CHAPTER 42

Gonococcal and Chlamydial Genital Infections and Pelvic Inflammatory Disease

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Infections caused by *Neisseria gonorrhoeae* and *Chlamydia trachomatis* are the most common of the bacterial sexually transmitted infections (STIs). Since 1995, genital chlamydial infections have been the most frequently reported bacterial infection in the United States; for gonorrhea, continued emergence of antimicrobial resistance remains a major threat. This chapter reviews the global epidemiology of these two pathogens, their associated clinical syndromes, and current guidelines for their management.

EPIDEMIOLOGY

While the annual incidence of gonococcal infections in the United States declined from the early 1980s to an all-time low in 2009, the rate began to creep up, and by 2013 it was 106.1 cases per 100,000. Notably, rates in men exceeded those in women for the first time in 2013, possibly representing either increased ascertainment or actual higher incidence among men who have sex with men. The highest reported rates of gonorrhea were in women 15-19 years of age and in men 20-24 years of age, with marked differences by race (higher in blacks). While gonorrhea typically infects the cervix or urethra, both rectal and pharyngeal infections occur and are an important reservoir of asymptomatic infection, which helps to promote sexual transmission.

An estimated 2 million new chlamydial infections occur annually in the United States, and 3 million in Europe. In contrast to gonorrhea, these infections are more widely geographically distributed, and peak in even younger age groups—at least in women, as the epidemiology in men has not been well defined. Biological and social factors (namely, cervical ectopy and choice of sex partners) likely play a role in placing adolescent females at highest risk for chlamydial infection. The incidence of this disease has declined dramatically in some areas, probably in response to widespread screening programs begun in the 1980s. However, these trends may be undergoing a reversal. Chlamydia prevalence also remains high in many areas of the country in which screening has not become routine, approaching or exceeding 15-25% in some adolescent populations.

The prevalence of gonorrhea and chlamydia infections, as well as other STIs, is higher in developing countries than in the United States, although surveillance data from many areas are not comprehensive. The impact of both of these diseases goes beyond the obvious clinical and economic concerns and their well-recognized sequelae for women (which include ectopic pregnancy, tubal infertility, and chronic pelvic pain). Both gonorrhea and chlamydia potentiate infectiousness for and susceptibility to HIV. Urethral infection with *N. gonorrhoeae* is associated with an eight-fold increase in the amount of HIV in semen. In a prospective study of commercial sex workers in Kenya, acquisition of cervical chlamydial infection was associated with a 2.5-fold increase in the likelihood of acquiring HIV. Thus, these infections further fuel the HIV epidemic throughout Africa, Asia, and Latin America, along with other factors such as migration of refugees, population shifts from rural to urban

environments, and persistence of commercial sex and illicit drug use. The spread of HIV in developing countries is discussed in more detail in Chapter 14.

URETHRITIS

Urethritis is the most common STI-related syndrome in males throughout the world, with *N. gonorrhoeae* most commonly associated with the prototypical purulent discharge characterizing this syndrome. However, in the United States, most urethritis is nongonococcal in origin (NGU); of all NGU, 30% is caused by *C. trachomatis*, and the remainder by a variety of etiologic agents including *Mycoplasma genitalium*, *Trichomonas vaginalis*, herpes simplex virus (HSV), and adenovirus. The role of *Ureaplasma urealyticum* in causing urethritis is still unclear (see below).

The situation in many parts of the developing world is strikingly different, with *N. gonorrhoeae* accounting for up to 80% of all urethritis. The reasons for this disparity are poorly understood; inability to accurately diagnose other causes of urethritis may be partly responsible. Many studies reported from developing countries to date have utilized sub-optimal methodologies for the detection of *C. trachomatis* and have probably underestimated its true contribution. The availability of nucleic acid amplified assays (NAATs) for both gonorrhea and chlamydia (discussed below) should continue to clarify their etiologic contributions. Finally, since NGU is usually a milder disease than gonococcal urethritis, differences in the threshold for medical evaluation may exist, particularly in countries where the availability of medical care is compromised.

Most men infected with *N. gonorrhoeae* at the urethra experience purulent or mucopurulent penile discharge and dysuria, although symptomatic status is likely influenced by the duration of infection and specific strain type. Complications include epididymitis and urethral strictures; although these are rare, they are more common in developing countries. Examination of Gram-stained smears of urethral secretions reveals the Gram-negative, kidney-shaped intracellular diplococci in 98% of cases and is 99% specific for the diagnosis. NAATs, including polymerase chain reaction and transcription mediated assay, offer some increase in sensitivity (5-8%) over culture, while maintaining specificity. Perhaps most importantly, NAATs can be performed on first-catch urine (not "clean-catch" or midstream urine), obviating the need for urethral swab collection. However, gonococcal cultures should be obtained in cases of treatment failure or if there is any suspicion of antimicrobial resistance, as NAATs do not currently provide a means for antibiotic susceptibility testing.

Until recently, *C. trachomatis* caused ~30-40% of cases of NGU, particularly in heterosexual men; however, the proportion of cases due to this organism has probably declined in some populations served by effective chlamydial-control programs, and older men with urethritis appear less likely to have chlamydial infection. HSV and *T. vaginalis* each cause a small proportion of NGU cases in the United States. Recently, multiple studies have consistently implicated *M. genitalium* as a probable cause of many *Chlamydia*-negative cases. Fewer studies than in the past have implicated *Ureaplasma*; the ureaplasmas have been differentiated into *U. urealyticum* and *U. parvum*, and a few studies suggest that *U. urealyticum*—but not *U. parvum*—is associated with NGU. Coliform bacteria can cause urethritis in men who practice insertive anal intercourse. The initial diagnosis of urethritis in men currently includes specific tests only for *N. gonorrhoeae* and *C. trachomatis*; it does not yet include testing for *Mycoplasma* or *Urealyticum* species.

Diagnostic testing is required to distinguish the etiology of urethritis, and both gonorrhea and chlamydia should be specifically sought if possible. The finding of significant numbers of polymorphonuclear leukocytes (PMNs) (more than two per high power field) *without* Gram-negative intracellular diplococci is sufficient to make a presumptive diagnosis of NGU. *N. gonorrhoeae* can be easily cultured on chocolate agar; culture for *C. trachomatis*, in contrast, is not widely available due to its technical demand. NAATs are the recommended assay for chlamydia and gonorrhea. The preferred specimen for evaluation of urethritis in men is first-catch urine.

In women, *C. trachomatis* may directly infect the urethra, inducing dysuria that may simulate bacterial cystitis. This presentation is generally characterized by the presence of PMNs but not bacteria in the urine, and is often accompanied by a history of a new sex partner. Up to 50% of these women are also infected at the cervix, and all should have diagnostic cervical testing done; while the urethra can be cultured, NAATs performed on urine are particularly advantageous in this situation.

CERVICITIS

Cervical gonococcal infections are usually asymptomatic. When symptoms are present, they include vaginal discharge, intermenstrual bleeding, dyspareunia, and/or abdominal pain. Similarly, only 10% of infected cervices will evidence signs, which include mucopurulent endocervical discharge, easily induced endocervical bleeding, and cervical edema. Up to 50% of women with gonococcal cervicitis may also have gonococcal urethritis with associated dysuria, but even more will have concomitant asymptomatic colonization of the urethra. Reports of disseminated gonococcal infection (DGI) to sites such as the skin and joints (causing rash and arthritis) in the United States have declined, but isolated tenosynovitis or acute arthritis is not uncommon as a manifestation of sexually acquired gonorrhea. In developing countries, the epidemiology of DGI is less well characterized. DGI occurs more commonly in women.

Gonococcal infection of the cervix should be diagnosed by NAAT, preferably obtained with a vaginal swab or, alternatively, endocervical swab. Urine NAAT testing is sensitive for the detection of cervical infection because it not only detects concomitant gonococcal urethral infection, which occurs frequently, but also tests cervicovaginal secretions that have collected in the vulvar area. Obtaining rectal and pharyngeal specimens may increase the yield of case detection, particularly if receptive oral or anal intercourse is reported. Gram stain of endocervical discharge suggests the diagnosis of gonorrhea if intracellular Gram-negative diplococci are seen, but this occurs in only 50% of cases, making the test too insensitive to use as the sole means of diagnosis. In cases of suspected DGI, NAATs of the genital tract should be done, as well as blood and joint aspirate cultures.

Like gonorrhea, chlamydial infections in women are usually asymptomatic (90%). Because the symptoms of cervicitis are nonspecific, if at all present, chlamydial cervical infection may present like gonococcal infection. Similarly, signs occur in the minority of patients (10%) and include induced endocervical bleeding, mucopurulent endocervical discharge, and edematous ectopy. Certainly, any of these should provoke diagnostic testing with NAAT. Given the high prevalence of chlamydia in many settings, particularly in adolescent females, routine testing of young women at any presentation for STI evaluation is recommended. This is especially critical because asymptomatic untreated chlamydial infections are capable of causing tubal scarring, which can lead to infertility, ectopic pregnancy, and chronic pelvic pain.

PELVIC INFLAMMATORY DISEASE

N. gonorrhoeae and *C. trachomatis* are the causal STIs implicated most often in pelvic inflammatory disease (PID), but in recent years the role of anaerobes, Gram-negative rods, and *M. genitalium* has been stressed, emphasizing that PID is usually a polymicrobial process. Serious consequences of PID include infertility, ectopic pregnancy, tubo-ovarian abscess, chronic pelvic pain, and pelvic adhesions.

Although clinical criteria for diagnosis of PID are inexact, the diagnosis should be suspected if cervical motion, adnexal, or lower abdominal tenderness are present on bimanual pelvic exam. Women evidencing any of these signs should be tested for gonorrhea and chlamydia, and pregnancy should be ruled out. Treatment of women with presumptive PID requires broad-spectrum coverage that includes activity against *N. gonorrhoeae* and *C. trachomatis*. A complete discussion of the diagnosis and treatment of PID is beyond the scope of this chapter; however, up-to-date reviews are referenced below (see also **Table 42.1**).

TABLE 42.1 Recommendations for Treatment of Pelvic Inflammatory Disease, 2015

Intramuscular/Oral Therapy
Ceftriaxone 250 mg i.m. once
or
Cefoxitin 2 g i.m. plus probenecid 1 g orally concurrently as a single dose
or
Other third-generation parenteral cephalosporin (ceftizoxime, cefotaxime)
plus
Doxycycline 100 mg orally twice daily ×14 days
with or without
Metronidazole 500 mg orally twice daily ×7 days
Parenteral Therapy
Recommended:
Cefotetan 2 g i.v. every 12 h
or
Cefoxitin 2 g i.v. every 6 h
or
Clindamycin 900 mg i.v. every 8 h
plus
Gentamicin loading dose i.v. or i.m. (2 mg/kg), followed by maintenance dose 1.5 mg/kg every 8 h. Single daily dosing (3-5 mg/kg) can be substituted
Alternative:
Ampicillin/Sulbactam 3 g i.v. every 6 h
plus
Doxycycline 100 mg orally or i.v. every 12 h

i.m., Intramuscular; *i.v.*, intravenous.

TREATMENT OF GONORRHEA AND CHLAMYDIA

Resistant strains of *N. gonorrhoeae* originally appeared in the United States as imported infections in servicemen returning from Southeast Asia in the mid-1970s. In 1994, approximately 16% of all gonococci in the United States were resistant to penicillin on the basis of either plasmid-mediated or chromosomal resistance; they are designated penicillinase-producing *N. gonorrhoeae* (PPNG). In some urban areas, the proportion of gonococcal isolates that are PPNG may approach 60-75%. Strains of gonococci that have also acquired plasmid-mediated tetracycline resistance are designated tetracycline-resistant *N. gonorrhoeae* (TRNG) and constituted 22% of isolates in 1994. Some multidrug-resistant strains are both PPNG and TRNG. Another 10-15% of gonococci studied in the United States have chromosomally mediated resistance to multiple drugs (penicillin, tetracycline, second-generation cephalosporins, and erythromycin). Most recently, gonococci have acquired resistance to fluoroquinolones (including ciprofloxacin and ofloxacin). This has progressed worldwide to the point that the US Centers for Disease Control and Prevention (CDC) removed fluoroquinolones from its list of recommended antibiotics in April 2007. Most recently, the appearance of gonococcal strains with increasingly high-level resistance to cephalosporins, including the third-generation cephalosporin used widely to treat this infection (ceftriaxone), has been reported; these strains have been associated with treatment failure of parenteral ceftriaxone therapy. Similarly, resistance to azithromycin—an agent that has been used as an alternative in cases where cephalosporins cannot be used—has also been reported in association with treatment failure. Thus, new agents are under investigation. In the meantime, the CDC

TABLE 42.2 Treatment for Uncomplicated Gonococcal and Chlamydial Infections in Adults

Recommended:
Ceftriaxone 250 mg i.m. (single dose)
plus
Azithromycin 1 g p.o. as single dose
Alternative, *if ceftriaxone is not available*:[a]
Cefixime 400 mg p.o. as single dose
plus
Azithromycin 1 g p.o. as single dose

[a]Not recommended for gonococcal infection of the pharynx; ceftriaxone plus azithromycin should be used.
i.m., Intramuscular; *i.v.*, intravenous; *p.o.*, by mouth.

TABLE 42.3 Treatment for Gonococcal and Chlamydial Infections in Pregnant Women[a]

Treatment for uncomplicated gonococcal infection:
Ceftriaxone 250 mg i.m. (single dose)
Treatment for uncomplicated chlamydial infection:[a]
Azithromycin 1 g p.o. as single dose

[a]Test of cure should be routine (3 weeks post-initiation of therapy).
i.m., Intramuscular; *p.o.*, by mouth.

recommends that all persons with gonorrhea be treated with parenteral ceftriaxone, if tolerated. This should be accompanied by treatment with azithromycin as a single dose for the theoretical benefit of exposing the organism to two classes of antibiotics.

Approved drug regimens are given in **Tables 42.2** and **Table 42.3**. The single-dose treatment of azithromycin for chlamydia is preferred, given its obvious advantage in compliance. Azithromycin is also the recommended regimen for the treatment of chlamydia in pregnant women. Regardless of the antibiotic chosen, a test of cure at 3 weeks post-completion of therapy is essential in pregnant women; no test of cure is otherwise routinely required. With the excellent sensitivity of NAAT for chlamydia, presumptive treatment for chlamydia in the setting of gonorrhea with a negative chlamydia NAAT is no longer recommended.

Recommendations for treating rectal gonorrhea, gonorrhea in children, neonatal gonococcal infections, gonococcal ophthalmia, and complicated or disseminated gonococcal infections are covered in the CDC treatment guidelines for sexually transmitted diseases.

FURTHER READING

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Kirkcaldy, R.D., Zaidi, A., Hook, E.W., et al., 2013. *Neisseria gonorrhoeae* antimicrobial resistance among men who have sex with men and men who have sex exclusively with women: the Gonococcal Isolate Surveillance Project, 2005–2010. Ann. Intern. Med. 158, 321–328.

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