86 Neisseria Infections

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Definition and Classification

Neisseria are aerobic, gram-negative, oxidase-positive coccoid bacteria, and most species are found in pairs (diplococci) on examination of the Gram stain. Two main pathogenic species exist, *N. meningitidis* (commonly referred to as meningococcus) and *N. gonorrhoeae* (commonly referred to as gonococcus). This chapter will focus on *N. meningitidis* and manifestations of *N. gonorrhoeae* outside the urogenital tract. For a detailed discussion of genitourinary infections caused by *N. gonorrhoeae*, please see Chap. 71, "Sexually Transmitted Diseases".

Other *Neisseria* species commonly colonize the human upper respiratory and female urogenital tracts, and can be distinguished from the more pathogenic *Neisseria* species on the basis of carbohydrate utilization and biochemical testing. These other species include *N. sicca*, *N. subflava*, *N. cinerea*, *N. lactamica*, *N. mucosa*, *N. flavescens*, *N. weaveri*, *N. polysaccharea*, and *N. elongata*.

Epidemiology

Annually, *N. meningitidis* causes disease in approximately 2,500 people in the United States, and 500,000 people worldwide, resulting in an estimated 50,000 deaths. Despite advances in therapy, the 10% mortality rate has remained unchanged in the last 20 years. Two incidence peaks exist for meningococcal infection: the first peak occurs in children less than 5 years of age, and the second peak in people 15–24 years of age. Although the vast majority of meningococcal cases (95%) are endemic, epidemic outbreaks have occurred in association with daycare centers, college dorms, and military barracks. Crowded living conditions promote the spread of the organism, placing those of low socioeconomic status at higher risk of meningococcal disease. In addition, tobacco smoke exposure and upper respiratory viral infections increase the risk of disease, likely through diminishing mucous membrane integrity. Meningococcal cases are reported more frequent in the winter months following influenza virus infections.

There are 13 identified *N. meningitidis* serogroups as determined by differences in the bacterial polysaccharide capsule. The serogroups have varying epidemiological features and are responsible for different disease manifestations. For example, serogroup C usually causes meningitis and septicemia, whereas serogroup W-135 also causes arthritis and pneumonia. Current meningococcal vaccines target specific serogroups and are likely going to change the epidemiology of disease in the future as vaccination rates increase.

Serogroups B, C, Y, and W-135 are the most common causes of endemic meningococcal disease in the United States. Of these, serogroups B and C are the most prevalent serogroups causing disease, but serogroup Y is emerging as a more common entity, causing up to a third of endemic cases in certain areas. Serogroup W-135 previously caused 20% of meningococcal cases but is now responsible for only 4% of cases in the United States.

Worldwide, the majority of endemic meningococcal cases are caused by serogroups A, B, and C. Serogroups B and C cause disease in Europe and the Americas, while serogroups A and C cause disease in Asia and Africa.

Although all serogroups have the potential to cause epidemic disease, certain serogroups have caused recurrent outbreaks. In the United States, the majority of these outbreaks are due to serogroup C, and more recently, due to serogroup Y. Although the frequency of epidemics has been increasing since the 1990s, epidemics in the United States typically account for only 2–3% of meningococcal cases.

Worldwide, serogroup A is the most common agent responsible for epidemics of meningococcal meningitis. Serogroup A causes outbreaks in the sub-Saharan "meningitis belt," which extends from Ethiopia to Senegal. In this region, serogroup A is responsible for both endemic meningococcal disease as well as recurrent epidemics occurring approximately every 7–10 years. Other serogroups that have caused epidemic disease include serogroup W-135, which was responsible for the Hajj epidemic in 2000, and serogroup B, which caused an epidemic in Oregon and Washington in 1990.

Overall, the incidence of gonococcal infections remains high, with an estimated 60 million cases annually

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worldwide, including approximately 300,000 annually in the United States. Disseminated gonococcal infection, however, is less common, with fewer than 5% of patients experiencing disseminated disease. Rates of disease in the United States have remained stable since the mid-1990s. Gonococcal infections are more common among those with lower socioeconomic status and earlier onset of sexual activity.

Resistance to multiple antibiotic classes has begun to develop among *Neisseria* species worldwide. In part, horizontal gene transfer between nonpathogenic colonizing *Neisseria* species and pathogenic *Neisseria* species is responsible for these increasing resistance patterns. Emerging resistance to penicillins, extended-spectrum cephalosporins, and fluoroquinolones has been documented.

Pathogenesis

Five to ten percent of adults are asymptomatic carriers of *N. meningitidis*. The organisms colonize the nasopharynx and are spread through secretions of aerosolized particles. Disease occurs when the epithelial cells engulf the bacteria, which then gain access to the bloodstream. For reasons that are still unclear, invasive disease tends to occur within 1 week of a new exposure to *N. meningitidis*.

People with deficiencies in antibody-dependent immunity are more susceptible to meningococcal disease. The specific immune deficiencies associated with meningococcal infection include infants with waning maternal antibodies, those with functional or anatomical asplenia, and those with terminal complement deficiencies. Terminal complement deficiencies are estimated to cause a 10,000-fold increased risk of acquiring meningococcal disease. However, the majority of meningococcal disease does not occur in people with intrinsic risk factors.

Clinical Manifestations

The common and uncommon clinical presentations of *N. meningitidis* and *N. gonorrhoeae* are presented in Table 86.1. *N. meningitidis* most commonly causes meningitis and meningococcal sepsis (meningococcemia), but can also cause less common infections such as arthritis, pneumonia, otitis media, conjunctivitis, epiglottitis, urethritis, pericarditis, and osteomyelitis.

Meningococcal sepsis manifests as an abrupt onset of fever and a characteristic petechial or purpuric rash. The rash that typically presents in meningococcemia is known as purpura fulminans and is a diffuse, non-blanching petechial or purpuric rash over the trunk and extremities. Progression of sepsis leads to hypotension and disseminated intravascular coagulation with end-organ failure. End-organ failure in meningococcal sepsis often involves the kidneys, lungs, and adrenal glands. Waterhouse–Friderichsen syndrome is an acute adrenal hemorrhage often seen in meningococcal sepsis, which leads to a subsequent cortisol deficiency.

Table 86.1
Clinical presentations *of Neisseria meningitidis and Neisseria gonorrhoeae* infections

Neisseria meningitidis	*Neisseria gonorrhoeae*
Most common	
Meningitis	Neonatal conjunctivitis
Bacteremia	Urethritis
Septic arthritis	Endocervicitis
	Salpingitis
Uncommon	
Otitis media	Septic arthritis
Pneumonia	Arthritis-dermatitis
Conjunctivitis	Bacteremia
Epiglottitis	Meningitis
Urethritis	Endocarditis
Pericarditis	
Vasculitis	
Osteomyelitis	

Chronic meningococcemia is a rare clinical manifestation of *N. meningitidis* and is defined as meningococcal sepsis of at least 1 week duration without meningeal symptoms. It is characterized by recurrent fevers, rash, migratory arthralgias, and headaches. The pathophysiology of chronic meningococcemia remains unclear.

The hematogenous spread of *N. meningitidis* can lead to meningitis, which is the most common presentation of invasive meningococcal disease (see Chap. 69, "Meningitis"). About 60% of patients with meningococcal meningitis present without septic shock. Clinical signs of meningococcal meningitis are typical of those of other causes of bacterial meningitis and include meningismus, headache, increased intracranial pressure, and mental status changes. In infants, meningitis can often present as poor feeding or lethargy without any focal signs.

N. meningitidis also causes arthritis. Two different types of arthritis result following infection: septic arthritis or an immune-complex-mediated arthritis. Septic

arthritis can occur as an isolated meningococcal infection, but it most commonly presents as a complication of meningococcemia or meningitis. Septic arthritis complicates approximately 10% of meningococcemia and is frequently preceded by an upper respiratory tract infection. It is usually monoarthritic, particularly affecting the knees, and is more common in men. The immune-mediated form of arthritis, which also primarily affects the large joints, results from the deposition of immune complexes in the joint space, and presents as a sterile effusion. The frequency of immune-mediated arthritis complicating acute meningococcal infection ranges from 4% to 50%.

N. meningitidis, particularly serogroup Y, can cause pneumonia as an isolated infection or concurrently with meningococcemia or meningitis. Meningococcal pneumonia occurs in approximately 5–15% of invasive meningococcal disease. Diagnosis of meningococcal pneumonia is challenging given that isolation of the organism in the sputum cannot distinguish between colonization and infection. Blood or pleural cultures that yield *N. meningitidis* can assist with the diagnosis.

Other meningococcal infections such as otitis media infections, epiglottitis, pericarditis, urethritis, and osteomyelitis are rare and may require consultation with an infectious diseases specialist.

Gonococcus is a common cause of neonatal conjunctivitis, also known as ophthalmia neonatorum. Neonates acquire the organism after exposure to maternal colonization; symptoms typically begin within 2–5 days after birth, though can arise in the first 3 weeks of life. Clinical features include prominent eyelid edema and significant mucopurulent discharge, often bilaterally. Rarely invasive gonococcal disease can occur with the microbial entry to the bloodstream via the conjunctivae.

Disseminated infections due to *N. gonorrhoeae* outside the genitourinary tract are uncommon, typically occurring in fewer than 5% of patients. The more common manifestations of disseminated gonococcal infection include bacteremia, septic arthritis, tenosynovitis, and an arthritis-dermatitis syndrome including multiple skin lesions with polyarthralgias. As with meningococcus, when septic arthritis is present, typically single large distal joints are affected, such as knees, wrists or ankles, but multiple joints and small joints (such as interphalangeal joints) can be affected. Likewise, arthritis in patients with gonococcal infections can also be immunologically mediated and sterile in nature. The skin lesions seen with disseminated gonococcal infections can be quite varied, including papules, pustules, and bullae. Gonococcal infections in children outside the neonatal period should prompt a consideration of sexual abuse; see Chap. 71, "Sexually Transmitted Diseases".

The other *Neisseria* species are typically nonpathogenic, but have been associated with bacteremia, meningitis, endocarditis, septic arthritis, and other invasive infections, most typically in immunocompromised hosts or after surgical procedures, but occasionally reported in previously healthy individuals. *N. cinerea* has been specifically linked to ocular infections in neonates. Because these *Neisseria* species are commensal oral flora, they have also occasionally been identified in bite wounds.

Diagnosis

Diagnosing meningococcal infection relies on recognition of clinical signs and symptoms and on isolating the organism from the appropriate body site. Gram stain and culture of blood, cerebrospinal fluid (CSF), and tissue remain the gold standard. In suspected meningococcal meningitis, diagnosis is made by performing a lumbar puncture and obtaining CSF for analysis. Typical CSF findings include an elevated opening pressure, a pleocytosis with a neutrophil predominance, an elevated protein level, and a low glucose level. While meningococcal meningitis can be diagnosed using an antigen test on the CSF, the antigen test is rapid but has poor sensitivity and is not commonly used. Narrowing empiric therapy based on the results of a rapid antigen test alone is therefore not recommended. Nucleic acid testing for *N. meningitidis*, although not commercially available in the United States, is being developed and used in other parts of the world.

Diagnosis of meningococcemia can be more challenging as typical clinical symptoms do not always manifest initially. Gram stain and culture of blood and skin lesions are most helpful in making the diagnosis. Diagnosis of septic arthritis should include joint aspiration with synovial fluid analysis for Gram stain and culture.

The diagnosis of meningococcal pneumonia is challenging as *N. meningitidis* isolated in the sputum cannot differentiate infection from colonization. Blood cultures positive for *N. meningitidis* support the diagnosis, but a pleural effusion sample or pleural biopsy confirms it.

Diagnosis of gonococcal infections can likewise be made in several ways. Diagnosis of genitourinary infections can be made rapidly using nucleic acid amplification methods on urine specimens (see Chap. 69, "Meningitis"). Blood cultures should be obtained if gonococcal bacteremia is suspected, and culture of synovial fluid is routinely indicated and may be positive in up to half of patients with gonococcal septic arthritis.

Differential Diagnosis

For a differential diagnosis of organisms that may cause a specific infectious syndrome (e.g., meningitis, septic arthritis, etc.), please refer to the appropriate chapter. Other gram-negative organisms that can appear coccoid upon microscopic examination include *Moraxella* species (formerly *Branhamella*) and *Kingella* species.

Treatment

The initial treatment of meningococcal disease depends on the severity of the presenting infection. If a patient presents with shock, disseminated intravascular coagulation, and increased intracranial pressure, resuscitation and supportive intensive care should be initiated. If septic shock or meningitis is the presenting illness and *N. meningitidis* is suspected, broad-spectrum antibiotics such as third-generation cephalosporins (cefotaxime or ceftriaxone) should be administered (see Chap. 69, "Meningitis"). Fluoroquinolones are not routinely recommended for empiric treatment of suspected invasive meningococcal disease due to reports of emerging resistance.

Once *N. meningitidis* has been identified on culture from a sterile site (such as blood, spinal fluid, or synovial fluid), antibiotics can be narrowed based on the susceptibility profile. Treatment of chronic meningococcemia is identical to that for acute meningococcemia. The majority of *N. meningitidis* isolates continue to be susceptible to penicillin, which is the preferred treatment. Treatment of meningococcemia for 5–7 days with penicillin is appropriate, although shorter antibiotic courses are being explored. However, cases of *N. meningitidis* infection with reduced susceptibility to penicillin have been documented in certain serogroups (W-135 and C) outside the United States. Alternative treatments in the case of penicillin-resistance or penicillin allergy include cefotaxime, ceftriaxone, and ampicillin. In the low-resource setting, a one-time intramuscular dose of chloramphenicol has also been shown to be effective.

If antibiotics are administered prior to obtaining CSF, interpretation of CSF analysis cannot be relied upon as *N. meningitidis* is killed within 3–4 h of antibiotic administration. Although a CSF pleocytosis may be seen, it is unlikely that culture will yield an organism. The benefit of corticosteroids in meningococcal meningitis has not been established.

In cases of less severe illness such as conjunctivitis, susceptibility testing is not always necessary and empiric treatment is recommended. Susceptibility testing should be initiated only in cases of treatment failures.

Recommended empiric treatment of disseminated gonococcal infections outside the central nervous system includes a third-generation cephalosporin (cefotaxime or ceftriaxone) for 7 days, and should be extended to 10–14 days if meningitis is confirmed or suspected. Antimicrobial treatment can be tailored when culture results are available.

Prognosis

Severe meningococcal disease such as meningitis and sepsis causes sequelae in up to 20% of survivors, including hearing loss, limb loss and skin scarring, seizures, and neurologic disabilities. Untreated neonatal conjunctivitis can progress to corneal ulceration and ultimately blindness, and was formerly a leading cause of blindness worldwide. Other *Neisseria* infections typically resolve without significant sequelae if diagnosed and treated in a timely manner.

Prevention

The quadrivalent conjugate meningococcal vaccine (MCV4) was licensed in 2005 and includes the four most common meningococcal serogroups encountered in the United States (serogroups A, C, Y, and W-135). Most meningococcal disease is caused by these four strains as well as serogroup B, which is not covered in any vaccine. More than 50% of disease in younger children is caused by serogroup B. The meningococcal vaccine is recommended routinely for adolescents 11–18 years of age, for children >2 years of age with risk factors (including terminal complement deficiencies and asplenia), children living in high-risk endemic areas, military recruits, and those living in college dormitories who were not previously vaccinated. A new, more affordably produced conjugate meningococcal vaccine against serogroup A was introduced to sub-Saharan Africa in late 2010 with a goal of widespread immunization to prevent epidemics of meningitis caused by *N. meningitidis* serogroup A. No vaccine is currently available for *N. gonorrhoeae.*

Close contacts of patients with invasive meningococcal disease are considered high risk and chemoprophylaxis is recommended. This includes all household members, persons sleeping in the same dwelling within 7 days of the index case, and all attendees of a daycare or preschool present within 7 days of the index case. Persons who

Table 86.2
Recommended chemoprophylaxis for exposed persons

Infants	Rifampin (2 days)
Children	Rifampin (2 days) or ceftriaxone (single dose)
Adolescents	Rifampin (2 days) or ceftriaxone (single dose) or azithromycin (single dose)
Adults	Rifampin (2 days) or ceftriaxone (single dose) or ciprofloxacin (single dose) or azithromycin (single dose)

came into contact with any secretions from the infected person, such as health care workers taking oral or nasal samples, or health care workers involved in airway management should receive chemoprophylaxis. Chemoprophylaxis is not necessary for health care workers coming into contact with secretions more than 24 h following antibiotic initiation. Persons seated next to the index case on a plane or confined space for more than 8 h should also receive chemoprophylaxis. All chemoprophylaxis should be initiated within 24 h of contact.

Rifampin should be used as chemoprophylaxis in children and rifampin, ceftriaxone, ciprofloxacin, or azithromycin can be used in older children and adults (*Table 86.2*). Chemoprophylaxis is also recommended in children treated for meningococcemia with penicillin or chloramphenicol as these antibiotics do not eradicate nasal carriage. Prophylaxis to prevent neonatal conjunctivitis is routinely and universally indicated, by applying either 1% tetracycline ophthalmic ointment or 0.5% erythromycin ointment to both eyes immediately after birth.

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