, in epidemic conditions such as some areas of Africa where there is limited health infrastructure and resources, ceftriaxone is the drug of choice.\(^5\)

**Prevention of *Neisseria meningitidis***

Over the last several decades, pharmaceutical companies have worked to develop preventative measures against *N. meningitidis*. There has been successful development of vaccines to prevent disease for many individuals. Vaccines for A, C, W and Y have been available and used since the 1970s.\(^9\) These vaccines were developed using serogroup-specific capsular polysaccharides. With serogroup B, this approach was not possible, as its capsular polysaccharide is poorly immunogenic.\(^1,7\) In 2014 and 2015, vaccines were successfully developed and released for serogroup B. These vaccines will defend against the most common U.S. cause of bacterial meningitis, serogroup B, and are FDA-approved for individuals between 10-25 years of age.\(^14\) Vaccines are now available to defend the human body from the five of the six serogroups which are responsible for the majority of disease. Though vaccines exist, 1 in 5 persons aged 13 to 17 are not vaccinated in the United States.\(^15\)

Since serogroup B causes around 40% of meningitis it is recommended that individuals at risk of encountering infection be vaccinated against serogroup B. Vaccination is routinely recommended for adolescents 10 years and older who are at increased risk for serogroup B, especially college age students (16-23), anyone whose spleen has been damaged or removed, anyone with the immune deficiency called “persistent complement component deficiency”, and those who work routinely with infected patients or their specimens. For adequate protection from serogroup B meningitis, more than one dose of the vaccine is recommended, and the same vaccine should be used for all doses. The timing and dosing amount are determined by the patient’s health care provider.\(^16\)

There are some individuals who should not receive a vaccination. These individuals include those who have had a previous allergic reaction to the vaccine, or have an allergy to any ingredient contained within the vaccine. Those who are pregnant or breastfeeding should not receive the vaccine, as there are no studies which assessed the risks for pregnant individuals. It is also important not to receive the vaccine during a time when the immune system is compromised by receiving chemotherapy or certain anti-rejection medication.\(^16,17\)

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**Laboratory Investigation**

*Neisseria meningitidis* is a Gram-negative diplococci. On a Gram stain prepared from CSF, it can be seen both extracellularly and intracellularly in polymorphonuclear (PMN) leukocytes. *Neisseria meningitidis* is cultured at normal body temperature of 35-37°C in an environment induced with 5% CO₂. Two common agar plates used to culture *N. meningitidis* are blood agar and chocolate agar. When growth is present on the blood agar plate it appears as grey colonies which are smooth, round and convex with defined edges. On the chocolate agar plate *N. meningitidis* appears as large colonies which appear as colorless to grey and opaque. Following colony growth, identification of bacterial species and antibiotic sensitivity is recommended. First, Gram staining is performed to verify the presence of Gram-negative diplococci, which is indicative of *Neisseria*. The next step in speciation is to perform manual biochemical testing. First is oxidase testing, for the presence of cytochrome oxidase or indophenol oxidase, an iron-containing hemoprotein contained within its electron transport chain. *Neisseria meningitidis* is oxidase positive. Following a positive oxidase test, the next step is to test for a reaction to four carbohydrates (sucrose, glucose, maltose and lactose) using cystine trypticase agar. *Neisseria meningitidis* is glucose and maltose positive and lactose and sucrose negative. There is also a Haemophilus-Neisseria identification (HNID) panel (MicroScan) which is a microdilution format system that can help to identify and differentiate *Haemophilus* and *Neisseria* spp., *Moraxella catarrhalis*, and *Gardnerella vaginalis*. Following these tests, one can be certain that *N. meningitidis* is present.

Since *N. meningitidis* has twelve serogroups, identifying and reporting the serogroup to public health officials is important, as this information can assist in identifying and controlling outbreaks, detecting emergence of a new strain, or identifying those causing sporadic disease. Serogroup testing is typically conducted at reference laboratories or public health laboratories. Serogroup B is most common in the United States, whereas serogroup A is most common in Africa and Asia, and C, W and X are more common in several parts of Africa as well. Testing for specific serogroups can be done using antisera in a slide agglutination test. This is typically done using a 5% saline formalin suspension (formalin is used to kill the bacteria to maintain a safe working environment) and antisera for particular serogroups. The CDC assigns a number to agglutination levels (Table). A rating of 3+ or 4+ is considered positive, whereas a result of 0, +/-, 1+, or 2+ is considered negative. This algorithm is used for evaluating all serogroups except B, where a 2+ and higher are considered positive. If agglutination is seen within one or more serogroups the culture is considered cross-reactive; no visible agglutination is considered to be non-reactive.
Table. Rating the intensity of the agglutination reaction that occurs when the antisera bind to the bacterial cells, making the cell suspension appear clearer.11

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Appearance of cell suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>4+</td>
<td>All of the cells agglutinate and the cell suspension appears clear</td>
</tr>
<tr>
<td>3+</td>
<td>75% of the cells agglutinate and the cell suspension remains slightly cloudy</td>
</tr>
<tr>
<td>2+</td>
<td>50% of the cells agglutinate and the cell suspension remains slightly cloudy</td>
</tr>
<tr>
<td>1+</td>
<td>25% of the cells agglutinate and the cell suspension remains slightly cloudy</td>
</tr>
<tr>
<td>+/-</td>
<td>Less than 25% of the cells agglutinate and a fine granular matter occurs</td>
</tr>
<tr>
<td>0</td>
<td>No visible agglutination; the suspension remains cloudy and smooth</td>
</tr>
</tbody>
</table>

Other methods for identifying serogroups include immunoassay and polymerase chain reaction (PCR). The identification of the serogroups and susceptibility testing to antibiotics are important to define control measures.5

Conclusion

*Neisseria meningitidis*, though rare, can have a poor prognosis if not treated quickly following onset. Over the last decade many advances have been made to institute preventative vaccination measures for five of the six most common serogroups: A, C, W, Y and B. These vaccines are available and recommended for the most commonly infected age group, those 10-25 years of age, as this is a bacteria that inhabits the nasopharynx and this age group is most likely to live in close quarters, share drinks and utensils, and engage in intimate activities.5,12 The ability to identify which serogroup is responsible for a particular outbreak is important for public health investigation in order to continue to reduce and prevent those impacted by *N. meningitidis*.

References

1. Feavers I, Pollard AJ, Sadarangani, M (eds.). *Handbook of Meningococcal Disease Management*. Springer International Publishing Switzerland, 2016. doi: 10.1007/978-3-319-28119-3_1


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