

Gonococcal Infections

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Author Disclosure

Dr Holder has disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives After completing this article, readers should be able to:

1. Understand the clinical importance of recognizing and treating gonococcal infections.
2. Describe the different types of infections that are caused by *Neisseria gonorrhoeae*.
3. Differentiate between cervicitis and pelvic inflammatory disease.
4. Discuss treatments for gonococcal infections.

Causes

Neisseria gonorrhoeae is a gram-negative diplococcus that is oxidase-positive and produces beta-lactamase. (1) This quality differentiates it from other species of *Neisseria* because it requires iron for growth and can metabolize only glucose, lactate, and pyruvate. It is nonmotile and does not produce spores. There are at least 70 different strains, characterized by the absence or presence of pili, opacity of colonies, auxotyping (nutritional requirements), serotyping, and genotyping. (2) Only humans have been reported to be infected by *N gonorrhoeae*.

Pathophysiology

Gonococcal infections tend to be associated with the acute onset of symptoms and purulent mucosal drainage due to the organism's ability to recruit polymorphonuclear leukocytes (PMNs). Piliated strains increase adherence and virulence of such organisms by enhancing their attachments to human cells (including sperm). Opacity-associated proteins also affect virulence by enhancing gonococcal adherence to host cells. The organism attacks cuboidal or columnar epithelial surfaces on mucosal cells. Subsequent mucosal damage and invasion lead to an inflammatory response due to PMN recruitment. *N gonorrhoeae* also has an affinity for blood. Hence, transmission may occur from lower genital structures (vagina and cervix) to higher genital structures (endometrium, fallopian tubes, ovaries) and possibly spread into the peritoneal space via refluxed menstrual blood or by attachment to sperm. It is common for female patients who have a gonococcal infection to present during menses with fever due to the inflammatory response.

Epidemiology

Gonococcal infection is the second most common bacterial disease in the United States that is classified as a reportable and notifiable infection. In 2005, the national rate was reported at 115.6 cases per 100,000, and it was estimated that 600,000 new cases would be reported annually. (3) Higher rates of gonococcal infection have been reported in African Americans as well as in rural areas of the southeastern United States. Rates are lower in other industrialized countries such as Sweden. Due to social and biologic factors, the incidence of gonococcal infections is highest in youth, especially females between 15 and 19 years of age, in whom 40% of reported cases occur. (2) In sexually active patients, coinfection with other sexually transmitted organisms (most commonly *Chlamydia trachomatis*) can occur. Recurrent infections from *N gonorrhoeae* increase the risk of tubal scarring and infertility in females. Gonococcal infections occur in neonates as well as in sexually active males and females because transmission can occur during parturition as well as through sexual activity. The incubation period is 2 to 7 days. (1) A child abuse evaluation must be performed in any prepubertal case of gonococcal infection. Due to

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Table 1. **Clinical Manifestations of Gonococcal Infections**

Neonates

- Conjunctivitis
- Scalp abscesses
- Vaginitis
- Bacteremia
- Arthritis
- Meningitis

Males

- Pharyngitis
- Urethritis
- Epididymitis
- Proctitis
- Disseminated gonococcal infection

Females

- Pharyngitis
- Cervicitis
- Pelvic inflammatory disease
- Proctitis
- Perihepatitis
- Menometrorrhagia
- Disseminated gonococcal infection
- Endometritis

different strains and degrees of virulence, some patients are infected with *N gonorrhoeae* but may not develop symptoms; such patients are referred to as asymptomatic carriers.

Burden of Illness (Table 1)

In neonates, *N gonorrhoeae* usually causes conjunctivitis due to mucosal transmission during vaginal delivery. Other types of neonatal infection include scalp abscess (from fetal monitoring during labor), vaginitis, bacteremia, arthritis, and meningitis. Neonatal conjunctivitis can be prevented by applying topical antibiotics (erythromycin, silver nitrate, or tetracycline) to the eyes of a newborn within 1 hour of birth. (1)

In males, *N gonorrhoeae* can cause pharyngitis, urethritis, epididymitis, proctitis, and disseminated gonococcal infection (DGI). DGI is defined as hematogenous spread of *N gonorrhoeae*. Patients may present with dermatitis, arthritis (typically a monoarticular, migratory arthritis), and rarely, meningitis or endocarditis.

In females, *N gonorrhoeae* can cause pharyngitis, cervicitis, pelvic inflammatory disease (PID), proctitis, perihepatitis (Fitz-Hugh-Curtis syndrome), menometror-

rhagia, and DGI. Endometritis can occur during the postpartum period (usually the first 6 weeks).

Pharyngitis

Gonococcal pharyngitis develops after genital-oral activity. Positive pharyngeal cultures for *N gonorrhoeae* have been demonstrated to be as high as 25% in sexually active individuals (range of 3% to 25%, highest in homosexual males), yet this infection is asymptomatic in most cases. Patients who have symptoms develop sore throat, fever, and cervical lymphadenopathy 3 to 7 days after exposure. Patients who have gonococcal pharyngitis have a significant public health impact and are at risk for developing DGI. Patients have been shown to clear pharyngeal infection spontaneously within 12 weeks. (2)

Urethritis

A 16-year-old male presents with a 1-week history of dysuria and penile discharge. He is sexually active (females only) and does not always use condoms. His past medical history is unremarkable. His urine specimen is positive for leukocyte esterase. Intracellular diplococci are noted on microscopic evaluation of his urethral swab.

In most cases of urethritis due to *N gonorrhoeae*, males present with dysuria and a mucopurulent penile discharge. They may be coinfecting with other sexually transmitted organisms, most commonly, *C trachomatis*. Evidence of intracellular diplococci in urethral discharge supports a diagnosis of gonococcal urethritis. (2)

Epididymitis

In addition to dysuria and a mucopurulent discharge, patients who have epididymitis also present with scrotal edema as well as scrotal, inguinal, or flank pain. Urinalysis may demonstrate white blood cells. In most cases, this infection is transmitted sexually and may be an extension of urethritis.

Proctitis

Most cases of proctitis due to *N gonorrhoeae* occur in homosexual males, but proctitis can occur in adult females as well as in children and neonates. Symptoms include anal discharge, rectal bleeding, anorectal pain, tenesmus, and constipation. Patients also should be screened for *Chlamydia*, herpes simplex virus, *Treponema pallidum*, and human immunodeficiency virus. Severe infections (extending beyond the rectum and involving the colon, ie, proctocolitis) usually are due to gram-negative enteric rods.

Disseminated Gonococcal Infection

A 16-year-old female is hospitalized for a “septic” knee. An initial elevated erythrocyte sedimentation rate suggests osteomyelitis. Additional history reveals that she had a similar lesion involving her wrist 2 weeks ago (with what appeared to be spontaneous resolution). In confidence, she discloses that she recently initiated sexual activity, has been monogamous with a male partner, and hence, did not think that they needed to use condoms. Blood cultures do not grow any pathogen. Her pelvic examination results are normal, but her cervical cultures grow *N gonorrhoeae*.

DGI infection occurs in 0.5% to 3% of people infected with *N gonorrhoeae*. (2) Strains associated with DGI usually cause an asymptomatic genital infection. Later, patients present with migratory arthritis, dermatitis, and tenosynovitis. Typically involved joints are the wrist, ankle, and knee. There may be associated findings of fever, chills, and an elevated white blood cell count. DGI occurs more commonly in females. Perhaps alteration in vaginal pH due to hormonal influences and menstrual flow account for this phenomenon. Other patients at risk include people who have complement deficiencies or systemic lupus erythematosus. Unless there is a high degree of suspicion, the diagnosis of DGI may be delayed. Because cultures for this organism are not performed routinely, *N gonorrhoeae* may not be detected in the blood or synovial fluid unless a culture is obtained within the first few days of illness. If DGI is suspected, a urethral or cervical specimen for additional testing may demonstrate the presence of *N gonorrhoeae*.

Menometrorrhagia

An 18-year-old mother of three presents with the acute onset of worsening abdominal pain, nausea, and vomiting. She also has been complaining of prolonged menstrual bleeding for 2 weeks. She has not had fever, loss of appetite, or dysuria. She cannot tell if she has had an abnormal vaginal discharge. Abdominal examination reveals a diffusely tender abdomen with rebound tenderness. She has cervical motion tenderness as well as right-sided adnexal tenderness. Ambulation is very difficult. She has a negative pregnancy test and normal urine study results. She is admitted for administration of intravenous antibiotics, and her symptoms resolve in 24 hours. Cervical specimens are positive for both *N gonorrhoeae* and *C trachomatis*.

The differential diagnosis for prolonged and irregular uterine bleeding is broad and includes hormonal, hematologic, structural, hypothalamic, endocrinologic, and infectious causes. In addition to ruling out pregnancy, the initial assessment should rule out *N gonorrhoeae* infection as the source of prolonged bleeding.

Cervicitis

Cervicitis caused by *N gonorrhoeae* is a sexually transmitted infection. Other organisms that can cause cervicitis include *C trachomatis*, *Trichomonas vaginalis*, *Candida albicans*, and herpes simplex virus. Coinfection may occur with *C trachomatis*. Symptoms of cervicitis include an increased or unusual vaginal discharge, dyspareunia, postcoital spotting, and dysuria. Because many cases of cervicitis are asymptomatic, periodic screening of sexually active females for both *N gonorrhoeae* and *C trachomatis* has been recommended. (4) Sexually active females may be screened every 6 months to 1 year or after intercourse with a new sexual partner. Findings consistent with cervicitis include mucopurulent endocervical discharge and endocervical friability on speculum examination. Bimanual examination yields normal results. Microscopic evaluation of a cervical swab demonstrates 10 or more white blood cells per high-power field. (5)

Pelvic Inflammatory Disease

If cervicitis is not treated, it can progress to an ascending genital tract infection, specifically salpingo-oophoritis or PID. PID refers to inflammation of the upper female genital tract, specifically the endometrium, fallopian tubes, and ovaries, as well as the adjacent peritoneum. As many as 10% to 40% of untreated gonococcal and chlamydial infections result in PID. (6) Other organisms associated with PID include anaerobes, *Gardnerella vaginalis*, *Haemophilus influenzae*, *Streptococcus agalactiae*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and enteric gram-negative rods. (7)

Patients who have PID present with abdominal pain and may disclose a history of sexual intercourse. Patients who have PID due to *N gonorrhoeae* typically present with symptoms during menses. On physical examination, patients have abdominal tenderness (occasionally with rebound tenderness) in addition to adnexal tenderness or cervical motion tenderness. Some patients may have difficulty with ambulation because of the pain. Patients who have this history and these symptoms meet the minimal criteria for the diagnosis of PID (Table 2). Other findings supportive of the diagnosis (but not necessary) include an elevated temperature, elevated white blood cell count, elevated erythrocyte sedimentation rate or C-reactive protein concentration, mucopurulent cervical discharge, and evidence of positive gonococcal or chlamydial infection. PID is diagnosed definitively by endometrial biopsy or laparoscopy. Pelvic ultrasonography may demonstrate fluid in the cul-de-sac, thickened fallopian tubes, or a tubo-ovarian abscess. (8)

Table 2. Diagnostic Criteria for Pelvic Inflammatory Disease

Minimal Findings (3 of 4 Required to Make the Diagnosis)

- Abdominal pain
- Abdominal tenderness
- Cervical motion tenderness OR adnexal tenderness

Supportive Findings (Helpful But Not Necessary)

- Fever
- Elevated white blood cell count
- Mucopurulent cervical discharge
- Elevated erythrocyte sedimentation rate or C-reactive protein concentration
- Positive screen for *N gonorrhoeae* or *C trachomatis*

Definitive Findings

- Endometritis on endometrial biopsy
- Radiographic evidence of thickened fallopian tubes or tubo-ovarian abscess
- Laparoscopic evidence

Patients who have a history suggestive of PID (sexually active female who has lower abdominal pain and tenderness) should undergo a diagnostic evaluation that can eliminate other causes. The differential diagnosis for PID includes gynecologic problems (ovarian cysts, ovarian torsion, ectopic pregnancy, endometriosis, or severe dysmenorrhea), gastrointestinal problems (appendicitis, pancreatitis, hepatitis, severe gastroenteritis, inflammatory bowel disease), urologic problems (urinary tract infection, pyelonephritis), and complications from chronic conditions such as systemic lupus erythematosus, diabetic ketoacidosis, or lymphoma.

The evaluation should include a detailed history as well as abdominal and pelvic examinations. Laboratory studies should include cervical cultures for *N gonorrhoeae* and *C trachomatis* and a wet prep for microscopic examination. Wet prep analysis is necessary to rule out concurrent infection such as candidiasis, bacterial vaginosis, or trichomoniasis. Also indicated are a pregnancy test, urinalysis, complete blood count, and erythrocyte sedimentation rate or C-reactive protein measurement. Clinicians also should consider obtaining a urine culture and pelvic ultrasonography.

If undiagnosed and untreated, PID can lead to additional problems with the female reproductive tract, including a tubo-ovarian abscess, Fitz-Hugh–Curtis syndrome (perihepatitis), chronic abdominal pain, and an

increased risk for ectopic pregnancy. There also is the public health risk of untreated sexually transmitted infections. (7) If mild, PID may be managed in the ambulatory setting with close follow-up. More severe disease necessitates inpatient treatment (Table 3). (8)

Fitz-Hugh–Curtis syndrome, also known as perihepatitis, can occur with either a gonococcal or chlamydial pelvic infection. If untreated, PID or salpingitis may extend onto the perineum and actually track superiorly through the hepatocolic gutter to cause inflammation of the hepatic capsule. Symptoms consist of colicky, right upper quadrant abdominal pain, sometimes with vomiting. Hepatic enzymes as well as ultrasonographic findings of the right upper quadrant often are normal. Treating the pelvic infection leads to resolution of symptoms. Fitz-Hugh–Curtis syndrome should be considered when evaluating a sexually active female who has right upper quadrant abdominal pain.

Screening Methods and Diagnostic Tests

N gonorrhoeae can be detected by several methods. The organism can be isolated in culture media or identified by using nucleic acid techniques. The gold standard for diagnosing a gonococcal infection is growth in chocolate agar or Thayer-Martin agar. (8) However, identification of *N gonorrhoeae* by growth in culture media should be confirmed by using other bacteriologic tests (such as enzyme substrate) because other *Neisseria* species also may grow in chocolate agar. (1)

Nucleic acid probes and nucleic acid amplification tests (NAATs) can be used to detect *N gonorrhoeae*, specifically in specimens from endocervical or urethral sites. NAATs use ligase chain reaction, polymerase

Table 3. Criteria for Inpatient Management of Pelvic Inflammatory Disease (8)

- Inability to tolerate oral medications
- Pregnancy
- Failed outpatient management
- Tubo-ovarian abscess
- Signs and symptoms of severe illness such as fever, nausea, or vomiting; elevated white blood cell count, erythrocyte sedimentation rate, or C-reactive protein values
- Inability to rule out surgical emergency such as appendicitis

Table 4. Treatment Strategies for Gonococcal Infections (8)

Disease	Treatment
Cervicitis, urethritis, proctitis	Ceftriaxone 125 mg IM $\times$ 1 OR Cefixime 400 mg PO $\times$ 1 OR Spectinomycin 2 g IM $\times$ 1 PLUS* #Azithromycin 1 g PO $\times$ 1 OR Doxycycline 100 mg PO twice daily $\times$ 7 d #Erythromycin 500 mg PO 4 $\times$ daily $\times$ 7 d OR #Amoxicillin 500 mg PO thrice daily $\times$ 7 d
Pharyngitis	Ceftriaxone 125 mg IM $\times$ 1 or Spectinomycin 2 g IM $\times$ 1
Conjunctivitis	Ceftriaxone 1 g IM $\times$ 1 PLUS saline lavage
Childhood infection (rule out sexual abuse) Vaginitis, urethritis, pharyngitis, proctitis	Ceftriaxone 125 mg IM $\times$ 1 or Spectinomycin 40 mg/kg (maximum of 2 g) IM $\times$ 1 PLUS* Erythromycin 50 mg/kg per day PO divided into 4 doses daily $\times$ 14 d (<45 kg) Azithromycin 1 g PO $\times$ 1 (>45 kg and <8 y of age) Azithromycin 1 g PO $\times$ 1 OR Doxycycline 100 mg PO twice daily $\times$ 7 d ($\geq$ 8 y of age)
Neonatal infection	Ceftriaxone 25 to 50 mg/kg (maximum of 125 mg) IV or IM as a single dose Hospitalize and monitor for disseminated infection
Epididymitis	Ceftriaxone 250 mg IM $\times$ 1 PLUS* Doxycycline 100 mg twice daily $\times$ 10 d
Pelvic Inflammatory Disease (Outpatient)	Ceftriaxone 250 mg IM $\times$ 1 Cefoxitin 2 g IM PLUS* Doxycycline 100 mg twice daily $\times$ 14 d
Pelvic Inflammatory Disease (Inpatient) (If a tubo-ovarian abscess is suspected, broaden antibiotic coverage to include anaerobes.)	Cefoxitin 2 g IV every 6 h PLUS Doxycycline 100 mg IV or PO twice daily for a total of 14 d OR Clindamycin 900 mg IV every 8 h PLUS Gentamicin 1.5 mg IV every 8 h
IM=intramuscular, IV=intravenous, PO=oral. *Treatment if a coinfection with <i>C trachomatis</i> is suspected or diagnosed. #May be used to treat a suspected or diagnosed coinfection with <i>C trachomatis</i> in pregnant patients. Inpatient treatment of pregnant patients should be with obstetric support and guidance regarding antimicrobial therapy.	

chain reaction, transcription-mediated amplification, or strand displacement assays to identify and amplify DNA. NAATs also may be used to detect *N gonorrhoeae* in urine specimens.

In the absence of culture or NAATs, Gram stains may be performed directly on exudates from several sites, such as the male urethra, synovial fluid, eye discharge, vagina in prepubertal girls, skin lesions, and cerebrospinal fluid. The presence of gram-negative intracellular diplococci on microscopy suggests the diagnosis of a gonococcal infection. (1)

Treatment

Treatment of *N gonorrhoeae* is based on the site and type of infection (Table 4). For those who have infections of the cervix, urethra, pharynx, or conjunctiva, a third-generation cephalosporin can be used as single-dose therapy. In cases of *N gonorrhoeae* in children, the clinician must investigate for possible child abuse.

Infections involving the upper genital tract (epididymitis in males and salpingo-oophoritis or PID in females) can be treated with third-generation cephalosporin single-dose treatment if the patient meets criteria for

outpatient therapy. Spectinomycin may be used as alternative treatment.

Penicillin and fluoroquinolones no longer are acceptable forms of therapy due to antimicrobial resistance. (9) Hence, the treatment of gonococcal infections is limited to the use of third-generation cephalosporins. Spectinomycin also can be used as an alternative. A follow-up screen or “test of cure” is not recommended routinely in patients who have completed treatment and are asymptomatic.

Treatment of a possible coinfection with *C trachomatis* should be considered when treating a gonococcal infection, (10) especially if the infection is diagnosed based on a technique other than NAAT. Given their high sensitivity, if NAATs are used to diagnose a gonococcal infection and *C trachomatis* is not identified specifically, treatment solely for *N gonorrhoeae* is recommended. (8) Because rates of chlamydial infection are significantly greater than rates of gonococcal infection, clinicians who do not have access to screening methods that employ NAATs should treat patients for both *N gonorrhoeae* and *C trachomatis*.

For infections acquired via consensual sexual activity, patients should be advised to be abstinent for at least 1 week after treatment to prevent reinfection. (8) Patients also should be advised to contact their sexual partners and to encourage their treatment. This strategy greatly reduces the public health burden of gonococcal disease. Some states in the United States allow “expedited partner treatment,” whereby the prescribing practitioner can give an advance prescription to patients to assist with treating sexual contacts. (11)

Summary

Based on strong research evidence:

- Gonococcal infections remain a substantial public health problem in the United States (Centers for Disease Control and Prevention, 2005).
- NAATs may be used to screen for *N gonorrhoeae* in most patients (Centers for Disease Control and Prevention, 2006).

- PID is high on the list of differential diagnoses for female patients who have a history of sexual activity and a complaint of lower abdominal pain (Centers for Disease Control and Prevention, 2006).
- Fluoroquinolones should not be offered as a treatment for gonococcal infection (Centers for Disease Control and Prevention, 2007).

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

5. A 16-year-old boy presents with a 2-day history of burning urination and urethral discharge. He recently initiated monogamous sexual activity. Gram stain of the urethral discharge reveals gram-negative diplococci. Which of the following is the *most* appropriate therapy at this time?
 - A. Cefixime plus azithromycin.
 - B. Ciprofloxacin alone.
 - C. Clindamycin plus erythromycin.
 - D. Penicillin V plus doxycycline.
 - E. Trimethoprim-sulfamethoxazole plus amoxicillin.
6. A 16-year-old girl was treated with an appropriate antibiotic for uncomplicated gonococcal cervicitis 1 month ago. She has remained asymptomatic. Of the following, the *most* appropriate course of action at this time is to:
 - A. Obtain polymerase chain reaction test for *N gonorrhoeae*.
 - B. Obtain urethral, cervical, and vaginal cultures to ascertain cure.
 - C. Perform pelvic ultrasonography.
 - D. Repeat antibiotic treatment once a month for 2 more months.
 - E. Undertake no additional testing.
7. A 17-year-old girl presents with fever, vomiting, and diffuse abdominal pain over the last 2 days. Her last menstrual period ended 4 days ago. For the last several hours she has been complaining of intermittent colicky right upper quadrant pain. Physical examination shows an oral temperature of 102.2°F (39°C), heart rate of 110 beats/min, respiratory rate of 24 breaths/min, and blood pressure of 100/55 mm Hg. Diffuse abdominal tenderness is most pronounced in the right upper quadrant. Pelvic examination documents cervical motion tenderness. Laboratory studies show leukocytosis with left shift. Serum transaminases and amylase values are normal. Cervical specimens are positive for both *N gonorrhoeae* and *C trachomatis*. Abdominal ultrasonography shows fluid accumulation in the right and left paracolic gutters. Of the following, the *most* likely diagnosis is:
 - A. Acalculous cholecystitis.
 - B. Fitz-Hugh-Curtis syndrome.
 - C. Liver abscess.
 - D. Ruptured appendix.
 - E. Suppurative pancreatitis.
8. A 17-year-old girl presents with fever, abdominal pain, and vaginal discharge for 2 days. Presence of which of the following features on bimanual pelvic and speculum examination is *most* helpful in determining that gonococcal cervicitis has progressed to pelvic inflammatory disease?
 - A. Cervical motion and adnexal tenderness.
 - B. Cervical specimen positive for both *N gonorrhoeae* and *C trachomatis*.
 - C. Cervical swab showing 10 or more white blood cells per high-power field.
 - D. Endocervical redness and friability.
 - E. Mucopurulent endocervical discharge.