Updates in the Treatment of Sexually Transmitted Diseases

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Sexually transmitted infections (STIs) represent a major burden of morbidity and mortality in the United States. In 2018, there were an estimated 26.2 million new STI diagnoses in the nation, almost half of these among persons ages 15-24.[1] STIs increase rates of infertility, ectopic pregnancy, cancer, and adverse birth outcomes. In addition, several STIs increase the risk of human immunodeficiency virus (HIV) transmission.[2]

In this article, we review the most clinically relevant updates from the 2021 Centers for Disease Control and Prevention (CDC) STI Treatment Guideline Update, as well as commonly asked questions regarding STI screening, diagnosis, and follow-up.

Of note, this article is not comprehensive, and an in-depth discussion of syphilis and HIV screening and treatment is beyond its scope. Please refer to the Fall 2022 *JLGH* article on syphilis[3] and the full CDC STI Treatment Guidelines[4] for further information.

Who should be screened for STIs?

The CDC recommends screening all adults at least once for HIV and hepatitis C. Other STI screening should be based on an individual and population-based risk assessment. A useful guide for risk assessment is the CDC's Five Ps method for collecting an accurate sexual history: partners, practices, protection from STIs, past history of STIs, and pregnancy intention. See Fig. 1 on page 68 for further information.[5]

Table 1 on page 71 summarizes screening recommendations for special populations. In addition, all patients with exposure or symptoms concerning for an STI or requesting STI evaluation should at minimum have testing for chlamydial and gonococcal infections in all sites of exposure, HIV, and syphilis. Testing for other STIs should be offered depending on symptoms and risk assessment.

How should clinicians perform screening for gonorrhea and chlamydia?

Clinicians should screen for chlamydia and gonorrhea at any site of possible infectious exposure with nucleic acid amplification testing (NAAT). When screening for gonorrhea and chlamydia, clinicians should offer screening at all sites with possible infectious exposure. Gonorrhea can affect the oropharynx, and both chlamydia and gonorrhea can affect the urogenital region and the anorectal region. Chlamydia can be found in the oropharynx, but the clinical significance is unknown. Negative testing in one site does not indicate that testing is negative in all sites, and pharyngeal and rectal testing may be positive even in the setting of negative urine testing.

KEY TAKEAWAY

Gonorrhea can affect the oropharynx, and both chlamydia and gonorrhea can affect the urogenital region and the anorectal region. Chlamydia can be found in the oropharynx, but the clinical significance is unknown. Negative testing in one site does not indicate that testing is negative in all sites, and pharyngeal and rectal testing may be positive even in the setting of negative urine testing.

Testing for oropharyngeal gonorrhea should be offered to all patients who practice receptive oral intercourse, and testing for anorectal chlamydia and gonorrhea should be offered to all patients who practice receptive anal intercourse. Clinicians can consider offering rectal gonorrhea and chlamydia testing to all women irrespective of participation in anal intercourse as positive results may be seen even in the absence of reported anal intercourse.[6,7]

The preferred method of testing for chlamydia and gonorrhea in all sites is with NAAT rather than culture.[8] For women, urogenital chlamydial and gonococcal infections can be diagnosed with NAAT vaginal or cervical swabs or first-void urine. Patient-collected vaginal swabs have equivalent sensitivity and specificity to clinician-collected swabs.[9] For men, urogenital chlamydial and gonococcal infections can be diagnosed

with NAAT first-void urine or urethral swab. Anorectal infection can be diagnosed with rectal NAAT swab; patient-collected rectal swabs have comparable efficacy to clinician-collected swabs.[10]

What are the updated recommendations for treatment of chlamydia?

Doxycycline 100 mg twice daily for seven days is the preferred regimen for treatment of urogenital and anorectal chlamydial infections in all patients.

Previously, single-dose azithromycin was the preferred treatment for chlamydial infections; however, studies show that doxycycline is more effective than azithromycin in treating anorectal chlamydia and chlamydia in men.[11,12] While azithromycin retains good efficacy in treating urogenital chlamydia in women, studies show high rates of concurrent anorectal chlamydia in women diagnosed with urogenital chlamydia, even in women who do not report receptive anal intercourse.

Inadequately treated anorectal infections increase transmission risk and place women at risk for reinfection through autoinoculation from the anorectal site. Because of the improved coverage for both urogenital and anorectal infection, treatment with doxycycline is now preferred.

The preferred treatment for non-pregnant adults and adolescents for chlamydial infection in any site is:

- Doxycycline 100 mg twice daily for seven days.

Alternative regimens are:

- Azithromycin 1 g in a single dose.
- Levofloxacin 500 mg daily for seven days.

Fig. 1. The Five Ps Approach to Taking a Sexual History

Partners	• Are you currently having sex of any kind? • What is the gender(s) of your partner(s)?
Practices	• To understand any risks for sexually transmitted infections (STIs), I need to ask more specific questions about the kind of sex you have had recently. What kind of sexual contact do you have or have you had? — Do you have vaginal sex, meaning "penis in the vagina" sex? — Do you have anal sex, meaning "penis in rectum/anus" sex? — Do you have oral sex, meaning "mouth on penis/vagina"?
Protection from STIs	• Do you and your partner(s) discuss prevention of STIs and human immunodeficiency virus (HIV)? • Do you and your partner(s) discuss getting tested? • What protection methods do you use? In what situations do you use condoms?
Past History of STIs	• Have you ever been tested for STIs and HIV? • Have you ever been diagnosed with an STI in the past? • Have any of your partners had an STI? ***Additional questions for identifying HIV and viral hepatitis risk:*** • Have you or any of your partner(s) ever injected drugs? • Is there anything about your sexual health that you have questions about?
Pregnancy Intention	• Do you think you would like to have (more) children in the future? • How important is it to you to prevent pregnancy (until then)? • Are you or your partner using contraception or practicing any form of birth control? • Would you like to talk about ways to prevent pregnancy?

Adapted from Centers for Disease Control and Prevention.[5]

Azithromycin should still be used for pregnant adults or if adherence to a multiday regimen is a significant concern.

Because doxycycline is highly efficacious for treatment, a test of cure is not required except in pregnancy, but because of high risk for reinfection, persons treated for chlamydia should be offered repeat testing in three months.

What are the updated recommendations for treatment of gonorrhea?

Ceftriaxone 500 mg IM (or 1 g IM if patient's weight is greater than or equal to 150 kg) is now the recommended treatment for oropharyngeal, urogenital, and anorectal gonococcal infections.

Gonorrhea has developed significant antibiotic resistance over the past 30 years, which has affected the treatment of this common infection. Gonorrhea now has significant fluoroquinolone resistance, and rates of resistance to cephalosporins and azithromycin are rising.[13,14]

Due to the rapidly rising rate of azithromycin resistance in gonococcal infections and rising azithromycin resistance in other pathogens (such as *M. genitalium* and enteric pathogens), the CDC now recommends against dual therapy for gonorrhea with ceftriaxone and azithromycin. The recommended dose of ceftriaxone for treatment has also increased due to increased gonococcal resistance to cephalosporins.

The preferred treatment regimen for uncomplicated gonococcal infections of the urogenital or anorectal region in adolescents and adults is:

- Ceftriaxone 500 mg IM for patients weighing less than 150 kg and ceftriaxone 1 g IM for patients weighing more than 150 kg. Doxycycline 100 mg twice daily for seven days should be administered if chlamydial infection is not excluded.

Alternative regimens include:

- Cefixime 800 mg oral once (if ceftriaxone is not available or not feasible as cefixime has lower efficacy than ceftriaxone).
- Gentamicin 240 mg IM in a single dose **PLUS** azithromycin 2 g orally in a single dose (in persons with a cephalosporin allergy).

Oropharyngeal gonorrhea, while usually asymptomatic, may be a major source of infection transmission and is more difficult to treat. Cefixime has limited efficacy for the treatment of oropharyngeal gonorrhea. The only reliable regimen for treatment is:

- Ceftriaxone 500 mg IM in a single dose for persons weighing less than 150 kg and 1 g IM in persons weighing more than 150 kg.

Test of cure is not required for urogenital or anorectal infections except during pregnancy. Test of cure is recommended in oropharyngeal gonorrhea infections 7-14 days after treatment, given lower efficacy of treatment. Persistent positive tests should undergo confirmatory gonococcal culture to evaluate for antimicrobial susceptibility. Thayer Martin Agar culture plates are available by request from the LG Health laboratory. All persons with gonococcal infection should be retested in three months to evaluate for reinfection.

What are the updated recommendations for treatment of pelvic inflammatory disease (PID)?

Treat patients with pelvic inflammatory disease with metronidazole in addition to agents treating gonococcal and chlamydial infections.

Pelvic inflammatory disease encompasses multiple inflammatory conditions of the upper female genital tract and can increase risk of infertility and pelvic pain in women. Though STIs, especially chlamydia and gonorrhea, are often associated with PID, the proportion of PID related to these infections has decreased. Currently, only approximately 50% of current PID cases are associated with gonorrhea or chlamydia.[15]

Other vaginal flora are increasingly associated with PID, including anaerobic bacteria and *Gardnerella vaginalis, H. influenzae,* and enteric gram-negative bacteria. The preferred treatment for PID thus not only includes agents that treat chlamydial or gonococcal infections, but also agents that treat these anaerobic organisms.

For severely ill patients requiring hospitalization (including persons with severe illness, tubo-ovarian abscess, pregnancy, or poor response or inability to tolerate outpatient regimen), preferred parental treatment options include:

- Ceftriaxone 1 g IV every 24 hours **PLUS** doxycycline 100 mg oral or IV every 12 hours **PLUS** metronidazole 500 mg oral or IV every 12 hours.
- Cefotetan 2 g IV every 12 hours **PLUS** doxycycline 100 mg oral or IV every 12 hours.
- Cefoxitin 2 g IV every 6 hours **PLUS** doxycycline 100 mg oral or IV every 12 hours.

If tolerated, clinicians should give doxycycline and metronidazole in oral form rather than IV. The preferred regimens for outpatient treatment for persons with mild to moderate PID include:

- Ceftriaxone 500 mg IM in a single dose (or 1 g IM if patient's weight is greater than or equal to 150 kg) **PLUS** doxycycline 100 mg orally twice daily for 14 days **PLUS** metronidazole 500 mg orally twice daily for 14 days.
- Cefoxitin 2 g IM in a single dose and probenecid 1 g orally administered concurrently **PLUS** doxycycline 100 mg orally twice daily for 14 days **PLUS** metronidazole 500 mg orally twice daily for 14 days.
- Other parental third-generation cephalosporin **PLUS** doxycycline 100 mg orally twice daily for 14 days **PLUS** metronidazole 500 mg orally twice daily for 14 days.

Fluoroquinolone-based regimens are an alternative for cephalosporin-allergic patients; however, there are high rates of gonococcal resistance to fluoroquinolones. Fluoroquinolones may be used if the individual risk and community prevalence of gonococcal infections are low and close follow-up is possible. Options include:

- Levofloxacin 500 mg orally daily **PLUS** metronidazole 500 mg orally twice daily for 14 days.
- Moxifloxacin 400 mg orally daily for 14 days.

What are the updated recommendations for the treatment of trichomoniasis?

Metronidazole 500 mg twice daily for seven days is now the preferred treatment for *Trichomonas vaginalis* infection in women. *Trichomonas vaginalis* is the most common nonviral STI worldwide; it affects 3.7 million people in the United States. Infections are frequently asymptomatic, and untreated infection might last for months to years.

Trichomoniasis is commonly diagnosed using wet prep microscopy; however, sensitivity of this technique is low (44% to 68%).[16] Microscopy must be performed immediately after collection because sensitivity drops to 20% within one hour of collection.[17] NAATs are highly sensitive at detecting trichomonas infections. Data show that multi-dose metronidazole in women results in an increased rate of cure compared to single-dose metronidazole.[18]

The preferred treatment regimen for adolescent and adult women is:

- Metronidazole 500 mg orally twice daily for seven days.

The preferred treatment regimen for adolescent and adult men is:

- Metronidazole 2 g orally in a single dose.

An alternative regimen for both men and women is:

- Tinidazole 2 g orally in a single dose.

A review of alcohol consumption during metronidazole treatment showed no animal or clinical studies providing convincing evidence of disulfiram-like interactions between alcohol and metronidazole. Refraining from alcohol use while taking metronidazole or tinidazole is unnecessary.

It is recommended to retest sexually active women with trichomoniasis approximately three months after initial treatment, regardless of partner treatment status, because of high rates of reinfection. A test of cure is not recommended for men due to insufficient data.

What should providers consider when encountering recurrent urethritis or cervicitis?

Consider *Mycoplasma genitalium* as a cause of recurrent urethritis or cervicitis.

Mycoplasma genitalium is an increasingly recognized pathogen causing urethritis among men. It represents 15% to 20% of non-gonococcal urethritis and 40% of persistent or recurrent urethritis. *Mycoplasma genitalium* has also been associated with PID, preterm delivery, spontaneous abortion, and infertility in women, although data remain limited. Men with recurrent non-gonococcal urethritis and women with recurrent cervicitis should be tested for *M. genitalium* using an FDA-cleared NAAT.

Table 1. **STI Screening Recommendations for Special Populations**	
Population	**Screening Recommendations for Asymptomatic Patients**
Anyone age 13-64	• Screen for HIV at least once in lifetime.
Anyone age 18+	• Screen for hepatitis C once in lifetime, except in settings where rate of positivity is less than 0.1%.
Women	• Test annually for gonorrhea and chlamydia in sexually active women under 25 years and in women at increased risk over 25 years.* • Consider pharyngeal gonorrhea and anorectal chlamydia and gonorrhea testing depending on exposure and reported sexual behaviors. • Screen for syphilis if at increased risk.** • Consider hepatitis B screening in women at high risk.***
Men who have sex only with women	• Consider screening for chlamydia, gonorrhea, and syphilis in high-prevalence settings or if other epidemiologic risk factors are present.**
Men who have sex with men (MSM)	***For sexually active MSM, screen at least annually for:*** • Gonorrhea and chlamydia at any site of exposure. • HIV. • Syphilis. *Consider screening every 3-6 months for persons at higher risk (such as those on HIV pre-exposure prophylaxis or those with multiple sexual partners).* ***For sexually active MSM, screen at least once for:*** • Hepatitis B (HBsAg, anti-HBcAb, anti-HBsAb). • Hepatitis C.
Transgender and gender-diverse patients	• Screening recommendations should be adapted based on anatomy and risk factors (e.g., annually screen for chlamydia and gonorrhea for transgender men and gender-diverse people with a cervix under age 25 years). Consider screening at pharyngeal and rectal sites, and yearly for syphilis, depending on reported sexual behavior and exposure.
Pregnant women	***At first visit, screen for:*** • Gonorrhea and chlamydia for all pregnant women under 25 years, and women 25 years and older with increased risk.* • Syphilis, HIV, and hepatitis B (HBsAg) in all pregnant women. • Hepatitis C in all pregnant women, except in setting where the HCV positivity rate is <0.1%. ***Repeat testing for the following in third trimester:*** • Gonorrhea and chlamydia in women under 25 years, or women 25 years and older with increased risk.* • Syphilis and HIV if at increased risk (recommended for all women in Pennsylvania).** ***Repeat testing for the following at delivery:*** • Syphilis and hepatitis B if increased risk (repeat syphilis testing recommended for all women in Pennsylvania).** • Rapid HIV testing if not previously screened for HIV.
Persons with HIV	***At first visit in sexually active individuals, screen for:*** • Syphilis. • Gonorrhea and chlamydia at any site of contact. • Trichomonas in sexually active women. • Hepatitis B (HBsAg, anti-HBcAb, anti-HBsAb). • Hepatitis C. ***Annually screen for:*** • Syphilis, gonorrhea, and chlamydia at any site of exposure. • Trichomonas in sexually active women. • Hepatitis C in men who have sex with men.

**Risk factors for chlamydia and gonorrhea in women over 25 years include: the presence of another STI, new sex partner, more than one sex partner, a sex partner with concurrent partners, a sex partner who has an STI, inconsistent condom use when not in a mutually monogamous relationship, history of exchanging sex for money or drugs, or a history of incarceration.*
***Risk factors for syphilis include history of incarceration, presence of other STIs or partner with STIs, sex in exchange for money or drugs, or living in a community with a high syphilis morbidity.*
****Risk factors for hepatitis B include more than one sex partner in the past six months, evaluation or treatment for an STI, past or current injection drug use, or hepatitis B positive sex partner.*

Source: Centers for Disease Control and Prevention.

Clinicians can consider testing women with PID for *M. genitalium*. At LG Health, order an "unidentified lab" and specify "*Mycoplasma genitalium* PCR," which can be performed on an endocervical, vaginal, urethral, or urine specimen. Note that *M. genitalium* has significant antibiotic resistance.

The preferred regimen for treatment if *M. genitalium* resistance testing is not available (such as at LG Health) is:

- Doxycycline 100 mg orally twice daily for seven days, followed by moxifloxacin 400 mg orally daily for seven days.

How should providers follow-up after treatment of gonorrhea or chlamydia?

Patients should abstain from sexual intercourse after treatment for gonorrhea or chlamydia for at least seven days after the initiation of treatment, until symptoms have resolved if present, and until completion of treatment by sexual partners. All persons diagnosed with an STI should be tested for chlamydia and gonorrhea in any susceptible site, as well as for HIV and syphilis if not already tested.

Repeat testing for gonorrhea and chlamydia infections in three months is recommended because of high rates of reinfection. HIV pre-exposure prophylaxis should be offered to any person who is HIV negative with an increased risk of HIV transmission, including any person diagnosed with syphilis or gonorrhea and any man who has sex with men who has anorectal chlamydia. Refer to the CDC Pre-Exposure Prophylaxis for the Prevention of HIV Infection in the United States guidelines for further information.[19]

What partner services should be available for patients?

Most health departments routinely provide partner services to patients with syphilis and newly diagnosed HIV but may not offer partner services for patients diagnosed with other STIs. Providers should encourage all patients with STIs to inform their sexual partners from the past 60 days of positive STI testing.

Expedited Partner Therapy (EPT) should be used by providers as a harm-reduction technique to treat sexual partners of persons with chlamydia or gonorrhea who are not able or not likely to seek treatment. This reduces rates of transmission and reinfection. EPT is permissible in Pennsylvania.

The preferred regimen for EPT for chlamydial infections is doxycycline 100 mg orally twice daily for seven days. The preferred regimen for EPT for gonococcal infections is cefixime 800 mg orally once. Note that cefixime has decreased efficacy compared to injectable cephalosporins, and thus efforts should be made to connect patient with treatment prior to prescribing EPT for gonococcal infections.

Packaged medication or prescriptions provided for EPT should be accompanied by educational material that includes treatment instructions, warnings about the medication (including safety in pregnancy), health counseling, and a statement advising that partners seek medical evaluation for STI testing.

Limited data are available regarding EPT for gonococcal or chlamydial infections among men who have sex with men (MSM). Persons in this population have a higher rate of coexisting STIs such as syphilis or HIV, which may not be detected if comprehensive STI testing is not obtained. The CDC recommends shared clinical decision-making regarding EPT and encourages connecting patients for comprehensive STI screening in the MSM population.

KEY TAKEAWAYS

Clinicians can consider testing women with PID for M. genitalium. *At LG Health, order an "unidentified lab" and specify "*Mycoplasma genitalium *PCR," which can be performed on an endocervical, vaginal, urethral, or urine specimen. Note that* M. genitalium *has significant antibiotic resistance.*

Providers should encourage all patients with STIs to inform their sexual partners from the past 60 days of positive STI testing. Expedited Partner Therapy should be used by providers as a harm-reduction technique to treat sexual partners of persons with chlamydia or gonorrhea who are not able or not likely to seek treatment.

CONCLUSION

STIs remain highly prevalent and have great morbidity and mortality in the United States. This article emphasizes important updates in treatment recommendations for STIs and offers tips for ensuring all patients presenting for STI evaluation receive comprehensive evaluation and treatment.

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