44 - 161 Gonococcal Infections

161 Gonococcal Infections

of the remainder over the next 6 weeks. In outbreaks of meningococcal disease, mass prophylaxis has been used; however, limited data support population intervention, and significant concerns have arisen about adverse events and the development of resistance. For these reasons, prophylaxis is usually restricted to (1) persons at greatest risk who are intimate and/or household contacts of the index case and (2) health care workers who have been directly exposed to respiratory secretions. In most cases, members of wider communities (e.g., at schools or col leges) are not offered prophylaxis. The aim of prophylaxis is to eradicate colonization of close contacts with the strain that has caused invasive disease in the index case. Prophylaxis should be given to all contacts at the same time to avoid recolonization by meningococci transmitted from untreated contacts and should also be used as soon as possible to treat early disease in secondary cases. If the index patient is treated with an antibiotic that does not reliably clear colonization (e.g., penicillin), the patient should be given a prophylactic agent at the end of treatment to prevent relapse or onward transmission. Although rifampin has been most widely used and studied, it is not the optimal agent because it fails to eradicate carriage in 15–20% of cases, rates of adverse events have been high, compliance is affected by the need for four doses, and emerging resis tance has been reported. Ceftriaxone as a single IM or IV injection is highly (97%) effective in carriage eradication and can be used at all ages and in pregnancy. Reduced susceptibility of isolates to ceftriaxone has occasionally been reported. Ciprofloxacin or ofloxacin is preferred in some countries; these agents are highly effective and can be adminis tered by mouth but are not recommended in pregnancy. Resistance to fluoroquinolones has been reported in some meningococci in North America, Europe, and Asia. In documented capsular group A, B, C, Y, or W disease, contacts may be offered immunization (with either the MenACWY conjugate vaccine or the MenB vaccine, as appropriate) in addition to chemo prophylaxis to provide protection beyond the duration of antibiotic therapy. Mass vaccination has been used successfully to control disease during outbreaks in closed communities (educational and military establishments) as well as during epidemics in open communities. ■ ■FURTHER READING Carr JP et al: Impact of meningococcal ACWY conjugate vaccines on pharyngeal carriage in adolescents: Evidence for herd protection from the UK MenACWY programme. Clin Microbiol Infect 28:1649. e1, 2022. Castilla J et al: Effectiveness of a meningococcal group B vaccine (4CMenB) in children. N Engl J Med 388:427, 2023. Christensen H et al: Meningococcal carriage by age: A systematic review and meta-analysis. Lancet Infect Dis 10:853, 2010. Haidara FC et al: Meningococcal ACWYX conjugate vaccine in 2-to29-year-olds in Mali and Gambia. N Engl J Med 388:1942, 2023. Ladhani SN et al: Vaccination of infants with

meningococcal group B vaccine (4CMenB) in England. N Engl J Med 382:309, 2020. Marshall HS et al: Meningococcal B vaccine and meningococcal car riage in adolescents in Australia. N Engl J Med 382:318, 2020. Mbaeyi SA et al: Meningococcal vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020. MMWR Recomm Rep 69:1, 2020. Pardo de Santayana C et al: Epidemiology of invasive meningococ cal disease worldwide from 2010–2019: A literature review. Epide miol Infect 151:e57, 2023. Pollard AJ et al: Maintaining protection against invasive bacteria with protein–polysaccharide conjugate vaccines. Nat Rev Immunol 9:213, 2009. Read RC et al: Effect of a quadrivalent meningococcal ACWY glyco conjugate or a serogroup B meningococcal vaccine on meningococcal carriage: An observer-blind, phase 3 randomised clinical trial. Lancet 384:2123, 2014. Vieusseux M: Memoire sur le maladie qui a regne a Geneva au print emps de 1805. J Med Clin Pharm 11:163, 1805. Wang B et al: 4CMenB sustained vaccine effectiveness against invasive meningococcal B disease and gonorrhoea at three years post pro gramme implementation. J Infect 87:95, 2023.

Sanjay Ram, Peter A. Rice

Gonococcal Infections ■ ■DEFINITION Gonorrhea is a sexually transmitted infection (STI) of epithelium and commonly manifests as cervicitis, urethritis, proctitis, and conjunctivi tis. If untreated, infections at these sites can lead to local complications such as endometritis, salpingitis, tuboovarian abscess, bartholinitis, peritonitis, and perihepatitis in female patients; periurethritis and epi didymitis in male patients; and ophthalmia neonatorum in newborns. Disseminated gonococcemia is an uncommon event whose manifesta tions include skin lesions, tenosynovitis, septic arthritis, and (in rare cases) endocarditis or meningitis. ■ ■MICROBIOLOGY Neisseria gonorrhoeae is a gram-negative, nonmotile, non-spore-forming organism that grows singly and in pairs (i.e., as monococci and dip lococci, respectively). Exclusively a human pathogen, the gonococcus contains, on average, three genome copies per coccal unit; this poly ploidy permits a high level of antigenic variation and the survival of the organism in its host. Gonococci, like all other Neisseria species, are oxidase positive. They are distinguished from other neisseriae by their ability to grow on selective media and to use glucose but not maltose, sucrose, or lactose. CHAPTER 161 ■ ■EPIDEMIOLOGY The incidence of gonorrhea had been declining steadily in the United States, but in 2021, there were ~710,000 newly reported cases—up 136% since their historic low in 2009. With 82.4 million cases esti mated by the World Health Organization to have occurred globally in 2020 among adults aged 15 to 49 years, gonorrhea remains a major public health problem worldwide, is a significant cause of morbidity in developing countries, and may play a role in enhancing transmission of HIV. Gonococcal Infections Gonorrhea predominantly affects young, nonwhite, unmarried, less educated members of urban populations. The number of reported cases probably represents half of the true number of cases—a dis crepancy resulting from underreporting, self-treatment, nonspecific treatment without a laboratory-proven diagnosis, and asymptomatic infection. The number of reported new cases of gonorrhea in the United States rose from ~250,000 in the early 1960s to a high of 1.01 million in 1978. The recorded incidence of gonorrhea in modern times peaked in 1975, with 468 reported new cases per 100,000 population in the United States. This peak was attributable to the interaction of several variables, including improved accuracy of diagnosis, changes in patterns of contraceptive use, and changes in sexual behavior. A decline in the overall incidence of gonorrhea in the United States over the past quarter-century may have reflected increased condom use resulting from public health efforts to curtail HIV transmission. Nevertheless, in 2019, 214 new cases per 100,000 population were reported in this

country, representing a 1-year increase of 4.6%; this figure is the highest among industrialized countries. Simultaneously, antibiotic resistance is increasing in the United States and other coun tries, prompting the U.S. Centers for Disease Control and Prevention (CDC) to name antibiotic-resistant N. gonorrhoeae as one of the three most urgent threats of its kind. At present, the attack rate in the United States is highest among 15- to 24-year-old women (730.5 per 100,000) and 20- to 29-year-old men (813.6 per 100,000); >70% of all reported cases occur in these two groups. From the standpoint of ethnicity, rates are highest among African Americans (652.9 per 100,000) and lowest among persons of Asian descent (37.8 per 100,000). The incidence of gonorrhea is higher in developing countries than in industrialized nations. The exact incidence of any STI is difficult to ascertain in developing countries because of limited surveillance and variable diagnostic criteria. Extremely high rates of gonorrhea have

been reported among aboriginal populations in Namibia and Australia. Studies in Africa have clearly demonstrated that nonulcerative STIs such as gonorrhea (in addition to ulcerative STIs) are an independent risk factor for the transmission of HIV (Chap. 208).

Gonorrhea is transmitted from males to females more efficiently than in the opposite direction. The rate of transmission to a woman during a single unprotected sexual encounter with an infected man is ~50–80%. Oropharyngeal gonorrhea occurs in ~20% of women who practice fellatio with infected partners. Transmission in either direc tion by cunnilingus is rare. In any population, there exists a small minority of individuals who have high rates of new-partner acquisition. These “core-group members” or “high-frequency transmitters” are vital in sustaining STI transmission at the population level. Another instrumental factor in sustaining gonorrhea in the population is the large number of infected individuals who are asymptomatic or have minor symptoms that are ignored. These persons, unlike symptomatic individuals, may not cease sexual activity and therefore may continue to transmit the infec tion. This situation underscores the importance of contact tracing and empirical treatment of the sex partners of index cases. ■ ■PATHOGENESIS, IMMUNOLOGY, AND ANTIMICROBIAL RESISTANCE Outer-Membrane Proteins • PILI Fresh clinical isolates of N. gonorrhoeae initially form piliated (fimbriated) colonies distinguish able on translucent agar. Pilus expression is rapidly switched off with unselected subculture because of rearrangements in pilus genes. This change is a basis for antigenic variation of gonococci. Piliated strains adhere better to cells derived from human mucosal surfaces and are more virulent in organ culture models and human inoculation experi ments than nonpiliated variants. In a fallopian tube explant model, pili mediate gonococcal attachment to nonciliated columnar epithelial cells. This event initiates gonococcal adherence, invasion and transport through these cells to intercellular spaces near the basement membrane or directly into the subepithelial tissue. Pili are also essential for genetic competence and transformation of N. gonorrhoeae, which permit horizontal transfer of genetic material between different gonococcal lineages in vivo. PART 5 Infectious Diseases OPACITY-ASSOCIATED PROTEIN Another gonococcal surface protein that is important in adherence to epithelial cells is opacity-associated protein (Opa; formerly called protein II). Opa contributes to inter gonococcal adhesion, which is responsible for the opaque nature of gonococcal colonies on translucent agar and the organism’s adherence to a variety of eukaryotic cells, including polymorphonuclear leuko cytes (PMNs). Certain Opa variants promote invasion of epithelial cells, and this effect has been linked with the ability of Opa to bind vitronectin, heparan sulfate proteoglycans, and several members of the carcinoembryonic antigen–related cell adhesion molecule (CEACAM) receptor family. Epithelial CEACAM-binding gonococci prevent exfo liation of

epithelium through a mechanism that involves nitric oxide that is produced during anaerobic bacterial metabolism and upregu lation of CD105 (a member of the transforming growth factor-beta receptor family), which may interfere with bacterial clearance.

N. gonorrhoeae Opa proteins that bind CEACAM1, which is expressed by primary CD4+ T lymphocytes, suppress the activation and pro liferation of these lymphocytes. Select Opa proteins can engage CEACAM3, which is expressed on neutrophils, with consequent non opsonic phagocytosis (i.e., phagocytosis independent of antibody and complement) and killing of bacteria. PORIN Porin (previously designated protein I) is the most abundant gonococcal surface protein. Porin molecules exist as trimers that provide anion-transporting aqueous channels through the otherwise hydrophobic outer membrane. Porin exhibits stable interstrain anti genic variation and forms the basis for gonococcal serotyping. Two main serotypes have been identified; PorB.1A strains are often associ ated with disseminated gonococcal infection (DGI), whereas PorB.1B strains usually cause local genital infections only. DGI strains are

generally resistant to the killing action of normal human serum and do not incite a significant local inflammatory response; therefore, they may not cause symptoms at genital sites. These characteristics may be related to the ability of PorB.1A strains to bind to complement-inhibitory molecules, resulting in a diminished inflammatory response. Porin can translocate to the cytoplasmic membrane of host cells—a process that could initiate gonococcal endocytosis and invasion. PorB.1B present in outer membrane vesicles shed during bacterial growth inhibits the abil ity of dendritic cells to induce T-cell proliferation and may contribute to the ability of gonococci to subvert adaptive immunity. OTHER OUTER-MEMBRANE PROTEINS Other notable outer-membrane proteins include H.8, a lipoprotein that is present in high concentra tion on the surface of all gonococcal strains and is an excellent target for antibody-based diagnostic testing. Transferrin-binding proteins (Tbp1 and Tbp2), lactoferrin-binding proteins (LbpA and LbpB), and hemoglobin/haptoglobin binding proteins (HpuA and HpuB) are required for scavenging iron from transferrin, lactoferrin, and heme in vivo. Transferrin and iron have been shown to enhance the attachment of iron-deprived N. gonorrhoeae to human endometrial cells. TdfH and TdfJ enable gonococci to scavenge host zinc from calprotectin and S100 calcium binding protein A7 (psoriasin). IgA1 protease is produced by N. gonorrhoeae and may protect the organism from the action of mucosal IgA. Lipooligosaccharide Gonococcal lipooligosaccharide (LOS) con sists of a lipid A and a core oligosaccharide that lacks the repeating O-carbohydrate antigenic side chain seen in many other gram-negative bacteria. Gonococcal LOS possesses marked endotoxic activity and contributes to the local cytotoxic effect in a fallopian tube model. LOS core sugars undergo a high degree of phase variation under different conditions of growth; this variation reflects genetic regulation and expression of glycotransferase genes that dictate the carbohydrate structure of LOS. These phenotypic changes may affect interactions of N. gonorrhoeae with elements of the humoral immune system (antibodies and complement) and may also influence direct binding of organisms to both professional phagocytes and nonprofessional phagocytes (epithelial cells). For example, gonococci that are sialylated at their LOS sites inhibit the classic pathway of complement by reduc ing binding of IgG and also bind complement factor H to inhibit the alternative pathway of complement. LOS sialylation may also decrease nonopsonic Opa-mediated association with neutrophils and inhibit the oxidative burst in PMNs. The binding of the unsialylated terminal lactosamine residue of LOS to an asialoglycoprotein receptor on male epithelial cells facilitates adherence and subsequent gonococcal inva sion of these cells. Moreover, oligosaccharide

structures in LOS can modulate host immune responses. For example, the terminal mono saccharide expressed by LOS determines the C-type lectin receptor on dendritic cells that is targeted by the bacteria. In turn, the specific C-type lectin receptor engaged influences whether a TH1- or TH2-type response is elicited; the latter response may be less favorable for clear ance of gonococcal infection. Host Factors In addition to gonococcal structures that interact with epithelial cells, host factors seem to be important in mediating entry of gonococci into nonphagocytic cells. Activation of phospha tidylcholine-specific phospholipase C and acidic sphingomyelinase by N. gonorrhoeae, which results in the release of diacylglycerol and ceramide, is a requirement for the entry of N. gonorrhoeae into epi thelial cells. Ceramide accumulation within cells leads to apoptosis, which may disrupt epithelial integrity and facilitate entry of gonococci into subepithelial tissue. Release of chemotactic factors as a result of complement activation contributes to inflammation, as does the toxic effect of LOS and peptidoglycan in provoking the release of inflamma tory cytokines. The importance of humoral immunity in host defenses against neisserial infections is best illustrated by the predisposition of persons deficient in terminal complement components (C5 through C9) to have recurrent bacteremic gonococcal infections and recurrent menin gococcal meningitis or meningococcemia. Gonococcal porin induces

T cell–proliferative responses in persons with urogenital gonococcal disease. A significant increase in porin-specific interleukin (IL)

4–producing CD4+ as well as CD8+ T lymphocytes is seen in individu als with mucosal gonococcal disease. A portion of these lymphocytes that show a porin-specific TH2-type response could traffic to mucosal surfaces and play a role in immune protection against the disease. Few data clearly indicate that protective immunity is acquired from a previ ous gonococcal infection, although bactericidal and opsonophagocytic antibodies to porin and LOS may offer partial protection. On the other hand, women who are infected and acquire high levels of antibody to another outer-membrane protein, Rmp (reduction modifiable protein, formerly called protein III), may be especially likely to become rein fected with N. gonorrhoeae because Rmp antibodies block the effect of bactericidal antibodies to porin and LOS. Rmp shows little, if any, interstrain antigenic variation; therefore, Rmp antibodies potentially may block antibody-mediated killing of all gonococci. The mechanism of blocking has not been fully characterized, but Rmp antibodies may noncompetitively inhibit binding of porin and LOS antibodies because of the proximity of these structures in the gonococcal outer membrane. In male volunteers who have no history of gonorrhea, the net effect of these events may influence the outcome of experimental challenge with N. gonorrhoeae. Because Rmp bears extensive homology to enterobac terial OmpA and meningococcal class 4 proteins, it is possible that these blocking antibodies result from prior exposure to cross-reacting proteins from these species and also play a role in first-time infection with N. gonorrhoeae. Gonococcal Resistance to Antimicrobial Agents It is no surprise that N. gonorrhoeae, with its remarkable capacity to alter its antigenic structure and adapt to changes in the microenvironment, has become resistant to numerous antibiotics. The first effective agents against gonorrhea were the sulfonamides, which were introduced in the 1930s and became ineffective within a decade. Penicillin was then used as the drug of choice for the treatment of gonorrhea. By 1965, 42% of gonococcal isolates had developed low-level resistance to penicillin G. Resistance due to the production of penicillinase arose later. Gonococci become fully resistant to antibiotics either by chromo somal mutations or by acquisition of R factors (plasmids). Two types of chromosomal mutations have been described. The first type, which is drug specific, is a single-step

mutation leading to highlevel resistance. The second type involves mutations at several chromo somal loci that combine to determine the level as well as the pattern of resistance. Strains with mutations in chromosomal genes were first observed in the late 1950s. As recently as 2007, chromosomal muta tions accounted for resistance to penicillin, tetracycline, or both in ~16% of strains surveyed in the United States. β-Lactamase (penicillinase)–producing strains of N. gonorrhoeae (PPNG) carrying β-lactamase plasmids had rapidly spread worldwide by the early 1980s. N. gonorrhoeae strains with plasmid-borne tetra cycline resistance (TRNG) can mobilize some β-lactamase plasmids, and PPNG and TRNG occur together, sometimes along with strains exhibiting chromosomally mediated resistance (CMRNG). Penicillin, ampicillin, and tetracycline are no longer reliable for the treatment of gonorrhea and should not be used. Quinolone-containing regimens also were recommended for treat ment of gonococcal infections; the fluoroquinolones offered the advan tage of antichlamydial activity when administered for 7 days. However, quinolone-resistant N. gonorrhoeae (QRNG) appeared soon after these agents were first used to treat gonorrhea. QRNG is particularly common in the Pacific Islands (including Hawaii) and Asia, where, in certain areas, all gonococcal strains are now resistant to quinolones. At present, QRNG is also common in parts of Europe and the Middle East. In the United States, QRNG has been identified in all areas but predominantly in states on the Pacific coast, where resistant strains were first seen. Alterations in DNA gyrase and topoisomerase IV have been implicated as mechanisms of fluoroquinolone resistance. Third-generation cephalosporins have remained highly effective as single-dose therapy for gonorrhea, but the recent isolation of strains highly resistant to ceftriaxone (minimal inhibitory concentrations

[MICs], 2 μg/mL) in Asia, some European countries and recently, in the United States, is cause for concern. Even though the MICs of ceftriaxone against certain strains may reach 0.015–0.125 μg/mL (higher than the MICs of 0.0001–0.008 μg/mL for fully susceptible strains), these levels are greatly exceeded in the blood, the urethra, and the cervix when the routinely recommended parenteral dose of ceftriaxone is administered. The rising MICs of oral cefixime (the pre viously recommended alternative oral third-generation cephalosporin) against N. gonorrhoeae, combined with this drug’s limited capacity to reach levels sufficiently higher than MICs in the blood, the urethra, the cervix, and especially the pharynx, have resulted in the removal of cefixime from the list of first-line agents for treatment of uncom plicated gonorrhea. N. gonorrhoeae strains with reduced susceptibility to ceftriaxone and cefixime (i.e., cephalosporin-intermediate/resistant strains) contain mutations in (1) the penA allele, which is the princi pal resistance determinant and encodes a penicillin-binding protein (PBP2) whose sequence can differ in up to 60–70 amino acids from that of wild-type PBP2; (2) the multiple transferable resistance regulator (mtrR) gene that results in increased drug efflux through the MtrCDE efflux pump; and (3) penB, which decreases drug influx through PorB.

Spectinomycin has been used as an alternative agent because it is not associated with resistance to other antibiotics and can be reserved for use against multidrug-resistant strains of N. gonorrhoeae. In China, spectinomycin is recommended as an alternative agent for primary treatment of urogenital gonorrhea and is often used there instead of ceftriaxone. Nevertheless, outbreaks caused by strains resistant to spectinomycin have been documented in Korea and England when the drug had been used for primary treatment of gonorrhea. CHAPTER 161 Resistance to azithromycin can result from alterations of the ribo somal binding target by azithromycin and—as with cephalosporins— the over- and underexpression of efflux and influx

systems. Combined resistance to cephalosporins and azithromycin has been reported in several instances throughout the world. Gonococcal Infections ■ ■CLINICAL MANIFESTATIONS Gonococcal Infections in Men Acute urethritis is the most com mon clinical manifestation of gonorrhea in male patients. However, there is a reservoir of infected men who remain asymptomatic. The usual incubation period after exposure is 2–7 days before symptoms develop although the interval can be longer. Strains of the PorB.1A serotype tend to cause a greater proportion of cases of mild and asymp tomatic urethritis than do PorB.1B strains. When they occur, urethral discharge and dysuria, usually without urinary frequency or urgency, are the major symptoms. The discharge initially is scant and mucoid but becomes profuse and purulent within a day or two. Gram staining of the urethral discharge may reveal PMNs and gram-negative intracel lular monococci and diplococci (Fig. 161-1). The clinical manifesta tions of gonococcal urethritis are usually more severe and overt than FIGURE 161-1 Gram stain of urethral discharge from a male patient with gonorrhea shows gram-negative intracellular monococci and diplococci. (Source: © All rights reserved. Canadian Guidelines on Sexually Transmitted Infections. Public Health Agency of Canada, modified 2020. Adapted and reproduced with permission from the Minister of Health, 2021.)

those of nongonococcal urethritis, including urethritis caused by Chla mydia trachomatis (Chap. 194); however, exceptions are common, and it is often impossible to differentiate the causes of urethritis on clinical grounds alone. The majority of cases of urethritis seen in the United States today are not caused by N. gonorrhoeae and/or C. trachomatis. Although a number of other organisms may be responsible, many cases do not have a specific etiologic agent identified. Certain clones of Neisseria meningitidis, the second member of the pathogenic Neisseria species, have been associated with urethritis in men who have sex with men (MSM) in Europe and in heterosexual men in the southern and midwestern United States.

Most symptomatic men with gonorrhea seek treatment and cease to be infectious. The remaining men, who are largely asymptomatic, accumulate in number over time and constitute the majority of all infected men at any point in time; together with men incubating the organism who shed the organism but have yet to become symptomatic, they serve as the source of spread of infection. Before the antibiotic era, symptoms of urethritis persisted for ~8 weeks. Epididymitis is now an uncommon complication, and gonococcal prostatitis occurs rarely, if at all. Other unusual local complications of gonococcal urethritis include edema of the penis due to dorsal lymphangitis or thrombophlebitis, submucous inflammatory “soft” infiltration of the urethral wall, peri urethral abscess or fistula, inflammation or abscess of Cowper’s gland, and seminal vesiculitis. Balanitis may develop in uncircumcised men. Gonococcal Infections in Women • GONOCOCCAL CERVICITIS

Mucopurulent cervicitis is a common STI diagnosis in American women and may be caused by N. gonorrhoeae, C. trachomatis, and other organisms, including Mycoplasma genitalium (Chap. 193). Cervicitis is often associated with more that one bacterial species, for example, coinfection with C. trachomatis, and may also coexist with candidal or trichomonal vaginitis. N. gonorrhoeae primarily infects the columnar epithelium of the cervical os. Bartholin’s glands occasionally become infected. PART 5 Infectious Diseases About one-half of women infected with N. gonorrhoeae develop symptoms. Women who either remain asymptomatic or have only minor symptoms may delay seeking medical attention. These minor symptoms may include scant vaginal discharge issuing from the inflamed cervix (without vaginitis or vaginosis per se) and dysuria (often without urgency or frequency) that may be associated with gonococcal urethritis. Although the incubation period of

gonorrhea is less well defined in women than in men, symptoms usually develop within 10 days of infection and are more acute and intense than those of chlamydial cervicitis. The speculum examination reveals a mucopurulent discharge (mucopus) issuing from the cervical os or a reddened (inflamed) cervix even in the absence of reported symptoms. Because Gram stain is not sensitive for the diagnosis of gonorrhea in women, specimens should be submitted for culture or a nonculture assay (see “Laboratory Diagnosis,” below). Edematous and friable cervical ectopy and endo cervical bleeding induced by gentle swabbing are more often seen in chlamydial infection. Gonococcal infection may extend deep enough to produce dyspareunia and lower abdominal or back pain. In such cases, it is imperative to consider a diagnosis of pelvic inflammatory disease (PID) and to administer treatment for that disease (Chaps. 141 and 194). N. gonorrhoeae may also be recovered from the urethra and rectum of women with cervicitis, but these are rarely the only infected sites. Urethritis in women may produce symptoms of internal dysuria, which is often attributed to “cystitis.” Pyuria in the absence of bacteriuria visi ble on Gram stain of unspun urine, accompanied by urine cultures that fail to yield >102 colonies of bacteria usually associated with urinary tract infection, signifies the possibility of urethritis usually due to C. trachomatis. Urethral infection with N. gonorrhoeae also may occur in this context, but in this instance, urethral cultures are usually positive. GONOCOCCAL VAGINITIS The vaginal mucosa of healthy women is lined by stratified squamous epithelium and is rarely infected by N. gonorrhoeae. However, gonococcal vaginitis can occur in anestro genic women (e.g., prepubertal girls and postmenopausal women),

in whom the vaginal stratified squamous epithelium is often thinned down to the basilar layer, which can be infected by N. gonorrhoeae. The intense inflammation of the vagina makes the physical (speculum and bimanual) examination extremely painful. The vaginal mucosa is red and edematous, and an abundant purulent discharge is often present. Infection in the urethra and in Skene’s and Bartholin’s glands often accompanies gonococcal vaginitis. Inflamed cervical erosion or abscesses in nabothian cysts may also occur. Coexisting cervicitis may result in pus in the cervical os. Anorectal Gonorrhea Because the female anatomy permits the spread of cervical exudate to the rectum, N. gonorrhoeae is sometimes recovered from the rectum of women with uncomplicated gonococcal cervicitis. The rectum is the sole site of infection in only 5% of women with gonorrhea. Such women are usually asymptomatic but occasion ally have acute proctitis manifested by anorectal pain or pruritus, tenesmus, purulent rectal discharge, and rectal bleeding. Among MSM, the frequency of gonococcal infection, including rectal infection, fell by ≥90% throughout the United States in the early 1980s. A resurgence of gonorrhea among MSM has been documented in several cities since the 1990s; the estimated rates of reported cases having more than doubled in a recent 3-year period. Gonococcal isolates from the rec tum of MSM tend to be more resistant to antimicrobial agents than are gonococcal isolates from other sites. Gonococcal isolates with a muta tion in mtrR or in the promoter region of the gene that encodes for this transcriptional regulator develop increased resistance to antimicrobial hydrophobic agents such as bile acids and fatty acids in feces and thus are found with increased frequency in MSM. This situation may have been responsible for higher rates of failure of treatment for rectal gon orrhea with older regimens consisting of penicillin or tetracyclines. Pharyngeal Gonorrhea Pharyngeal gonorrhea is usually mild or asymptomatic, although symptomatic pharyngitis does occasion ally occur with cervical lymphadenitis. The mode of acquisition is oral–genital sexual exposure, with fellatio being a more efficient means of transmission than cunnilingus. In certain female adolescent populations in the United States, pharyngeal gonorrhea has become as common as genital gonorrhea. Most cases resolve spontaneously and transmission from the pharynx to sexual

contacts is rare. Pharyngeal infection almost always coexists with genital infection. Swabs from the pharynx should be plated directly onto gonococcal selective media. Pharyngeal colonization with N. meningitidis needs to be differentiated from that with other Neisseria species. Because commensal oropha ryngeal neisseriae are often resistant to antimicrobials, horizontal gene transfer between these organisms and N. gonorrhoeae may be impor tant in the development of antimicrobial resistance of N. gonorrhoeae. Ocular Gonorrhea in Adults Ocular gonorrhea in an adult usu ally results from autoinoculation of N. gonorrhoeae from an infected genital site. As in genital infection, the manifestations range from severe to occasionally mild or asymptomatic disease. The variability in clinical manifestations may be attributable to differences in the ability of the infecting strain to elicit an inflammatory response. Infection may result in a markedly swollen eyelid, severe hyperemia and chemosis, and a profuse purulent discharge. The massively inflamed conjunctiva may be draped over the cornea and limbus. Lytic enzymes from the infiltrating PMNs occasionally cause corneal ulceration and rarely cause perforation. Prompt recognition and treatment of this condition are of para mount importance. Gram stain and culture of the purulent discharge establish the diagnosis. Genital cultures also should be performed. Gonorrhea in Pregnant Women, Neonates, and Children Gon orrhea in pregnancy can have serious consequences for both the mother and the infant. Recognition of gonorrhea early in pregnancy also identifies a population at risk for other STIs, particularly chlamyd ial infection, syphilis, and trichomoniasis. The risks of salpingitis and PID—conditions associated with a high rate of fetal loss—are highest during the first trimester. Pharyngeal infection, most often asymptom atic, may be more common during pregnancy because of altered sexual

practices. Prolonged rupture of the membranes, premature delivery, chorioamnionitis, funisitis (infection of the umbilical cord stump), and sepsis in the infant (with N. gonorrhoeae detected in the newborn’s gas tric aspirate during delivery) are common complications of maternal gonococcal infection at term. Other conditions and microorganisms, including Mycoplasma hominis, Mycoplasma genitalium, Ureaplasma urealyticum, C. trachomatis, and bacterial vaginosis (often accompa nied by infection with Trichomonas vaginalis), have been associated with similar complications. The most common form of gonorrhea in neonates is ophthalmia neonatorum, which results from exposure to infected cervical secre tions during parturition. Ocular neonatal instillation of 0.5% erythro mycin ophthalmic ointment, a prophylactic agent, prevents ophthalmia neonatorum but is not effective for its treatment, which requires systemic antibiotics. One-percent (1%) silver nitrate eye drops and ointments that contain silver nitrate or tetracycline can also be used for prophylaxis but are no longer available in the United States. The clini cal manifestations are acute and usually begin 2–5 days after birth. An initial nonspecific conjunctivitis with a serosanguineous discharge is followed by tense edema of the eyelids, chemosis, and a profuse, thick, purulent discharge. Corneal ulcerations that result in nebulae or per foration may lead to anterior synechiae, anterior staphyloma, panoph thalmitis, and blindness. Infections described at other mucosal sites in infants, including vaginitis, rhinitis, and anorectal infection, are likely to be asymptomatic. Pharyngeal colonization has been demonstrated in 35% of infants with gonococcal ophthalmia, and coughing is the most prominent symptom in these cases. Septic arthritis (see below) is the most common manifestation of systemic infection or disseminated gonococcal infection (DGI) in the newborn. The onset usually comes at 3–21 days of age, and polyarticular involvement is common. Sepsis, meningitis, and pneumonia are seen in rare instances. Any STI in children beyond the neonatal period raises the possibil ity of sexual abuse. Gonococcal vulvovaginitis is the most common manifestation of gonococcal infection in children beyond

infancy. Anorectal and pharyngeal infections are common in these children and are frequently asymptomatic. The urethra, Bartholin's and Skene's glands, and upper genital tract are rarely involved. All children with gonococcal infection should also be evaluated for chlamydial infection, syphilis, and possibly HIV infection. Gonococcal Arthritis Dissemi nated gonococcal infection (DGI; gono coccal arthritis) results from gonococcal bacteremia. In the 1970s, DGI occurred in ~0.5–3% of persons with untreated gonococcal mucosal infection. The lower incidence of DGI at present is probably attributable to a decline in the preva lence of particular strains that are likely to disseminate. Nonetheless, sporadic outbreaks of DGI still occur in North America. DGI strains resist the bacteri cidal action of human serum and gener ally do not incite inflammation at genital sites, probably because of limited gen eration of chemotactic factors. Strains recovered from DGI cases in the 1970s were often of the PorB.1A serotype, were highly susceptible to penicillin, and had special growth requirements—including arginine, hypoxanthine, and uracil—that made the organism more fastidious and more difficult to isolate. A B C Menstruation is a risk factor for dis semination, and approximately twothirds of cases of DGI are in women. In about half of affected women, symptoms of DGI begin within 7 days of onset of menses. Complement deficiencies, D E F FIGURE 161-2 Characteristic skin lesions in patients with proven gonococcal bacteremia. The lesions are in various stages of evolution. A. Very early petechia on finger. B. Early papular lesion, 7 mm in diameter, on lower leg. C. Pustule with central eschar resulting from early petechial lesion. D. Pustular lesion on finger. E. Mature lesion with central necrosis (black) on hemorrhagic base. F. Bullae on anterior tibial surface. (Reprinted with permission from KK Holmes et al: Disseminated gonococcal infection. Ann Intern Med 74:979, 1971.)

especially of the components involved in the assembly of the mem brane attack complex (C5 through C9), predispose to neisserial bac teremia, and persons with more than one episode of DGI should be screened with an assay for total hemolytic complement activity. DGI is also associated with the use of the complement C5–blocking monoclo nal antibody eculizumab.

The clinical manifestations of DGI have sometimes been classified into two stages: a bacteremic stage, which is less common today, and a joint-localized stage with suppurative arthritis. A clear-cut progres sion usually is not evident. Patients in the bacteremic stage have higher temperatures, and chills more frequently accompany their fever. Painful joints are common and often occur together with tenosynovitis and skin lesions. Polyarthralgias usually include the knees, elbows, and more distal joints; the axial skeleton is generally spared. Skin lesions are seen in ~75% of patients and include papules and pustules, often with a hem orrhagic component (Fig. 161-2; see also Fig. A1-43 in the Atlas of Rashes Associated with Fever). Other manifestations of noninfectious dermatitis, such as nodular lesions, urticaria, and erythema multiforme, have been described. These lesions are usually on the extremities and number between 5 and 40. The differential diagnosis of the bacteremic stage of DGI includes reactive arthritis, acute rheumatoid arthritis, sarcoidosis, erythema nodosum, drug-induced arthritis, and viral infec tions (e.g., hepatitis B and acute HIV infection). The distribution of joint symptoms in reactive arthritis differs from that in DGI (Fig. 161-3), as do the skin and genital manifestations (Chap. 374). Suppurative arthritis involves one or two joints, most often the knees, wrists, ankles, and elbows (in decreasing order of frequency); other joints occasionally are involved. Most patients who develop gonococcal septic arthritis do so without prior polyarthralgias or skin lesions; in the absence of symptomatic genital infection, this disease cannot be distinguished from septic arthritis caused by other patho gens. The differential diagnosis of acute arthritis in young adults is dis cussed in Chap. 135. Rarely,

osteomyelitis complicates septic arthritis involving small joints of the hand. CHAPTER 161 Gonococcal Infections Gonococcal endocarditis, although rare today, was a relatively common complication of DGI in the preantibiotic era, accounting for about one-quarter of reported cases of endocarditis. Another unusual complication of DGI is meningitis.

Disseminated gonococcal infection (N = 102) Reactive arthritis (N = 173) Hand and fingers Wrist Elbow Shoulder Sternal* Spine and SI† Hip Knee Ankle Foot and toes

Percent of patients FIGURE 161-3 Distribution of joints with arthritis in 102 patients with disseminated gonococcal infection and 173 patients with reactive arthritis. *Includes the sternoclavicular joints. †SI, sacroiliac joint. Gonococcal Infections in HIV-Infected Persons The asso ciation between gonorrhea and the acquisition of HIV has been demonstrated in several well-controlled studies, mainly in Kenya and Zaire. The nonulcerative STIs enhance the transmission of HIV three- to fivefold; transmission of HIV-infected immune cells and increased viral shedding by persons with urethritis or cervicitis may contribute (Chap. 208). HIV has been detected by polymerase chain reaction (PCR) more commonly in ejaculates from HIV-positive men with gonococcal urethritis than in those from HIV-positive men with nongonococcal urethritis. PCR positivity diminishes twofold after appropriate therapy for urethritis. Not only does gonorrhea enhance the transmission of HIV, but it may also increase the individual’s risk for acquisition of HIV. A proposed mechanism is the significantly greater number of CD4+ T lymphocytes and dendritic cells that can be infected by HIV in endocervical secretions from women with nonul cerative STIs than in those from women with ulcerative STIs. PART 5 Infectious Diseases ■ ■LABORATORY DIAGNOSIS A rapid diagnosis of gonococcal infection in men may be obtained by Gram staining of urethral exudates (Fig. 161-1). The detection of gram-negative intracellular monococci and diplococci is usually highly specific and sensitive in diagnosing gonococcal urethritis in symptomatic males but is only ~50% sensitive in diagnosing gono coccal cervicitis. Samples should be collected with Dacron or rayon swabs. Part of the sample should be inoculated onto a plate of modi fied Thayer-Martin or other gonococcal selective medium for culture. It is important to process all samples immediately because gonococci do not tolerate drying. If plates cannot be incubated immediately, they can be held safely for several hours at room temperature in can dle extinction jars prior to incubation. If processing is to occur within 6 h, transport of specimens may be facilitated by the use of nonnu tritive swab transport systems such as Stuart or Amies medium. For longer holding periods (e.g., when specimens for culture are to be mailed), culture media with self-contained CO2-generating systems (such as the JEMBEC or Gono-Pak systems) may be used. Specimens should also be obtained for the diagnosis of chlamydial infection (Chap. 194). PMNs are often seen in the endocervix on a Gram stain, and an abnormally increased number (≥30 PMNs per field in five 1000× oil-immersion microscopic fields) establishes the presence of an inflammatory discharge. Unfortunately, the presence or absence of gram-negative intracellular monococci or diplococci in cervical smears does not accurately predict which patients have gonorrhea, and the

diagnosis in this setting should be made by culture or another suitable nonculture diagnostic method. The sensitivity of a single endocervical culture is ~80–90%. If a history of rectal sex is elicited, a rectal wall swab (uncontaminated with feces) should be cultured. A presumptive diagnosis of gonorrhea cannot be made on the basis of gram-negative diplococci in Gram-stained smears from the pharynx, where other Neisseria species are also components of the pharyngeal flora. Several nucleic acid amplification tests (NAATs), including the Roche COBAS AMPLICOR, Gen-

Probe Aptima Combo 2, Cepheid Xpert® CT/NG Assay and BD ProbeTec ET, are now widely available on semiautomated or fully automated platforms and are commonly employed diagnostic tests for gonorrhea. These tests also detect C. trachomatis and are more sensitive than culture for identification of either

N. gonorrhoeae or C. trachomatis. These tests offer the advantage that urine samples can be tested with a sensitivity similar to or greater than that obtained when urethral or cervical swab samples are assessed by other non-NAATs or culture, respectively. NAAT tests performed on self-collected vaginal swabs are as sensitive and specific as physiciancollected samples and may be used in women to facilitate sample collection when a pelvic exam is not indicated as part of their clinic evaluation. A point-of-care NAAT-based test (Binx io®) for gonorrhea and chlamydia with a 30-minute turnaround time is now approved by the U.S. Food and Drug Administration (FDA). In MSM, it is impor tant to screen the rectum and pharynx because screening urine alone will miss the majority of cases. A disadvantage of non-culture-based assays is that N. gonorrhoeae cannot be grown from the transport systems. Thus, a culture-confirmatory test and formal antimicrobial susceptibility testing, if needed, cannot be performed. Because of the legal implications, the preferred method for the diag nosis of gonococcal infection in children is a standardized culture. Two positive NAATs, each targeting a different nucleic acid sequence, may be substituted for culture of the cervix or the urethra as legal evidence of infection in children. Although nonculture tests for gonococcal infection have not been approved by the FDA for use with specimens obtained from the pharynx and rectum of infected children, NAATs from these sites are preferred for diagnostic evaluation in adult victims of suspected sexual abuse, especially if the NAATs have been evalu ated by the local laboratory and found to be superior. Cultures should be obtained from the pharynx and anus of both girls and boys, the urethra of boys, and the vagina of girls; cervical specimens are not rec ommended for prepubertal girls. For boys with a urethral discharge, a meatal specimen of the discharge is adequate for culture. Presumptive colonies of N. gonorrhoeae should be identified definitively by at least two independent methods. Blood should be cultured in suspected cases of DGI. The use of Isolator blood culture tubes may enhance the yield. The probability of positive blood cultures decreases after 48 h of illness. Synovial fluid should be inoculated into blood culture broth medium and plated onto chocolate agar rather than selective medium because this fluid is not likely to be contaminated with commensal bacteria. Gonococci are infrequently recovered from early joint effusions containing <20,000 leukocytes/μL but may be recovered from effusions containing >80,000 leukocytes/μL. The organisms are seldom recovered from blood and synovial fluid of the same patient. TREATMENT Gonococcal Infections Treatment failure can lead to continued transmission and the emergence of antibiotic resistance. The importance of adequate treatment with a regimen that the patient will adhere to cannot be overemphasized. Single-dose regimens have been developed for uncomplicated gonococcal infections. The Centers for Disease Control and Prevention (CDC) Gonorrhea Treatment Recom mendations in 2020 and the 2021 Sexually Transmitted Infections (STI) Treatment Guidelines are summarized in Table 161-1. The third-generation cephalosporin ceftriaxone is now recommended as the first-line regimen for use at twice the previous dose (now,

TABLE 161-1 Recommended Treatment for Gonococcal Infections: Adapted from the 2021 Guidelines for Gonococcal Infection of the Centers for Disease Control and Prevention DIAGNOSIS TREATMENT OF CHOICEa Uncomplicated gonococcal infection of the cervix, urethra, pharynx,b or rectum First-line regimen Ceftriaxone (500 mg IM, single dose) plus Doxycycline (100 mg orally

twice a day for 7 days) for treatment of chlamydial infection if chlamydial infection cannot be excluded Alternative regimens if ceftriaxone is not available Gentamicin (240 mg IM, single dose) plus azithromycin (2 g orally as a single dose)c or Cefixime (800 mg PO, single dose) or spectinomycin (2 g IM, single dose)d,e plus Doxycycline (100 mg orally twice a day for 7 days) for treatment of chlamydial infection if chlamydial infection cannot be excluded Epididymitis See Chap. 141 Pelvic inflammatory disease See Chap. 141 Gonococcal conjunctivitis in an adult Ceftriaxone (1 g IM, single dose)f Ophthalmia neonatorumg Ceftriaxone (25–50 mg/kg IV, single dose, not to exceed 125 mg) Disseminated gonococcal infectionh Initial therapyi Patient tolerant of β-lactam drugs Ceftriaxone (1 g IM or IV q24h; recommended) or cefotaxime

(1 g IV q8h) or ceftizoxime (1 g IV q8h) Patients allergic to β-lactam drugs Spectinomycin (2 g IM q12h)d Continuation therapyj Cefixime (400 mg PO bid) Meningitis or endocarditis See text for specific recommendationsk aTrue failure of treatment with a recommended regimen is rare and should prompt an evaluation for reinfection, infection with a drug-resistant strain, or an alternative diagnosis. bCeftriaxone is the most reliable agent recommended for treatment of pharyngeal infection. cIn vitro synergistic killing of N. gonorrhoeae by gentamicin plus azithromycin is mild to moderate; azithromycin is for treatment chlamydial infection, primarily. dSpectinomycin is unavailable in the United States; in uncomplicated gonococcal infection it should be used at a higher dose (4 g IM, single dose) in areas of the world where increased resistance to spectinomycin exists. eSpectinomycin may be ineffective for the treatment of pharyngeal gonorrhea. fPlus lavage of the infected eye with saline solution (once). gProphylactic regimens are discussed in the text. hHospitalization is indicated if the diagnosis is uncertain, if the patient has the joint-localized stage with suppurative arthritis, or if the patient cannot be relied on to adhere to treatment. iAll initial regimens should also include doxycycline (100 mg orally twice a day for 7 days) for treatment of chlamydial infection if chlamydial infection cannot be excluded; jgonococcal therapy should be continued for 24–48 h after clinical improvement begins, at which time the switch may be made to an oral agent (e.g., cefixime) if antimicrobial susceptibility can be documented by culture of the causative organism. If no organism is isolated and the diagnosis is secure, then treatment with ceftriaxone should be continued for at least 1 week. kHospitalization is indicated to exclude suspected meningitis or endocarditis. 500 mg IM, single dose) based on doubling of mean inhibitory concentrations (MICs) of current strains compared with MICs over 20 years ago. The development of decreased sensitivity to ceftri axone throughout the world will require the development of new effective regimens. Azithromycin, which had been recommended to provide additional treatment of gonorrhea (also to include treat ment of chlamydial infection) is no longer recommended as part of a first line regimen. Resistance to azithromycin of U.S. isolates of N. gonorrhoeae, which had been less than 0.6% over a number of years, has increased more than sevenfold to 4.7% in 2021. If chla mydial infection cannot be excluded, concurrent treatment with doxycycline (100 mg orally twice a day for 7 days) is recommended.

The recommendations for uncomplicated gonorrhea apply to HIVinfected as well as HIV-uninfected patients.

The currently recommended regimen for the treatment of uncom plicated gonococcal infection of the urethra, cervix, rectum, or pharynx (a single IM dose of ceftriaxone) almost always results in an effective cure. Quinolone-containing regimens are no longer recommended in the United States as first-line treatment because of widespread resistance. Rising MICs of cefixime worldwide have led

the CDC to discontinue its recommendation of this agent as first-line treatment for uncomplicated gonorrhea. Multicenter trials of treat ment for uncomplicated gonorrhea in the United States have shown ≥99.5% efficacy of two combination regimens and 96% efficacy in one single-agent regimen: gemifloxacin (320 mg, single oral dose) plus azithromycin (2 g, single oral dose); gentamicin (a single IM dose of 240 mg or, in individuals who weigh ≤45 kg, 5 mg/kg) plus azithromycin (2 g, single oral dose), and zoliflodacin (2 or 3 g, single oral dose). At this time, however, none of these regimens is recom mended by CDC as first-line treatment; gentamicin plus azithromy cin is recommended as an alternative regimen. Co-infection with C. trachomatis occurs frequently; concurrent treatment with doxycycline (100 mg orally twice daily for 7 days) is effective against chlamydial infection. Spectinomycin has been used as an alternative agent for the treatment of uncomplicated gonococcal infections in penicillin-allergic persons outside the United States but is not currently available in the United States. Of note, the limited effectiveness of spectinomycin and gentamicin for the treatment of pharyngeal infection reduces the utility of this regi men in populations among whom gonococcal infection is common, such as MSM. CHAPTER 161 Persons with uncomplicated genital or rectal infections who receive ceftriaxone or an alternative regimen do not need a test of cure; however, cultures for N. gonorrhoeae should be performed if symptoms persist after therapy with an established regimen, and any gonococci isolated should be tested for antimicrobial suscep tibility. Persons with pharyngeal infection should undergo a test of cure regardless of the treatment regimen, 7–14 days after treatment to ensure eradication or detection of a possible treatment failure. Symptomatic gonococcal pharyngitis is more difficult to eradicate than genital infection. Persons who cannot tolerate cephalosporins may be treated with an alternative regimen. Treatment with spec tinomycin results in a cure rate of ≤52%; persons given spectino mycin should have a subsequent pharyngeal sample cultured early (3–5 days) following treatment as a test of cure. A single 2-g dose of azithromycin may be used if the infecting organism is known to be sensitive or in areas where rates of resistance to azithromycin are low. Quinolones may be used if the infecting organism is known to be sensitive. If culture is not readily available and NAAT is positive, every effort should be made to perform a confirmatory culture. All isolates from test-of-cure cultures should undergo antimicrobial susceptibility testing. Because of high rates of reinfection with

N. gonorrhoeae (and C. trachomatis) within 6–12 months, persons previously treated for gonorrhea should be retested 3 months after treatment. Gonococcal Infections Treatments for gonococcal epididymitis and PID are discussed in Chap. 141. Ocular gonococcal infections in older children and adults should be managed with a single dose of ceftriaxone com bined with saline irrigation of the conjunctivae (both undertaken expeditiously), and patients should undergo a careful ophthalmo logic evaluation that includes a slit-lamp examination. DGI, particularly the joint-localized stage with suppurative arthritis, may require higher dosages and longer durations of therapy (Table 161-1). Hospitalization is indicated if the diagnosis is uncertain, if the patient has localized suppurative arthritis that requires aspiration, or if the patient cannot be relied on to comply with treatment. Open drainage is necessary only occasionally— e.g., for management of hip infections that may be difficult to drain percutaneously. Nonsteroidal anti-inflammatory agents may be indicated to alleviate pain and hasten clinical improvement of affected joints.

Revision #1
Created 2026-01-06 16:33:07 UTC by Omar Ayman
Updated 2026-01-06 16:33:07 UTC by Omar Ayman