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Gonococcal Infections

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Educational Gaps

1. Adolescents (15–19 years of age) and young adults (20–24 years of age) account for the majority of new cases of gonorrhea reported each year. Gonococcal infections in postpubertal females are commonly asymptomatic. Complications such as pelvic inflammatory disease (PID) and disseminated gonococcal infection (DGI) occur more often in females, probably because of delays in diagnosis and treatment.
2. A major difficulty in the treatment of gonococcal infections is the increasing incidence of multidrug-resistant strains. In August 2012, the Centers for Disease Control and Prevention (CDC) updated gonorrhea treatment guidelines and no longer recommends oral cephalosporins as routine treatment. (1)

Objectives

After finishing this article, readers should be able to:

1. Discuss the risk factors for acquisition of *Neisseria gonorrhoeae.*
2. Recognize the different clinical manifestations of gonococcal infections.
3. Understand the importance of following current treatment recommendations for *N gonorrhoeae.*

Epidemiology

Neisseria gonorrhoeae is an oxidase-positive diplococcus that grows in warm, moist environments. The optimal temperature for growth is 35° to 37°C. (2) Typically an intracellular organism, *N gonorrhoeae* cannot live outside of its human host and is differentiated from other species of *Neisseria* by its ability to ferment glucose instead of other carbohydrates. The organism survives and replicates within host macrophages after phagocytosis but is killed by polymorphonuclear leukocytes. *N gonorrhoeae* is shed in exudates and secretions transmitted through intimate contact, such as sexual contact or vaginal delivery.

N gonorrhoeae is the second most commonly occurring reportable sexually transmitted disease (STD), or sexually transmitted infection (STI; currently the more accepted term), after *Chlamydia trachomatis.* Incidence of gonococcal infections is estimated at 700,000 new cases in the United States per year. (1) Although incidence rates had declined to historically low levels since 1998, statistics from 2010 show a slight increase in the amount of new cases reported. (3) Adolescents (15–19 years of age) and young adults (20–24 years of age) account for the majority of new cases reported each year. However, ethnic minority groups (African Americans, Hispanics, and Native Americans) continue to account for a disproportionate number of cases. Males and females continue to account for an equal amount of new cases per year, and the Southeastern region of the United States remains the most affected geographic region. (4) Additionally, men who have sex with men (MSM) comprise a population experiencing increasing rates of infection. The STD Surveillance Network noted an increased prevalence of gonococcal infections in MSM infected with human immunodeficiency virus (HIV) compared to MSM not infected with HIV. (3)

Any sexually active person can be infected with *N gonorrhoeae*. Behavioral factors predisposing adolescents

Abbreviations

DGI:	disseminated gonococcal infection
EPT:	expedited partner therapy
MSM:	men who have sex with men
NAAT:	nucleic acid amplification test
PID:	pelvic inflammatory disease
STD/I:	sexually transmitted disease/infection
USPSTF:	United States Preventative Services Task Force

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and young adults to infection include (1) having multiple or new sex partners; (2) inconsistent, incorrect, or no condom use; and (3) lack of screening by health care providers. Additionally, adolescent females are biologically predisposed to infection due to the larger number of columnar epithelial cells that are exposed on the ectocervix during the teenage years.

Pathogenesis

N gonorrhoeae invades mucosal and glandular surfaces lined with columnar or cuboidal, noncornified epithelium, resulting in a local inflammatory response that involves recruitment of polymorphonuclear leukocytes and macrophages.

Virulence is mediated by several distinct characteristics associated with the bacterial outer cell wall membrane. The endotoxin activity of lipooligosaccharides assists in cytotoxicity and acts as a target for the bactericidal antibody. In turn, opacity-associated proteins are thought to aid in the binding to human cells, and expression of variant pili helps the bacteria adhere to tissues, thereby protecting the bacteria from phagocytosis.

Clinical Aspects

Neonates

Gonococcal infections can occur throughout the entire lifespan of the human host. Neonates exposed to infected exudate during vaginal delivery can develop ophthalmia neonatorum, scalp abscesses, or disseminated disease. Characterized by purulent conjunctivitis, ophthalmia neonatorum presents 1 to 4 days after birth. All neonates who have conjunctivitis should have exudates cultured and tested for antibiotic susceptibility. Examination of exudate-yielding intracellular gram-negative diplococci should raise suspicion for gonococcal ophthalmia, and presumptive treatment should be started after collecting appropriate cultures. Lack of prevention or delay in treatment of ophthalmia neonatorum can lead to corneal ulceration, globe rupture, and blindness. Currently, prophylaxis with erythromycin (0.5%) ophthalmic ointment is recommended for all newborn infants regardless of method of delivery. (1)

Prepubertal Children

Acquisition of gonococcal infections during childhood occurs typically via sexual abuse; but, rarely, infections can be acquired through household exposure to affected caretakers or through childhood sexual play. Any child diagnosed as having gonorrhea should be evaluated for sexual abuse. Providers should refer any affected child to local Child Protection Service agency and other appropriate authorities, and specifically trained and experienced professionals should do the sexual abuse evaluation.

Gonococcal infections in children can occur in the pharynx, the rectum, and most commonly, the vagina. Because *N gonorrhoeae* can invade the thin noncornified epithelium of the vagina in prepubertal girls, gonococcal infections of the vagina are symptomatic and are characterized by purulent vaginal discharge, vaginitis, and an erythematous, swollen vulva.

Adolescents and Adults

Infections in adolescents may be either symptomatic or asymptomatic and therefore may be more difficult to diagnosis without proper screening. (Table 1) Infections in males are more likely to be symptomatic than those in females, but the appearance of symptoms may be delayed for weeks. Typical infections in males cause urethritis, proctitis, pharyngitis, and. Infection in females typically causes cervicitis, urethritis, proctitis, menometrorrhagia, pharyngitis, PID, perihepatitis, and DGI. Gonococcal infections in postpubertal females are commonly asymptomatic. Consequently, PID and DGI occur more often in females and probably develop from a spread of infection into the upper genital tract that is related to delay in diagnosis and treatment.

Pharyngitis

An overwhelming majority of pharyngeal gonococcal infections are asymptomatic. However, if symptomatic, the most common symptoms associated with infection are sore throat, fever, and cervical adenopathy. Patients who have a history of penile–oral contact are at increased risk for throat infection. Diagnosis of pharyngitis from

Table 1. Signs and Symptoms of Gonococcal Infection

Asymptomatic (women and men)
Burning and pain with urination, increased urination (women and men)
Penile discharge with redness at penile meatus (men)
Vaginal discharge (women)
Sore throat (gonococcal pharyngitis) (women and men)
Sore or swollen testicles (men)
Pain with intercourse (women)
Fever and abdominal pain (Pelvic inflammatory disease) (women)
Fever, arthritis, and rash (Disseminated gonococcal infection) (women and men)

positive throat cultures can be made in up to 20% to 25% of heterosexual females and homosexual males who have genital gonorrhea; however, cultures must be plated on special media for growth; therefore, routine swabs used for group A *Streptococcus* are not appropriate for the detection of gonorrhea. (4) Elimination of the organism may occur spontaneously after 12 weeks.

Urethritis

Urethritis is characterized by urethral discharge, dysuria, and meatal pruritus. Unlike females, who generally display no symptoms of urethritis, most males exhibit symptoms 2 to 5 days after exposure; however, symptoms may resolve spontaneously after a few weeks. Untreated infections can lead to epididymitis, prostatitis, seminal vesiculitis, or infection of Cowper and Tyson glands. Diagnosis can be made by a Gram stain of urethral discharge that demonstrates polymorphonuclear leukocytes with intracellular gram-negative intracellular diplococci. (1)

Cervicitis

In contrast to prepubertal females, postpubertal females do not experience vulvovaginitis associated with gonococcal infections. Similar to chlamydial infections, gonococcal genital infections in postpubertal females result in cervicitis and endocervicitis. Sixty to 90 percent of females are at risk for infection after one exposure to an infected male. (4) Cervicitis may be asymptomatic or may be characterized by purulent vaginal discharge or erythema, edema, and friability of the cervix. Dyspareunia may result from endocervicitis.

Pelvic Inflammatory Disease

Untreated gonococcal infections of the lower genital tract may ascend the urogenital tract, causing acute endometritis, salpingitis, tuboovarian abscess, and peritonitis, which are collectively characterized as PID. Inflammation of the liver capsule may cause perihepatitis (Fitz-Hugh–Curtis syndrome). Ten to 20 percent of women with acute genital gonorrhea may manifest with PID, and presenting signs and symptoms can include vaginal discharge, abdominal pain, dyspareunia, or abnormal vaginal bleeding. (4) Complications of PID after one episode can include a six- to tenfold increased risk for ectopic pregnancy, 13% to 21% risk for infertility, and 18% risk for chronic pelvic pain. (5) *N gonorrhoeae* is one of the common causes of PID. However, *C trachomatis*, anaerobes, *Gardnerella vaginalis*, *Haemophilus influenzae*, enteric gram-negative rods, and *Streptococcus agalactiae* also have been associated with PID.

The diagnosis of PID is made clinically. Empiric treatment should be started if the patient meets the minimal diagnostic criteria for PID (Table 2). Table 2 also lists additional criteria that may support a specific diagnosis of PID. For an in-depth review of PID, see the April issue of *Pediatrics in Review* (pedsinreview.aappublications.org/content/34/4/163.extract).

Table 2. Diagnostic Criteria for Pelvic Inflammatory Disease

Empiric treatment for PID should be initiated in sexually active young women and other women at risk for sexually transmitted infections if they are experiencing pelvic or lower abdominal pain if no cause for the illness other than PID can be identified and if one or more of the following minimum criteria are present on pelvic examination:

- Cervical motion tenderness OR
- Uterine tenderness OR
- Adnexal tenderness

One or more of the following additional criteria can be used to enhance the specificity of the minimum criteria and support a diagnosis of PID:

- Oral temperature >101˚F (>38.3˚C)
- Abnormal cervical or vaginal mucopurulent discharge
- Presence of abundant numbers of white blood cells on saline microscopy of vaginal fluid
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein level
- Laboratory documentation of cervical infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*

The most specific criteria for diagnosing PID include the following:

- Endometrial biopsy with histopathologic evidence of endometritis
- Transvaginal ultrasonography or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies suggesting pelvic infection (eg, tubal hyperemia)
- Laparoscopic abnormalities consistent with PID

Disseminated Gonococcal Infection

Disseminated disease typically is characterized by fever, arthritis, and rash. Occurring more frequently in females than males, it is thought that DGI is associated often with persistent asymptomatic infection, which results in delayed diagnosis and delayed treatment. In addition, females are at risk also during menstruation, pregnancy, and the postpartum period because of maximal endocervical shedding and decreased bactericidal activity of cervical mucus. (2)

Two common classifications of DGI are tenosynovitis–dermatitis syndrome and suppurative arthritis syndrome. Tenosynovitis–dermatitis, the more common, is characterized by fever, chills, skin lesions, and polyarthralgia, which primarily affects the hands and fingers. Monoarticular arthritis is the predominant manifestation of suppurative arthritis syndrome. (2)

Skin manifestations of DGI present as hemorrhagic or vesiculopapular lesions. Frequently, these lesions are painful and appear on palmar and plantar surfaces. Twenty to 30 percent of these lesions may contain gonococci.

Less common manifestations of DGI include acute endocarditis, pericarditis, and meningitis. In cases of suspected DGI, cultures of blood, pharynx, rectum, urethra, cervix, and synovial fluid (if involved) should be collected. An elevated peripheral white blood cell count and increased erythrocyte sedimentation rate commonly occur.

Screening and Diagnostic Methods

Initial screening for suspected STIs such as gonorrhea begins with performing an appropriate history. A proper sexual history, including questions about high-risk behaviors and sites of sexual contact, must be obtained to direct laboratory screening to the appropriate anatomic site. Those inexperienced with taking a sexual history should refer to the CDC website (http://www.cdc.gov/std/treatment/SexualHistory.pdf).

Because the clinical manifestations of gonococcal infections can mimic, or even coincide with, other infections such as chlamydial infection, bacterial vaginosis, and trichomoniasis, it is important to appropriately distinguish gonococcal infections from these other entities. Furthermore, untreated gonococcal disease can have complications that produce significant morbidity and mortality.

Specific diagnostic testing for gonorrhea consists of culture, nucleic hybridization tests, and nucleic acid amplification tests (NAATs). Culture can be performed on selective (eg, Thayer–Martin) or nonselective (eg, chocolate agar) media. Because of the limitation of genital specimens—endocervical swab specimens in females and urethral swab specimens in males—culture and nucleic hybridization tests are not used as commonly as NAATs, which allow for the widest variety of specimen types: endocervical swabs, vaginal swabs, urethral swabs, and urine. Rectal swabs even may be processed in some laboratories. In addition, NAATs demonstrate high specificity and sensitivity and may be considered as less invasive and easier to perform (urine and vaginal specimens). Patient-collected vaginal swabs have demonstrated similar specificity and improved sensitivity compared with provider-collected swabs. Gram stain may be used to diagnose urethritis in males, as stated above, but should not be used to rule out gonorrhea in symptomatic individuals.

Cultures must be obtained in affected children because of legal implications and concerns for antibiotic resistance and antimicrobial susceptibility. Cultures must be performed as well on nongenital specimens from the rectum, pharynx, and conjunctiva.

Current recommendations advocate annual screening of sexually active adolescents for chlamydial infection and gonorrhea. Adolescents at higher risk, such as those with multiple partners or a history of STI, should be screened for both infections every 6 months. (1) Additionally, clinicians should recommend routine HIV and syphilis screening to all patients at increased risk for these infections. This group includes adolescents who seek screening for STIs, MSM, and those who exchange sex for money or drugs. (6,7) Clinicians should report STI cases in accordance with local and state requirements. Gonorrhea, along with syphilis, chlamydial infection, chancroid, HIV infection, and AIDS are reportable diseases in every state. (1)

Management

The largest hurdle in the treatment of gonococcal infections is the increase in multidrug-resistant strains. In 2007, quinolones were no longer recommended for the treatment of gonorrhea because of drug resistance. (8) In 2010, the preferred management of uncomplicated infections became intramuscular injection of ceftriaxone rather than oral administration of a third-generation cephalosporin. (1) Ceftriaxone produces a higher and more sustained bactericidal level than cefixime. Ceftriaxone also has remained the preferred treatment for pharyngitis caused by *N gonorrhoeae*.

In August 2012, the CDC updated treatment guidelines for gonorrhea and no longer recommends oral cephalosporins as routine treatment for gonococcal infections. (9) This recommendation stems from declining effectiveness of

cefixime. Currently, combination therapy of ceftriaxone with either doxycycline or azithromycin is the recommended treatment for uncomplicated genital, rectal, and pharyngeal infections for two reasons: (1) to provide cotreatment of *C trachomatis* infection and (2) to assist in preventing further drug resistance because gonococci are susceptible to both drugs. (1)

Cefixime, in combination therapy, may be used only if ceftriaxone is not available; however, a test of cure is recommended 1 week after treatment with cefixime. (8) Further efforts are being made to curb this increasing drug resistance. Table 3 lists the current recommendations for treatment of uncomplicated *N gonorrhoeae* in older children, adolescents, and adults according to the CDC.

Table 3. Updated Recommended Treatment Regimens for Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum[1]

Recommended Regimen
Ceftriaxone 250 mg in a single intramuscular dose
PLUS
Azithromycin 1 g orally in a single dose
or doxycycline 100 mg orally twice daily for 7 days*
Alternative Regimens
If ceftriaxone is not available:
Cefixime 400 mg in a single oral dose
PLUS
Azithromycin 1 g orally in a single dose
or doxycycline 100 mg orally twice daily for 7 days*
PLUS
Test-of-cure in 1 week
If the patient has severe cephalosporin allergy:
Azithromycin 2 g in a single oral dose
PLUS
Test-of-cure in 1 week

[1]The recommended regimen for uncomplicated gonococcal infections of the pharynx is ceftriaxone 250 mg in a single intramuscular dose plus either azithromycin 1 g orally in a single dose or doxycycline 100 mg orally twice daily for 7 days.*

*Because of the high prevalence of tetracycline resistance among Gonococcal Isolate Surveillance Project isolates, particularly those with elevated minimum inhibitory concentrations to cefixime, the use of azithromycin as the second antimicrobial is preferred.

 Data from *MMWR Morb Mortal Wkly Rep.* 2012;61(31):590–594.

Ceftriaxone is also the mainstay of treatment for infections in neonates, prepubertal children, and patients who have DGI or other complicated forms of gonococcal infection. Neonates with suspected ophthalmia neonatorum should receive one dose of ceftriaxone (25–50 mg/kg, intravenously or intramuscularly, not to exceed 125 mg) and should undergo frequent eye irrigations with saline solution until the discharge is gone. Neonates with disseminated infections, such as arthritis and septicemia, should be treated for 7 days with ceftriaxone, and neonates with meningitis should be treated for 10 to 14 days.

Management of prepubertal children is dependent on weight and age. Prepubertal children who weigh less than 45 kg and have uncomplicated gonococcal disease should be treated with 125 mg of ceftriaxone, and those above 45 kg should be treated with the adult dose. For children who weigh less than 45 kg and have DGI, treatment should consist of 50 mg/kg of ceftriaxone for 7 days, and the treatment of children above 45 kg or older than 8 years should consist of 1 g of ceftriaxone for 7 days. Meningitis should be treated for 10 to 14 days and endocarditis for 28 days with ceftriaxone. Further details on these therapies can be found in *Red Book: 2012 Report of the Committee on Infectious Diseases.* (10) Readers are urged to consult *Red Book* for complete management of gonococcal infection occurring in these special circumstances, which often requires the addition of a macrolide antibiotic.

Empiric management of sex partners must be undertaken to prevent reinfection and to stop further transmission. Counseling for the use of barrier protection methods (male latex condom) during all types of sexual contact also should be undertaken to prevent the spread of disease. Current recommendations require evaluation and treatment for both *N gonorrhoeae* and *C trachomatis* infection for all sexual partners of patients within 60 days of onset of symptoms or diagnosis. In patients whose last intercourse was greater than 60 days before the onset of symptoms or diagnosis, the most recent sexual partner should be treated.

When treatment of a sexual partner cannot be ensured or is unlikely, clinicians should consider expedited partner therapy (EPT). In EPT, the practitioner provides the partners of the infected patient with a prescription or medication for treatment of infection without an evaluation or examination. Currently, not all states allow this treatment, and clinicians should check the legal status of EPT in their jurisdictions. (11) Abstinence from sexual contact is recommended until therapy is completed and the signs and symptoms have resolved.

Summary

- Gonococcal infections commonly are asymptomatic, especially in females.
- Clinicians miss opportunities to identify and treat infections because of the lack of symptoms and suboptimal screening, which allow for disease transmission.

Based on strong research evidence:

- The United States Preventative Services Task Force (USPSTF) recommends prophylactic ocular topical medication for all newborns for the prevention of gonococcal ophthalmia neonatorum. (12)
- The USPSTF recommends that clinicians screen all sexually active women, including those who are pregnant, for gonorrhea infection if they are at increased risk for infection (ie, if they are young or have other individual or population risk factors). (13)
- Fluoroquinolones are no longer recommended as treatment of gonococcal infections. (8)
- Oral cephalosporins are no longer recommended as routine treatment of gonococcal infections. (9)

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1. A 16-year-old sexually active boy presents with complaints of pain in both hands. He has a temperature of 39°C and says he has chills. During the physical examination, you suspect disseminated gonococcal infection when you note
   - A. Hemorrhagic lesions on both palms.
   - B. Jaundice.
   - C. Pallor.
   - D. Target lesions.
   - E. Urticaria.

2. An 18-year-old girl presents with purulent vaginal discharge. On pelvic examination, you note erythema, edema, and friability of her cervix. You suspect gonococcal infection and seek to confirm your impression by obtaining a
   - A. Culture of endocervical swab specimens on chocolate agar.
   - B. Culture of urethral swab specimens on Thayer-Martin medium.
   - C. Nucleic acid amplification test of a patient-collected vaginal specimen.
   - D. Nucleic acid amplification test of a provider-collected vaginal specimen.
   - E. Nucleic hybridization testing of a urine specimen.

3. You are seeing a 17-year-old male prostitute for a first visit. You recommend that he be tested for sexually transmitted infection whenever he is symptomatic and at least every
   - A. 3 months.
   - B. 6 months.
   - C. 9 months.
   - D. 12 months.
   - E. 18 months.

4. The patient tests positive for *N gonorrhoeae*. You recommend testing and treatment of all of his sexual partners over the past
   - A. 7 days.
   - B. 14 days.
   - C. 30 days.
   - D. 60 days.
   - E. 90 days.

5. The patient tells you that not all of his contacts will agree to testing in your office. In states that allow it, your BEST course of action is to
   - A. Give the patient information sheets about symptoms of gonorrhea to give to his contacts.
   - B. Have the local health department collect specimens from all contacts.
   - C. Have the patient collect specimens; treat those who are infected.
   - D. Provide prescriptions to treat all contacts without an evaluation.
   - E. Treat all of those who present to your office for testing.

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