

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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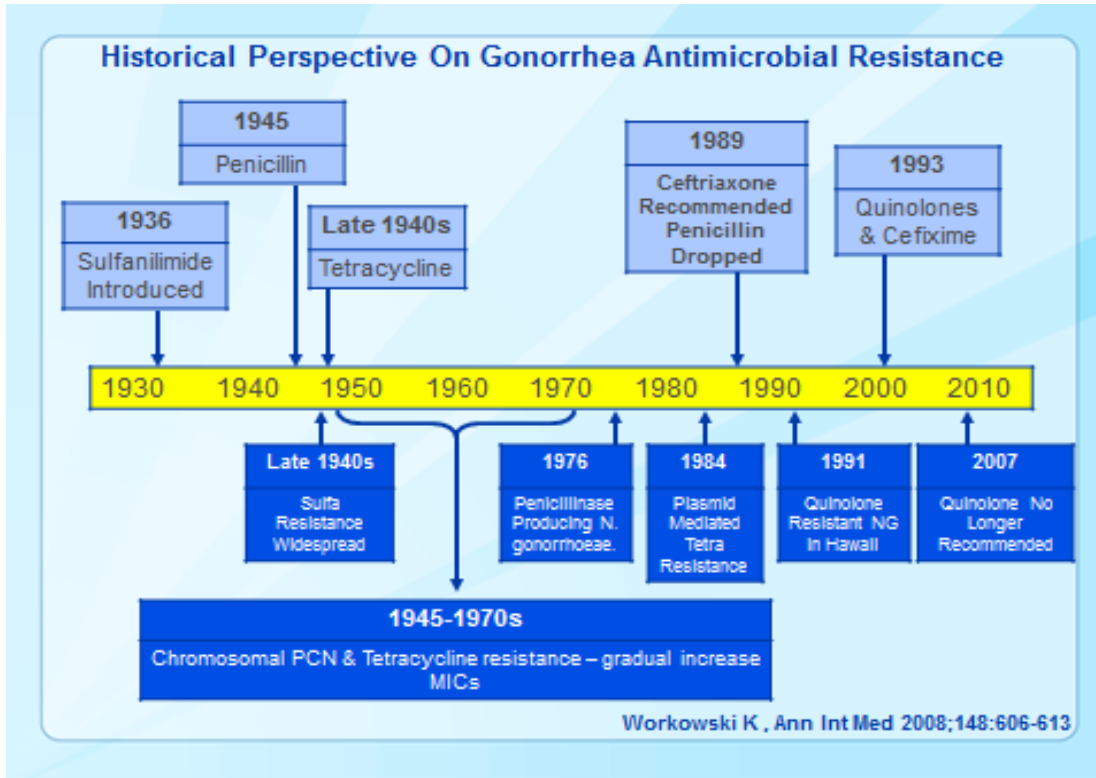
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I. Epidemiology

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. Reported gonorrhea cases have **declined steadily in recent years** – 10% over 2009 and 17% since 2006 – and are now at the lowest level since CDC began tracking the disease in 1941.
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) Age: peak incidence in men 20-24 years, women 15-19 years; >80% of cases occur in men and women between age 15-29 years.
 - c) Sex: since 2002, national gonorrhea rates have been slightly higher in women than in men. In 2010, the gonorrhea rate was 106.5 cases per 100,000 population among women and 64.1 among men.
 - d) Race/ethnicity: During 2009–2010, gonorrhea rates increased 21.5% among American Indians/Alaska Natives (87.0 to 105.7), 13.1% among Asians/Pacific Islanders (13.7 to 15.5), 11.9% among Hispanics (44.6 to 49.9), 9.0% among whites (21.2 to 23.1) and 0.3% among blacks (431.1 to 432.5). In 2012, gonorrhea rates remained highest among blacks (432.5 cases per 100,000 population). The gonorrhea rate among blacks is 18.7 times higher than whites This disparity has changed little in recent years and is larger for black men (22.2 times) than for black women (16.2 times).
5. Gonococcal Isolate Surveillance Project: Antimicrobial resistance remains an important consideration in the treatment of gonorrhea. In 1986, the [Gonococcal Isolate Surveillance Project \(GISP\)](#), a national sentinel surveillance system, was established to monitor trends in antimicrobial susceptibilities of strains of *N. gonorrhoeae* in the United States. Data are collected from selected STD clinics at 25–30 GISP sentinel sites and from 4–5 regional laboratories.



B. Risk factors and risk markers:

1. Multiple or new sex partners or inconsistent condom use.
2. Urban residence (in areas with high disease incidence), age less than 25 years adolescent females at particular risk), lower socio-economic status, use of drugs including alcohol, exchange of sex for drugs or money.

C. Efficiency of Transmission

1. Female-to-male transmission (vagina to male urethra): 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 anal intercourse has not been quantified but also appears to be efficient.
4. Transmission less efficient by fellatio, however transmission from pharynx to

- penis in men who have sex with men who only report being recipients of fellatio appears to be as efficient as unprotected insertive anal sex; transmission thought to be 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.

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 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, often 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: Gram stain 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 FDA cleared 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) should be used for specimens collected from sites that are normally sterile (blood, CSF, joint fluid).
 2. Sensitivity: male urethra 95%; cervix 95%, rectum 70-90% , and pharynx as low as 40% .
 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, rectum-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 assault or abuse in children, 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 2010 CDC STD Treatment Guidelines. (p 93)
- E. In cases of suspected sexual assault or abuse in adults, NAAT is the preferred technology for evaluation of adult/adolescent sexual assault victims See sexual assault or abuse of adults and adolescents section in 2010 CDC STD Treatment Guidelines. (p 90)
- F. If gonorrhea is detected, provide dual antibiotic therapy to treat for gonorrhea and chlamydia 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, 27.2% of isolates collected in 2005 by the Gonococcal Isolate Surveillance Project (GISP) were resistant to penicillin, tetracycline, ciprofloxacin or some combination of those antibiotics.
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. Fluoroquinolone resistance: **The CDC has not recommended quinolone antibiotics for the treatment of gonorrhea since 2007 due to high levels of resistance (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.
 5. Cephalosporin
 - a) Ceftriaxone in a single injection of 250 mg provides sustained, high bactericidal blood levels and is the treatment of choice for uncomplicated gonorrhea at all anatomic sites. Ceftriaxone is the only recommended antibiotic for pharyngeal gonorrhea infection.
 - 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 but these do not offer therapeutic advantage over ceftriaxone.
 - c) Oral alternative regimens if ceftriaxone is not available include cefixime given in a single 400 mg dose. Cefixime has similar cure rates to parenteral cephalosporins for urogenital and anorectal gonorrhea; cefixime is not recommended for treatment of pharyngeal gonorrhea.
 - d) Other oral cephalosporins (cefuroxime, cefpodoxime) are no longer considered alternative regimens.

6. For persons with documented severe penicillin or cephalosporin allergies, A single oral dose of azithromycin 2 grams is effective against uncomplicated gonococcal infections. 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. An intramuscular dose of spectinomycin 2 grams could be a potential alternative, however, spectinomycin is not currently available in the United States.

B. 2012 Gonorrhea Treatment recommendations

UNCOMPLICATED CERVICAL, URETHRAL, OR RECTAL GONORRHEA		
<i>Recommended Dual Antibiotic Regimen</i>		
<i>Antibiotic 1</i>		<i>Antibiotic 2</i>
Ceftriaxone 250 mg IM in a single dose (preferred)	PLUS	Azithromycin 1 g orally in a single dose (preferred) or Doxycycline 100 mg orally twice daily for 7 days
<ul style="list-style-type: none"> • <i>Dual therapy with a cephalosporin plus azithromycin or doxycycline is recommended regardless of the chlamydia test result.</i> 		

PHARYNGEAL GONORRHEA: <i>Recommended Dual Antibiotic Regimen</i>		
<i>Antibiotic 1</i>		<i>Antibiotic 2</i>
Ceftriaxone 250 mg IM in a single dose (preferred)	PLUS	Azithromycin 1 g orally in a single dose (preferred) or Doxycycline 100 mg orally twice daily for 7 days

UNCOMPLICATED CERVICAL, URETHRAL, OR RECTAL GONORRHEA <i>Alternative Regimen</i>		
<i>Antibiotic 1</i>		<i>Antibiotic 2</i>
Cefixime 400 mg orally in a single dose	PLUS	Azithromycin 1 g orally in a single dose (preferred) or Doxycycline 100 mg orally twice daily for 7 days
<ul style="list-style-type: none"> • A test of cure should be performed 1 week after treatment with an alternative regimen 		

UNCOMPLICATED CERVICAL, URETHRAL, OR RECTAL GONORRHEA <i>Alternative Regimen for patients with allergy to cephalosporins or severe penicillin allergy</i>
Azithromycin 2 g orally in a single dose
<ul style="list-style-type: none"> • A test of cure should be performed 1 week after treatment with an alternative regimen

Note- The test of cure should be performed with culture or with a NAAT for *N. gonorrhoeae* if culture is not available. If the NAAT is positive, perform a confirmatory culture. All positive cultures for test of cure should undergo phenotypic antimicrobial susceptibility testing.

C. Management of gonorrhea in pregnancy:

1. Avoid tetracyclines.
2. Recommend dual therapy with cephalosporin plus azithromycin.
3. If woman is penicillin-allergic, or cannot tolerate a cephalosporin, azithromycin 2 g orally in a single dose can be considered for therapy. A test of cure should be performed 1 week after therapy if azithromycin monotherapy is used.
4. Either azithromycin or amoxicillin is recommended for treatment of presumptive or diagnosed *C. trachomatis* infection.

Women diagnosed with gonorrhea during the first trimester should be retested within 3-6 months after treatment, preferably in the 3rd trimester.

- 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 at least a 1 week antibiotic course.

Disseminated Gonorrheal Infection <i>Initial Regimens</i>
<i>Recommended regimen</i> Ceftriaxone 1 g IM or IV every 24 hours
<i>Alternative regimen</i> Cefotaxime 1 g IV every 8 hours Ceftizoxime 1 g IV every 8 hours

Disseminated Gonorrheal Infection <i>Recommended oral regimens after improvement</i>
Cefixime 400 mg orally twice daily Cefixime suspension 500 mg (25 cc) orally twice daily Cefpodoxime 400 mg orally twice daily

Recommended oral regimen after improvement

E. Follow-up:

1. A test of cure is not recommended if treated with the recommended regimen (ceftriaxone plus azithromycin or doxycycline), but clinicians should advise all patients with gonorrhea to be retested approximately 3 months after treatment. If patients do not present for retesting in 3 months, providers should retest 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.
2. Although cephalosporins remain an effective treatment for gonococcal infections, health-care providers should be vigilant for treatment failure and are requested to report its occurrence to state and local health departments. State and local public health departments should promote maintenance of laboratory capability to culture *N. gonorrhoeae* to allow testing of isolates for cephalosporin resistance. They also should develop enhanced surveillance and response protocols for gonorrhea treatment failures and report gonococcal treatment failures to CDC.

VI. Prevention

A. Screening recommendations (testing of asymptomatic individuals): active screening in high-risk populations:

1. Sexually active adolescents, especially if local prevalence is >2%.
2. Persons with new or multiple sex partners.
3. High prevalence geographic areas (especially in the Southern U.S.).
4. Screening during pregnancy depends on age, risk history and local prevalence.
5. MSM should be screened 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. (See 2010 CDC STD Treatment Guidelines p.11 “Persons in Correctional Facilities”)
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 heterosexual patients with gonorrhea whose partners’ treatment cannot be assured or is unlikely, patient delivered partner therapy (PDPT) may be an

option. PDPT is a partner management strategy whereby the patient delivers antibiotic therapy for gonorrhea (either a prescription or medications) directly to the partner. PDPT is not intended as the first-line or optimal partner management strategy. Providers should use their best judgment to determine whether partners will or will not come in for treatment, and to decide whether or not to dispense or prescribe additional medication to the index patient.

Male patients should be instructed to inform their female partner(s) that she should still seek medical care to be evaluated for PID.

Providers should consult with local and state practice regulations regarding PDPT in their jurisdiction. The CDC updates the status of expedited partner therapy and PDPT in the United States on their website at www.cdc.gov/std/ept/legal/default.htm

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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www.cdc.gov/mmwr/preview/mmwrhtml/mm6131a3.htm.

Internet resources

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