



Gonorrhea

Learning Objectives

Upon completion of this content the learner will be able to:

1. Discuss the epidemiology and clinical manifestations of gonococcal infections.
2. Describe the rationale for diagnostic testing and the advantages and disadvantages of currently available diagnostic tests.
3. Describe the current antibiotic resistance patterns of *Neisseria gonorrhoeae* and the impact on treatment recommendations.
4. Describe patient follow-up and partner management.
5. Describe prevention strategies and screening guidelines

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I. Epidemiology

A. Incidence and prevalence:

1. Still a significant public health problem in U.S and is the second most common reported notifiable disease.
2. Historically, the rate rose steadily between 1960 and 1975, declined by 74% from 1975 to 1997 after implementation of national gonorrhea control program in the mid-1970s, appeared to plateau for several years, but increased slightly in 2005, which was the first increase since 1999.
3. Numbers of reported cases underestimates incidence.
4. Incidence remains high in some groups defined by geography, age and race/ethnicity or sexual orientation.
 - a) Geographic and demographic variability, highest rates reported from the South.
 - b) In the West, increasing rates among men having sex with men.
 - c) Age: peak incidence in men 20-24 years, women 15-19 years; >80% of cases occur between age 15-29 years.
 - d) Sex: since 2000, national gonorrhea rates have been slightly higher in women than in men.
 - e) Race/ethnicity: disproportionately high rates in African-Americans, Hispanic and Native Americans compared with whites and Asians. From 2001 through 2005, rates have decreased 18% for African Americans, but increased 28% among Native Americans, 20% among whites, 6% among Hispanics, and 5% among Asian/Pacific Islanders.
5. Proportion of gonococcal infections caused by quinolone resistant organisms has increased dramatically nationwide. **Consequently, the CDC issued revised gonorrhea treatment guidelines early in 2007 and no longer recommends the use of quinolones for the treatment of gonorrhea (www.cdc.gov/std/treatment).** Elevated mean inhibitory concentrations (MICs) for Azithromycin have been observed but the significance of this is yet to be determined.

B. Risk factors and risk markers:

1. Multiple or new sex partners or inconsistent condom use.
2. Urban residence (in areas with disease incidence), adolescence (females particularly), lower socio-economic status, use of drugs, exchange of sex for

drugs or money.

C. Transmission: efficiently transmitted:

1. Infected woman to the urethra of male sexual partner: 20% per episode of vaginal intercourse and increases to 60-80% after four or more exposures.
2. Male to female transmission approximates 50-70% per contact.
3. Transmission by rectal intercourse has not been quantified but appears to be efficient.
4. Transmission less efficient by fellatio; rare by cunnilingus.
5. Perinatal transmission from infected mother to newborn through vaginal delivery.

D. Gonorrhea and HIV interaction: gonorrhea is associated with increased susceptibility to HIV infection and increased HIV viral load in men with gonococcal urethritis.

II. Pathogenesis

A. Microbiology:

1. Etiologic agent = *Neisseria gonorrhoeae*.
2. Gram-negative diplococcus, oxidase-positive, utilizes glucose, but not sucrose, maltose, or lactose.
3. Infects mucus-secreting epithelial cells.
4. Divides by binary fission (every 20-30 minutes).

B. Pathology:

1. GC attach to different types of epithelial cells via a number of different structures located on the surface of gonococci and are ingested.
2. GC has ability to alter surface structures, particularly pili, lipooligo-saccharide antigens and, less frequently, protein 1 (porin) antigens, helping the organism to evade an effective host response.

3. GC employs several mechanisms to disarm the complement system, which may result in a survival advantage in the human host.

C. Typing systems:

1. Protein 1 serovar determination by monoclonal antibodies and genotyping both based on protein 1 variation; auxotyping.
2. Antimicrobial susceptibility testing: these are not used generally to provide population-based typing. They are useful for clinical typing to link cases that are contacts of each other.
3. Plasmid typing.

III. Clinical Manifestations

A. Genital infection in men:

1. Urethritis:
 - a) Many male patients develop overt, symptomatic urethritis.
 - b) However, asymptomatic (unrecognized) infection does occur and appears to be linked to individual gonococcal phenotypes. Asymptomatic GC represents the reservoir in the community that perpetuates transmission from men to women.
 - c) Incubation period: for symptomatic disease, usually 2-7 days, but may be longer.
 - d) Symptoms: typically purulent urethral discharge often accompanied by dysuria.
 - e) Clinical presentation: purulent or mucopurulent urethral discharge is common, but discharge may be clear or cloudy.
2. Epididymitis:
 - a) Infrequent, but most common local complication in males.
 - b) Symptoms: unilateral testicular pain and swelling.
 - c) Usually associated with overt or subclinical urethritis.
 - d) Testicular swelling, epididymal tenderness.
3. Uncommon complications include: inguinal lymphadenitis, penile edema, periurethral abscess or fistula, accessory gland infection (Tyson's glands), balanitis, urethral stricture, and perhaps prostatitis.

B. Genital infection in women: fewer than half of women have symptoms suggestive of

gonococcal infection.

1. Cervicitis:
 - a) 50% of women with clinical cervicitis have no symptoms.
 - b) Incubation period unclear, but symptoms may occur within 10 days of infection.
 - c) Symptoms: often nonspecific and may include abnormal vaginal discharge, intermenstrual bleeding, dysuria, lower abdominal pain or dyspareunia.
 - d) Signs: mucopurulent, or purulent cervical discharge or easily induced cervical bleeding.
2. Urethritis:
 - a) In women with cervical gonococcal infection, 40-90% may have urethral infection.
 - b) Symptoms: dysuria; most are asymptomatic.
3. Accessory gland infection (Skene's, Bartholin's gland infections). Often unilateral. Occlusion of the duct results in abscess formation.
4. PID:
 - a) Refers to ascending infection to the endometrium and/or fallopian tubes.
 - b) May be "silent" or asymptomatic.
 - c) Symptoms: lower abdominal pain, discharge, dyspareunia, intermenstrual bleeding and fever.
 - d) Exam findings: uterine, adnexal tenderness or cervical motion tenderness. Evidence of cervicitis may be present.
 - e) Clinical diagnosis of PID is imprecise.
 - f) Long-term sequelae: chronic pelvic pain, tubal infertility, and ectopic pregnancy.
5. Perihepatitis (Fitz-Hugh-Curtis Syndrome):
 - a) Inflammation of the liver capsule.
 - b) Initially attributed to gonococcal infection, but now more often associated with chlamydial infection.
 - c) Characterized by right upper quadrant pain, almost always normal liver function tests.
6. Pregnancy morbidity: associated with premature rupture of membranes, preterm delivery, and postpartum endometritis.

C. Syndromes in men and women:

1. Anorectal infection:

- a) Acquired by anal intercourse.
 - b) The rectal mucosa has also been reported to be infected in 35 to 50% of women with gonococcal cervicitis who do not acknowledge rectal sexual contact. These infections are assumed to result from perineal contamination with infected cervical secretions. However, in several pre-AIDS studies, the rectum was the only site of infection in approximately 5% of women with gonorrhea.
 - c) Most cases asymptomatic, but occasional severe proctitis.
 - d) Symptoms: anal irritation, painful defecation, constipation, rectal bleeding and/or discharge, tenesmus.
 - e) Evaluation utilizing an anoscopic examination is recommended if gonococcal proctitis is suspected.
 - f) Signs: mucosa may appear normal, purulent discharge, erythema or easily induced bleeding may be observed under anoscopy.
2. Pharyngeal infection:
- a) May be sole site of infection if oral-genital contact is the only exposure.
 - b) Most often asymptomatic. Exudative pharyngitis is rare.
3. Conjunctivitis:
- a) In adults, a result of autoinoculation.
 - b) Symptoms/signs: purulent conjunctival exudate.
4. Disseminated gonococcal infection (DGI):
- a) Occurs infrequently, more common in women.
 - b) DGI associated with gonococci that have a propensity to produce bacteremia due to resistance to killing by normal human serum.
 - c) Also, persons deficient in complement components C5-C8 are at greater risk.
 - d) Clinical manifestations include skin lesions, arthralgias, tenosynovitis, arthritis, hepatitis, myocarditis, endocarditis, meningitis.

D. Infections in children:

- 1. Perinatal: during childbirth, the neonatal conjunctiva, pharynx, respiratory tract, or anal canal may become infected. Conjunctivitis (ophthalmia neonatorum) is preventable by ocular prophylaxis.
- 2. Older children (>1 year):
 - a) All cases should be considered possible evidence of sexual abuse.
 - b) Vulvovaginitis (not cervicitis) is most common manifestation in prepubertal girls. Symptoms/signs: vaginal discharge (often purulent), dysuria, odor, pruritis.
 - c) The anorectum and the pharynx are the most frequently infected sites in

- abused boys. Urethritis is less frequently seen.
- d) If specimens are to be collected, proper guidelines for collecting forensic evidence must be followed. Individual state laws should be consulted.

IV. Diagnosis

- A. Gram-stained smear: positive = any polymorphonuclear leukocytes (PMNs) with intracellular Gram-negative diplococci.
1. Male urethra in symptomatic urethritis: >95% sensitivity and >99% specificity; reliable both to diagnose and exclude gonorrhea. Sensitivity less for asymptomatic urethritis; decreases to 50% in asymptomatic men.
 2. Cervix: ~ 50% sensitivity, >95% specificity; positive predictive value varies with prevalence of GC in the population but varies with the severity of the cervicitis, the quality of the smear specimen, and the skills of the microscopist.
 3. Female urethra, Skene's glands, Bartholin's gland: similar to male urethra if overt exudate expressed.
 4. Rectum: Sensitivity of blind anorectal Gram stain 40-60%; with symptomatic rectal gonorrhea Gram stain sensitivity was 79% when obtained via anoscopy, compared to 53% when obtained via a rectally inserted swab.
 5. Pharynx: not useful.
- B. Non-culture tests: rely on detection of bacterial products (proteins, nucleic acid) in patient samples.
1. Non-amplified tests: enzyme immunoassay (EIA), DNA probe (Gen-Probe PACE II), direct fluorescent antibody (DFA):
 - a) Less sensitive to handling than culture, potential for more timely results than culture.
 - b) Sensitivity (85-90%) and specificity of EIA and Gen-Probe (95%) good, although both are less in asymptomatic populations.
 - c) Antimicrobial susceptibility cannot be determined.
 - d) For some tests, same sample can be evaluated for *C. trachomatis*.
 - e) Not approved for pharyngeal or rectal specimens.
 2. Nucleic Acid Amplified Tests (NAATs): Polymerase Chain Reaction (PCR - Amplicor®), Transcription-Mediated Amplification (TMA- GenProbe Aptima Combo2 ®), Strand Displacement Amplification (SDA- ProbeTec®): Sensitivity

as good as culture or in settings where transport conditions are sub-optimal may be better than culture.

- a) Approved for use on cervical and urethral specimens. TMA is also approved for vaginal swabs.
- b) All tests except PCR of female urine are also FDA cleared for use with urine.
- c). Antimicrobial susceptibility cannot be tested.
- d) Same sample can be also evaluated for *C. trachomatis*.
- e) Not FDA cleared for pharyngeal or anorectal specimens, although some sites have validated their use in local studies. Preliminary data appear to suggest good results.

C. Culture:

1. Selective media containing antimicrobial antibiotics to inhibit competing bacteria (e.g., Modified Thayer Martin medium); non-selective media (chocolate agar) may/should be used for specimens collected from sites that are normally sterile (blood, CSF, joint fluid).
2. Sensitivity: male urethra 95%; cervix 95%, rectum, and pharynx 70 -90% in most laboratories.
3. Direct inoculation is best; inoculated culture plate should be promptly placed into CO₂ enriched (3-10%) environment and incubated at 35-37° C within 4 hours.
4. Anatomic sites to test: test in response to complaints/clinical findings and exposure history in persons at significant risk of gonococcal infection.
 - a) In men: urethra in all; pharynx and rectum, depending on symptoms, and exposure history; pharynx, if history of performing fellatio, if history of receptive anal sex.
 - b) In women: cervix; rectal or a second cervical culture increases overall yield by 5%; pharynx, if history of performing fellatio; rectum and urethra or vagina may be tested if cervix absent.

D. In cases of suspected sexual abuse, culture with multiple means of confirmation of the identity of *Neisseria gonorrhoeae* is the legal standard. See sexual assault or abuse of children section in CDC STD Treatment Guidelines.

E. If gonorrhea is detected, treat for CT and screen for other STDs:

1. *Chlamydia trachomatis*.
2. Syphilis.
3. HIV.

V. Treatment

- A. Antimicrobial susceptibility of *N. gonorrhoeae*: one or more types of resistance is present in 20-30% of gonococci in U.S. Overall, 20% of isolates collected in 2005 by the Gonococcal Isolate Surveillance Project (GISP) were resistant to penicillin, tetracycline, or both.
1. B-Lactamase (penicillinase) production (PPNG): plasmid-mediated.
 2. High-level tetracycline resistance (TRNG): plasmid-mediated.
 3. Chromosomal resistance (CMRNG): penicillins, tetracyclines, spectinomycin, erythromycin, cephalosporins, quinolones.
 4. No decreased susceptibility to cefixime or to ceftriaxone has been reported.
 5. Fluoroquinolone resistance: **The CDC issued revised gonorrhea treatment guidelines early in 2007 and no longer recommends the use of quinolones for the treatment of gonorrhea (www.cdc.gov/std/treatment).**
 - a) Chromosomal (DNA gyrase, membrane permeability).
 - b) The incidence of quinolone-resistant GC (QRNG) has increased steadily in the U.S. since 1992.
 - c) In 2005, 9.4% of isolates collected by the GISP were quinolone-resistant.
 - d) QRNG has become relatively common in parts of Europe, Asia, Central Asia and the Pacific.
 6. Cephalosporins
 - a) Ceftriaxone in a single injection of 125 mg provides sustained, high bactericidal blood levels and is the treatment of choice for uncomplicated gonorrhea at all anatomic sites
 - b) Alternative parenteral single-dose regimens for urogenital and anorectal gonorrhea include ceftizoxime 500 mg, cefoxitin 2 grams with probenecid 1 gram orally, or cefotaxime 500 mg.
 - c) Cefixime given in a single 400 mg dose has similar cure rates, but is not currently marketed in the United States.
 - c) Cefpodoxime proxetil 200 mg orally is less active than ceftriaxone and only 79% efficacious in treating pharyngeal gonorrhea. Cefpodoxime 400 mg PO is an acceptable oral alternative for the treatment of urogenital and anorectal infection.
 - d) Cefuroxime axetil 1 gm PO might be an additional oral alternative for the treatment of urogenital and anorectal gonorrhea, but has a shorter duration of bacteriocidal activity, may select for resistance, and should be avoided.
 7. For persons with penicillin or cephalosporin allergies, a single intramuscular

dose of spectinomycin 2 grams is an alternative regimen. However, spectinomycin is not currently available in the United States. A single oral dose of Azithromycin 2 grams is effective against uncomplicated gonococcal infections, but CDC does not recommend widespread use of Azithromycin because of concerns regarding rapid emergence of resistance, documented since 1999 in the United States and internationally. It may, however, be used in persons with documented severe penicillin or cephalosporin allergies.

B. 2002 recommendations for uncomplicated genital, rectal and pharyngeal infection in adults and adolescents.

¹ Cefixime	400 mg	PO	Once	or
¹ Ceftriaxone	125 mg	IM	Once	or

PLUS (for treatment of chlamydial infection – if CT infection not ruled out)⁴

³ Azithromycin	1.0 g	PO	Once	or
² Doxycycline	100 mg	PO	BID x7 days	

Key: ¹If penicillin-allergic, consider potential cephalosporin cross-reactivity (3-5%).

²Contraindicated in pregnancy and children. ³Safety and efficacy in pregnancy not established. Not recommended for GC treatment. Azithromycin 2.0 g dose is effective for uncomplicated GC, but is expensive and causes gastrointestinal distress too often to be recommended, and concerns for developing resistance exist..

⁴If co-infection rate is high and sensitive chlamydia tests not available, or patient is unlikely to return for chlamydia treatment.

C. Management in pregnancy:

1. Avoid tetracyclines.
2. Recommend cephalosporin.
3. If woman is penicillin allergic, or cannot tolerate a cephalosporin, 2 g dose of IM spectinomycin should be given, if available..
4. Either erythromycin or amoxicillin is recommended for treatment of presumptive or diagnosed *C. trachomatis* infection.

D. DGI: Requires initial parenteral therapy, which should be continued for 24-48 hours after improvement begins, at which time the patient may be switched to an oral regimen to complete a full week antibiotic course.

Recommended Initial Regimen

Ceftriaxone	1 gram IM or IV	Every 24 hours	or
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Alternate Regimens

Cefotaxime	1 gram IV	Every 8 hours	or
Ceftizoxime	1 gram IV	Every 8 hours	or
Spectinomycin	2 grams IM	Every 12 hours	

Recommended oral regimen after improvement

Cefixime	400 mg PO	Twice daily	or
Cefixime suspension	500 mg (25 cc)	Twice daily	
Cefpodoxime	400mg	Twice daily	

E. Follow-up:

1. 1. In general, test of cure is not recommended, but clinicians should advise all patients with gonorrhea to be retested 3 months after treatment. If patients do not present for retesting in 3 months, providers should repeat test patients whenever they next present for care within the following 12 months, even if the patient believes that their sex partners were treated. If symptoms persist, perform culture for *N. gonorrhoeae*, and any gonococci isolated should be tested for antimicrobial susceptibility. Repeat test for incident, repeat or resistant infection.

VI. Prevention

- A. Screening recommendations (testing of asymptomatic individuals): active screening in high-risk populations:
 1. Sexually active adolescents, especially if prevalence is >2%.
 2. Persons with new or multiple sex partners.

3. High prevalence geographic areas (inner city, [both urban and rural] not clear, especially in the South).
4. Screening during pregnancy depends on age, risk history and local prevalence.
5. MSM annually; MSM with high risk behaviors (multiple or anonymous partners, partners met through the internet, unprotected anal intercourse, having sex in conjunction with substance use), should be screened every 3 to 6 months.
6. Patients with other STDs.
7. Correctional populations depending on prevalence.
8. Sex workers and other potential core group members.

B. Partner management:

1. Patients should be instructed to refer their sex partners for evaluation and treatment.
2. All sex partners of patients who have *N. gonorrhoeae* infection should be evaluated and treated for *N. gonorrhoeae* and *C. trachomatis* infections if their last sexual contact with the patient was within 60 days before onset of symptoms or diagnosis of infection in the patient. If a patient's last sexual intercourse was >60 days before onset of symptoms or diagnosis, the patient's most recent sex partner should be treated.
3. Patients should be instructed to avoid sexual intercourse until therapy is completed and they and their sex partners no longer have symptoms.
4. For patients with gonorrhea whose partners' treatment cannot be assured or is unlikely, delivery of antibiotic therapy for gonorrhea and chlamydia (either a prescription or medications) by heterosexual male or female patients to their partner is an option. Male patients should be instructed to inform their female partners about still seeking medical care to be evaluated for PID. Providers must consult with local and state practice regulations before proceeding with patient delivered partner therapy.

C. Reporting:

Laws and regulations in all states require that persons diagnosed with gonorrhea are reported to public health authorities by clinicians, labs, or both.

D. Patient counseling/education: risk reduction:

1. Assess client's behavior-change potential.
2. Discuss prevention strategies (abstinence, monogamy, condoms, limit number of sex partners, etc.). Latex condoms, when used consistently and correctly, can reduce the risk of transmission of gonorrhea.
3. Develop individualized risk-reduction plans.

VII. References

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Internet resources

CDC. National Center for Infectious Diseases homepage: <http://www.cdc.gov/ncidod>