Gonorrhea

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Disease Type 1: Pathogen-Based Diseases
Disease 6: Gonorrhea

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Epidemiology in the United States

Infection with *Neisseria gonorrhoeae* (gonorrhea) is a significant public health problem in the United States. A total of 468,514 cases of gonorrhea were reported in the United States in 2016 and this was a significant increase from the 395,216 reported cases in 2015.[1] The number of reported gonorrhea cases probably underestimates the true incidence and the reporting has been influenced by changes in screening practices, use of diagnostic tests with different performance characteristics, and reporting practices. In the United States, the rate of gonorrhea declined by 74% from 1975 to 1997 after implementation of a national gonorrhea control program in the mid-1970s. After 1997, gonorrhea rates declined further, reaching a historic low of 98.1 cases per 100,000 population in 2009.[1] During 2009–2012, the gonorrhea rate increased each year, with 106.7 cases per 100,000 population reported in 2012. A slight decline occurred in 2013, but the rates then increased again during 2014, 2015, and 2016 (Figure 1).[1] In 2016, the gonorrhea rate was 145.8 cases per 100,000 population, an increase of 18.5% from 2015; since 2006, the gonorrhea rate of reported gonorrhea cases has increased 48.6%.[1] Based on the estimated incident cases among all ages in 2008, the total lifetime direct medical cost of gonorrhea in the United States was estimated at $162.1 million.

Epidemiology by Demographics

The incidence of gonorrhea remains high in some groups as defined by geography, age, race/ethnicity, or sexual risk behavior.[1] Gonorrhea rates have increased among men and women, and in every region of the United States.[1]

Rates by Region and State

In the United States, in 2016, the highest reported rates of gonorrhea are in the South, followed by equivalent rates in the Midwest and West, and lowest rates in the Northeast (Figure 2).[1] During 2012 to 2016, gonorrhea rates increased the most in the West (96%), but it increased significantly in all regions (Figure 3).[1] The highest rates by state (in descending order) are Mississippi, Louisiana, Georgia, Alaska, North Carolina, Oklahoma, Arkansas, and Missouri; the rates in the District of Columbia (479.9 per 100,000 population) was markedly higher than the rates in any state (Figure 4).

Rates by Sex

For 2016, the rate of reported gonorrhea cases among men (170.7 cases per 100,000 males) was significantly higher than among women (121.0 cases per 100,000 females). Over the 1-year period of 2015–2016, the rates of reported gonorrhea increased 22.2% among men and 13.8% among women.[1] During 2012 to 2016, the gonorrhea rate among men increased 62.6%, while the rate among women increased 12.1% (Figure 5).[1] The significant increase among males in recent years is predominantly attributed to marked increase in gonorrhea among men who have sex with men (MSM).[2]
Rates by Race/Ethnicity

The incidence of gonorrhea is by far highest among blacks, with the next highest rates in American Indian/Alaska Natives (Figure 6).[1] The rate of gonorrhea in blacks is approximately 8.6 times greater than in whites. During 2012 to 2016, the gonorrhea rate increased among all race and ethnic groups.

Rates by Age Group

In 2016, the highest rates of gonorrhea among women were observed among those aged 20-24 years (595.5 cases per 100,000 females) and 15-19 years (482.1 cases per 100,000 females). Among men, the rate was highest among those aged 20-24 years (616.8 cases per 100,000 males) and 25–29 years (545.1 cases per 100,000 males) (Figure 7).

Antimicrobial Susceptibility of *N. gonorrhoeae*

Antimicrobial resistance remains an important consideration in the treatment of gonorrhea.[3,4,5,6,7,8,9] Much of the information regarding antimicrobial susceptibility of *N. gonorrhoeae* isolates in the United States comes from the CDC’s Gonococcal Isolate Surveillance Project (GISP).[3] This microbiologic surveillance project has performed ongoing antibiotic susceptibility testing and tracks minimum inhibitory concentrations (MICs) in clinical isolates from men to determine the antimicrobial concentration needed to kill *N. gonorrhoeae* in the laboratory. Higher MICs indicate the need for higher antibiotic concentrations to effectively treat the bacteria. Increases above a defined cut-off indicate resistance to that antibiotic, and progressive increases in MICs below that cut-off suggest that resistance might eventually emerge. Laboratory-based data demonstrate that more widespread resistance has emerged with some antimicrobials and might develop in the near future with others, thus highlighting the need for ongoing surveillance. The GISP tracks primary antimicrobial drugs used to treat gonorrhea in the United States and *N. gonorrhoeae* susceptibility to 7 antimicrobials: ceftriaxone, cefixime, azithromycin, spectinomycin, ciprofloxacin, penicillin, and tetracycline (Figure 8).[1,3] These specific drugs are tested because they either are currently or were previously used for gonorrhea treatment.

- **Ceftriaxone**: During 2006–2016, the percentage of isolates with reduced ceftriaxone susceptibility (defined as MIC ≥0.125 μg/mL) fluctuated between 0.05% and 0.4%.[1] In 2016, the percentage of isolates with reduced susceptibility to ceftriaxone (MICs ≥0.125 μg/mL) was approximately 0.3%. In the GISP program, five isolates have been reported with a ceftriaxone MIC of 0.5 μg/mL.[1]
- **Cefixime**: The proportion of *N. gonorrhoeae* isolates in the United States with elevated cefixime minimum inhibitory concentrations (≥0.25 μg/mL) increased from 2009 to 2011, fell in 2012 and 2013, increased in 2014, and decreased in 2015 and 2016.[1] In 2016, the percentage of elevated cefixime MICs (≥0.25 μg/mL) was approximately 0.3%, which is a significant decline from the peak of 1.4% in 2010 and 2011.[1]
- **Azithromycin**: Gonococcal azithromycin resistance has been tracked since 1992. From 2012–2016, the percentage of isolates with reduced azithromycin susceptibility (MICs ≥2 μg/mL) ranged from 0.02% to 3.6%; between 2014 and 2016, the percentage increased from 2.4% to 3.6%.[1]
- **Ciprofloxacin**: Fluoroquinolone-resistant *N. gonorrhoeae* is widely disseminated throughout the United States and the world. In 2016, 26.8% of GISP isolates were resistant to fluoroquinolones, such as ciprofloxacin.[1] Because of these high rates of resistance, fluoroquinolones are no longer recommended as therapy for gonorrhea.
- **Other Antimicrobials**: In 2016, 44.1% of isolates were resistant to one or more of the following three antimicrobials that were previously to treat gonorrhea: penicillin, tetracycline, and ciprofloxacin.[1] Although these antimicrobials are no longer recommended for treating gonorrhea, phenotypes that have resistance to these antimicrobials remain common.
Microbiology and Pathogenesis

Microbiology

Gonorrhea is a common bacterial sexually transmitted disease caused by *N. gonorrhoeae*, an oxidase-positive, gram-negative diplococcus that utilizes glucose, but not sucrose, maltose, or lactose. Every 20 to 30 minutes *N. gonorrhoeae* divides by binary fission (Figure 9) and infects mucous-secreting epithelial cells.

Pathology

*N. gonorrhoeae* attaches to different types of epithelial cells via a number of structures located on the surface of gonococci (Figure 10), rendering it capable of infecting a wide variety of mucosal surfaces, such as the urogenital epithelium, oropharyngeal tract, and conjunctival tissue.[10] By altering its surface structures, including pili, lipo-oligosaccharide antigens, and protein (porin) antigens, this organism has the ability to evade the host immune response. In addition, *N. gonorrhoeae* employs several other mechanisms of immune evasion that cause inherent resistance to phagocytosis and killing by macrophages and neutrophils.[11] These multiple mechanisms of immune evasion explain how an individual can reacquire identical strains of *N. gonorrhoeae* at multiple distinct times.

Transmission

The transmission of *N. gonorrhoeae* can occur in several ways:

- Male-to-female transmission of *N. gonorrhoeae* via semen occurs at a rate of approximately 50% to 70% per episode of vaginal intercourse with ejaculation; male-to-female transmission of *N. gonorrhoeae* can occur without ejaculation.[12]
- An infected woman can transmit *N. gonorrhoeae* to the urethra of a male sex partner; the rate of transmission is approximately 20% per episode from vaginal intercourse, and it increases to approximately 60% to 80% after four or more intercourse exposures.[13]
- Pharyngeal gonorrhea is readily acquired by fellatio; it is less efficiently acquired by cunnilingus. Gonorrhea can also be transmitted from the pharynx to the urethra during fellatio (and presumably to vagina with cunnilingus).
- Perinatal transmission (mother-to-infant) can occur during vaginal delivery, when the infected mother has not been treated during the perinatal period.
- Rectal intercourse transmission rates have not been quantified, but rectal intercourse appears to be an efficient mode of transmission.
- Gonorrhea is associated with increased susceptibility to HIV acquisition. It is also associated with an increase in HIV transmission, because gonococcal urethritis increases HIV shedding in men.[14]

Risk Factors for Acquisition

Risk factors and risk markers for acquiring gonorrhea include:

- Multiple or new sex partners
- Inconsistent or incorrect condom use
- Living in an urban area where gonorrhea prevalence is high
- Being adolescent (especially female)
- Having a lower socio-economic status
- Using drugs including alcohol (in association with higher risk sex)
- Exchanging sex for drugs or money
- African American race
Clinical Manifestations

*N. gonorrhoeae* infection can potentially cause an array of clinical syndromes, including urogenital, pharyngeal, and rectal infections in males and females, conjunctivitis in adults and neonates, and uncommonly, disseminated gonococcal infection (DGI). If untreated, gonorrhea can cause pelvic inflammatory disease (PID), tubal infertility, ectopic pregnancy, and chronic pelvic pain.

Genital Infection in Men

Urethritis

Urethritis is a common manifestation of gonorrhea in men. Most men develop overt, symptomatic urethritis, but a small percentage will develop asymptomatic (unrecognized) infection. Asymptomatic gonorrhea may act as a reservoir that perpetuates transmission in the community. The typical symptoms of gonococcal urethritis, when present, include a purulent or mucopurulent urethral discharge ([Figure 11](#)), often accompanied by dysuria. The discharge may also be clear or cloudy. The incubation period ranges from 1 to 14 days, with most men becoming symptomatic within 2 to 5 days after exposure ([Figure 12](#)).

Anorectal Infections

Anorectal infection most often occurs in men who have sex with men, with acquisition of rectal *N. gonorrhoeae* occurring through receptive anal intercourse, but it also has been reported in women with gonococcal cervicitis who do not acknowledge rectal sexual contact. These infections may result from perineal contamination with infected cervical secretions. Most patients with anorectal infection are asymptomatic, although proctitis can occur. Symptoms of proctitis include anal irritation, painful defecation, constipation, scant rectal bleeding, painless mucopurulent discharge, anal pruritus, and tenesmus. When proctitis is suspected, an anoscopy examination is recommended to assess for inflammation and mucosal injury. The anorectal mucosa may appear normal, but purulent discharge, erythema, or easily induced bleeding may be observable under anoscopy.

Complications of Genital Infection in Men

Men with untreated gonococcal genital infection can develop epididymitis, with typical symptoms of unilateral testicular pain and swelling, and epididymal tenderness. Epididymitis is infrequent following gonococcal infection, but it is the most common local complication of gonorrhea infection in men. When it does occur, epididymitis is often associated with overt or subclinical urethritis. Urethral discharge may or may not be present. Notably, up to 70% of epididymitis caused by a sexually transmitted pathogen are due to *Chlamydia trachomatis*. Other less common complications associated with gonococcal infection in men include inguinal lymphadenitis, penile edema, periurethral abscess or fistula, accessory gland infection (Tyson's glands), balanitis, urethral stricture, and prostatitis, and rarely perirectal abscess.

Genital Infection in Women

Cervicitis

Symptomatic gonococcal infection in women most often manifests as cervicitis and/or urethritis, but at least 50% of women with genital gonococcal infection are asymptomatic. Symptoms of cervicitis vary and may include a nonspecific vaginal discharge, intermenstrual bleeding, dysuria, lower abdominal pain, and dyspareunia. Clinically, examination of the cervix may show mucopurulent or purulent cervical discharge and easily bleed with minimal contact. The incubation period in women is variable, but symptoms, when they do occur, usually develop within 10 days of the exposure. Seventy to ninety percent of women with genital gonococcal infection have laboratory evidence of urethral infection (urethritis); dysuria may be present, but these women frequently do not have
specific urethral symptoms.

**Anorectal Infections**

Anorectal gonococcal infection is uncommon in women, but can occur via anal intercourse. Anorectal infection has been reported in women with gonococcal cervicitis who do not acknowledge rectal sexual contact, presumably these infections result from perineal contamination with infected cervical secretions.

**Complications in Genital Infection in Women**

There are several complications associated with gonorrhea in women:

- **Accessory gland infections**: Infection of female sex accessory glands (Bartholin's glands or Skene's glands) is often a unilateral infection. Occlusion of the ducts of these glands due to inflammation may result in the formation of an abscess (Figure 13).

- **Pelvic inflammatory disease (PID)**: If cervical gonococcal infection ascends to the endometrium and/or fallopian tubes, PID may develop, typically causing symptoms that include lower abdominal pain, vaginal discharge, dyspareunia, intermenstrual bleeding, and fever.[19] In some women, PID may also be asymptomatic. Presumptive treatment for PID should be considered if one or more of the following minimum criteria are present on pelvic examination—uterine or adnexal tenderness or cervical motion tenderness. The long-term sequelae of untreated PID can include chronic pelvic pain, tubal infertility, and increased risk for ectopic pregnancy.

- **Perihepatitis (Fitz-Hugh-Curtis Syndrome)**: In situations where gonococcal infection ascends from the cervix, infection may produce inflammation of the liver capsule and the adjacent peritoneum. Most women with perihepatitis have associated PID, but perihepatitis can occur independently. Historically, perihepatitis was attributed only to gonococcal infection, but now it is often associated with chlamydial infection. Gonococcal perihepatitis is characterized by right upper quadrant pain, and may be accompanied by abnormal liver function tests.

**Additional Syndromes Seen in Men and Women**

**Pharyngeal Infection**

Gonococcal pharyngeal infection is most often asymptomatic. The pharynx may be the sole site of infection if the only exposure was receptive orogenital intercourse. Exudative pharyngitis is rare. Symptoms of pharyngeal infection may include pharyngitis, tonsillitis, fever, and cervical adenitis.

**Ocular Infection**

Gonococcal conjunctivitis in adults most often results from autoinoculation in persons with genital gonococcal infection. Patients may initially develop a mild non-purulent conjunctivitis, that, if untreated, typically progress to marked conjunctival redness, copious purulent discharge, and conjunctival edema (Figure 14).[20] Less often, the manifestations include an ulcerative keratitis. Untreated gonococcal conjunctivitis can cause complications that may include corneal perforation, endophthalmitis, and blindness.

**Disseminated Gonococcal Infection**

Disseminated gonococcal infection, a systemic gonococcal infection, occurs infrequently and is more common in women than in men. Disseminated gonococcal infection is associated with some gonococcal strains that have a propensity to produce bacteremia without associated urogenital
symptoms. In addition, patients with complement deficiency have greater risk of developing disseminated gonococcal infection. Clinical manifestations of disseminated gonococcal infection include skin lesions (Figure 15), arthralgia, tenosynovitis, arthritis (Figure 16), hepatitis, myocarditis, endocarditis, and meningitis. Rates of disseminated gonococcal infection have decreased due to the declining proportion of gonococcal strains prone to disseminate.[21]

### Infection in Children

Perinatal infections most often occur during childbirth when the neonatal conjunctiva, pharynx, respiratory tract, or anal canal may become infected. Conjunctivitis (ophthalmia neonatorum) is preventable by ocular antimicrobial prophylaxis in the newborn. All cases of gonorrhea beyond the newborn period should be considered possible evidence of sexual abuse. Vulvovaginitis (not cervicitis) is the most common manifestation in prepubescent girls. Signs and symptoms may include vaginal discharge (often purulent or crusting), dysuria, odor, irritation, and pruritus. The anorectum and the pharynx are the most frequently infected sites in abused boys; urethritis is less frequently seen. If specimens are to be collected, proper guidelines for collecting forensic evidence must be followed. When evaluating a child who has potentially suffered sexual abuse, the clinician should consult individual state laws concerning reporting and counseling.
Laboratory Diagnosis

The approach to diagnostic testing for *N. gonorrhoeae* has evolved from traditional cultivation to widespread use of nucleic acid amplification tests (NAAT).[22] Gram’s stain, another non-culture test, is used for the diagnosis of urethral gonorrhea in symptomatic males. Culture is still recommended if antimicrobial resistance is a concern, especially in cases of treatment failure.

Nucleic Acid Detection Tests

There are two types of nucleic acid detection tests: non-amplified tests and amplified tests:

- **Amplified Tests**: The nucleic acid amplification tests (NAATs) include polymerase chain reaction (PCR) (Roche Amplicor; Cepheid GeneXpert CT/NG), transcription-mediated amplification (TMA) (Gen-Probe Aptima), and strand displacement amplification (SDA) (Becton-Dickinson BDProbeTec ET). Amplified tests are FDA-cleared for endocervical specimens from women, urethral specimens from men, and urine specimens from men and women.[22,23,24] Some NAATs are also cleared for vaginal swabs. For many of the commercially available tests, the same specimen can be used to test for *C. trachomatis* infection. NAATs are the most sensitive test to detect *N. gonorrhoeae* infections. NAATs are not FDA-cleared for rectal or oropharyngeal specimens, though many individual laboratories have validated NAAT for non-genital sites and this practice is becoming increasingly common.[25] At present, antimicrobial susceptibility cannot be determined with NAATs, but research in this area is ongoing.

- **Non-Amplified Tests**: Non-amplified tests used for *N. gonorrhoeae* include the DNA probe (e.g. Gen-Probe PACE 2 and Digene Hybrid Capture II). A non-amplified test is less likely to be affected by transport conditions than culture, and has the potential for more timely results. These tests are FDA-cleared for endocervical specimens from women and urethral specimens from men. They are not FDA-cleared for pharyngeal, rectal, or urine specimens. The same specimen can be evaluated for *Chlamydia trachomatis* infection.[22] Antimicrobial susceptibility cannot currently be determined with non-amplified tests.

**Gram’s Stain**

The use of Gram's stain is a non-culture test that can make a presumptive diagnosis of gonorrhea. In the clinical setting, a Gram's stain to detect *N. gonorrhoeae* is most often performed on a male with purulent urethral discharge. A Gram’s stain on a specimen positive for *N. gonorrhoeae* shows polymorphonuclear leukocytes (PMNs) with intracellular gram-negative diplococci (Figure 17). A Gram’s stain, with proper laboratory technique, has greater than 95% sensitivity and greater than 99% specificity for diagnosing symptomatic male gonococcal urethritis.[22] Thus, the Gram’s stain is considered reliable both to diagnose and to exclude gonococcal urethritis in symptomatic men.[26] The sensitivity of a Gram’s stain is lower for males with asymptomatic urethral infection and thus not considered adequate to rule out infection in asymptomatic men.[26] Performing a Gram’s stain is not recommended on endocervical, pharyngeal, or rectal specimens due to poor sensitivity.[26]

**Culture**

Obtaining a bacterial culture is the historic standard for detection of *N. gonorrhoeae*. It has several advantages over non-culture tests, including low cost, use for a variety of specimen sites, and antimicrobial susceptibility testing can be performed if *N. gonorrhoeae* is isolated from the specimen. Despite having some advantages, culture is not as sensitive as NAAT and is more laboratory intensive, which has led to infrequent use in modern practice. At present, culture is primarily used for antimicrobial resistance surveillance by collecting specimens from either symptomatic urethral infections or from screen-positive sites of infection prior to treatment.
Diagnosis in Sexual Abuse/Assault

In cases of suspected sexual abuse or assault, the legal standard is to obtain culture samples combined with additional tests in an attempt to identify *N. gonorrhoeae*. Due to the legal complexity of these cases, it is imperative that all positive specimens be retained for additional confirmatory testing. In adults, NAATs are preferred for the diagnostic evaluation of sexual assault regardless of whether penetration occurred with the assault. In evaluating children with suspected sexual abuse, use of culture to detect *N. gonorrhoeae* is recommended. This is because data on use of NAATs for detection of *N. gonorrhoeae* in children are limited, and performance varies with each commercial test. NAATs are an acceptable alternative to culture for vaginal specimens or urine from girls, but consultation with an expert is recommended before using NAATs in this context. This is to minimize the possibility of cross-reaction with nongonococcal *Neisseria* species and other commensals and to ensure appropriate interpretation of results. Culture remains the only preferred method for urethral specimens or urine from boys and for extragenital specimens (pharynx and rectum) from children of both genders. Gram's stain is inadequate for evaluating prepubertal children for gonorrhea and should not be used to diagnose or exclude gonorrhea.
Screening for Gonococcal Infection

Routine screening for gonococcal infection in women is recommended in order to decrease morbidity as well as to reduce the burden of disease in the community. Urethral infections caused by *N. gonorrhoeae* among men usually produce symptoms that cause them to seek curative treatment soon enough to prevent sequelae, but transmission to others may occur in this interim. Among women, gonococcal infections are commonly asymptomatic until complications (such as pelvic inflammatory disease with resultant risk for infertility and ectopic pregnancy) have occurred. The following summarizes *N. gonorrhoeae* screening recommendations issued by the CDC and the U.S. Preventive Services Task Force (USPSTF) for different patient populations:[26,27]

- **Sexually Active Women Who Have Sex with Men**: The CDC and the USPSTF recommend (1) annual screening for *N. gonorrhoeae* in all sexually active women younger than 25 years of age, and (2) annual screening for *N. gonorrhoeae* in sexually active women age 25 years and older if they are considered to have increased risk for gonococcal infection.[26,27] The most important identified risk factors for gonococcal infection include a new sex partner, multiple sex partners, a sex partner with concurrent partners, or a sex partner with a sexually transmitted infection; additional factors that indicate risk of gonococcal infection include inconsistent condom use in persons not in a mutually monogamous relationship, exchange of sex for money or drugs, one or more previous sexually transmitted infections, or a coexistent sexually transmitted infection. Women diagnosed with *N. gonorrhoeae* infection should have repeat testing approximately 3 months after completing treatment.

- **Women Who Have Sex with Women**: The CDC recommends gonococcal screening for women who have sex with women should occur according to the current screening guidelines for sexually active women who have sex with men.[28]

- **Women Who are Pregnant**: The CDC recommends screening for *N. gonorrhoeae* should be performed at the first prenatal visit for (1) women younger than age 25 and (2) women age 25 years and older who are at increased risk for gonorrhea (e.g. women with a new sex partner, a sex partner who has a sexually transmitted infection, more than one sex partner, or a sex partner with concurrent partners).[28] Additional factors associated with increased risk of gonococcal infection include inconsistent condom use in persons not in a mutually monogamous relationship, exchange of sex for money or drugs, and previous or coexisting sexually transmitted infections. A repeat test for gonococcal infection should be performed during the third trimester for those at continued risk. Pregnant women diagnosed with *N. gonorrhoeae* infection should have repeat testing approximately 3 months after completing treatment.[28]

- **Men Who Have Sex Only with Women**: Routine screening for gonococcal infection is not recommended by either the CDC or the USPSTF for men who have sex only with women.[26,27]

- **Men Who Have Sex with Men**: The CDC recommends screening for gonococcal infection in men who have sex with men at least annually, regardless of a history of condom use during sexual contact; the sites tested should correspond with sites involved in sexual activity with other men during the prior year (e.g. urethral testing if insertive intercourse, rectal testing if receptive anal intercourse, and pharyngeal testing with receptive oral intercourse).[28] The USPSTF does not recommend routine screening for gonorrhea in men, including men who have sex with men.[27]

- **Transgender Men and Women**: The CDC recommends screening for gonorrhea in transgender men ("trans-men") and transgender women ("trans-women") should be based on age, current anatomy, and sexual practices.[28]

- **Persons with HIV Infection**: The CDC recommends performing routine screening for gonorrhea for persons with HIV infection who are sexually active; testing for gonorrhea should be performed at the initial evaluation and at least annually thereafter (more frequent screening may be indicated based on risk).[29] The testing should consist of obtaining samples from the anatomic sites of sexual exposure.

- **Persons in Correctional Facilities**: The CDC recommends performing routine gonococcal
screening at the initial intake in a correctional facility for women 35 years of age and younger and men younger than age 30.[28]
Treatment

Principles of Treating Gonococcal Infections in Adults and Adolescents

The CDC treatment guidelines recommend using dual therapy for the treatment of gonococcal infections in adults and adolescents. Ceftriaxone is the most effective cephalosporin for treatment of gonorrhea and should be used in combination with azithromycin. The recommendation for dual therapy is based on the premise that using two antimicrobials with different mechanisms of action (e.g., a cephalosporin plus azithromycin) may improve treatment efficacy and potentially slow the emergence and spread of resistance. In addition, azithromycin and doxycycline will effectively treat concomitant *C. trachomatis* infection, if present. Azithromycin is preferred over doxycycline as a second agent due to convenience (single-dose therapy versus 7-day therapy) and the substantially lower prevalence of gonococcal resistance to azithromycin than with doxycycline, particularly for gonococcal strains that have an elevated cefixime MIC. In the case of azithromycin allergy or severe intolerance, doxycycline (100 mg orally twice a day for 7 days) can be used as a substitute for azithromycin, but doxycycline should only be used as an alternative, primarily because of the high prevalence of gonococcal tetracycline resistance. For details regarding these alternative regimens, refer to the section on gonococcal infections in the 2015 STD Treatment Guidelines.[26] The following recommendations for treatment are based on the 2015 STD Treatment Guidelines.

Uncomplicated Infections of the Cervix, Urethra, and Rectum

For patients with uncomplicated gonococcal infections of the cervix, urethra, or rectum, the recommended treatment consists of a single dose of ceftriaxone and azithromycin (**Table 1**).[26] If ceftriaxone is not available, cefixime 400 mg orally as a single dose (in place of ceftriaxone) plus azithromycin 1 g orally as a single dose can be used for uncomplicated gonococcal infections of the cervix, urethra, and rectum; this regimen, however, should only be considered for use as an alternative regimen due to concern for lower and less sustained bactericidal blood levels and increasing frequency of elevated MIC’s to cefixime. Other less optimal alternative regimens include oral gemifloxacin plus azithromycin, and intramuscular gentamicin plus oral azithromycin.[30]

Uncomplicated Infections of the Pharynx

Gonococcal infections of the pharynx are more difficult to eradicate than infections at urogenital and anorectal sites. Few antimicrobial regimens can reliably cure greater than 90% of pharyngeal gonococcal infections. As with other gonococcal infections, ceftriaxone-based dual therapy in combination with azithromycin is recommended (**Table 2**). Notably, cefixime has demonstrated limited efficacy for treatment of pharyngeal gonorrhea. Thus, if an alternative treatment regimen is used to treat pharyngeal gonorrhea, a test-of-cure 14 days after treatment using either culture or NAAT is recommended. If the NAAT is positive, effort should be made to perform a confirmatory culture before retreatment. All positive cultures for test-of-cure should undergo antimicrobial susceptibility testing.

Conjunctivitis

In the only published study of the treatment of gonococcal conjunctivitis among adults, all 12 study participants responded to a single 1 g intramuscular injection of ceftriaxone.[31] Nevertheless, due to concerns for emergence of antimicrobial resistance with *N. gonorrhoeae*, the CDC’s recommendation is to treat with ceftriaxone 1 g intramuscular injection once and azithromycin 1 g orally as a single dose (**Table 3**). In addition, a one-time lavage of the infected eye with saline should be considered.

Disseminated Gonococcal Infection
Disseminated gonococcal infection (DGI) frequently results in petechial or pustular acral skin lesions, asymmetric polyarthralgia, tenosynovitis, or oligoarticular septic arthritis. The infection is complicated occasionally by perihepatitis and rarely by endocarditis or meningitis. Because of the possibility of potentially severe sequelae associated with these complications, the 2015 STD Treatment Guidelines recommend hospitalization and consultation with an infectious diseases specialist for patients suspected of having disseminated gonococcal infection. The recommended initial therapy is ceftriaxone 1 g intramuscularly or intravenously every 24 hours plus azithromycin 1 g orally in a single dose. The first dose is given ideally after promptly obtaining cultures and NAATs from multiple sites, as indicated, including skin, synovial fluid, blood, and cerebrospinal fluid. The duration of therapy for disseminated gonococcal infection with arthritis-dermatitis syndrome is at least 7 days and the ceftriaxone can transition to oral therapy if antimicrobial sensitivity testing shows an effective oral choice (Table 4).[26] For patients with meningitis, parenteral therapy should continue for 10 to 14 days and with endocarditis parenteral therapy should be given for at least 4 weeks (Table 5).[26]

Allergy to Penicillins or Cephalosporin

Allergic reactions to first-generation cephalosporins occur in less than 2.5% of persons with a history of penicillin allergy and are less common with third-generation cephalosporins such as ceftriaxone and cefixime.[32] Ceftriaxone is contraindicated in patients with a history of IgE-mediated anaphylaxis to penicillin. Given these considerations, expert consultation with an infectious diseases specialist (and possibly also an allergy specialist), is recommended for treating gonorrhea among persons who have documented severe cephalosporin allergy. Cephalosporin desensitization is preferred but impractical in many settings. Potential therapeutic options in this situation for adults and adolescents include (1) dual treatment with single doses of oral gemifloxacin 320 mg plus a single dose of oral azithromycin 2 g, or (2) dual treatment with single doses of intramuscular gentamicin 240 mg plus a single dose of oral azithromycin 2 g.[26] Note that since May 2015, gemifloxacin has not available for use in the United States because of a legal dispute regarding the license to manufacture and distribute this drug. For patients with documented severe cephalosporin allergy, recent evidence supports superior effectiveness of dual therapy when compared with azithromycin monotherapy. In this setting, spectinomycin monotherapy has been effective in clinical trials, curing 98.2% of uncomplicated urogenital and anorectal gonococcal infections, but it has poor efficacy against pharyngeal infection and is not currently available in the United States. Although true allergic reactions to third-generation cephalosporins are uncommon among persons who report a history of penicillin allergy, use of ceftriaxone is contraindicated in persons with a history of IgE-mediated penicillin allergy.

Gonococcal Infections in Pregnancy

As with other patients, pregnant women infected with N. gonorrhoeae should be treated with recommended cephalosporin-based therapy in combination with azithromycin. Pregnant women should not be treated with any fluoroquinolone or any tetracycline drug. Because spectinomycin is not available in the United States, pregnant women who cannot tolerate a cephalosporin should be evaluated by an infectious diseases specialist.

Management of Antibiotic-Resistant Gonorrhea

Although there are no confirmed cases of treatment failure due to cephalosporin-resistant N. gonorrhoeae in the United States, the gradual upwards trend of MICs documented by the United States Gonococcal Isolate Surveillance Project (GISP) remains worrisome.[5,6,9,33] Criteria for resistance to cefixime and ceftriaxone have not been defined by the Clinical and Laboratory Standards Institute (CLSI), but isolates with cefixime or ceftriaxone MICs equal to or greater than 0.5 μg/mL are considered to have decreased susceptibility. Only five isolates with ceftriaxone MIC equal to or greater than 0.5 μg/mL have been reported during the history of the GISP. Notably, isolates
with high-level cefixime and ceftriaxone MICs (cefixime MICs 1.5–8 μg/mL and ceftriaxone MICs 1.5–4 μg/mL) have been identified in Japan, France, and Spain.[34,35,36,37]

### Defining Gonococcal Treatment Failure

Treatment failure should be suspected in patients who have recurrence of symptoms or a positive culture after a documented, appropriate treatment.[26] The majority of cases of suspected treatment failure are reinfection rather than true treatment failure. A true treatment failure should be considered in: (1) a person whose symptoms do not resolve within 3 to 5 days after appropriate treatment and they report no sexual contact during the post-treatment follow-up period and (2) a person with a failed test-of-cure (i.e. positive culture at least 72 hours or positive NAAT at least 7 days after receiving recommended treatment) when no sexual contact is reported during the post-treatment follow-up period. Risk factors for treatment failure due to resistant organisms include multiple prior treatment courses for gonorrhea, international travel, or pharyngeal disease.

### Management of Suspected Gonococcal Treatment Failure

Clinicians who diagnose *N. gonorrhoeae* infection in a person with suspected cephalosporin treatment failure should (1) perform culture and susceptibility testing of all relevant clinical specimens; (2) obtain expert opinion for guidance in clinical management (through the [STD Clinical Consultation Network](https://std.consultnet.org), a local STD/HIV Prevention Training Center clinical expert, the CDC, or an infectious diseases specialist); and (3) report the case to the CDC through state and local public health authorities.[26] Isolates that grow *N. gonorrhoeae* should be saved and sent to the CDC through state public health laboratory mechanisms. Health departments should prioritize notification and culture evaluation for sex partner(s) of persons with *N. gonorrhoeae* infection suspected for cephalosporin treatment failure or persons whose isolates demonstrate decreased susceptibility to cephalosporins. In this setting, a test-of-cure at relevant clinical sites should be obtained 7 to 14 days after retreatment; culture is the recommended test, preferably with simultaneous NAAT and susceptibility testing of *N. gonorrhoeae* if isolated. For patients considered to have high likelihood of true treatment failure, especially those with a documented elevated cephalosporin MIC for *N. gonorrhoeae*, the 2015 STD Treatment Guidelines suggested options consist of (1) single dose oral therapy with gemifloxacin 320 mg plus azithromycin 2 g, or (2) single dose oral therapy with azithromycin 2 g plus a single intramuscular injection of a 240 mg dose of gentamicin. Note that since May 2015, gemifloxacin has not available for use in the United States because of a legal dispute regarding the license to manufacture and distribute this drug.

### Follow-Up

In general, a test-of-cure is not recommended for patients who have uncomplicated gonorrhea and are treated with any of the recommended regimens. Patients who have persistent symptoms should be evaluated by culture for *N. gonorrhoeae*, and any gonococci isolated should be tested for antimicrobial susceptibility. A routine test-of-cure at day 14 after treatment with NAAT or culture is recommended for patients with pharyngeal gonorrhea treated with an alternative regimen. All patients diagnosed with gonorrhea should have repeat testing in 3 months at the anatomic site of exposure, regardless of whether they have symptoms. Infections identified after treatment with one of the recommended regimens usually result from reinfection rather than treatment failure, indicating a need for improved patient education and referral of sex partners. Patients who have persistent infection despite treatment with a recommended regimen and who deny sexual exposure after treatment should be evaluated with culture of clinical specimens and susceptibility testing. Clinicians should promptly notify the local STD program of such cases, and local or state STD programs should notify the CDC.

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Recent sex partners (within the 60 days preceding onset of symptoms or gonorrhea diagnosis) should be referred for evaluation, testing, and presumptive dual treatment. The most recent sex partner should be treated regardless of interval from diagnosis. To avoid reinfection, sex partners should be instructed to abstain from unprotected sexual intercourse for 7 days after they and their sex partner(s) have completed antimicrobial treatment and symptoms have resolved.

**Expedited partner therapy**

In settings where prompt referral and treatment are unavailable or impractical, providers should consider expedited partner therapy. This entails provision of appropriate antibiotics as well as educational and pharmacy information for the partner. The documentation should include notification that partner(s) have been exposed, information about the importance of treatment, signs and symptoms of potential complications, as well as possible therapy-related potential allergic reactions and adverse effects. The expedited partner therapy regimen for sex partners of patients with *N. gonorrhoeae* infection is cefixime 400 mg and azithromycin 1 g, with delivery of the prescription to the partner by either the patient, a disease investigation specialist, or a collaborating pharmacy as permitted by law. It is essential to check with one's state health department to clarify the policies, as the use of expedited partner therapy is not legal in all states. The CDC maintains an updated information page [Legal Status of Expedited Partner Therapy](#) that identifies the legal status of expedited partner therapy in each state in the United States, as well as providing links to each state for more detailed state policies. Notably, provision of expedited partner therapy alone is not sufficient and each partner should ideally be seen in follow-up for repeat testing to confirm resolution of infection and check for reinfection. Although offering expedited partner therapy to female partners is acceptable, this approach may result in undertreatment of pelvic inflammatory disease. The use of expedited partner therapy for gonorrhea is contraindicated in a female partner who have current signs or symptoms that are suggestive of PID. Female partners who have current signs and symptoms suggestive of PID should undergo prompt evaluation by a health care provider. In addition, the use of expedited partner therapy should not be considered a routine partner management strategy in MSM with gonorrhea for several reasons, including the high risk for coexisting infections (especially HIV and syphilis infection), inadequate data regarding the efficacy of expedited partner therapy in this patient population, and concerns regarding the increased proportion of gonococcal isolates among MSM with reduced susceptibility to cefixime.

**Reporting Requirements**

Laws and regulations in all states require clinicians, laboratories, or both to report persons with gonorrhea to public health authorities.
Patient Counseling and Education

Patient counseling and education should cover the nature of the disease, transmission issues, and risk reduction.

Nature of the Disease

- Genitourinary infection with gonorrhea is most often symptomatic in males and asymptomatic in females.
- Untreated cervical gonorrheal infection in women can result in upper genital tract infection, which may result in pelvic inflammatory disease, tubal infertility, and ectopic pregnancy.
- Untreated urethral gonorrhea in men can result in epididymitis and other less common complications such as penile edema, abscess, and stricture.

Transmission Issues

- *N. gonorrhoeae* is efficiently transmitted from males to females via vaginal intercourse, rectal intercourse, and fellatio.
- *N. gonorrhoeae* can be transmitted from females to males via vaginal intercourse and less efficiently by cunnilingus.
- Patients with gonorrhea are more likely to transmit and acquire HIV.
- Patients and their partners should abstain from intercourse for 7 days after completing treatment and until they and their sex partners have complete resolution of any symptoms.

Risk Reduction

The clinician should provide the following counseling information for the patients as a risk reduction plan:

- Assess the patient’s potential to change behavior,
- Develop individualized risk-reduction plans with the patient,
- Discuss prevention strategies such as abstinence, mutual monogamy with an uninfected partner, use of condoms, and limiting the number of sex partners. Latex condoms, when used consistently and correctly, can reduce the risk of transmission of *N. gonorrhoeae*.
Summary Points

- Rates of *Neisseria gonorrhoeae* infection have increased in recent years, especially among men who have sex with men and in the southern and western regions of the United States.
- *N. gonorrhoeae* can cause a wide array of urogenital, pharyngeal, and rectal symptoms as well as serious complications, such as pelvic inflammatory disease, tubal infertility, ectopic pregnancy, periurethral fistula or abscess, neonatal conjunctivitis, and rarely, disseminated gonococcal infection.
- Gonorrhea is associated with an increased susceptibility to HIV acquisition as well as an increased risk of HIV transmission.
- Screening for gonorrhea is recommended in sexually active women under 25 years of age and in other persons at high risk of infection.
- Dual therapy with a cephalosporin and azithromycin is recommended in all persons (including pregnant women) for treatment of uncomplicated infections of the cervix, urethra, and rectum. Alternative antimicrobial therapies are available to treat persons with penicillin or cephalosporin allergy (though cephalosporin desensitization is preferred).
- Antimicrobial resistance is a key concern in the treatment of gonorrhea: in 2016, 26.8% of isolates demonstrated resistance to ciprofloxacin and 44.1% of isolates demonstrated resistance to either ciprofloxacin, penicillin, tetracycline, or a combination of these antimicrobials.
- The majority of cases of suspected treatment failures represent reinfection with *N. gonorrhoeae*, but if true cephalosporin treatment failure is suspected, clinicians should perform culture and sensitivity testing and seek expert consultation.
- Patients who are diagnosed with gonorrhea should receive counseling about the nature of infection, transmission, and risk reduction, and their sex partners should be referred for treatment; expedited partner therapy should be considered where permitted.


References


[PubMed Abstract]

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[PubMed Abstract]

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[PubMed Abstract]

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Figures

Figure 1 Gonorrhea–Rates of Reported Cases by Year, United States, 1941-2016

Figure 2 Gonorrhea — Rates of Reported Cases by Region, United States, 2016

Figure 3 Gonorrhea — Rates of Reported Cases by Region, United States, 2012-2016

Figure 4 Gonorrhea — Rates of Reported Cases by State, United States and Outlying Areas, 2016

NOTE: The total rate of reported cases of gonorrhea for the United States and outlying areas (Guam, Puerto Rico, and Virgin Islands) was 144.4 cases per 100,000 population.

Figure 5 Gonorrhea — Rates of Reported Cases by Sex, United States, 2012-2016

Figure 6 Gonorrhea — Rates of Reported Cases by Race/Ethnicity, 2016

Figure 7 Gonorrhea — Rates of Reported Cases by Age Group and Sex, United States, 2016

Figure 8 (Image Series) - Gonococcal Isolate Surveillance Project (GISP) (Image Series)

Image 8A: Antimicrobial Drugs Used to Treat Gonorrhea, GISP 1988-2016

NOTE: For 2016, “Other” includes azithromycin 2g (0.7%), no therapy (0.1%), and other less frequently used drugs (0.8%).

Figure 8 (Image Series) - Gonococcal Isolate Surveillance Project (GISP)

Image 8B: *Neisseria gonorrhoeae* — Isolates (%) with Elevated Ceftriaxone MICs (≥0.125 μg/ml) & Elevated Cefixime MICs (≥0.25 μg/ml), GISP 2006-

*Isolates not tested for cefixime susceptibility in 2007 and 2008. MICs = minimum inhibitory concentrations

Figure 8 (Image Series) - Gonococcal Isolate Surveillance Project (GISP)
Image 8C: Neisseria gonorrhoeae — Distribution of Azithromycin MICs, GISP, 2012-2016

MICs = minimum inhibitory concentrations

NOTE: PenR = penicillinase-producing *Neisseria gonorrhoeae* and chromosomally-mediated penicillin-resistant *N. gonorrhoeae*; TetR = chromosomally- and plasmid-mediated tetracycline-resistant *N. gonorrhoeae*; and QRNG = quinolone-resistant *N. gonorrhoeae*.

Figure 9 *Neisseria gonorrhoeae* and Binary Fission

Transmission electron micrograph (TEM) showing *Neisseria gonorrhoeae* undergoing binary fission.

Source: Centers for Disease Control and Prevention Public Health Image Library (Dr. Wiesner, 1972).
**Figure 10 Neisseria gonorrhoeae**

This illustration shows a three-dimensional computer-generated image of *Neisseria gonorrhoeae* diplococci. The illustration is an artistic recreation based on scanning electron microscopic (SEM) imagery. Note the hair-like appendages extending from the organisms’ exterior; these are type IV pili that promote motility and improve surface adherence.

Source: Centers for Disease Control and Prevention Public Health Image Library (Medical Illustration—James Archer, 2013).
Figure 11 Purulent Urethral Discharge with Gonococcal Infection

Photograph from Negusse Ocbamichael, PA; Public Health—Seattle & King County STD Clinic
Figure 12 Incubation Period with Gonococcal Urethritis

This graph illustrates the timing of onset of urethral symptoms in 44 men following exposure to *N. gonorrhoeae*.

Figure 13 Bartholin Gland Abscess

Photograph showing right labial Bartholin gland abscess (white arrow) caused by *Neisseria gonorrhoeae*.

Source: Centers for Disease Control and Prevention Public Health Image Library (Susan Lindsley, 1973).
Figure 14 Gonococcal Conjunctivitis

This photograph illustrates a severe case of gonococcal conjunctivitis. Note the purulent material on the upper and lower lids.

Source: Centers for Disease Control and Prevention Public Health Image Library. CDC, 1977.
Figure 15 Disseminated Gonococcal Infection with Skin Lesions

This patient had disseminated gonococcal infection including multiple cutaneous lesions on the feet (black arrows).

Source: Centers for Disease Control and Prevention Public Health Image Library (J. Pledger and Dr. S. E. Thompson, VDCD, 1979).
**Figure 16 Disseminated Gonococcal Infection with Arthritis**

This image taken from a woman with disseminated gonococcal infection and right elbow arthritis.

Source: Centers for Disease Control and Prevention Public Health Image Library (Emory, Tom Sellers, 1963).
Figure 17 Urethral Swab Gram's Stain in Patient with Gonorrhea

This Gram's stain of a smear of a urethral discharge in a man diagnosed with acute gonococcal urethritis.

Source: Centers for Disease Control and Prevention Public Health Image Library (Joe Miller, 1979).
Table 1. 2015 STD Treatment Guidelines: Gonococcal Infections
Treatment of Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum

<table>
<thead>
<tr>
<th>Recommended Treatment of Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ceftriaxone</strong> 250 mg IM in a single dose + <strong>Azithromycin</strong> 1 g orally in a single dose</td>
</tr>
</tbody>
</table>

Note: As dual therapy, ceftriaxone and azithromycin should be administered together on the same day, preferably simultaneously and under direct observation.

Alternative if Ceftriaxone is not available:

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Cefixime</strong> 400 mg orally in a single dose + <strong>Azithromycin</strong> 1 g orally in a single dose</td>
</tr>
</tbody>
</table>

Table 2. 2015 STD Treatment Guidelines: Gonococcal Infections
Treatment of Uncomplicated Gonococcal Infections of the Pharynx

Recommended for Treatment of Uncomplicated Gonococcal Infections of the Pharynx

<table>
<thead>
<tr>
<th>Ceftriaxone</th>
<th>Azithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 mg IM in a single dose</td>
<td>1 g orally in a single dose</td>
</tr>
</tbody>
</table>

## Table 3. 2015 STD Treatment Guidelines: Gonococcal Infections
### Treatment of Gonococcal Conjunctivitis

<table>
<thead>
<tr>
<th>Recommended for Treatment of Gonococcal Conjunctivitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>1 g IM in a single dose</td>
</tr>
</tbody>
</table>

Table 4. 2015 STD Treatment Guidelines: Gonococcal Infections
Treatment of Disseminated Gonococcal Infection (DGI): Arthritis-Dermatitis Syndrome

### Recommended for Treatment of Disseminated Gonococcal Infection (DGI): Arthritis-Dermatitis Syndrome

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>1 g IM or IV every 24 hours</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1 g orally in a single dose</td>
</tr>
</tbody>
</table>

Note: The provider can switch to an oral agent guided by antimicrobial susceptibility testing 24–48 hours after substantial clinical improvement, for a total treatment course of at least 7 days. The duration of treatment of DGI has not been systematically studied and should be determined in consultation with an infectious-disease specialist.

### Alternative for Treatment of Disseminated Gonococcal Infection (DGI): Arthritis-Dermatitis Syndrome

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefotaxime</td>
<td>1 g IV every 8 hours</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1 g orally in a single dose</td>
</tr>
</tbody>
</table>

Note: The provider can switch to an oral agent guided by antimicrobial susceptibility testing 24–48 hours after substantial clinical improvement, for a total treatment course of at least 7 days. The duration of treatment of DGI has not been systematically studied and should be determined in consultation with an infectious-disease specialist.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
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</thead>
<tbody>
<tr>
<td>Ceftizoxime</td>
<td>1 g IV every 8 hours</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1 g orally in a single dose</td>
</tr>
</tbody>
</table>

Note: The provider can switch to an oral agent guided by antimicrobial susceptibility testing 24–48 hours after substantial clinical improvement, for a total treatment course of at least 7 days. The duration of treatment of DGI has not been systematically studied and should be determined in consultation with an infectious-disease specialist.

Table 5. 2015 STD Treatment Guidelines: Gonococcal Infections
Treatment of Disseminated Gonococcal Infection: Meningitis and Endocarditis

Recommended for Treatment of Disseminated Gonococcal Infection: Meningitis and Endocarditis

<table>
<thead>
<tr>
<th>Ceftriaxone</th>
<th>+</th>
<th>Azithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 g IV every 12-24 hours</td>
<td></td>
<td>1 g orally in a single dose</td>
</tr>
</tbody>
</table>

Note: Therapy for meningitis should be continued with recommended parenteral therapy for 10-14 days. Parenteral antimicrobial therapy for endocarditis should be administered for at least 4 weeks. The duration of treatment of DGI has not been systematically studied and should be determined in consultation with an infectious-disease specialist.
