Chapter 8: Meningococcal Disease

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I. Disease Description

Meningococcal disease is a serious and potentially life-threatening infection caused by the bacterium *Neisseria meningitidis*. *N. meningitidis* can be classified into 12 serogroups based on its capsular polysaccharide; serogroups A, B, C, W, X, and Y are the primary causes of meningococcal disease worldwide.

Signs and symptoms of meningococcal disease include sudden onset of high fever, neck stiffness, confusion, nausea, vomiting, lethargy, and/or petechial or purpuric rash. Without prompt and appropriate treatment, the infection can progress rapidly and result in death.

II. Background

Epidemiology

The incidence of meningococcal disease has been steadily declining in the United States since the late 1990s. During 2012–2015, the incidence of meningococcal disease was 0.1–0.2 cases per 100,000 population in the United States, with 350–550 cases reported annually (CDC, unpublished data). Meningococcal disease incidence varies by age and is highest in infants less than 1 year of age, particularly during the first 6 months of life.[1,2]

Serogroups B, C, and Y each cause approximately one-third of meningococcal disease cases in the United States.[1,3] The relative importance of each serogroup varies by age; serogroup B causes over 60% of cases in children <5 years of age, while serogroups C, Y, and W135 cause 75% of all cases of meningococcal disease among persons ≥11 years of age.[3] Although serogroup A was responsible for most large meningococcal disease outbreaks during the first half of the twentieth century, serogroup A disease is now exceedingly rare in the United States (CDC, unpublished data). During 2009–2016, eleven outbreaks of serogroup B meningococcal disease occurred on college campuses (range: 2–13 cases), resulting in 50 cases and 3 deaths. In addition, outbreaks of serogroup C meningococcal disease have been reported among men who have sex with men (MSM) in major metropolitan areas (CDC, unpublished data).

Meningococcal disease incidence has historically had a cyclical pattern, with peaks in incidence occurring every 7–10 years (CDC, unpublished data). However, the declining incidence of meningococcal disease observed over the last 20 years does not reflect the previously observed cyclical periodicity of disease. Although it occurs year-round, the disease has a seasonal pattern with peak incidence in later winter and early spring.[1,4]

Natural history

Humans are the only natural reservoir for *N. meningitidis*. *N. meningitidis* organisms are Gram-negative, aerobic diplococci that can attach to the surface of mucosal cells of the nasopharynx. In the nasopharynx, the bacteria multiply, bind to specific receptors, and are taken up by epithelial cells, which transport the meningococci across the mucosal epithelium. In a small number of persons, the bacteria penetrate the mucosa and gain access to the bloodstream, resulting in systemic disease.

Meningococcal bacteria can be transmitted from person-to-person, by asymptomatic carriers or persons with invasive disease, through direct contact with large droplet respiratory secretions or saliva.

Carriage

Asymptomatic nasopharyngeal carriage of *N. meningitidis* is common; f5-10% of the population are asymptomatic nasopharyngeal carriers of *N. meningitidis* at any given time.[5] The frequency of carriage, like that of invasive disease, varies by age. Adolescents and young adults have the highest rates of meningococcal carriage.[5] Although asymptomatic carriage of both pathogenic and nonpathogenic *N. meningitidis* is common, few carriers develop invasive disease. For the majority of people, carriage is an immunizing process that results in a systemic, serogroup-specific protective antibody response.[4]

Risk factors

Risk factors for meningococcal disease include organism, host, and environmental factors. Persons with anatomic or functional asplenia, persistent complement component deficiencies (e.g., C3, C5—C9, properdin, factor H, or factor D), human immunodeficiency virus (HIV), and those who are receiving eculizumab (Soliris®, Alexion Pharmaceuticals) are at increased risk for meningococcal disease.[3,6]

Crowded living conditions can facilitate respiratory droplet transmission of meningococci. College freshmen residing in residence halls were historically shown to be at greater risk of acquiring meningococcal disease than college students not living in residence halls.[7] Active or passive smoking and recent upper respiratory tract infections also increase risk of disease.[8] Historically, black individuals and persons of low socioeconomic status have been found to be at higher risk for meningococcal disease than white individuals and persons of high socioeconomic status; however, these differences have diminished in ecent years.[1,9] Race and socioeconomic status are likely markers for differences in risk factors such as household crowding, exposure to tobacco smoke, and urban residence.

Meningococcal disease is more commonly diagnosed among infants and adolescents and young adults compared to other age groups. Infants less than 1 year of age have the highest incidence of meningococcal disease; the majority of cases in infants occur during the first 6 months of life.[1,2] In time, children gradually become exposed to meningococci and develop bactericidal antibodies. By the time they reach adulthood, 65%–85% of persons possess bactericidal antibody against meningococcal disease.[10]

Those who have close contact with case-patients, such as household members, are at substantially increased risk for acquiring carriage and disease.[11] Rates of secondary disease are also elevated among childcare workers and attendees as well as among schoolchildren.[12,13]

Clinical characteristics

Diagnosing meningococcal disease is often challenging because its initial clinical manifestations are similar to more common but less serious illnesses. In addition, it can progress rapidly.

The common clinical presentations of meningococcal disease include meningitis, bacteremia, and bacteremic pneumonia. Meningitis is observed in approximately 50% of invasive cases and is characterized by abrupt onset of fever, headache, and stiff neck.[1] These clinical features may be accompanied by nausea, vomiting, photophobia, and altered mental status. In infants, symptoms may have a slower onset, signs may be nonspecific, and neck stiffness may not be present. Approximately 40% of meningococcal disease cases present as bacteremia.[1] A portion of these cases will present as meningococcemia, the most severe manifestation of meningococcal bacteremia.[9] Signs of meningococcemia include sudden onset of fever and a characteristic petechial or purpuric rash, which may progress to purpura fulminans. The clinical course can include hypotension, acute adrenal hemorrhage, multiorgan failure, shock, and death. Patients with severe meningococcemia often respond poorly to treatment, and death can occur within hours of onset. Bacteremic pneumonia occurs in approximately 10% of cases and occurs most frequently in older persons.[1] Diagnosing meningococcal pneumonia is difficult because isolation of the organism from sputum does not distinguish persons who are carriers from those with pneumonia caused by the organism.[14]

Much less common manifestations of meningococcal disease include myocarditis, endocarditis or pericarditis, arthritis, conjunctivitis, urethritis, pharyngitis, and cervicitis.

The use of antibiotics has dramatically reduced mortality due to meningococcal disease. Before antibiotics were available, the case-fatality ratio for meningococcal disease was between 70% and 85%. Now with the widespread use of antibiotics, the case-fatality ratio for meningococcal disease is 10%–15%, although mortality may be as high as 40% among patients with meningococcemia.[4] Even with prompt and appropriate antimicrobial treatment the case-fatality ratio remains high. Of those who survive invasive disease, 10%–20% experience sequelae, including limb loss from gangrene, extensive skin scarring, or cerebral infarction. Persons with meningococcal meningitis who do not develop septic shock are less likely to die or experience these sequelae but are at risk of developing neurosensory hearing loss, mild to moderate cognitive defects, or seizure disorders.

Treatment

Because of the risks of severe morbidity and death, effective antibiotics should be administered promptly to patients suspected of having meningococcal disease. Multiple antimicrobial agents, including penicillins, are effective against *N. meningitidis*.[4] Empirical therapy for suspected meningococcal disease should include an extended-spectrum cephalosporin, such as cefotaxime or ceftriaxone.[4] Once the microbiologic diagnosis is established, definitive treatment with penicillin G, ampicillin, or an extended-spectrum cephalosporin (cefotaxime or ceftriaxone) is recommended.[15] Ceftriaxone clears nasopharyngeal carriage effectively after 1 dose; if antimicrobial agents other than ceftriaxone or cefotaxime are used for treatment of meningococcal disease, eradication of nasopharyngeal carriage with rifampin (4 doses over 2 days) or single doses of ciprofloxacin or ceftriaxone are recommended prior to discharge from the hospital.

Chemoprophylaxis

Close contacts of persons with meningococcal disease should receive antimicrobial chemoprophylaxis, regardless of immunization status, because they are at increased risk for infection.[15] Close contacts include, 1) household members, 2) childcare center contacts, and 3) anyone else directly exposed to an infected patient's oral secretions (e.g., via kissing, mouth-to-mouth resuscitation, endotracheal intubation or endotracheal tube management) in the 7 days before symptom onset. Health care personnel should receive chemoprophylaxis if they were managing an airway or exposed to respiratory secretions of a patent with meningococcal disease.

Chemoprophylaxis is not recommended for close contacts of patients with evidence of *N. meningitidis* only in non-sterile sites such as an oropharyngeal swab, endotracheal secretions, or conjunctival swab. Furthermore, there is no indication to treat persons who are asymptomatic nasopharyngeal carriers.

Risk of secondary disease among close contacts is highest during the first few days after the onset of disease, which requires that chemoprophylaxis be administered as soon as possible. If given more than 14 days after the onset of disease, chemoprophylaxis is probably of limited or no benefit.[15] Oropharyngeal or nasopharyngeal cultures are not useful in determining the need for chemoprophylaxis and may unnecessarily delay the use of effective preventive measures.

Rifampin, ceftriaxone, and ciprofloxacin are 90%–95% effective in reducing nasopharyngeal carriage of *N. meningitidis* and are all acceptable antimicrobial agents for chemoprophylaxis (Table 1). Although azithromycin is not recommended for use as a first-line chemoprophylaxis agent, azithromycin has been recommended for chemoprophylaxis in the rare circumstance of sustained ciprofloxacin-resistance in a community. Use of azithromycin as a single oral dose has been shown to be effective for eradication of nasopharyngeal carriage and can be used on a limited basis where ciprofloxacin resistance has been detected.[16]

Table 1. Recommended chemoprophylaxis regimens for high-risk contacts and persons with invasive meningococcal disease

Drug	Age	Dose	Duration	Efficacy (%)	Cautions
Rifampin	<1 month	5 mg/kg, orally, every 12 h	2 days		
	≥1 month	10 mg/kg (maximum 600 mg), orally, every 12 h	2 days	90–95	Can interfere with efficacy of oral contraceptives and some seizure prevention and anticoagulant medications; may stain soft contact lenses. Not recommended for pregnant women.
Ceftriaxone	<15 years	125 mg, intramuscularly	Single dose	90–95	To decrease pain at injection site, dilute with 1% lidocaine.
	≥15 years	250 mg, intramuscularly	Single dose	90–95	
Ciprofloxacin	≥1 month	20mg/kg (maximum 500 mg), orally	Single dose	90	Not recommended for pregnant women.
Azithromycin[a]		*10 mg/kg (maximum 500 mg)*	*Single dose*	*90*	Not recommended routinely. Equivalent to rifampin for eradication of *Neisseria meningitidis* from nasopharynx in one study

Source: American Academy of Pediatrics. Meningococcal Infections. In: Kimberly DW, Brady MT, Jackson MA, Long SS, editors. Red Book: 2015 Report of the Committee on Infectious Diseases, 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015. 550–8.

[a]*Use only if fluoroquinolone-resistant strains of* N meningitidis *have not been identified in the community.*

III. Importance of Rapid Identification

Immediate recognition and treatment of meningococcal disease is critical. Persons with suspected meningococcal disease should be treated promptly without waiting for laboratory confirmation. All suspect, probable, and confirmed meningococcal disease cases should be promptly reported to the appropriate health department to ensure that the proper prevention and control measures can be implemented .

IV. Importance of Surveillance

Surveillance data are used to monitor the impact of meningococcal disease in the United States, and to evaluate changes in the epidemiology of meningococcal disease over time. Surveillance data are also used to guide public health policy and development of prevention and control strategies. Laboratory surveillance to monitor the molecular epidemiology of *N. meningitidis* is also important. High-quality surveillance data and collection of circulating isolates from a broad and representative population are key to follow disease trends, make vaccine policy recommendations, monitoring vaccine impact, and guide development of new vaccines.

V. Disease Reduction Goals

The *Healthy People 2020* goal is to reduce incidence of meningococcal disease to 0.3 cases/100,000 population.

VI. Case Definition

The following case definition has been approved by the Council of State and Territorial Epidemiologists (CSTE) and was published in 2014.[17]

Confirmed case:

- Detection of *N. meningitidis*-specific nucleic acid in a specimen obtained from a normally sterile site (e.g., blood or cerebrospinal fluid [CSF]), using a validated polymerase chain reaction (PCR) assay; or
- Isolation of *N. meningitidis*
  - from a normally sterile body site (e.g., blood or CSF, or less commonly, synovial, pleural, or pericardial fluid); or
  - from purpuric lesions.

Probable case:

- Detection of *N. meningitidis* antigen
  - in formalin-fixed tissue by immunohistochemistry (IHC); or
  - in CSF by latex agglutination

Suspected case:

- Clinical purpura fulminans in the absence of a positive blood culture; or
- Gram-negative diplococci, not yet identified, isolated from a normally sterile body site (e.g., blood or CSF)

VII. Laboratory Testing

Rapid and reliable laboratory results are critical for prompt diagnosis and implementation of appropriate prevention and control measures. Refer to the CDC website (https://www.cdc.gov/meningococcal/laboratory.html) and Chapter 22 for specific information on specimen collection, identifying *N. meningitidis*, determining *N. meningitidis* serogroups, and antimicrobial susceptibility testing.

Specimen collection

Specimen collection and shipping are important steps in obtaining laboratory diagnosis or confirmation for vaccine preventable diseases. Guidelines have been published for specimen collection and handling for microbiologic agents.[18] Information is also available on using CDC laboratories as support for reference and disease surveillance;[19,20] this includes

- a central website (https://www.cdc.gov/laboratory/specimen-submission/index.html) for requesting lab testing;
- the form required for submitting specimens to CDC (See Appendix 23, Form # CDC 50.34);
- information on general requirements for shipment of etiologic agents (Appendix 24, https://www.cdc.gov/vaccines/pubs/surv-manual/appx/appendix24-etiologic-agent.pdf)—although written to guide specimen submission to CDC, this information may be applicable to submission of specimens to other laboratories; and
- the CDC Infectious Diseases Laboratories Test Directory (https://www.cdc.gov/laboratory/specimen-submission/list.html), which not only contains a list of orderable tests for that institution, but also detailed information on appropriate specimen types, collection methods, specimen volume, and points of contact.

VIII. Reporting and Case Notification

Case reporting within a jurisdiction

Each state and territory has regulations and laws governing the reporting of diseases and conditions of public health importance.[21] These regulations and laws list the diseases that are to be reported, and describe those persons or institutions responsible for reporting, such as health-care providers, hospitals, laboratories, schools, daycare and childcare facilities, and other institutions. Detailed information on reportable conditions in each state is available through the CSTE.[22] The Meningococcal Disease Surveillance Worksheet is included in Appendix 9 to serve as a guide for data collection during investigation of reported cases.

Case notification to CDC

Notification for suspect, probable, and confirmed cases of meningococcal disease should be sent to CDC using the eventcode 10150 in the National Notifiable Disease Surveillance System (NNDSS).[23] Case information should be reported through the (NNDSS), via the National Electronic Telecommunications System for Surveillance (NETSS), or the National Electronic Disease Surveillance System (NEDSS) within 14 days of the initial report to the state or local health department. The state in which the patient resides at the time of diagnosis should submit the case notification to CDC. The Meningococcal Disease Surveillance Worksheet is included in Appendix 9 to serve as a guide for data collection to be included in case investigations and case notification to CDC. Case notifications should not be delayed because of incomplete information or lack of confirmation; data can be updated electronically as more information becomes available.

IX. Vaccination

In the United States, two quadrivalent meningococcal conjugate vaccines, are available that protect against serogroups A, C, W, and Y: [MenACWY-D (Menactra®, Sanofi Pasteur) and MenACWY-CRM (Menveo®, Novartis)]. MenACWY-D is licensed and approved for use in persons 9 months through 55 years of age and MenACWY-CRM is licensed and approved for use in persons 2 months through 55 years of age.[24,25]

Two serogroup B meningococcal (MenB) vaccines [MenB-FHbp (Trumenba®, Pfizer)] and MenB-4C (Bexsero®, GlaxoSmithKline) are licensed and approved for use in persons 10 through 25 years of age.[26,27] MenB-4C is licensed as a 2-dose series (with doses administered at least 1 month apart) and MenB-FHbp is licensed as both a 2-dose series (administered at 0 and 6 months) and 3-dose series (administered at 0, 1–2, and 6 months of age).[26,27] Approximately 7–10 days are required after vaccination for development of protective antibody levels. The complete Advisory Committee on Immunization Practices (ACIP) recommendations for use of meningococcal vaccines can be found at https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/mening.html.

ACIP recommends routine MenACWY vaccination of adolescents at age 11 or 12 years, with a booster dose at age 16 Table 2).[3] For adolescents who receive the first dose at 13 through 15 years of age, a one-time booster dose should be administered preferably at 16 through 18 years of age. Persons who receive their first dose of MenACWY at or after age 16 do not need a booster dose, unless they remain at increased risk for meningococcal disease. Routine MenACWY vaccination of healthy persons who are not at increased risk for exposure to N. meningitidis is not recommended after age 21 years of age.[3]

ACIP does not recommend routine MenB vaccination for adolescents, but does recommend that adolescents and young adults 16 through 23 years of age may be vaccinated with MenB vaccines to provide short-term protection against most strains of serogroup B meningococcal disease.[28]

Meningococcal vaccination is also recommended for certain persons who have an increased risk for meningococcal disease (Tables 2 and 3).

ACIP recommends MenACWY vaccination for persons ≥2 months of age who are at increased risk for disease including 1) persons who have persistent complement component deficiencies (including inherited or chronic deficiencies in C3, C5–C9, properdin, factor D, factor H, or who are taking eculizumab [Soliris®]); 2) persons who have anatomic or functional asplenia, (including sickle cell disease); 3) persons with HIV; 4) microbiologists who are routinely exposed to isolates of *N. meningitidis*; 5) persons identified to be at increased risk during an outbreak due to serogroups A, C, W, or Y

meningococcal disease; 6) persons who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, particularly if contact with the local population will be prolonged; 7) college freshmen living in residence halls; and 8) military recruits (Table 2).[3,6]

Data indicate that the immune response to a single dose of MenACWY vaccine is not sufficient in persons with certain medical conditions.[3] As a result, persons who have functional or anatomic asplenia, persistent complement component deficiencies, or HIV infection should receive a 2-dose primary series administered 2 months apart instead of a single dose.[3,6] All other persons at increased risk for meningococcal disease (e.g., microbiologists or travelers to an epidemic or highly endemic country) should receive a 1-dose primary series.

Persons who remain at increased risk for meningococcal disease should receive booster doses of MenACWY vaccine. If the person was ≥7 years of age at their previous MenACWY dose, they should be revaccinated after 5 years, and should continue to receive boosters every 5 years thereafter as long as they remain at increased risk. Persons <7 years of age at their previous dose of MenACWY, they should be revaccinated after 3 years, and should continue to receive boosters every 5 years thereafter as long as they remain at increased risk. ACIP also recommends MenB vaccination for certain persons ≥10 years of age at increased risk for disease including 1) persons with persistent complement component deficiencies (including inherited or chronic deficiencies in C3, C5–C9, properdin, factor D, factor H, or who are taking eculizumab [Soliris®]); 2) persons with anatomic or functional asplenia (including sickle cell disease); 3) microbiologists routinely exposed to isolates of *N. meningitidis*; and 4) persons identified to be at increased risk because of a serogroup B meningococcal disease outbreak (Table 2).[29]

Table 2. Summary of recommendations for meningococcal conjugate (MenACWY) vaccine, by risk group—Advisory Committee on Immunization Practices[3,6]

Risk group	Primary series	Booster dose
Persons aged 11 through 18 years	1 dose, preferably at 11 or 12 years of age	At 16 years of age if primary dose was administered at 11 or 12 years of age
		At 16 through 18 years of age if primary dose was administered at 13 through 15 years of age
		No booster needed if primary dose was administered on or after 16 years of age
Persons ≥2 months of age with persistent complement component deficiency* or functional or anatomical asplenia**, or HIV infection	2 doses, 2 months apart	Every 5 years‡; children who received their last dose before their 7th birthday should receive a booster dose in 3 years and subsequent booster doses every 5 years.
Other persons ≥2 months of age at increased risk for meningococcal disease†	2 doses, 2 months apart	Every 5 years‡; children who received their last dose before their 7th birthday should receive a booster dose in 3 years and subsequent booster doses every 5 years.

** Including persons with inherited or chronic deficiencies in C3, C5–C9, properdin, factor D, or factor H, or who are taking eculizumab (Soliris®).*

*** Including persons with sickle cell disease† Including: microbiologists who are routinely exposed to isolates of* Neisseria meningitidis*; persons identified to be at increased risk during an outbreak due to serogroups A, C, W, or Y meningococcal disease; persons; persons whotravel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, particularly if contact with the local population will be prolonged; college freshmen living in residence halls; and military recruits.*

‡ If the person remains at increased risk.

Table 3. Summary of recommendations for serogroup B meningococcal (MenB) vaccine for persons at increased risk of serogroup B meningococcal disease—Advisory Committee on Immunization Practices[26]

Risk group	Primary series
Persons ≥10 years of age with persistent complement component deficiency*, functional or anatomical asplenia**, microbiologists routinely working with *N. meningitidis*, or persons identified as at increased risk because of a serogroup B meningococcal disease outbreak	2-dose series of MenB-4C (0 and ≥1 month) or 3-dose series of MenB-FHbp (0, 1–2, and 6 months)

** Including persons with inherited or chronic deficiencies in C3, C5–C9, properdin, factor D, factor H, or who are taking eculizumab (Soliris®)*

*** Including person with sickle cell disease*

X. Enhancing Surveillance

Active population-based and laboratory-based surveillance

CDC coordinates active, population- and laboratory-based surveillance for invasive meningococcal disease as part of the Active Bacterial Core surveillance (ABCs) system, through the Emerging Infections Program (EIP). ABCs operates in 10 sites which collect data from all patients from whom *N. meningitidis* was isolated from a normally sterile body site. This surveillance program allows for collection of detailed information on meningococcal cases, including estimation of serogroup and age-specific incidence rates. ABCs data have been used to track meningococcal disease trends over time;the ABCs web site is https://www.cdc.gov/abcs/index.html.

In addition, CDC has implemented enhanced surveillance for meningococcal disease through the Epidemiology and Laboratory Capacity (ELC) Vaccine Preventable Diseases (VPD) surveillance project. Data on key variables for monitoring meningococcal disease epidemiology and vaccine policy decisions, along with meningococcal isolates, are routinely collected from most state and territorial health departments.

Streamlining reporting using electronic methods

Although many surveillance systems still rely on paper and pencil for data collection, use of data from sources such as electronic medical records, electronic case reporting,[30–36] and clinical laboratory information systems (LIMS) can significantly improve reporting speed, enhance data quality, and reduce workload.

XI. Case Investigation

All reports of suspected meningococcal disease should be investigated immediately. CDC is available to assist with epidemiologic and laboratory investigations during outbreaks. A critical component of case investigation is ensuring that all close contacts (see definitions) receive appropriate chemoprophylaxis to eradicate nasopharyngeal carriage of meningococci and prevent secondary disease. Approximately 70% of secondary cases occur within 7 days of disease onset in the index patient. Antibiotic administration within 24 hours of identifying a case is ideal; after 14 days it is unlikely that antibiotic chemoprophylaxis is helpful.[6] Rifampin, ciprofloxacin, ceftriaxone, and azithromycin are all effective as chemoprophylaxis against meningococcal disease (Table 1).[6,27]

XII. Outbreaks

Approximately 98% of meningococcal disease cases in the United States are sporadic; the other 2% are associated with outbreaks. Guidance on the control of meningococcal disease outbreaks can be found on the CDC website (https://www.cdc.gov/meningococcal/outbreaks/index.html).

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