Neisseria, Moraxella, Kingella, and Acinetobacter

Neisseria, Moraxella, Kingella, and Eikenella

Neisseria gonorrhoeae

- **Clinical Manifestations**

Symptomatic or asymptomatic localized infections include urethritis, cervicitis, proctitis, pharyngitis, and conjunctivitis. Disseminated infections occur either by extension to adjacent organs (pelvic inflammatory disease, epididymitis) or by bacteremic spread (skin lesions, tenosynovitis, septic arthritis, endocarditis, and meningitis).

- **Structure**

Cells are Gram-negative cocci, usually seen in pairs with the adjacent sides flattened.

- **Classification and Antigenic Types**

N gonorrhoeae strains have been typed on the basis of their growth requirements (auxotyping) or by antigenic differences in the porin protein (serotyping). More recently, restriction fragment length polymorphisms in genes encoding ribosomal RNA (ribotyping) and the separation of large DNA fragments by pulsed-field gel electrophoresis have been used to type isolates.

- **Pathogenesis**

Gonorrhea is usually acquired by sexual contact. Gonococci adhere to columnar epithelial cells, penetrate them, and multiply on the basement membrane. Adherence is facilitated through pili and opa proteins. Gonococcal lipopolysaccharide stimulates the production of tumor necrosis factor, which causes cell damage. Gonococci may disseminate via the bloodstream. Strains that cause disseminated infections are usually resistant to serum and complement.

- **Host Defenses**

Infection stimulates inflammation and local immunity; however, it is not known whether the secretory immune response is protective. Serum antibodies also appear. Individuals with genetic defects in late-
acting complement components are at increased risk for disseminated infections. Protection, if it exists, may be strain specific.

- **Epidemiology**

Gonorrhea is a sexually transmitted disease of worldwide importance. The highest attack rate in both men and women occurs between 15 and 29 years of age. Host-related factors such as the number of sexual partners, contraceptive practices, sexual preference, and population mobility contribute to the incidence of gonorrhea.

- **Diagnosis**

Gonorrhea cannot be diagnosed solely on clinical grounds. For men, a Gram-stained smear of urethral exudate showing intracellular Gram-negative diplococci is diagnostic. For women, and for men when a direct smear is not definitive, culturing on selective medium is often required. N. gonorrhoeae must be differentiated from other Neisseria species. Where appropriate, isolates should be examined for antibiotic resistance. A non-amplified DNA probe test is commercially available. This test does not require viable organisms and is useful where maintenance of viability during specimen transport is a problem; however, it is not as sensitive as culture. Serologic tests are not recommended for uncomplicated infections.

- **Control**

Recommended treatment for uncomplicated infections is a third-generation cephalosporin or a fluoroquinolone plus an antibiotic (e.g., doxycycline) effective against possible co-infection with Chlamydia trachomatis. Sex partner(s) should be referred and treated. No effective vaccine yet exists. Condoms are effective in preventing gonorrhea.

**Neisseria meningitidis**

- **Clinical Manifestations**

Infection with N. meningitidis has two presentations, meningococcemia, characterized by skin lesions, and acute bacterial meningitis. Fulminant disease (with or without meningitis) is characterized by multisystem involvement and high mortality.

- **Structure**

Cell morphology is identical to that of N. gonorrhoeae. The antiphagocytic polysaccharide capsule is a prominent feature.
Classification and Antigenic Types

N meningitidis is grouped, on the basis of capsular polysaccharides, into 12 serogroups, some of which are subdivided according to the presence of outer membrane protein and lipopolysaccharide antigens.

Pathogenesis

Infection is by aspiration of infective particles, which attach to epithelial cells of the nasopharyngeal and oropharyngeal mucosa, cross the mucosal barrier, and enter the bloodstream. If not cleared blood-borne bacteria may enter the central nervous system and cause meningitis.

Host Defenses

Meningococci establish systemic infections only in individuals who lack serum bacterial antibodies directed against the capsular or noncapsular antigens of the invading strain, or in patients deficient in the late-acting complement components.

Epidemiology

Asymptomatic carriage of meningococci in the nasopharynx provides a reservoir for infection but also enhances host immunity. Attack rates peak in infants 3 months to 1 year old. Meningococcal meningitis occurs both sporadically (mainly groups B and C meningococci) and in epidemics (mainly group A meningococci), with the highest incidence during late winter and early spring.

Diagnosis

Symptoms are suggestive; diagnosis is confirmed by identifying N meningitidis in specimens of blood, cerebrospinal fluid, and nasopharyngeal secretions collected before antibiotic administration.

Control

Penicillin is the drug of choice. Household contacts require chemoprophylaxis with rifampin. Groups A, C, AC, and ACYW135 capsular polysaccharide vaccines are available. In children under 1 year old, antibody levels decline rapidly after immunization. Routine vaccination is not recommended.

Other Genera and Species

Moraxella is an oxidase-positive bacterium, sometimes mistaken for Neisseria, that may be isolated from eye infections and respiratory tract infections. M catarrhalis causes lower respiratory infection in adults with chronic lung disease and is a common cause of otitis media, sinusitis, and conjunctivitis in
Bacteriology

Neisseria, Moraxella, Kingella, and Acinetobacter

children. Kingella and Eikenella species are short bacilli or coccoid bacteria that act as opportunistic pathogens. They are sometimes secondary invaders of damaged tissues.

- **Introduction**

The family Neisseriaceae comprises the genera Neisseria, Moraxella, Kingella, and Acinetobacter. The only significant human pathogens are N gonorrhoeae, the agent of gonorrhea, and N. meningitidis, an agent of acute bacterial meningitis. N gonorrhoeae infections have a high prevalence and low mortality, whereas N meningitidis infections have a low prevalence and high mortality.

Gonococcal infections are acquired by sexual contact and usually affect mucous membranes of the urethra in men and the endocervix in women, although the infection may disseminate to a variety of tissues. The pathogenic mechanism involves the attachment of the gonococci to nonciliated epithelial cells via pili (fimbriae) and the production of cytotoxic factors (endotoxin). Similarly, the lipopolysaccharide of meningococci is highly toxic, but an additional virulence factor is the antiphagocytic capsule. Both pathogens produce proteases that cleave and inactivate human immunoglobulin A1 (IgA1), a major mucosal immunoglobulin of humans. Many normal individuals harbor meningococci, whereas gonococci are present only if sexual contact with an infected person has occurred. Epidemics of meningococcal meningitis occur sporadically. Gonococcal infections occur frequently and affect large numbers of sexually active people. Other species in this genus are primarily parasites on mucosal surfaces of humans and other animals. Human disease caused by these organisms usually is associated with opportunistic infections in compromised patients.

**Neisseria meningitidis**

**Clinical Presentation**

N meningitidis infection results from the bloodborne dissemination (meningococcemia) of the meningococcus, usually following an asymptomatic or mildly symptomatic nasopharyngeal carrier state or a mild rhinopharyngitis (Fig. 14-3). The mildest form is a transient bacteremic illness characterized by a fever and malaise; symptoms resolve spontaneously in 1 to 2 days. Acute meningococcemia is more serious and is often complicated by meningitis. The manifestations of meningococcal meningitis are similar to acute bacterial meningitis caused by organisms such as Streptococcus pneumoniae, Haemophilus influenzae, and E coli. The manifestations result from both infection and increased intracranial pressure. Chills, fever, malaise, and headache are the usual manifestations of infection; headache, vomiting, and rarely, papilledema may result from increased intracranial pressure. Signs of
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Meningeal inflammation are also present. The onset of meningococcal meningitis may be abrupt or insidious.

Infants with meningococcal meningitis rarely display signs of meningeal irritation. Irritability and refusal to take food are typical; vomiting occurs early in the disease and may lead to dehydration. Fever is typically absent in children younger than 2 months of age. Hypothermia is more common in neonates. As the disease progresses, apneic episodes, seizures, disturbances in motor tone, and coma may develop.

In older children and adults, specific symptoms and signs are usually present, with fever and altered mental status the most consistent findings. Headache is an early, prominent complaint and is usually very severe. Nausea, vomiting, and photophobia are also common symptoms.

Neurologic signs are common; approximately one-third of patients have convulsions or coma when first seen by a physician. Signs of meningeal irritation such as cervical rigidity (Brudzinski sign), thoracolumbar rigidity, hamstring spasm (Kernig sign), and exaggerated reflexes are common.

Petechiae (minute hemorrhagic spots in the skin) or purpura (hemorrhages into the skin) occurs from the first to the third day of illness in 30 to 60 percent of patients with meningococcal disease, with or without meningitis. The lesions may be more prominent in areas of the skin subjected to pressure, such as the axillary folds, the belt line, or the back.

Fulminant meningococcemia (Waterhouse-Friderichsen syndrome) occurs in 5 to 15 percent of patients with meningococcal disease and has a high mortality rate. It begins abruptly with sudden high fever, chills, myalgias, weakness, nausea, vomiting, and headache. Apprehension, restlessness, and frequently, delirium occur within the next few hours. Widespread purpuric and ecchymotic skin lesions appear suddenly. Typically, no signs of meningitis are present. Pulmonary insufficiency develops within a few hours, and many patients die within 24 hours of being hospitalized despite appropriate antibiotic therapy and intensive care.
Meningococcal capsular polysaccharides provide the basis for grouping these organisms. Twelve serogroups have been identified (A, B, C, H, I, K, L, X, Y, Z, 29E, and W135). The most important...
serogroups associated with disease in humans are A, B, C, Y, and W135. The chemical composition of these capsular polysaccharides, where known, is listed in Table 14-2. The prominent outer membrane proteins of N meningitidis have been designated class 1 through class 5. The class 2 and 3 proteins function as porins and are analogous to gonococcal Por. The class 4 and 5 proteins are analogous to gonococcal Rmp and Opa, respectively. Serogroup B and C meningococci have been further subdivided on the basis of serotype determinants located on the class 2 and 3 proteins. A few serotypes are associated with most cases of meningococcal disease, whereas other serotypes within the same serogroup rarely caused disease. All known group A strains have the same protein serotype antigens in the outer membrane. Another serotyping system is based on the antigenic diversity of meningococcal LOS. The LOS types are independent of the protein serotypes, although certain combinations frequently occur together.

**Pathogenesis**

The human nasopharynx is the only known reservoir of N meningitidis. Meningococci are spread via respiratory droplets, and transmission requires aspiration of infective particles. Meningococci attach to the nonciliated columnar epithelial cells of the nasopharynx. Attachment is mediated by pili and possibly by other outer membrane components. Invasion of the mucosal cells occurs by a mechanism similar to that observed with gonococci. However, once internalized, meningococci remain in an apical location within the epithelial cell; the route by which they gain access to the subepithelial space remains unclear. Trimers of class 2 and 3 proteins have the ability to translocate from intact cells and insert into eukaryotic cell membranes to form voltage-dependent channels. This process may be important in invasion. Purified meningococcal LOS is highly toxic and is as lethal for mice as the LOS from E coli or Salmonella typhimurium; however, meningococcal LOS is 5 to 10 times more effective than enteric LPS in eliciting a dermal Shwartzman reaction in rabbits. Meningococcal LPS suppresses leukotriene B4 synthesis in human polymorphonuclear leukocytes. The loss of leukotriene B4 deprives the leukocytes of a strong chemokinetic and chemotactic factor. The events after bloodstream invasion are unclear. Relatively little information is known about how the meningococcus enters the central nervous system.
Host Defenses

The integrity of the pharyngeal and respiratory epithelium may be important in protection from invasive disease. Chronic irritation of the mucosa due to dust or low humidity, or damage to the mucosa resulting from a concurrent viral or mycoplasmal upper respiratory infection, may be predisposing factors for invasive disease.

The presence of serum bactericidal IgG and IgM is probably the most important host factor in preventing invasive disease. These antibodies are directed against both capsular and noncapsular surface antigens. The antibodies are produced in response to colonization with carrier strains of *N. meningitidis*, *N. lactamica*, or other nonpathogenic *Neisseria* species. Protective antibodies are also stimulated by cross-reacting antigens on other bacterial species. The role of bactericidal antibodies in prevention of invasive disease explains why high attack rates are seen in infants from 6 to 9 months old, the age at which maternally acquired antibodies are being lost.

The immunity conferred by specific antibody may not be absolute. Illness has been documented in individuals with levels of antibodies considered to be protective. It has been postulated that the activity of the bactericidal antibodies might be blocked by IgA, induced by other meningococcal strains, or by cross-reacting antigens on enteric or other respiratory bacteria. Since IgA does not bind complement, it may block binding sites for the bactericidal IgG and IgM. Persons with complement deficiencies (C5, C6, C7, or C8) may develop meningococcemia despite protective antibody. This underscores the importance of the complement system in protection from meningococcal disease.

Epidemiology

The meningococcus usually inhabits the human nasopharynx without causing detectable disease. This carrier state may last for a few days to months and is important because it not only provides a reservoir for meningococcal infection but also enhances host immunity. Between 5 and 30 percent of normal individuals are carriers at any given time, yet few develop meningococcal disease. Even during epidemics of meningococcal meningitis in military recruits, when the carrier rate may reach 95 percent, the incidence of systemic disease is less than 1 percent. Meningococcal carriage rates are highest in older children and young adults, but the attack rates are higher in children, peaking at 5 years of age (group B) and 4 to 14 years of age (group C). The low incidence of disseminated disease following colonization suggests that host rather than bacterial factors play an important determining role.
Meningococcal meningitis occurs sporadically and in epidemics, with the highest incidence during late winter and early spring. Most epidemics are caused by group A strains, but small outbreaks have occurred with group B and C strains. Sporadic cases generally are caused by group B, C, and Y strains. Whenever group A strains become prevalent in the population, the incidence of meningitis increases markedly.

**Diagnosis**

The most characteristic manifestation of meningococcemia is the skin rash, which is essential for its recognition. Petechiae are the most common type of skin lesion. Ill-defined pink macules and maculopapular lesions also occur. Lesions are sparsely distributed over the body. They tend to occur in crops and on any part of the body; however, the face is usually spared and involvement of the palms and soles is less common. The skin rash may progress from a few ill-defined lesions to a widespread eruption within a few hours.

Acute bacterial meningitis has characteristic signs and symptoms. Except in epidemic situations, it is difficult to identify the causative agent without laboratory tests.

In cases of suspected meningococcal disease, specimens of blood, cerebrospinal fluid, and nasopharyngeal secretions should be collected before administration of any antimicrobial agents and examined for the presence of *N. meningitidis*. Success in isolation is reduced by prior therapy; however, the microscopic diagnosis is not significantly affected. The cerebrospinal fluid should be concentrated by centrifugation and a portion of the sediment cultured on chocolate or blood agar. The plates should be incubated in a candle jar or CO2 incubator. The presence of oxidase-positive colonies and Gram-negative diplococci provides a presumptive identification of *N. meningitidis*. Production of acid from glucose and maltose but not sucrose, lactose, or fructose may be used for confirmation (Table 14-1). The serologic group may be determined by a slide agglutination test, using first polyvalent and then monovalent antisera.

Nasopharyngeal specimens must be obtained from the posterior nasopharyngeal wall behind the soft palate and then should be inoculated onto a selective medium such as Thayer-Martin medium and processed as above.

Blood specimens are inoculated in 10- to 15-ml aliquots onto each of three blood bottles to give a final concentration of 10% (vol/vol). Evacuated bottles should be vented. Some strains of *N. meningitidis* are inhibited by the sodium polyanetholsulfonate contained in blood medium. Toxicity may be overcome
by the addition of gelatin. Sodium amylosulfate is not toxic for the meningococcus. Blood cultures are subcultured blindly onto chocolate or blood agar for confirmation. Gram-stained smears of cerebrospinal fluid may be diagnostic; however, finding neisseriae in these smears is often more difficult than finding the strains that cause pneumococcal meningitis. Quellung tests may be of value.

Control

Group A, C, Y, and W135 capsular polysaccharide vaccines are available and can be used to control outbreaks due to the meningococcal serogroups covered by the vaccine. The A, C, AC, and ACYW135 polysaccharide formulations are currently licensed in the United States. The polysaccharide vaccines are ineffective in young children, and the duration of protection is limited in children vaccinated at 1 to 4 years of age. Routine vaccination of the civilian population in industrialized countries is not currently recommended because the risk of infection is low and most endemic disease occurs in young children. The group B capsular polysaccharide is a homopolymer of sialic acid and is not immunogenic in humans. A group B meningococcal vaccine consisting of outer membrane protein antigens has recently been developed but is not licensed in the United States.

Meningococcal disease arises from association with infected individuals, as evidenced by the 500- to 800-fold greater attack rate among household contacts than among the general population. Because such household members are at high risk, they require chemoprophylaxis. Sulfonamides were the chemoprophylactic agent of choice until the emergence of sulfonamide-resistant meningococci. At present, approximately 25 percent of clinical isolates of N meningitidis in the United States are resistant to sulfonamides; rifampin is therefore the chemoprophylactic agent of choice. Penicillin is the drug of choice to treat meningococcemia and meningococcal meningitis. Although penicillin does not penetrate the normal blood-brain barrier, it readily penetrates the blood-brain barrier when the meninges are acutely inflamed. Either chloramphenicol or a third-generation cephalosporin such as cefotaxime or ceftriaxone is used in persons allergic to penicillins.

Moraxella

Moraxella species are parasites of the mucous membranes of humans and other warm-blooded animals. Many species are nonpathogenic. M lacunata can be isolated from the eyes and may cause conjunctivitis
in humans living under conditions of poor hygiene. *M. nonliquefaciens* is found in the upper respiratory tract, especially the nose, and may be a secondary invader in respiratory infections. *M. urethralis* can be isolated from urine and the female genital tract. Some strains formerly designated as *Mima polymorpha* subsp oxidans belong in this species. These organisms can be mistaken for *N. gonorrhoeae* unless appropriate biochemical characteristics are determined.

*M. catarrhalis* organisms are cocci that morphologically resemble *Neisseria* cells. Other relevant characteristics are presented in Table 14-1. *M. catarrhalis* was formerly placed in the genus *Neisseria*; however, studies of DNA base content, fatty acid composition, and genetic transformation showed that this organism did not belong in that genus. *M. catarrhalis* is a member of the normal flora in 40-50% of normal school children; however, it should be considered more than a harmless commensal of the mucous membranes of humans. It is an infrequent, yet significant, cause of severe systemic infections such as pneumonia, meningitis, and endocarditis. It is an important cause of lower respiratory tract infections in adults with chronic lung disease and a common cause of otitis media, sinusitis, and conjunctivitis in otherwise healthy children and adults. *M. catarrhalis* may cause clinical syndromes indistinguishable from those caused by gonococci, and so it is important to distinguish these organisms from one another. Many strains produce β-lactamase.

**Kingella**

*Kingella kingae* and *K. denitrificans* are oxidase-positive non-motile organisms that are hemolytic when grown on blood agar. They are gram-negative rods, but may resemble coccobacilli or diplococci. They are part of the normal oral flora and occasionally cause infections of bone, joints, and tendons. The organism may enter the circulation with minor oral trauma such as tooth brushing. It is susceptible to penicillin, ampicillin, and erythromycin.

**Eikenella**

*Eikenella corrodens* is a small oxidase-positive, fastidious gram-negative rod, which requires carbon dioxide for growth. Many isolates form pits in agar during growth on solid medium. *E. corrodens* is part of the gingival and bowel flora in 40-70% of humans and may be found in mixed flora infections associated with contamination from these sites. It occurs frequently.
Clinical Manifestations

Gonorrheal infection is generally limited to superficial mucosal surfaces lined with columnar epithelium. The area’s most frequently involved are the cervix, urethra, rectum, pharynx, and conjunctiva (Fig. 14-1). Squamous epithelium, which lines the adult vagina, is not susceptible to infection by the gonococcus. However, the prepubertal vaginal epithelium, which has not been keratinized under the influence of estrogen, may be infected. Hence, gonorrhea in young girls may present as vulvovaginitis. Mucosal infections are usually characterized by a marked local neutrophilic response (purulent discharge).

The most common symptom of uncomplicated gonorrhea is a discharge that may range from a scanty, clear, or cloudy fluid to one that is copious and purulent. Dysuria is often present. Men with asymptomatic urethritis are an important reservoir for transmission. In addition, such men and those who ignore their symptoms are at increased risk for developing complications.

Endocervical infection is the most common form of uncomplicated gonorrhea in women. Such infections are usually characterized by vaginal discharge and sometimes by dysuria (because of coexistent urethritis). The cervical os may be erythematous and friable, with a purulent exudate. About 50 percent of women with cervical infections are asymptomatic. Local complications include abscesses in Bartholin’s and Skene’s glands.

Rectal infections with N gonorrhoeae occur in about one-third of women with cervical infection. They most often result from autoinoculation with cervical discharge and are rarely symptomatic. Rectal infections in homosexual men usually result from anal intercourse and are more often symptomatic. The symptoms and signs of gonococcal proctitis range from mild burning on defecation to itching to severe tenesmus and from mucopurulent discharge to frank blood in the stools.
Pharyngeal infections are diagnosed most often in women and homosexual men with a history of fellatio. Such infections may be a focal source of gonococcemia. Ocular infections can have serious consequences (corneal scarring or perforation); prompt diagnosis and treatment are therefore important. Ocular infections (ophthalmia neonatorum) occur most commonly in newborns who are exposed to infected secretions in the birth canal. Keratoconjunctivitis is occasionally seen in adults as a result of autoinoculation. Disseminated gonococcal infections result from gonococcal bacteremia. Asymptomatic infections of the pharynx, urethra, or cervix often serve as focal sources for bacteremia. The most common form of disseminated gonococcal infection is the dermatitis-arthritis syndrome. It is characterized by fever, chills, skin lesions, and arthralgias (usually involving the hands, feet, and elbows), which are due to periarticular inflammation of the tendon sheaths. Occasionally, a patient develops a septic joint with effusion. Skin lesions may be macular, pustular, centrally necrotic, or hemorrhagic. Rarely, disseminated gonococcal infection causes endocarditis or meningitis. Gonococci may ascend from the endocervical canal through the endometrium to the fallopian tubes and ultimately to the pelvic peritoneum, resulting in endometritis, salpingitis, and finally, peritonitis. Women usually present with pelvic and abdominal pain, fever, chills, and cervical motion tenderness. This complex of signs and symptoms is referred to as pelvic inflammatory disease (PID). This disease may also be caused by other sexually transmitted organisms (e.g., Chlamydia trachomatis) as well as by non-sexually transmitted bacteria that are part of the normal vaginal flora. Complications of pelvic inflammatory disease include tubo-ovarian abscesses, pelvic peritonitis, or Fitz-Hugh and Curtis syndrome, which is an inflammation of Glisson’s capsule of the liver. As many as 15 percent of women with uncomplicated cervical infections may develop pelvic inflammatory disease. The disease may have serious consequences, including an increased probability of infertility and ectopic pregnancy.

**Structure**

Neisseria species are Gram-negative cocci, 0.6 to 1.0 μm in diameter. The organisms are usually seen in pairs with the adjacent sides flattened. Pili, hairlike filamentous appendages extend several micrometers from the cell surface and have a role in adherence. The outer membrane is composed of proteins, phospholipids, and lipopolysaccharide (LPS). Features that distinguish gonococcal LPS from enteric LPS are the highly branched basal oligosaccharide structure and the absence of repeating O-antigen subunits. For these reasons gonococcal LPS, as well as that of other mucosal pathogens, is
referred to as lipooligosaccharide (LOS). Gonococci characteristically release outer membrane fragments (blebs) during growth. These blebs contain LOS and may have a role in pathogenesis.

**Classification and Antigenic Types**

<table>
<thead>
<tr>
<th>TABLE 14-1 Differential Characteristics of <em>Neisseria</em> and related species of human origin*</th>
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<tr>
<td>Species</td>
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<td><em>N. gonorrhoeae</em></td>
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<td><em>N. meningitidis</em></td>
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<td><em>M. catarrhalis</em></td>
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<td><em>K. menetamur</em></td>
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*Symbols and abbreviations: + stains typically positive but genetic variants may be negative; 0, most strains negative; x, strain dependent; NT, not tested; GLU, glucose; MAL, maltose; LAC, lactose; SUC, sucrose; FRU, fructose; MTM, modified Thayer-Martin medium; ML, Martin-Levis medium; NYC, New York City medium. All species contain catalase and cytochrome oxidase.

*Some strains grow on selective media even though they are catalase susceptible.

*Includes *b. subflava*, *flava*, and *pentflava*. *N. subflava* is *flava* strains produce acid from sucrose and fructose and produce polysaccharide from sucrose; *N. subflava* is *flava* strains produce acid from fructose; *N. subflava* is *flava* and *N. subflava* is *subflava* do not produce polysaccharide from sucrose.

The gonococcus is an obligate human pathogen. It is one of two Neisseria species that cause significant human infections. The genus also includes several nonpathogenic species (Table 14-1), which may be part of the normal flora and therefore can be confused with *N. gonorrhoeae*. Gonococcal strains can be characterized according to their nutritional requirements (auxotyping). A panel of monoclonal antibodies specific for epitopes on protein I have also been used to type strains. Strains exhibiting specific reaction patterns are termed serovars. A combined auxotype-serovar classification provides greater resolution among gonococcal isolates and is useful in epidemiologic investigations.
Gonococci can invade columnar epithelial cells, although they do not invade ciliated columnar epithelium of the genitourinary tract.

Our knowledge of the molecular basis of gonococcal pathogenesis is incomplete (Fig. 14-2). Attachment of gonococci to mucosal cells is mediated in part by pili, although nonspecific factors such as surface charge and hydrophobicity may be important. Pili undergo both phase and antigenic variation. Opa proteins (protein II), which are located in the outer membrane, are also involved in attachment to host cells. Gonococci attach only to microvilli of nonciliated columnar epithelial cells; attachment to ciliated cells is not observed.
Much of our knowledge of gonococcal invasion comes from studies with tissue culture cells and human fallopian tube organ culture. After gonococci attach to the nonciliated epithelial cells of the fallopian tube, they are surrounded by the microvilli, which draw them to the surface of the mucosal cell. The gonococci appear to enter the epithelial cells by a process called parasite-directed endocytosis. This process seems to be initiated by microbial factors because it does not occur unless the gonococci are viable and because it involves host cells that are not normally phagocytic. An unidentified factor in serum enhances engulfment of gonococci. The process is inhibited by drugs that block the actions of the microtubule (demecolcine) and microfilament (cytochalasin B) systems. During endocytosis the membrane of the mucosal cell retracts, pinching off a membrane-bound vacuole that contains gonococci; this vacuole is rapidly transported to the base of the cell, where gonococci are released by exocytosis into the subepithelial tissue. Gonococci are not destroyed within the phagocytic vacuole; it is not clear whether they replicate in the vacuoles.

The major porin protein of the gonococcal outer membrane, Por (protein I), has been proposed as a candidate invasin (a substance that helps mediate invasion into a host cell). The insertion of Por into neutrophils treated with the chemotactic peptide, fMLP and leukotriene B4, inhibits degranulation but not the generation of the superoxide anion. The significance of these observations with respect to the pathogenesis of gonorrhea remains to be determined. Each gonococcal strain expresses only one type of Por; however, the Por of different strains may exhibit antigenic differences.

Gonococci can produce one or several outer membrane proteins called Opa proteins (proteins II). These proteins are subject to phase variation and are usually found on cells from colonies possessing an opaque phenotype (O+). At any one time, a gonococcus may express zero, one, or several different Opa proteins, though each strain has 10 or more genes for different Opas. Trypsin-like proteases present in cervical mucus may help select for protease-resistant transparent (O–) colony phenotypes. O+ colony phenotypes (protease sensitive) predominate in cultures taken during the middle portion of the menstrual cycle. Cervical proteases increase during the second half of the cycle, resulting in an increase in the O– phenotype. The O– colony types can be isolated from tubal as well as endocervical cultures; O+ colony phenotypes have been isolated more often from endocervical cultures than from tubal cultures.

Rmp (Protein III) is an outer membrane protein found in all strains of N gonorrhoeae. It does not undergo phase variation and is found in a complex with Por and LOS. It shares partial homology with
the Omp A protein of Escherichia coli. Antibodies to Rmp, induced either by a neisserial infection or by colonization with E coli, block bactericidal antibodies directed against Por and LOS. Rmp antibodies may facilitate infection with N gonorrhoeae.

LOS has a profound effect on the virulence and pathogenesis of N gonorrhoeae. Gonococci can express several antigenic types of LOS and can alter the type of LOS they express by an as yet unknown mechanism. Gonococcal LOS produces mucosal damage in fallopian tube organ cultures and brings about the release of enzymes, such as proteases and phospholipases, that may be important in pathogenesis. More recent evidence suggests that gonococcal LOS stimulates the production of tumor necrosis factor (TNF) in fallopian tube organ cultures; inhibition of tumor necrosis factor with specific antiserum prevents tissue damage. Thus, gonococcal LOS appears to have an indirect role in mediating tissue damage. Gonococcal LOS is also involved in the resistance of N gonorrhoeae to the bactericidal activity of normal human serum. Oligosaccharides containing epitopes defined by specific monoclonal antibodies are associated with a serum-resistant phenotype.

Gonococci can utilize host-derived cytidine monophospho-N-acetylneuraminic acid (CMP-NANA) in vivo to sialylate the oligosaccharide component of its LOS, converting a serum-sensitive organism to a serum-resistant one. When such organisms are grown in vitro without CMP-NANA, their resistance to killing by normal human serum is rapidly lost. Organisms with non-sialylated LOS are more invasive than those with sialylated LOS. There is antigenic similarity between neisserial LOS and antigens present on human erythrocytes. This similarity to self may preclude an effective immune response to these LPS antigens.

Gonococci are highly autolytic and release peptidoglycan fragments during growth. These fragments, released by bacterial and/or host peptidoglycan hydrolases, are toxic for fallopian tube mucosa and may contribute to the intense inflammatory reactions characteristic of gonococcal disease.

N gonorrhoeae is highly efficient at utilizing transferrin-bound iron for in vitro growth; many strains can also utilize lactoferrin-bound iron. Gonococci (and meningococci) bind only human transferrin and lactoferrin. This specificity is thought to be the reason these organisms are exclusively human pathogens. Nevertheless, the role of transferrin- and lactoferrin-bound iron in in vivo growth is unknown. Gonococci express several new proteins when grown under iron-restricted conditions similar to the conditions occurring in the host. Some of these proteins function as receptors for
transferrin, lactoferrin, heme, and hemoglobin; others function in the transport of iron into the cell. Gonococci cannot grow anaerobically unless low concentrations of the alternative electron acceptor nitrite are present. Under these conditions they produce novel proteins. These proteins are apparently produced during an infection because antibodies against them are present in the serum specimens of patients with uncomplicated gonorrhea, disseminated gonococcal infection, or pelvic inflammatory disease. These data suggest that some gonococci in the host are growing under anaerobic conditions. Further studies will determine the relevance of these proteins to pathogenesis.

Strains of N gonorrhoeae (and N meningitidis) produce two distinct extracellular IgA1 proteases, which cleave the heavy chain of human immunoglobulin A1 (IgA1) at different points within the hinge region. Type 1 protease cleaves a prolyl-seryl peptide bond and type 2 protease cleaves a prolyl-threonyl bond in the hinge region of the heavy chain. This region is missing in human IgA2, and so this isotype is not susceptible to cleavage. Each gonococcal or meningococcal isolate elaborates only one of these two enzymes. Split products of IgA1 have been found in the genital secretions of women with gonorrhea, suggesting that the gonococcal IgA1 protease is present and active during genital infection. Fab fragments of IgA1 may bind to the gonococcal cell surface and block the Fc-mediated functions of intact immunoglobulins.

**Host Defenses**

Not everyone exposed to N gonorrhoeae acquires the disease. This may be due to variations in the size or virulence of the inoculum, to nonspecific resistance, or to specific immunity. A 50 percent infective dose (ID50) of about 1,000 organisms has been established, based on the experimental urethral inoculation of male volunteers. There is no reliable ID50 for women, although it is assumed to be similar.

Nonspecific factors have been implicated in natural resistance to gonococcal infection. In women, changes in the genital pH and hormones may increase resistance to infection at certain times of the menstrual cycle. Urinary solutes exhibit bactericidal and bacteriostatic activity of N gonorrhoeae. Factors in urine that seem to be important are pH, osmolarity, and the concentration of urea. The variability in the susceptibility of gonococcal strains to the bactericidal and bacteriostatic properties of urine is thought to be one of the reasons some men do not develop a gonococcal infection when exposed.
Most uninfected individuals have serum antibodies that react with gonococcal antigens. These antibodies probably result from colonization or infection with various Gram-negative bacteria that possess cross-reactive antigens. These “natural” antibodies differ, both qualitatively and quantitatively, from person to person, but may be important in an individual's natural resistance or susceptibility to infection.

Infection with N. gonorrhoeae stimulates both mucosal and systemic antibodies to a variety of gonococcal antigens. Mucosal antibodies are primarily IgA and IgG. In genital secretions, antibodies have been identified that react with Por, Opa and LOS, and some of the iron-regulated proteins. Vaccine trials have suggested that antipilus antibodies inhibit the pilus-mediated attachment of the homologous gonococcal strain. Complement is present in endocervical secretions, but in a much lower concentration than in blood. However, there is little evidence to support a role for a complement-mediated bactericidal defense mechanism on the genital mucosa. In general, the IgA response is brief and declines rapidly after treatment; IgG levels decline more slowly.

More information is available about the function of systemic humoral immune mechanisms in gonococcal infection. Gonococcal antigens such as pili, Por, Opa, Rmp, and LOS elicit a serum antibody response during an infection. Antipilus antibody levels tend to be higher in women than in men and are related to the number of previous infections. The predominant IgG subclass that reacts with a variety of gonococcal antigens is IgG3, followed by IgG1 and IgG4. IgG2 is minimal, suggesting that polysaccharides are not important in the immune response to gonococcal infection. Anti-Por antibodies may be bactericidal for the gonococcus. IgG that reacts with Rmp blocks the bactericidal activity of antibodies directed against Por and LOS. Genital infection with N. gonorrhoeae stimulates a serum antibody response against the LOS of the infecting strain. Disseminated gonococcal infection results in higher levels of anti-LOS antibody than do genital infections.

Strains that cause uncomplicated genital infections usually are killed by normal human serum and are termed serum sensitive. This bactericidal activity is mediated by IgM and IgG that recognize sites on the LOS. Strains that cause disseminated infections are not killed by most normal human serum and are referred to as serum resistant. Resistance is mediated, in part, by IgA that blocks the IgG-mediated bactericidal activity of the serum. Serum specimens from convalescent patients with disseminating infections contain bactericidal IgG to the LOS of the infecting strain.
Individuals with inherited complement deficiencies have a markedly increased risk of acquiring systemic neisserial infections and are subject to recurring episodes of systemic gonococcal and meningococcal infections, indicating that the complement system is important in host defense. Gonococci activate complement by both the classic and alternative pathways. Complement activation by gonococci leads to the formation of the C5b-9 complex (membrane attack complex) on the outer membrane. In normal human serum, similar numbers of C5b-9 complexes are deposited on serum-sensitive and serum-resistant organisms, but the membrane attack complex is not functional on serum-resistant organisms. Other complement-mediated functions, such as opsonophagocytosis and chemotaxis, are more efficient with serum-sensitive than with serum-resistant gonococci. This may be a significant factor in the pathogenesis of disseminated gonococcal infection and probably contributes to the relative lack of genital symptoms observed with this disease.

Normal human serum contains opsonic anti-Por IgG. Antibodies to various surface-exposed antigens are also present in cervical and urethral secretions of patients with gonorrhea and probably contribute to the opsonophagocytosis of the organism. Opa is important in gonococcus-neutrophil interactions. Gonococci expressing certain Opas interact with neutrophils in the absence of antibodies. Once phagocytosed, gonococci are killed by both oxygen-dependent and oxygen-independent mechanisms. The survival of gonococci within neutrophils has been the subject of considerable controversy, with no clear-cut answer yet available. The opsonization and phagocytosis of gonococci are comparatively more important in mucosal infections than in protection from systemic gonococcal (and meningococcal) infections.

**Epidemiology**

The only natural host for N gonorrhoeae is the human. Gonorrhea has all but disappeared in Scandinavia and several other European countries. In the United States, gonorrhea remains the most frequently reported infectious disease. Between 1977 and 1993, the number of reported cases decreased 56 percent, from 1 million to 439,673 cases per year. The Centers for Disease Control (CDC) estimates that there are two unreported cases for every reported case of gonorrhea. Gonorrhea is transmitted almost exclusively by sexual contact. The highest rates occur in women between the ages of 15 and 19 years and in men 20 and 24 years of age. Persons who have multiple sex partners are at highest risk. Rates of gonorrhea are higher in males and in minority and inner-city populations.
Gonorrhea is usually contracted from a sex partner who is either asymptomatic or has only minimal symptoms. It is estimated that the efficiency of transmission after one exposure is about 35 percent from an infected woman to an uninfected man and 50 to 60 percent from an infected man to an uninfected woman. More than 90 percent of men with urethral gonorrhea will develop symptoms within 5 days; fewer than 50 percent of women with anogenital gonorrhea will do so. Women with asymptomatic infections are at higher risk of developing pelvic inflammatory disease and disseminated gonococcal infection.

**Diagnosis**

Gonococcal infection produces several common clinical syndromes that have multiple causes or that mimic other conditions. Laboratory tests are often required to differentiate among the etiologic agents causing urethritis or cervicitis. The etiologic diagnosis of salpingitis and pelvic peritonitis is quite difficult because mixed infections are common and laparoscopy is required to obtain appropriate cultures. Gonococcal perihepatitis may mimic acute cholecystitis. All of the above syndromes are also caused by C trachomatis, a sexually transmitted bacterium that causes more infections in the United States than N gonorrhoeae. The gonococcal arthritis-dermatitis syndrome, must be, differentiated from meningococcemia and Reiter syndrome, in particular, and from other causes of septic arthritis.

Customarily, the laboratory diagnosis of gonorrhea is made presumptively and then confirmed; the latter process involves identifying characteristics that distinguish N gonorrhoeae from other Neisseria spp. that may be present in the specimen. Nonpathogenic Neisseria are normal inhabitants of the oropharynx and nasopharynx and occasionally are isolated from other sites infected by N gonorrhoeae. A presumptive diagnosis of gonorrhea may be made from Gram-stained smears of urethral, cervical, and rectal specimens if Gram-negative diplococci are observed within leukocytes; it is equivocal if only extracellular Gram-negative diplococci are seen and negative if no Gram-negative diplococci are seen. Gram stain diagnosis has a sensitivity and specificity of >95 percent in men with symptomatic urethritis. The specificity of Gram stain diagnosis in women is also high if the cervix is wiped clean to remove cervical secretions before collecting the specimen; however, the sensitivity is only about 50 percent. The sensitivity and specificity of the Gram stain for rectal specimens are lower than with cervical specimens.
Specimens for the laboratory diagnosis of gonorrhea should be collected before treating the patient. Ideally, specimens should be inoculated onto appropriate media and incubated immediately after collection at 35 to 36.5°C in a CO2-enriched atmosphere, which can be obtained by using a candle extinction jar or a CO2 incubator. Urethral specimens are normally obtained from heterosexual men; urethral, rectal, and pharyngeal specimens are normally obtained from homosexual men; and cervical and rectal specimens are normally obtained from women. Specimens are collected with cotton, polyester, or calcium alginate swabs. When appropriate, specimens may also be obtained from the urethra and from Bartholin’s and Skene’s glands of infected women. Blood cultures should be performed for patients with suspected disseminated infection. Synovial fluid cultures should be performed for patients with septic arthritis.

Urethral, cervical, and pharyngeal specimens are inoculated onto selective medium such as modified Thayer-Martin, Martin-Lewis, or NYC medium. These are complex media that contain antimicrobial and antifungal agents to inhibit the growth of unwanted organisms. Rectal specimens should be inoculated onto modified Thayer-Martin medium which contains trimethoprim lactate to inhibit the growth and swarming of Proteus species. Specimens collected from normally sterile sites such as blood, synovial fluid, and conjunctivae may be inoculated onto a nonselective medium such as chocolate agar.

The combination of oxidase-positive colonies and Gram-negative diplococci provides a presumptive identification of *N. gonorrhoeae*. Fluorescent-antibody staining, coagglutination, specific biochemical tests (Table 14-1), and DNA probes may be used for confirmation. DNA probes have also been used to detect gonococci in urethral and cervical specimens. A commercial test based on this approach is available. Serologic tests for uncomplicated gonorrhea have not proved satisfactory.

**Control**

There is no effective vaccine to prevent gonorrhea. Candidate vaccines consisting of pilus protein or Por are of little benefit. The development of an effective vaccine has been hampered by the lack of a suitable animal model and the fact that an effective immune response has never been demonstrated. Condoms are effective in preventing the transmission of gonorrhea.
Contact tracing to identify source contacts (i.e., those who infected the index patient) has been useful in identifying asymptomatic individuals or those with ignored symptoms. Contact tracing has also been used to identify contacts who were exposed to the index patient and who may have become infected.

The evolution of antimicrobial resistance in N gonorrhoeae may ultimately affect the control of gonorrhea. Strains with multiple chromosomal resistance to penicillin, tetracycline, erythromycin, and cefoxitin have been identified in the United States and most other parts of the world. Sporadic high-level resistance to spectinomycin and fluoroquinolones have been reported.

Penicillinase-producing strains of N gonorrhoeae were first described in 1976. Five related β-lactamase plasmids of different sizes have been identified in these strains. The strains cause more than one-half of all gonococcal infections in parts of Africa and Asia. Their prevalence has increased dramatically in the United States since 1984 and has affected nearly every major metropolitan area.

Plasmid-mediated high-level resistance of N gonorrhoeae to tetracycline was first described in 1986 and has now been reported in most parts of the world. This resistance is due to the presence of the streptococcal tet M determinant on a gonococcal conjugative plasmid.

The current CDC Treatment Guidelines recommend treatment of all gonococcal infections with antibiotic regimens effective against resistant strains. The recommended antimicrobial agents are ceftriaxone, cefixime, ciprofloxacin, or oflaxacin. Since a significant proportion of patients with gonorrhea are also infected with C trachomatis, doxycycline or erythromycin has been added to treat this concomitant infection.