Neisserial Infections

Neisseria are gram-negative diplococci that are flattened on the adjoining sides, giving the pair the shape of a coffee bean. These aerobic bacteria have stringent nutritional requirements and grow best on enriched media such as lysed sheep's blood agar. The two clinically significant *Neisseria* are *N. meningitidis* and *N. gonorrhoeae*.

***N. meningitidis* is a significant cause of bacterial meningitis, particularly among adolescents and young adults.** The organism is a common colonizer of the oropharynx and is spread by the respiratory route. An immune response leads to elimination of the colonizing organism in most people, and this response is protective against subsequent infection with the same serotype of bacteria. There are several capsular serotypes of *N. meningitidis*, however five of them cause most cases of disease. Invasive disease mainly occurs when people encounter new strains to which they are not immune, as may happen to young children or to young adults living in crowded quarters such as military barracks or college dormitories. *N. meningitidis* is endemic in the United States, but epidemics occur periodically in sub-Saharan Africa and cause thousands of deaths. Conjugate vaccines for *N. meningitidis* composed of capsular polysaccharides conjugated to antigenic proteins are available and are highly effective at preventing disease.

Even in the absence of preexisting immunity, only a small fraction of people infected with *N. meningitidis* develop meningitis. The bacteria must invade respiratory epithelial cells and travel to their basolateral side to enter the blood. In the blood, the bacterial capsule inhibits opsonization and destruction of the bacteria by complement proteins. The importance of complement as a first-line defense against *N. meningitidis* is shown by the increased rates of serious infection among people who have inherited defects in the complement proteins (C5 to C9) that form the membrane attack complex, or patients with paroxysmal nocturnal hemoglobinuria (Chapter 14) who are being treated with an antibody inhibitor of the membrane attack complex. If *N. meningitidis* escapes the host response, the consequences can be severe. Although antibiotic treatment greatly reduces the mortality of *N. meningitidis* infection, about 10% of infected patients still die The pathology of pyogenic meningitis is discussed in Chapter 28.

***N. gonorrhoeae* is an important cause of sexually transmitted disease (STD)**, with more than 300,000 cases reported each year in the United States. It is second only to *C. trachomatis* among bacterial STDs. Infection in men causes urethritis. In women, *N. gonorrhoeae* infection is often asymptomatic and so may go unnoticed. Untreated gonorrhea may lead to pelvic inflammatory disease, which can cause infertility or ectopic pregnancy (Chapter 22). Infection is diagnosed by culture and PCR tests.

Although *N. gonorrhoeae* infection usually manifests locally in the genital or cervical mucosa, pharynx, or anorectum, disseminated infections may occur. Like *N. meningitidis*, *N. gonorrhoeae* is much more likely to become disseminated in people who lack the complement proteins that form the membrane attack complex. Disseminated infection of adults and adolescents usually causes septic arthritis accompanied by a rash of hemorrhagic papules and pustules. Neonatal *N. gonorrhoeae* infection causes conjunctivitis that may lead to blindness and, rarely, sepsis. The eye infection, which is preventable by instillation of silver nitrate or antibiotics in the newborn's eyes, remains an important cause of blindness in some developing nations.

Pathogenesis. *Neisseria* organisms adhere to and invade nonciliated epithelial cells at the site of entry (nasopharynx, urethra, or cervix). Adherence of *N. gonorrhoeae* to epithelial cells is initially mediated by long pili, which bind to CD46, a protein expressed on all human nucleated cells. OPA proteins (so named because they make bacterial colonies opaque), located in the outer membrane of the bacteria, increase binding of *Neisseria* organisms to epithelial cells and promote entry of bacteria into cells.

Neisseria use antigenic variation as a strategy to escape the immune response. The existence of multiple capsular serotypes of *N. meningitidis* results in meningitis in some people on exposure to a new strain, as discussed above. In addition, *Neisseria* species also can generate new antigens by special genetic mechanisms, which permit a single bacterial clone to change its expressed antigens and escape immune defenses. Such mechanisms involve both pili and OPA proteins:

- Recombination of genes encoding pili proteins. The pili are composed of polypeptides encoded by the pilin gene, which consists of a promoter and coding sequences for 10 to 15 pili protein variants. At any point in time, only one of these coding sequences is adjacent to the promoter, allowing it to be expressed. Periodically, homologous recombination shuttles one of the other pilin coding sequences next to the promoter, resulting in expression of a different pili variant.
- Expression of different OPA proteins. Each *OPA* gene has several repeats of a five-nucleotide sequence, which are frequently deleted or duplicated. These changes shift the reading frame of the gene so that it encodes new sequences. Stop codons are also introduced by the additions and deletions, which determine whether each *OPA* gene is expressed or silent. Thus, *Neisseria* can express one, none, or multiple OPA proteins at any time.

Pertussis

Pertussis, or whooping cough, caused by the gram-negative coccobacillus *Bordetella pertussis*, is an acute, highly communicable illness characterized by paroxysms of violent coughing followed by a loud inspiratory "whoop." In the United States, the incidence of pertussis has risen dramatically, with large epidemics occurring in 2005, 2010, and 2012. Although the reasons for this increase are not clear, the acellular pertussis vaccine currently in use is less effective than the vaccine used before 1997, and this may be a factor in the changing epidemiology of this disease. In areas of the developing world where vaccination is not widely practiced, pertussis kills hundreds of thousands of children each year. The diagnosis is best made by PCR, because culture is less sensitive.

Pathogenesis. *B. pertussis* colonizes the brush border of the bronchial epithelium and also invades macrophages. It contains a filamentous hemagglutinin that binds to carbohydrates on the surface of respiratory epithelial cells, as well as to CR3 (Mac-1) integrins on macrophages. Pertussis