Extragenital Manifestations of *Neisseria gonorrhoeae*

Steven E. Spencer, MD, and Margaret C. Bash, MD, MPH

Corresponding author
Margaret C. Bash, MD, MPH
Center for Biologics Evaluation and Research, US Food and Drug Administration, HFM-428, 1401 Rockville Pike, Rockville, MD 20852, USA.
E-mail: margaret.bash@fda.hhs.gov

Current Infectious Disease Reports 2006, **8**:132–138
Current Science Inc. ISSN 1523-3847

Neisseria gonorrhoeae is a common cause of genitourinary sexually transmitted infections. *N. gonorrhoeae* is an obligate human pathogen that has evidence of tissue-specific host interactions and diverse extragenital manifestations of infection both in adult and pediatric populations. The clinical presentation of extragenital gonorrhea, diagnostic methods, treatment and preventive measures are reviewed.

Introduction

Neisseria gonorrhoeae (gonococcus or GC) remains not only the second most common cause of bacterial sexually transmitted infection (STI) in the United States but also the second most common reportable disease of any kind, *Chlamydia trachomatis* being the most common. GC infections mainly present as cervicitis, urethritis, and pelvic inflammatory disease in adolescents and young adults [1]. However, GC also has numerous other presentations both inside and outside of the genitourinary tract in all ages of patients. In this article, we will review non-genitourinary presentations of GC, diagnostic methods, indicated treatments, and preventative measures directed against the gonococcus.

Microbiology

GC is an aerobic, gram negative diplococcus that is nonmotile and non-sporeforming. Gonococci closely resemble the related pathogen *Neisseria meningitidis*, as well as species of nonpathogenic Neisseria. The species lacks a true polysaccharide capsule but produces a polyphosphate that provides a hydrophilic, negatively charged surface, and the cell envelope is similar in basic structure to that of other gram-negative bacteria. GC is frequently seen within phagocytes in gram stains of clinical specimens. When grown under conventional culture conditions, some bacterial colonies appear opaque whereas others are transparent. The opaque colonies represent organisms expressing opacity-associated proteins (Opa) on the outer-membrane [2,3••]. Different Opa proteins increase adherence between gonococci themselves and to a variety of host cells. Certain Opa variants appear to promote invasion of epithelial cells or result in down regulation of immune responses by CEACAM receptors on B and T cells, perhaps accounting for the poor immune response to natural infection [4]. The bacterial pilus and porin are also associated with pathogenesis. Piliated gonococci are better able than nonpilated variants to attach to human mucosal surfaces and tend to be more virulent. Porin has been implicated in invasion and plays a role in serum resistance through binding of complement regulatory proteins and Factor H [5,6•]. Lipo-oligosaccharide is also implicated in pathogenesis [7]. The relationship of each of these cell surface components to disease presentation and host tissue trophism is the focus of ongoing research efforts.

Epidemiology

Humans are the only natural reservoir of infection. In 2004, the Centers for Disease Control and Prevention (CDC) received reports of 330,132 cases of gonorrhea in the United States. The 2004 rate of reported gonorrhea, 113.5 cases per 100,000 population, is the lowest ever reported. Following a substantial decrease in the rates of reported gonorrhea from 1975 (467.7 cases per 100,000 population) to 1997 (120.2 cases per 100,000 population), overall rates appeared to plateau. From 2000 to 2004, rates have gradually decreased, but remain considerably higher than the Healthy People 2010 (HP2010) target of 19 cases per 100,000 population. The reported rates of infection are believed to be underestimates due to two important factors: underreporting of symptomatic cases by health care providers who often treat the disease without laboratory confirmation and under diagnosis of asymptomatic cases [1,8]. The highest rates of GC occur in the Southeastern United States. In the United States, African Americans have more than a fourfold higher inci-

dence than whites and Latinos, and although traditionally thought of as an urban disease, the population-based incidence of gonorrhea is as high in many rural settings in the United States as in urban ones [1,9].

Maternal and Fetal Infection

GC infection in expectant mothers is not uncommon and is easily treated with standard treatment regimens. Although rare, women who acquire GC during pregnancy are at risk of vertically transmitting the infection to the developing fetus [10]. However, chorioamnionitis and septic abortions are fairly common complications of maternal infection, with up to 13% of pregnancies resulting in septic abortion, 23% in preterm delivery and 29% in premature rupture of the membranes [3,11,12]. Early detection and treatment has been shown to avert adverse fetal outcomes [13]. GC infection should be considered in any preterm infant born to a mother with suspected chorioamnionitis. GC can be readily cultured using standard techniques from the blood, urine or cerebrospinal fluid (CSF) although maternal pretreatment with antibiotics may confound these cultures. Postpartum patients may also acquire GC.

Neonatal GC

The most common presentation of GC in the neonate is ophthalmia neonatorum. This condition was described by the ancient Greeks and Romans, who advised washing the eyes of infants [3••]. In the United States, prophylaxis for ophthalmia neonatorum is recommended for all infants, immediately after birth, and is required by law in most states. Conjunctival infection of the newborn can be rapidly destructive and lead to corneal scarring and blindness. After passage through an infected birth canal, there is usually an incubation period of 2 to 5 days (usually 3 days), but cases may arise 2 to 3 weeks after delivery [14]. The disease is usually characterized by copious mucopurulent discharge, although initially the discharge may be scant and watery. Chemosis often occurs and perioribital edema is prominent. In severe cases, corneal ulceration may result, with occasional perforation of the globe and endophthalmitis. The conjunctivitis of GC is usually more rapidly progressive than that of other organisms causing conjunctivitis in the newborn such as *C. trachomatis* or *Haemophilus influenzae*. With quick, appropriate recognition and treatment, most cases have good outcomes with little to no permanent vision changes [15].

Maternal screening and antibiotic prophylaxis of the eyes does not ensure that the newborn may not acquire invasive GC infection [16], and gonococcal colonization of the oropharynx or gastric fluid occurs relatively frequently in exposed infants [17]. Because of this potential failure of prophylaxis in maternal infection, infants born to mothers with known GC infections should be treated with a single parenteral dose of a third-generation cephalosporin [18•]. There is disagreement in the literature as to whether blood and CSF cultures need to be obtained in infants with gonococcal conjunctivitis [3••]. The American Academy of Pediatrics Red Book advocates admission with lumbar puncture [18•]. Gonococcal infections of minor scalp abrasions associated with fetal monitoring are not unusual in infants whose mothers are infected with GC. Necrosis and scalp abscess can occur, as well as disseminated infection. Scalp wounds in neonates should be cultured for gonococci as well as for other likely pathogens [19].

Disseminated disease occurs in less than 1% of infants perinatally exposed to GC; septic arthritis is the most commonly seen manifestation. Clinical findings usually occur in infants from 1 to 4 weeks of age. Signs and symptoms are indistinguishable from those associated with other pathogens causing arthritis in the newborn period but usually include polyarticular involvement. The neonate may or may not appear systemically ill. The most frequently affected joints are the ankles, knees, wrists, and hands [3••,20]. Disseminated GC disease in the neonate is treated with ceftriaxone or cefotaxime for 7 days for arthritis or septicemia or 10 to 14 days for meningitis. Cefotaxime is recommended for infants with hyperbilirubinemia (Table 1).

Disseminated Gonococcal Infection in Adolescents and Adults

Little recent information is available on the occurrence of disseminated gonococcal infection (DGI) in the United States. Studies conducted in the 1970s and 1980s indicate that dissemination occurs in approximately 0.5% to 3% of gonococcal infections, with the majority of DGI (78%–97%) occurring in women. The onset of symptoms of DGI occurs within a week of the start of menses in approximately one half of cases [21].

The pathogenesis of DGI has been associated with both microbial and host factors. DGI has been associated with strains that have similar porin proteins (PI or PorB) identified either serologically or by molecular typing [22–24]. DGI strains are resistant to the bactericidal effects of normal human serum. This characteristic has been attributed at least in part to the binding of complement regulatory proteins by the major outer membrane porin protein of DGI strains [6•,25]. In addition, phase variation in pilin glycosylation, presence of peptidoglycan hydrolase gene *atlA* associated with secretion of DNA and an additional serum resistance locus are associated with strains isolated from patients with DGI [26,27]. The importance of serum resistance in the pathogenesis of DGI is also apparent by the high rate of complement deficiencies among individuals with DGI (up to 13%) [21].

The clinical manifestations of DGI include a characteristic gonococcal arthritis-dermatitis syndrome, suppurative

Table 1. Treatment guidelines for gonococcal infections*

Uncomplicated infections of the cervix, urethra, and rectum	Cefixime 400 mg orally in a single dose†, or
	Ceftriaxone 125 mg IM in a single dose, or
	Ciprofloxacin 500 mg orally in a single dose‡ , or
	Ofloxacin 400 mg orally in a single dose, or
	Levofloxacin 250 mg orally in a single dose‡ plus, if chlamydial infection is not ruled out:
	Azithromycin 1.0 g orally in a single dose, or
	Doxycycline 100 mg orally twice daily for 7 days
	Alternative regimens:
	Spectinomycin 2.0 g in a single IM dose
Disseminated gonococcal infection (DGI)	Recommended initial parenteral regimen:
	Ceftriaxone 1.0 g IM or IV every 24 hours, or
	Cefotaxime 1.0 g IV every 8 hours, or
	Ceftizoxime 1.0 g IV every 8 hours, or
	Ciprofloxacin 400 mg IV every 12 hours‡, or
	Ofloxacin 400 mg IV every 12 hours‡, or
	Levofloxacin 250 mg IV daily‡, or
	Spectinomycin 2.0 g IM every 12 hours
	After 24–48 hours of improvement, may switch to an oral regimen to complete at least 1 week of therapy
	Cefixime 400 mg orally twice daily†, or
	Ciprofloxacin 500 mg orally twice daily‡, or
	Ofloxacin 400 mg orally twice daily‡, or
	Levofloxacin 500 mg orally daily‡
Uncomplicated gonococcal infections of the pharynx	Ceftriaxone 125 mg IM in a single dose, or
	Ciprofloxacin 500 mg orally in a single dose‡ plus, if chlamydial infection is not ruled out:
	Azithromycin 1.0 g orally in a single dose, or
	Doxycycline 100 mg orally twice daily for 7 days
Gonococcal conjunctivitis	Ceftriaxone 1.0 g IM in a single dose. Consider lavage of the infected eye with saline solution once.
Gonococcal meningitis	Ceftriaxone 1–2 g every 12 h for 10–14 days
Gonococcal endocarditis	Ceftriaxone 1–2 g every 12 h for at least 4 weeks
Newborn gonococcal conjunctivitis	Ceftriaxone 25–50 mg/kg, not to exceed 125 mg in a single dose. Consider use of cefotaxime in hyberbilrubenemic patients. Use frequent eye irrigation.
Gonococcal conjunctivitis prophylaxis of newborns, single application	Silver nitrate (1%) aqueous solution
	Erythromycin (0.5%) ophthalmic ointment
	Tetracycline ophthalmic ointment (1%)
DGI or scalp abscesses in newborns	Ceftriaxone 25–50 mg/kg/day IV or IM in a single daily dose for 7 days (10–14 days if meningitis)
	Cefotaxime 25 mg/kg IV or IM every 12 h for 7 days (10–14 days if meningitis)
Prophylactic treatment for infants whose mothers have gonococcal infection	Ceftriaxone 25–50 mg/kg IV or IM, not to exceed 125 mg, in a single dose.

*For children > 45 kg, adult regimens may be used.
†Currently not available due to manufacturing issues.
‡Quinolones should not be used for infections acquired in Asia or the Pacific, including Hawaii, the United Kingdom, California and in other areas with increased prevalence of quinolone resistance or in infections acquired in the United States by men who have sex with men. Use of quinolones is not recommended in children < 45 kg.
IM—intramuscularly; IV—intravenously.
Adapted from Centers for Disease Control and Prevention [51].

arthritis, and rarely, endocarditis, meningitis, or other localized infections. Gonococcal arthritis-dermatitis syndrome often includes high fever, rigors, tenosynovitis, and rash. The joint disease in this form of DGI is usually tenosynovitis rather than actual arthritis. Polyarthralgia is typical and most often involves the wrists, fingers ankles and toes. Skin lesions typically occur on the extremities, but can also be seen on the trunk and rarely the face [28••,29••]. Erythematous macules, papules, or pustules are most common, but petechia and vesicles can occur and erythema nodosum, erythema multiforme, and urticaria have been described in association with DGI [21]. Blood cultures may be positive in up to 50%, but cultures of synovial fluid and skin lesions are typically negative.

Suppurative gonococcal arthritis is usually mono- or pauci-articular most often involving the knee, wrist, ankle or elbow. Osteomyelitis has been reported. Synovial fluid analysis is similar to that seen with other forms of suppurative arthritis with leukocyte counts of 40,000 to 60,000 cells/mL and a predominance of polymorphonuclear cells. Blood cultures are usually negative but synovial fluid culture and gram stain may be positive. In some cases, suppurative arthritis follows a period of illness more consistent with bacteremic DGI as described above, but this history is not typical [21,22].

DGI often occurs in individuals with no genitourinary, rectal or pharyngeal symptoms; however, *N. gonorrhoeae* can be isolated from DGI patients or their partners in 70% to 80% of cases. When DGI is suspected, cultures of mucosal sites should be obtained regardless of symptoms prior to initiation of antibiotic therapy. Hospitalization is indicated when the diagnosis is unclear or compliance is uncertain and for suppurative arthritis. The primary treatment for DGI is ceftriaxone 1 g intravenously per day for adult patients. The initial therapy is generally continued for 24 to 48 hours after clinical improvement at which time change to a fluroquinolone can be considered based on risk factors for resistance and availability of sensitivity data. The recommended duration of therapy is seven days.

Gonococcal endocarditis, though common in the pre-antibiotic era, is rare and occurs in 1% to 2% of patients with DGI [30]. Vegetations are found on echocardiography in 90%, and the aortic valve is the most common site of infection. Most individuals do not have a history of previous valvular heart disease. Valvular abscesses are common, surgery is required in over half of patients and the mortality rate is exceptionally high, 19% in one series [30–32].

Pharyngeal and Rectal Gonorrhea

The US STI surveillance data for gonorrhea reports site of infection only in enhanced surveillance projects tracing STIs in men who have sex with men (MSM).

In 2004, the MSM Prevalence Monitoring Project identified that 80% (range: 57%–95%) of MSM were tested for urethral gonorrhea, 34% (range: 3%–65%) were tested for rectal gonorrhea, and 50% (range: 5%–92%) were tested for pharyngeal gonorrhea. The median clinic urethral gonorrhea positivity in MSM was 11% (range: 7%–13%), median rectal gonorrhea positivity was 8% (range: 3%–19%), and median pharyngeal gonorrhea positivity was 5% (range: 3%–14%) [1]. Rectal GC in MSM is considered indicative of unprotected receptive anal intercourse and is a marker of risk for transmission of other STDs, including HIV, however, McMillan et al. [33] reported acquisition of rectal GC in 20% of MSM via an alternative exposure. Oropharyngeal and rectal GC infections occur in women and heterosexual men, but current surveillance data regarding rates are not available for the United States.

Currently, only culture is recommended for diagnosis of rectal or pharyngeal gonorrhea though the use of nucleic acid amplification tests may provide increased sensitivity for detection of *N. gonorrhoeae* from these sites [34–36]. The high rate of *N. meningitidis* and commensal *Neisseria* species, especially in the oropharynx, may result in lower specificity [37] when nucleic acid amplification tests are used due to the genetic similarities among pathogenic and nonpathogenic species.

Treatment recommendations for pharyngeal and rectal gonorrhea are similar to those for urogenital gonorrhea except that spectinomycin is not sufficiently effective for pharyngeal infections and is not recommended as an alternative therapy for infections at this site unless followed by a test of cure [38]. Manavi et al. [39•] recently reported treatment failures following treatment of oropharyngeal gonorrhea with single dose ciprofloxacin 500 mg (11%) or amoxacillin 3 g plus probenecid 1 g (29%). Although higher resistance patterns were seen in strains isolated from the pharynx, all individuals who failed treatment were infected with a strain that was sensitive to the initial treatment regimen administered. These data suggest that a test of cure may be indicated for oropharyngeal infections treated with single-dose quinolone therapy or consideration should be given to the use of ceftriaxone as primary treatment. In the United States, fluroquinolones are no longer recommended as first line therapy for gonorrhea in MSM [38]. As with infections acquired in areas of high quinolone resistance such as Asia, Pacific Islands, the United Kingdom, Hawaii, California, and other selected parts of the United States, Ceftriaxone 125 mg intramuscularly is recommended for all uncomplicated gonococcal infections in MSM. Updated treatment recommendations are available at http://www.cdc.gov/std/gisp.

Diagnostics

Isolation of *N. gonorrhoeae* in culture remains the standard for diagnosis of gonococcal infections. Nonculture DNA based tests have become widely used in recent years however none of these are approved for the diagnosis

of GC outside of the genitourinary tract. Serologic tests are of limited clinical utility because of low sensitivity. Because gonococci die quickly when dried, inoculating clinical specimens onto appropriate media as soon as possible is important. Transport bottles that contain medium and a CO_2-enriched atmosphere are preferred if processing of the specimen is delayed. Selective media, such as modified Thayer-Martin which contains antibiotics to suppress normal flora, is required for cultures of vaginal, rectal, and pharyngeal specimens to prevent overgrowth of the GC by commensal bacteria. Selective or nonselective media (chocolate agar) can be used for CSF, blood, eye, and skin cultures [3••]. For medico-legal purposes, culture is currently the only acceptable method of isolation in a suspected abuse case, even if the GC is found as a urogenital infection. However, studies are ongoing to determine if other diagnostic modalities may eventually be substituted for diagnosis of urogeneital GC in suspected abuse [40].

Infection Control and Prevention

Gonorrhea infection is a reportable disease in all states in the United States, which in turn report the cases to the CDC. Sexual contacts (in the last 60 days) of infected persons need to be identified and treated to prevent complications and further spread of the disease. All infected individuals and their contacts should be counseled on the preventive measures such as the use of condoms. Notably in the United States, gonorrhea has been the STI most frequently recognized in sexually abused children [3••]. Any GC infection in a pre-adolescent child should immediately be investigated for abuse. All children with gonococcal infection from abuse should be evaluated for other STIs, including *C. trachomatis*, syphilis, hepatitis B virus, and HIV [3••].

Multiple studies have shown male condoms to be highly effective in decreasing the transmission of GC, with an expert panel from the National Institutes of Health suggesting a 49% to 75% risk reduction [41]. The development of a vaccine against gonorrhea has been slowed by a limited understanding of what formulates protective immunity. The fact that GC has multiple strains and also has and the potential to cause some immunosuppression may result in a weak GC-specific immune response. Antibodies to GC in convalescing patients have not demonstrated protective immunity [42,43].

Multi-strain variability will need to be considered in vaccine development to ensure that the proteins selected will afford protection against multiple GC strains. Current strategies target various gonococcal antigens, such as porin proteins, pilus proteins, opacity proteins, membrane lipooligosaccharide, and iron-regulated proteins. No vaccine candidates are currently in clinical trials, although Sanofi-Pasteur has identified gonococcal vaccines as a target for long-term vaccine development [44•]. A human male urethral gonococcal challenge model has been developed and used to examine protection against mucosal infection. However, this model is not useful in assessing upper genital tract infection [45]. A mouse model of female genital tract GC infection has been developed, and studies are ongoing to better understand the immune response to both GC infection and immunization [46,47].

Recent evidence has indicated that vaginal spermicides containing nonoxynol-9 (N-9) are not effective in preventing cervical gonorrhea, chlamydia, or HIV infection. Frequent use of spermicides containing N-9 has resulted in genital lesions, which may be associated with an increased risk of HIV transmission [48]. The vaginal contraceptive sponge appears to protect against cervical gonorrhea, but its use increases the risk for candidiasis. Diaphragm use has also been demonstrated to protect against cervical gonorrhea. However, both diaphragms and spermicides have been associated with an increased risk of bacterial urinary tract infection in women [49]. In recent years, vaginal microbicides have become attractive as a preventative barrier to STIs. Topical microbicides are chemical barriers that are used vaginally or rectally to prevent transmission of STIs. Several promising microbicides are in various stages of phase I to phase III human trials for the prevention of HIV. These products have also been shown to effectively inhibit GC both in vitro and in vivo and further study may determine if they are effective in preventing GC transmission in humans [50].

Conclusions

Extragenital manifestations of GC infection remain an important presentation of this STI. Systemic disease is seen less frequently than in previous decades, but it is not clear if the decrease has been greater than or proportional to the overall decrease in GC infections. Although the overall rates of disease in the United States have gradually declined in recent years, rates in some populations at risk, such as MSM and women have increased. The risk-group specific increases in extragenital manifestations of gonorrhea, especially in the setting of increasing antibiotic resistance in *N. gonorrhoeae*, are of concern. The observed increases may portend a similar increase for GC in general. Therefore, clinicians will need to include nongenital, GC-related manifestations in their differential diagnostic armamentarium when caring for sexually active adolescents and adults. Familiarity with the full spectrum of GC is important.

Disclaimer

The opinions and assertions contained herein are those of the authors alone and do not reflect the views of the United States Army, the Uniformed Services University of the Health Sciences, or the Food and Drug Administration.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Centers for Disease Control and Prevention: *Sexually Transmitted Disease Surveillance, 2003.* Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention; 2004.
2. Sparling PF, Handsfield HH: **Neisseria gonorrhoeae.** In *Principles and Practice of Infectious Diseases, edn 5.* Edited by Mandell GL, Bennett JE. Philadelphia: Churchill Livingstone; 2000:2242–2258.

3.•• Woods CR: **Gonococcal infections in neonates and young children.** *Semin Pediatr Infect Dis* 2005, **16:**258–270.
An excellent comprehensive review of GC in children, as well as of overall epidemiology, diagnostics, and treatment.

4. Boulton IC, Gray-Owen SD: **Neisserial binding to CEACAM1 arrests the activation and proliferation of CD4+ T lymphocytes.** *Nat Immunol* 2002, **3:**229–236.
5. Gorby GL, Ehrhardt AF, Apicella MA, Elkins C: **Invasion of human fallopian tube epithelium by Escherichia coli expressing combinations of a gonococcal porin, opacity-associated protein, and chimeric lipo-oligosaccharide.** *J Infect Dis* 2001, **184:**460–472.

6.• Ngampasutadol J, Ram S, Blom AM, et al.: **Human C4b-binding protein selectively interacts with Neisseria gonorrhoeae and results in species-specific infection.** *Proc Natl Acad Sci U S A* 2005, **102:**17142–17147.
Important report regarding pathogenesis of and protection from neisserial infections.

7. Edwards JL, Apicella MA: **The role of lipooligosaccharide in Neisseria gonorrhoeae pathogenesis of cervical epithelia: lipid A serves as a C3 acceptor molecule.** *Cell Microbiol* 2002, **4:**585–598.
8. American Social Health Association: *Sexually transmitted diseases in America: How many cases and at what cost?* Research Triangle Park, NC: American Social Health Association; 1998.
9. Thomas JC, Schoenbach VJ, Weiner DH, et al.: **Rural gonorrhea in the southeastern United States: a neglected epidemic?** *Am J Epidemiol* 1996, **143:**269–277.
10. Oppenheimer EH, Winn KJ: **Fetal gonorrhea with deep tissue infection occurring in utero.** *Pediatrics* 1982, **69:**74–76.
11. Pantanowitz L, Hodkinson J, Zeelie R, Jones N: **Gonococcal endocarditis after a threatened abortion. A case report.** *J Reprod Med* 1998, **43:**1043–1045.
12. Nickerson CW: **Gonorrhea amnionitis.** *Obstet Gynecol* 1973, **42:**815–817.
13. Stoll BJ, Kanto WP Jr, Glass RI, Pushkin J: **Treated maternal gonorrhea without adverse effect on outcome of pregnancy.** *South Med J* 1982, **75:**1236–1238.
14. Friendly DS: **Gonorrheal ophthalmia.** *Trans Am Acad Ophthalmol Otolaryngol* 1970, **74:**975–983.
15. Gutman LT: **Gonococcal infections.** In *Infectious Diseases of the Fetus and Newborn Infant,* edn 5. Edited by Remington JS, Klein JO. Philadelphia: W.B. Saunders Co.; 2001:1199–1215.
16. Babl FE, Ram S, Barnett ED, et al.: **Neonatal gonococcal arthritis after negative prenatal screening and despite conjunctival prophylaxis.** *Pediatr Infect Dis J* 2000, **19:**346–349.
17. Woods C: **Gonorrhea.** In *Textbook of Pediatric Infectious Diseases,* edn 5. Edited by Feigin RD, Cherry CJ. Philadelphia: W.B. Saunders, Co.; 2003:1280–1304.

18.• Committee on Infectious Diseases, American Academy of Pediatrics: **Gonococcal infections.** In *Red Book: 2003 Report of the Committee on Infectious Diseases,* edn 26. Edited by Pickering LK, Baker CJ, Overturf GD, Prober CG. Elk Grove Village, IL: American Academy of Pediatrics; 2003:285–291.
AAP recommendations on infectious disease reflecting the composite summary of consensus opinions of the members of the AAP Committee on Infectious Diseases.

19. Varady E, Nsanze H, Slattery T: **Gonococcal scalp abscess in a neonate delivered by caesarean section.** *Sex Transm Infect* 1998, **74:**451.
20. Glaser S, Boxerbaum B, Kennell JH: **Gonococcal arthritis in the newborn. Report of a case and review of the literature.** *Am J Dis Child* 1966, **112:**185–188.
21. Rice PA: **Gonococcal arthritis (disseminated gonococcal infection).** *Infect Dis Clin North Am* 2005, **19:**853–861.
22. O'Brien JP, Goldenberg DL, Rice PA: **Disseminated gonococcal infection: a prospective analysis of 49 patients and a review of pathophysiology and immune mechanisms.** *Medicine (Baltimore)* 1983, **62:**395–406.
23. Brunham RC, Plummer F, Slaney L, et al.: **Correlation of auxotype and protein I type with expression of disease due to Neisseria gonorrhoeae.** *J Infect Dis* 1985, **152:**339–343.
24. Bash MC, Zhu P, Gulati S, et al.: **por Variable-region typing by DNA probe hybridization is broadly applicable to epidemiologic studies of Neisseria gonorrhoeae.** *J Clin Microbiol* 2005, **43:**1522–1530.
25. Ram S, Mackinnon FG, Gulati S, et al.: **The contrasting mechanisms of serum resistance of Neisseria gonorrhoeae and group B Neisseria meningitidis.** *Mol Immunol* 1999, **36:**915–928.
26. Ghosh SK, Zhao J, Philogene MC, et al.: **Pathogenic consequences of Neisseria gonorrhoeae pilin glycan variation.** *Microbes Infect* 2004, **6:**693–701.
27. Dillard JP, Seifert HS: **A variable genetic island specific for Neisseria gonorrhoeae is involved in providing DNA for natural transformation and is found more often in disseminated infection isolates.** *Mol Microbiol* 2001, **41:**263–277.

28.•• Mehrany K, Kist JM, O'Connor WJ, DiCaudo DJ: **Disseminated gonococcemia.** *Int J Dermatol* 2003, **42:**208–209.
Wonderful photographs.

29.•• Russ S, Wrenn K: **Images in clinical medicine. Disseminated gonococcal infection.** *N Engl J Med* 2005, **352:**e15.
Wonderful photographs.

30. Shetty A, Ribeiro D, Evans A, Linnane S: **Gonococcal endocarditis: a rare complication of a common disease.** *J Clin Pathol* 2004, **57:**780–781.
31. Jackman JD Jr, Glamann DB: **Gonococcal endocarditis: twenty-five year experience.** *Am J Med Sci* 1991, **301:**221–230.
32. Sobel JL, Maisel AS, Tarazi R, Blanchard DG: **Gonococcal endocarditis: assessment by transesophageal echocardiography.** *J Am Soc Echocardiogr* 1997, **10:**367–370.
33. McMillan A, Young H, Moyes A: **Rectal gonorrhoea in homosexual men: source of infection.** *Int J STD AIDS* 2000, **11:**284–287.
34. Whiley DM, Buda PP, Freeman K, et al.: **A real-time PCR assay for the detection of Neisseria gonorrhoeae in genital and extragenital specimens.** *Diagn Microbiol Infect Dis* 2005, **52:**1–5.
35. Young H, Manavi K, McMillan A: **Evaluation of ligase chain reaction for the non-cultural detection of rectal and pharyngeal gonorrhoea in men who have sex with men.** *Sex Transm Infect* 2003, **79:**484–486.
36. Gaydos CA: **Nucleic acid amplification tests for gonorrhea and chlamydia: practice and applications.** *Infect Dis Clin North Am* 2005, **19:**367–386, ix.

37. Palmer HM, Mallinson H, Wood RL, Herring AJ: **Evaluation of the specificities of five DNA amplification methods for the detection of Neisseria gonorrhoeae.** *J Clin Microbiol* 2003, **41:**835–837.

38. **Increases in fluoroquinolone-resistant Neisseria gonorrhoeae among men who have sex with men—United States, 2003, and revised recommendations for gonorrhea treatment, 2004.** *MMWR Morb Mortal Wkly Rep* 2004, **53:**335–338.

39.• Manavi K, Young H, McMillan A: **The outcome of oropharyngeal gonorrhoea treatment with different regimens.** *Int J STD AIDS* 2005, **16:**68–70.

Concise study showing poor response to single-dose oral ciprofloxacin for pharyngeal gonorrhea.

40. Palusci VJ, Reeves MJ: **Testing for genital gonorrhea infections in prepubertal girls with suspected sexual abuse.** *Pediatr Infect Dis J* 2003, **22:**618–623.

41. National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services: *Scientific evidence on condom effectiveness for sexually transmitted disease prevention. 2000.* Bethesda, MD: National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services; 2001.

42. Zenilman JM, Deal CD: **Gonorrhea: epidemiology, control and prevention.** In *Sexually Transmitted Disease: Vaccines, Prevention and Control.* Edited by Stanberry LR, Bernstein BD. San Diego: Academic Press; 2000:369–386.

43. Price GA, Hobbs MM, Cornelissen CN: **Immunogenicity of gonococcal transferrin binding proteins during natural infections.** *Infect Immun* 2004, **72:**277–283.

44.• Stanberry LR, Rosenthal SL: **Progress in vaccines for sexually transmitted diseases.** *Infect Dis Clin North Am* 2005, **19:**477–490.

A comprehensive review of the progress of candidate vaccines against various STIs.

45. Schmidt KA, Schneider H, Lindstrom JA, et al.: **Experimental gonococcal urethritis and reinfection with homologous gonococci in male volunteers.** *Sex Transm Dis* 2001, **28:**555–564.

46. Jerse AE: **Experimental gonococcal genital tract infection and opacity protein expression in estradiol-treated mice.** *Infect Immun* 1999, **67:**5699–5708.

47. Plante M, Jerse A, Hamel J, et al.: **Intranasal immunization with gonococcal outer membrane preparations reduces the duration of vaginal colonization of mice by Neisseria gonorrhoeae.** *J Infect Dis* 2000, **182:**848–855.

48. Roddy RE, Cordero M, Cordero C, Fortney JA: **A dosing study of nonoxynol-9 and genital irritation.** *Int J STD AIDS* 1993, **4:**165–170.

49. Hooton TM, Scholes D, Hughes JP, et al.: **A prospective study of risk factors for symptomatic urinary tract infection in young women.** *N Engl J Med* 1996, **335:**468–74.

50. Spencer SE, Valentin-Bon IE, Whaley K, Jerse AE: **Inhibition of Neisseria gonorrhoeae genital tract infection by leading-candidate topical microbicides in a mouse model.** *J Infect Dis* 2004, **189:**410–419.

51. Centers for Disease Control and Prevention: **Sexually transmitted diseases treatment guidelines 2002.** *MMWR Recomm Rep* 2002, **51(RR-6):**1–78. Available at http://www.cdc.gov/STD/treatment/.