

## **Chlamydia and Gonorrhea: The Most Common Treatable STIs**

### ***Introduction***

*Chlamydia trachomatis* (*C. trachomatis*) and *Neisseria gonorrhoeae* (*N. gonorrhoeae*) infections are the most and second most frequently reported sexually transmitted infections (STIs) in the U.S and can result in serious consequences.<sup>1,2</sup> In women, they can lead to pelvic inflammatory disease (PID), tubal infertility, ectopic pregnancy, and chronic pelvic pain.<sup>1,3</sup> Reactive arthritis can also occur in both men and women following symptomatic or asymptomatic chlamydial infection. The arthritis sometimes occurs as part of a triad of symptoms with urethritis and conjunctivitis, which is sometimes referred to as Reiter's Syndrome.<sup>4</sup>

Symptomatic PID occurs in about 10% to 15% of women with untreated chlamydia.<sup>5</sup> Chlamydia can also cause subclinical inflammation of the upper genital tract or "subclinical PID." Both symptomatic and subclinical PID can cause permanent damage to the fallopian tubes, uterus, and surrounding tissues.<sup>6</sup> Some patients with chlamydial PID develop liver perihepatitis (Fitz-Hugh-Curtis Syndrome).<sup>3</sup> In pregnant women, untreated chlamydia has been associated with preterm delivery, as well as ophthalmia neonatorum (conjunctivitis) and pneumonia in the newborn.<sup>7</sup> With regard to gonorrhea, if left untreated, gonorrhea can spread to the blood and cause disseminated gonococcal infection. This is most commonly characterized by arthritis, tenosynovitis, and/or dermatitis.<sup>8</sup>

Due to these serious complications, increasing the awareness and adoption of current CDC STI diagnosis and treatment guidelines relative to chlamydia and gonorrhea is essential. And as testing methods continue to improve and evolve, it is also important that healthcare providers know how to utilize appropriate testing methods that are more sensitive and accurate to screen and diagnose these STIs.

### ***Epidemiology and Burden of Disease***

In 2017, 1,708,509 cases of chlamydia and 555,608 cases of gonorrhea in the U.S. were reported to the CDC.<sup>2</sup> A large additional number of cases are often not reported as most chlamydial and gonorrheal infections are asymptomatic, which is why some patients do not seek screening or testing. Both infections are most common among young people. Almost two-thirds of new chlamydia infections occur among 15 to 24-year olds,<sup>9</sup> and it is estimated that one in 20 sexually active young women aged 14 to 24 years has chlamydia.<sup>10</sup>

Substantial racial/ethnic disparities in these infections also exist. Prevalence among non-Hispanic blacks is 5.6 times the prevalence among non-Hispanic whites (1,175.8 and 211.3 cases per 100,000 population, respectively).<sup>2</sup> The rate of reported cases of gonorrhea remained highest among Blacks (548.1 cases per 100,000 population) and among American Indians/Alaska Natives (301.9 cases per 100,000 population).<sup>2</sup> Chlamydia and gonorrhea are also common among men who have sex with men (MSM) since chlamydial and gonorrheal infections can be transmitted by oral or anal sex.<sup>1</sup> Among MSM screened for rectal chlamydial infection, positivity has ranged from 3.0% to 10.5%.<sup>11,12</sup> The prevalence of pharyngeal gonorrhea and pharyngeal chlamydia among MSM has been found to be 7.3% and 2.3%, respectively.<sup>1</sup>

Chlamydia can also be spread perinatally from an untreated mother to her baby during childbirth, resulting in ophthalmia neonatorum (conjunctivitis) or pneumonia in some exposed infants. Studies show that chlamydial conjunctivitis has been identified in 18% to 44% of infants and chlamydial pneumonia in 3.0% to 16% of infants born to women with untreated chlamydial cervical infection at the time of delivery.<sup>13-16</sup> The prevalence of gonorrhea infection in infants depends on the prevalence of infection among pregnant women, whether they are screened and treated, and whether newborns receive eye prophylaxis. Other manifestations of neonatal gonorrhea infections range from rhinitis, vaginitis, and urethritis to arthritis, meningitis, and sepsis.<sup>1</sup>

### **Groups at Risk**

Patient groups at increased risk for chlamydial and gonorrheal infections are listed in **Table 1**. The highest reported rates of chlamydia and gonorrhea infections among females and males are during their adolescent and early adult years.<sup>2</sup> Fortunately, all 50 states and the District of Columbia explicitly allow minors to consent for their own health services for STDs.<sup>1</sup> Other factors associated with increased risk of *C. trachomatis* and *N. gonorrhoeae* infection include a new sex partner, a sex partner with concurrent partners, or a sex partner who has a sexually-transmitted infection. Women  $\leq 35$  and men  $< 30$  years in correctional facilities are also at increased risk of infections.<sup>1</sup> MSM are at increased risk for chlamydial and gonorrheal infections since infection can be transmitted by oral or anal sex.<sup>1</sup> Among MSM screened for rectal chlamydial infection, positivity has ranged from 3.0% to 10.5%.<sup>11, 12</sup> Among MSM screened at STD clinics for pharyngeal chlamydial infection, positivity has ranged from 0.5% to 2.3%.<sup>12, 17</sup>

**Table 1. Groups at risk for *Chlamydia trachomatis* and *N. gonorrhoeae* Infections<sup>1, 11, 12, 17</sup>**

- Adolescent females and males
- A new sex partner
- A sex partner with concurrent partners
- A sex partner who has a STI
- Women  $\leq 35$  years in correctional facilities
- Men  $< 30$  years in correctional facilities
- Men who have sex with men

### **Screening**

Studies have shown that chlamydia screening programs reduce the rates of PID in women.<sup>18</sup> Women with chlamydia or gonorrhea are at risk of serious complications, regardless of the presence or severity of symptoms.<sup>19, 20</sup> The USPSTF and the CDC recommend routine annual screening for *C. trachomatis* and *N. gonorrhoeae* for all sexually active females  $< 25$  years. Screening is also recommended in older women who may be at increased risk, such as those with a new sex partner, a sex partner who has an STI, or who have concurrent multiple sex partners.<sup>1, 21</sup> Although routine screening of men is not recommended, the screening of sexually active young men should be considered in clinical settings with a high prevalence of chlamydia (e.g. adolescent clinics, correctional facilities, and STD clinics) or in populations with high burden of infection, such as MSM.<sup>1, 21</sup> Recommended screening for MSM include a

test for *N. gonorrhoeae* and *C. trachomatis* of the urethra or rectum in men who have had insertive intercourse during the preceding year. Urine testing using a nucleic acid amplification test (NAAT) is the CDC recommended screen.<sup>1</sup> The CDC also recommends testing for *N. gonorrhoeae* in men who have had receptive oral intercourse during the preceding year using a NAAT of a pharyngeal sample. Testing for *C. trachomatis* pharyngeal infection is not recommended. Women <35 and men <30 years in correctional facilities should be screened for chlamydia and gonorrhea at intake.<sup>1</sup>

## ***Diagnosis***

Chlamydial and gonorrheal infections are commonly referred to as ‘silent’ because many infections are asymptomatic.<sup>4, 8</sup> Only about 10% of men and between 5% to 30% of women with laboratory-confirmed chlamydial infection develop recognizable symptoms.<sup>22</sup> Symptoms in women, especially of gonorrhea, are often so mild and nonspecific that they are mistaken for other urogenital issues such as dysuria, vaginal discharge, and/or intermenstrual vaginal bleeding. Signs of infection may include a mucopurulent endocervical discharge and easily induced endocervical bleeding.<sup>4</sup>

Urethral infections in men caused by *N. gonorrhoeae* can produce symptoms that cause them to seek treatment. Men who are symptomatic typically have urethritis with a mucoid or watery urethral discharge and dysuria.<sup>1</sup> A minority of infected men develop epididymitis presenting with unilateral testicular pain, tenderness, and swelling.<sup>23</sup> Symptoms of rectal infection in both men and women may be absent or may include anal discharge, itching, soreness, bleeding, or painful bowel movements.<sup>24</sup> Pharyngeal infections are typically asymptomatic but may present as a sore throat.<sup>25</sup>

## **Laboratory Testing**

For *C. trachomatis* and *N. gonorrhoeae* testing, the CDC states that NAATs have the advantage that they have high sensitivity for the widest variety of specimen types, including endocervical swabs, vaginal swabs, during Pap collection, urethral swabs in men, and urine from both men and women.<sup>1</sup> Different tests from different NAAT manufacturers have specific collection methods and different approved specimen types.<sup>1</sup> Second-generation NAATs may be more reliable than first generation NAATs due to technical improvements that reduce the rate of false positive results.<sup>26,27</sup> As the most sensitive screen, NAATs are recommended by the CDC for detecting *C. trachomatis* infection. FDA-cleared specimens to diagnose urogenital *C. trachomatis* infection can be collected in women as first-catch urine or swabs from the cervix or vagina. NAATs that are FDA-cleared for use with vaginal swab specimens can be collected by a provider or self-collected in a clinical setting. Self-collected vaginal swab specimens are equivalent in sensitivity and specificity to those collected by a clinician using NAATs.<sup>28</sup> Patients find this screening strategy to be acceptable.<sup>29</sup> Diagnosis of *C. trachomatis* urethral infection in men can be made by testing a urethral swab or first-catch urine specimen.<sup>1</sup>

In the 2015 CDC STD guidelines NAATs were not FDA-cleared for use with rectal or oropharyngeal swab specimens although they had been demonstrated to have improved sensitivity.<sup>1</sup> However, on May 23, 2019 FDA cleared two tests that can detect the presence of extragenital chlamydia and gonorrhea. The test(s) were the Aptima Combo 2 Assay and the Xpert CT/NC; both had previously only been cleared for testing urine, vaginal, and endocervical samples.

Bacterial culture and gram stain are also available for the detection of genitourinary *N. gonorrhoeae* infection but are becoming much less common.<sup>1</sup> Culture requires endocervical swab specimens in women or urethral swab specimens in men. Culture may be used for detection of rectal, oropharyngeal, and conjunctival gonococcal infection. *N. gonorrhoeae* is a fastidious organism that has demanding nutritional and environmental growth requirements. The best results are achieved when specimens are inoculated directly to specific growth medium and then promptly placed and incubated in an increased CO<sub>2</sub> environment.<sup>30</sup>

Gram stain of urethral secretions in symptomatic men that demonstrate polymorphonucleocytes with intracellular Gram-negative diplococci is considered diagnostic for *N. gonorrhoeae* infection. This approach has >99% specificity and >95% sensitivity, although sensitivity is lower in asymptomatic men.<sup>1</sup>

### **Treatment**

Recommended treatment regimens for urogenital chlamydial and gonorrheal infections are shown in **Table 2**. The recommended chlamydia regimen produces microbial cure rates of 97% to 98%.<sup>31</sup> The urogenital gonorrhea recommended regimen produces microbial cure rates of 99.2% for uncomplicated urogenital and anorectal infections and a 98.9% cure rate with pharyngeal infections.<sup>32</sup> When azithromycin allergy is present, doxycycline 100 mg orally twice a day for 7 days may be substituted for azithromycin.<sup>1</sup> More detailed treatment information can be found at <https://www.cdc.gov/std/tg2015/default.htm>.

Expedited Partner Therapy (EPT) involves treating the sex partners of persons who are diagnosed with an STI and is recommended by the CDC unless it is prohibited by law. It usually consists of providing prescriptions or medications in sufficient quantity for both patient and partner. EPT is legal in most but not all states; providers can check the legal status of EPT at <http://www.cdc.gov/std/ept>. As of the end of 2019, all states allow some form of EPT except South Carolina. Clinical trials indicate that more partners are treated when patients are offered EPT, with statistically significant declines in the rate of reinfection.<sup>1, 33</sup> Reduction in chlamydia prevalence at follow-up is about 20% and gonorrhea about 50%.<sup>1</sup> EPT should not be used in MSM with gonorrhea because of the high risk for coexisting infections (including HIV infection) and since no data exist for efficacy in this population.

**Table 2. CDC 2015 Recommended Treatments for Uncomplicated *C. trachomatis* & *N. gonorrhoeae* Infections<sup>1\*</sup>**

Drug	Dose and Regimen
Chlamydia trachomatis recommended regimens	
Azithromycin	1 g orally in a single dose
Doxycycline	100 mg orally twice a day for 7 days
Chlamydia trachomatis alternative regimens	
Erythromycin base	500 mg orally four times a day for 7 days
Erythromycin ethylsuccinate	800 mg orally four times a day for 7 days
Levofloxacin	500 mg orally once daily for 7 days
Ofloxacin	300 mg orally twice a day for 7 days
Neisseria gonorrhea recommended regimens	
Ceftriaxone <b>PLUS</b> Azithromycin	250 mg in a single IM dose 1g in a single oral dose
Neisseria gonorrhea alternative regimens	
Cefixime <b>PLUS</b> Azithromycin	400 mg orally in a single dose 1 g orally in a single dose

\* Azithromycin may have low cure rates in some patients with rectal chlamydia, therefore doxycycline may be preferred.

### **Test-of-Cure**

The 2015 CDC STD Guidelines recommend that a test-of-cure to detect therapeutic failure (i.e., repeat testing 3 to 4 weeks after completing therapy) is not advised for persons treated with the recommended or alternative regimens, unless therapeutic adherence is in question, symptoms persist, or reinfection is suspected. Moreover, the use of chlamydial NAATs at <3 weeks after completion of therapy is not recommended because the continued presence of nonviable organisms can lead to false-positive results. However, men and women who have been treated for chlamydia should be retested approximately 3 months after treatment, regardless of whether they believe that their sex partners were treated.<sup>1</sup> If retesting at 3 months is not possible, clinicians should retest whenever persons next present for medical care in the year following initial treatment. The CDC also suggests that in cases of suspected treatment failure, perform cultures with antimicrobial susceptibility testing to determine if antimicrobial resistance is present.<sup>1</sup>

A patient diagnosed with and treated for uncomplicated urogenital or rectal gonorrhea with any of the recommended or alternative regimens does not require a test-of-cure. All persons with pharyngeal gonorrhea should return 14 days after treatment for a test-of-cure. If a NAAT is positive, a confirmatory culture with antimicrobial susceptibility testing should be performed. If symptoms persist after treatment, the patient should receive a culture for *N. gonorrhoeae* with antimicrobial susceptibility testing.<sup>1</sup>

A high prevalence of *C. trachomatis* and *N. gonorrhoeae* infection has been observed in women and men who were treated during the preceding several months.<sup>34</sup> Most post-treatment infections do not

result from treatment failure, but rather from reinfection caused by the failure of sex partners to receive treatment or the initiation of sexual activity with a new infected partner. Repeat infections confer an elevated risk for PID and other complications in women. These findings reinforce the importance of EPT.<sup>1</sup>

### **Summary**

In the U.S., the best practices for the diagnosis and treatment of STIs are described in the 2015 Sexually Transmitted Diseases Treatment Guidelines.<sup>1</sup> Diagnosis and treatment of patients with chlamydia or gonorrhea is important to reduce the risk of serious complications. NAATs have the advantage of testing for these diseases because they have high sensitivity for the widest variety of specimen types. They also give providers and patients the widest range of choices to test since self-collected vaginal swab specimens for use in NAATs have a similar sensitivity and specificity compared to those collected by a clinician.

### **References**

1. Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015 Jun 5;64(RR-03):1-137.
2. Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2016. Atlanta: U.S. Department of Health and Human Services; 2017. <https://www.cdc.gov/std/stats17/default.htm>
3. CDC. Chlamydia - CDC Fact Sheet. [https://www.cdc.gov/std/chlamydia/stdfact-chlamydia-detailed.htm#\\_ENREF\\_3](https://www.cdc.gov/std/chlamydia/stdfact-chlamydia-detailed.htm#_ENREF_3). Accessed 11/23/17
4. Carter JD, Inman RD. Chlamydia-induced reactive arthritis: hidden in plain sight? Best practice & research *Clin Rheumatol*. 2011;25:359-374.
5. Oakeshott P, Kerry S, Aghaizu A, et al. Randomized controlled trial of screening for Chlamydia trachomatis to prevent pelvic inflammatory disease: the POPI (prevention of pelvic infection) trial. *BMJ*. 2010;340:c1642.
6. Westrom L, Joesoef R, Reynolds G, Hagdu A, Thompson SE. Pelvic inflammatory disease and fertility. A cohort study of 1,844 women with laparoscopically verified disease and 657 control women with normal laparoscopic results. *Sex Transm Dis*. 1992;19:185-192.
7. Rours GI, Duijts L, Moll HA, et al. Chlamydia trachomatis infection during pregnancy associated with preterm delivery: a population-based prospective cohort study. *Eur J Epidemiol*. 2011;26:493-502.
8. CDC. Gonorrhea - CDC Fact Sheet (Detailed Version) <https://www.cdc.gov/std/gonorrhea/stdfact-gonorrhea-detailed.htm>
9. Satterwhite CL, Torrone E, Meites E, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. *Sex Transm Dis*. 2013;40:187-193.

10. Torrone E, Papp J, Weinstock H. Prevalence of chlamydia trachomatis genital infection among persons aged 14–39 Years — United States, 2007–2012. *MMWR*. 2014;63:834-838.
11. Marcus JL, Bernstein KT, Stephens SC, et al. Sentinel surveillance of rectal chlamydia and gonorrhea among males—San Francisco, 2005-2008. *Sex Transm Dis*. 2010;37:59-61.
12. Pinsky L, Chiarilli DB, Klausner JD, et al. Rates of asymptomatic nonurethral gonorrhea and chlamydia in a population of university men who have sex with men. *J Am Coll Health*. 2012;60:481-484.
13. Frommelt GT, Rothenberg R, Wang S, McIntosh K. Chlamydial infection of mothers and their infants. *J Pediatr*. 1979;95:28-32.
14. Hammerschlag MR, Chandler JW, Alexander ER, English M, Koutsky L. Longitudinal studies on chlamydial infections in the first year of life. *Pediatr Infect Dis J*. 1982;1:395-401.
15. Heggie AD, Lumicao GG, Stuart LA, Gyves MT. Chlamydia trachomatis infection in mothers and infants. A prospective study. *Am J Dis Child*. 1981;135(6):507-511.
16. Schachter J, Grossman M, Sweet RL, et al. Prospective study of perinatal transmission of Chlamydia trachomatis. *JAMA*. 1986; 255:3374-3377.
17. Park J, Marcus JL, Pandori M, Snell A, Philip SS, Bernstein KT. Sentinel surveillance for pharyngeal chlamydia and gonorrhea among men who have sex with men—San Francisco, 2010. *Sex Transm Dis*. 2012;39:482-484.
18. Low N, Redmond S, Uusküla A, et al. Screening for genital chlamydia infection. *Cochrane Database Syst Rev*. 2016;13;9:CD010866.
19. McCormack WM, Johnson K, Stumacher RJ, Donner A, Rychwalski R. Clinical spectrum of gonococcal infection in women. *Lancet*. 1977;1:1182-1185.
20. Curran J, Rendtorff R, Chandler R, Wiser W, Robinson H. Female gonorrhea: its relation to abnormal uterine bleeding, urinary tract symptoms, and cervicitis. *Obstet Gynecol*. 1975;45: 195-198.
21. Final Recommendation Statement: Chlamydia and Gonorrhea: Screening. U.S. Preventive Services Task Force. December 2016.  
<https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/chlamydia-and-gonorrhea-screening>.
22. Korenromp EL, Sudaryo MK, de Vlas SJ, et al. What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? *Int J STD AIDS*. 2002;13:91-101.
23. Berger RE, Alexander ER, Monda GD, et al. Chlamydia trachomatis as a cause of acute “idiopathic” epididymitis. *N Eng J Med*. 1978;298(6):301-304.

24. Klein EJ, Fisher LS, Chow AW, Guze LB. Anorectal gonococcal infection. *Ann Intern Med.* 1997;86:340-346.
25. Bro-Jorgensen A, Jensen T. Gonococcal pharyngeal infections: report of 110 cases. *Brit J Vener Dis.* 1973;49: 491-499.
26. Chong S, Jang D, Song X, et al. Specimen processing and concentration of Chlamydia trachomatis added can influence false-negative rates in the LCx assay but not in the Aptima Combo 2 Assay when testing for inhibitors. *J Clin. Microbiol.* 2003;41:778-782.
27. Gaydos, CA, Quinn TC, Willis D, et al. Performance of the Aptima Combo 2 Assay for detection of Chlamydia trachomatis and Neisseria gonorrhoeae in female urine and endocervical swab specimens. *J. Clin. Microbiol.* 2003;41:304-309.
28. Masek BJ, Arora N, Quinn N, et al. Performance of three nucleic acid amplification tests for detection of Chlamydia trachomatis and Neisseria gonorrhoeae by use of self-collected vaginal swabs obtained via an Internet-based screening program. *J Clin Microbiol.* 2009;47:1663-1667.
29. Doshi JS, Power J, Allen E. Acceptability of chlamydia screening using self-taken vaginal swabs. *Int J STD AIDS.* 2008;19:507-509.
30. Papp JR, Schachter J, Gaydos C, et al. Recommendations for the laboratory-based detection of Chlamydia trachomatis and Neisseria gonorrhoeae-2014. *MMWR Recomm Rep.* 2014;63 (No. RR-02).
31. Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a meta-analysis of randomized clinical trials. *Sex Transm Dis.* 2002;29:497-502.
32. Moran JS, Levine WC. Drugs of choice for the treatment of uncomplicated gonococcal infections. *Clin Infect Dis.* 1995;20:S47-S65.
33. Schillinger JA, Kissinger P, Calvet H, et al. Patient-delivered partner treatment with azithromycin to prevent repeated Chlamydia trachomatis infection among women - a randomized, controlled trial. *Sex Transm Dis.* 2003;30:49-56.
34. Hosenfeld CB, Workowski KA, Berman S, et al. Repeat infection with chlamydia and gonorrhea among females: a systematic review of the literature. *Sex Transm Dis.* 2009;36:478-489.