Pharyngeal Gonorrhea: An Important Reservoir of Infection?

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(See the article by Bernstein et al on pages XXX–XX)

In 2008, >330,000 cases of gonorrhea were reported to the Centers for Disease Control and Prevention (CDC). The actual number of infections per year is thought to be much higher because of underdetection and underreporting [1]. *Neisseria gonorrhoeae* can cause cervicitis, urethritis, proctitis, pelvic inflammatory disease with long-term sequelae (eg, infertility, ectopic pregnancy, and chronic pelvic pain), adverse outcomes of pregnancy, and increased susceptibility to and facilitated transmission of human immunodeficiency virus (HIV) infection. An essential element in gonorrhea control is the availability and provision of effective antimicrobial therapy. Effective treatment not only eradicates infection in the affected individual and prevents the development of complications, it also has an important public health benefit by shortening the duration of infection, thus decreasing transmission and eliminating reservoirs of infection. However, gonorrhea treatment has been complicated by the development of resistance to multiple classes of antimicrobials over the past 60 years [2].

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Because of the recent emergence of quinolone-resistant *N. gonorrhoeae* (QRNG) in the United States, there is only a single class of antimicrobials among the recommended gonorrhea treatment options: the cephalosporins. Ceftriaxone, available only as an injection, is the recommended regimen for uncomplicated urogenital, anorectal, and pharyngeal infection. Cefixime (400 mg) is the only oral regimen recommended for urogenital and anorectal gonorrhea treatment. Several other alternative oral cephalosporins are active against *N. gonorrhoeae* for urogenital and anorectal infection, but none have substantial advantages over the recommended regimens. Oral cephalosporins have insufficient efficacy for treating gonococcal infections of the pharynx and should not be used in persons in whom pharyngeal infection is suspected [3]. *N. gonorrhoeae* infections of the pharynx are more difficult to eradicate than infections at urogenital and anorectal sites, and ceftriaxone is the only recommended regimen for treating pharyngeal infections.

Diagnosis of *N. gonorrhoeae* requires testing at specific anatomic sites of infection. Nucleic acid amplification tests (NAATs) permit testing of the widest range of specimen types and are Food and Drug Administration (FDA)–approved for use with endocervical, vaginal, and male urethral swabs and urine specimens from females and males. Unlike culture, NAATs are currently not FDA approved for use in the rectum, pharynx, and conjunctiva; however, some public and large private laboratories [4] have conducted validation tests to meet Clinical Laboratory Improvement Amendment requirements, allowing them to perform these tests at pharyngeal and rectal sites. The percentage of tests for gonorrhea that are performed with NAATs has been increasing over time, reflected by a recent CDC survey indicating that only 5% of all gonorrhea tests performed in public health laboratories were by culture [5, 6]. What is not clear, but is concerning, is that with the diminished use and availability of culture for diagnostic purposes, fewer tests are being performed to detect gonorrhea at rectal and pharyngeal sites.

In this issue of *Clinical Infectious Diseases,* Bernstein et al [7] demonstrate a 4.8% and a 4.1% prevalence of urethral chlamydia and urethral gonorrhea infection, respectively, in men who have sex with men (MSM) attending a municipal sexually transmitted disease (STD) clinic in San Francisco, California, whose only reported sexual exposure in the previous 3 months was receiving fellatio. The authors reported that 47% and 88% of the men who presumably acquired urethral chlamydial and gonococcal infection, respectively, through oral sex described urethral symptoms, suggesting that a substantial number of these infections, if not all of them, were recently acquired. Although the conclusions were limited by several factors noted by the authors, such as small numbers, a cross sectional design,

and self-reported behaviors, their analysis of available clinic data does raise important questions about the role of pharyngeal gonococcal infection, which is mostly asymptomatic, as a reservoir of infection in the population. The prevalence of gonococcal pharyngeal infection varies according to the population studied and the diagnostic method used for detection. Recent studies involving NAATs have demonstrated a high prevalence of pharyngeal gonoccocal infection among MSM [8–11].

Because of the substantial prevalence of gonorrhea and other STDs, routine screening for STDs, including HIV infection, is recommended for sexually active MSM [12]. Specific recommendations include annual tests for gonorrhea and chlamydia on urethral or urine specimens in men who have had insertive intercourse, a test for gonococcal pharyngeal infection in men with orogenital exposure, and a test for gonorrhea and chlamydia rectal infection in men who have had receptive anal intercourse in the previous year [12]. More-frequent screening (at 3–6-month intervals) may be indicated for MSM at greater risk: those with multiple or anonymous partners, those who have sex in conjunction with illicit drug use, who use methamphetamines, or those whose partners participate in these activities. Adherence to these screening recommendations is an important strategy for gonorrhea control in sexually active MSM, because asymptomatic infection at pharyngeal and rectal sites is common among this population, and gonococcal transmission is efficient with insertive or receptive rectal intercourse and fellatio [11]. Despite these recommendations, in surveys of sexually active MSM who attend venues frequented by MSM, 36% self-reported being tested for gonorrhea in the past year [13].

With few effective treatment options and limited screening for pharyngeal infection, the pharynx may not only be a reservoir of gonococcal infection, it may be a reservoir of antimicrobial-resistant gonococcal infection, as well. This could have implications for the prevention and control of gonorrhea in MSM and in heterosexuals who participate in oral-genital sexual practices. Providers should inquire about oral sexual exposures in MSM; patients reporting such exposures should be tested and, if infection is present, a regimen with enhanced efficacy against pharyngeal infection should be provided [12].

Clearly, more research is necessary to understand the role of pharyngeal infection as a source of genital infection and, potentially, a reservoir of gonorrhea resistant to various antimicrobials, including fluoroquinolones and cephalosporins. Could infection in the pharynx, for example, have contributed to the rapid emergence of quinolone-resistant *N. gonorrhoeae* in MSM? After first becoming established in Hawaii and then in California, QRNG became prevalent in the MSM population throughout the United States [14], followed by expansion into the heterosexual population a few years later [15]. Quinolone-resistant *N. gonorrhoeae* strains are now widely disseminated throughout the world [3], and fluoroquinolones are no longer recommended in the United States for the treatment of gonorrhea and associated conditions. Urogenital and pharyngeal treatment failures and decreased susceptibility to oral cephalosporins have also been reported, mostly from Japan and other Asian countries [16]. To date, few isolates in the United States have demonstrated decreased susceptibility to ceftriaxone or cefixime, the 2 cephalosporins now recommended for treating *N. gonorrhoeae*. However, decreased susceptibility of *N. gonorrhoeae* to cephalosporins is expected to spread, just as resistance to every other antimicrobial regimen used for the treatment of *N. gonorrhoeae* infection has spread throughout the world. Although the CDC conducts national sentinel surveillance for antimicrobial susceptibility, surveillance by clinicians is also critical. Clinicians who identify patients with suspected cephalosporin treatment failure (ie, a test result positive for *N. gonorrhoeae* after receiving recommended therapy and no history of sexual contact during the post-treatment period) should perform culture and susceptibility testing of relevant clinical specimens and consult a specialist for guidance in clinical management. Those cases with isolates indicating decreased susceptibility to cephalosporins should be reported to the CDC through state and local public health authorities.

Although the study by Bernstein et al [7] describes the pharynx as a potential reservoir for gonorrhea in MSM, similar studies are warranted in heterosexual populations engaging in receptive oral sexual practices if they have a high prevalence of gonorrhea. Further progress in the control of gonorrhea will require careful attention to an integrated comprehensive prevention strategy that includes enhancement of surveillance systems to monitor antimicrobial resistance; new approaches to maximize the benefit of available antimicrobials, such as combination therapy; novel antimicrobials; adherence to screening guidelines for those at high risk for infection; and prompt and effective treatment for infected persons and their sexual partners.

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