Highlights of updated recommendations in the 2021 CDC sexually transmitted infections treatment guidelines

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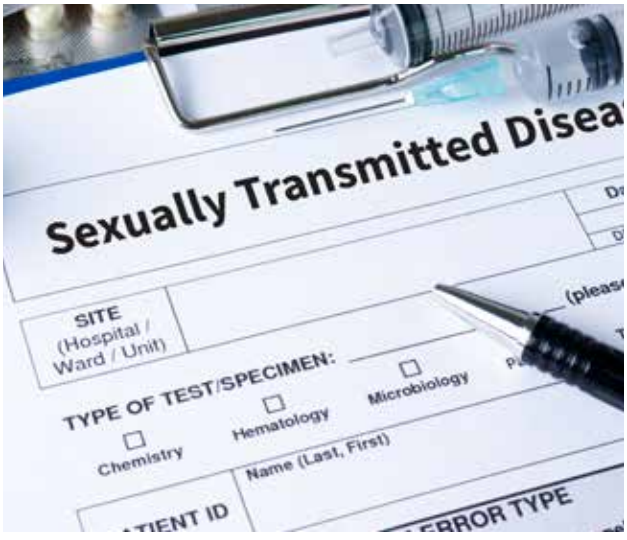
The Centers for Disease Control and Prevention (CDC) has provided clinicians with guidelines for the treatment of sexually transmitted infections (STIs) for more than three decades. Updates have been made on a regular basis through a multiple step process that includes engaging subject matter experts, conducting systematic literature reviews, ranking evidence, and convening meetings for discussion and decision making. The process is guided by four principal outcomes of therapy for each disease or infection: microbiologic eradication of infection, alleviation of signs and symptoms, prevention of sequelae, and prevention of transmission.[1]

Recommended and alternative treatment regimens consider efficacy, drug resistance, cost effectiveness, availability, adherence facilitation, and adverse reactions.[1] The guidelines are intended to assist clinicians in the prevention and treatment of STIs and are not meant to be prescriptive standards. The clinician should always consider the clinical circumstances of each patient. We also are reminded of the diversity of the patients we serve in a section on STI detection among special populations.[1] As clinicians, we should be aware of signs and symptoms consistent with common STIs and we should make decisions about screening for asymptomatic infections based on the patient's sexual practices and anatomy.



The most recent update of the guidelines was published in July 2021.[1] This article highlights changes in recommendations in the 2021 edition compared with the 2015 guidelines.[2]

Updated treatment guidelines

The 2021 guidelines include updated recommendations for treatment of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, pelvic inflammatory disease (PID) and *Mycoplasma genitalium*, and alternative treatment options for bacterial vaginosis (BV). Updated recommendations for testing include expanded risk factors for syphilis testing among pregnant persons, one-time testing for hepatitis C infection, and two-step testing for serologic diagnosis of genital herpes simplex virus.

Recommended regimen for treatment of chlamydial infection

Azithromycin 1 g orally in a single dose has been moved out of the recommended regimen category for treatment of *C. trachomatis* among adolescents and adults and into the alternative regimen category. Doxycycline 100 mg orally 2 times/day for 7 days is now the only medication in the recommended regimen category.[1] See *Box 1* for recommended and alternative treatment regimens.

Doxycycline is effective for *C. trachomatis* infections of urogenital, rectal, and oropharyngeal sites. Although azithromycin is highly effective for urogenital *C. trachomatis* infection among women, concern exists about its effec-

Box 1. Treatment for chlamydial infection among adolescents and adults[1]

Recommended regimen
Doxycycline 100 mg orally 2 times/day for 7 days
Alternative regimens
Azithromycin 1 g orally in a single dose (when nonadherence to doxycycline is a substantial concern)

or

Levofloxacin 500 mg orally once daily for 7 days (more expensive option)

tiveness for rectal infections.[3] Concomitant urogenital and rectal *C. trachomatis* infection is common in women and is not associated with reports of receptive anorectal activity. If not adequately treated, a rectal infection can increase the risk for repeat urogenital infection through autoinoculation from the anorectal site.[4] Doxycycline also is more effective than azithromycin in the treatment of rectal *C. trachomatis* infection among men who have sex with men.[5] Erythromycin has been removed from the alternative regimens category because of the frequency of gastrointestinal side effects, which can result in nonadherence. Azithromycin remains the recommended treatment for pregnant individuals with chlamydial infection.[1]

Recommended regimen for treatment of gonococcal infection

The treatment of gonorrhea has presented challenges for more than 20 years because of the ability of *N. gonorrhoeae* to develop resistance to antimicrobials. Dual therapy with a combination of two antimicrobials with different mechanisms of action has previously been recommended on the theoretical basis that this would improve efficacy and potentially slow the emergence of resistance to cephalosporins. The recommended regimen in the 2015 CDC guidelines was ceftriaxone 250 mg IM plus azithromycin even if chlamydial infection were ruled out.[2] Although this dual therapy might have mitigated the emergence of reduced susceptibility to ceftriaxone, concerns regarding the effect on other pathogens has diminished the benefits. Emergence of azithromycin resistance is not isolated to *N. gonorrhoeae*, as it has also been demonstrated in *M. genitalium* and some enteric pathogens.

The 2021 guidelines recommend ceftriaxone in an increased dose alone for the treatment of gonococcal infection of the cervix, urethra, or rectum. If chlamydial infection has not been excluded, doxycycline should be added rather than azithromycin. See *Box 2* for recommended and alternative treatment regimens. Clinicians are encouraged to remain vigilant for treatment failures with the use of ceftriaxone.

Recommended regimen for treatment of trichomoniasis

The recommended regimen for the treatment of *T. vaginalis* infection has been changed based on a meta-analysis of studies evaluating data on trichomoniasis and metronidazole. Findings demonstrated that women who received metronidazole 500 mg orally 2 times/day for 7 days were less likely to have treatment failure compared with those receiving metronidazole 2 g in a single dose.[6]

Box 2. Treatment for uncomplicated gonococcal infection of the cervix, urethra, or rectum among adolescents and adults[1]

Recommended regimen
Ceftriaxone 500 mg IM in a single dose for persons weighing < 150 kg and 1 g dose for persons weighing ≥ 150 kg; if chlamydial infection has not been excluded, treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.

Alternative regimens if ceftriaxone is not available
Gentamicin 240 mg IM in a single dose plus azithromycin 2 g orally in a single dose

or

Cefixime 800 mg orally in a single dose; if chlamydial infection has not been excluded, treat for chlamydia with doxycycline 100 mg orally for 2 times/day for 7 days.

Uncomplicated oropharyngeal gonococcal infection should be treated with ceftriaxone in the same doses as for infections of the cervix, urethra, or rectum.

Box 3. Treatment for trichomoniasis[1]

Recommended regimen among women
Metronidazole 500 mg orally 2 times/day for 7 days

Recommended regimen among men
Metronidazole 2 g orally in a single dose

Alternative regimen for women and men
Tinidazole 2 g orally in a single dose (more expensive option)

No published randomized trials are available to compare these doses among men. See *Box 3* for recommended and alternative treatment regimens.

Alternative regimens for treatment of bacterial vaginosis

The recommended regimens for the treatment of BV remain the same. Secnidazole 2 g oral granules in a single dose has been added to the list of alternative regimens. It is listed as an alternative regimen due to its higher cost and lack of long-term outcomes compared with the recommended BV treatments.[1]

Additionally, the guidelines note that restricting alcohol use while taking metronidazole is not necessary. Previous warnings about the risk for disulfiram-like interaction between metronidazole and alcohol were based on laboratory experiments and individual case histories. Metronidazole does not inhibit acetaldehyde as happens with disulfiram.[1]

Recommended regimen for treatment of pelvic inflammatory disease

In the 2015 CDC guidelines, the recommended intramuscular/oral treatment regimen for PID included consideration of the addition of metronidazole using the words "with" or "without."[2] The rationale was that anaerobic bacteria have been isolated from the upper reproductive tract with PID and that some anaerobes can cause tubal and epithelial damage. As well, BV is often present in individuals with PID. The recommended third-generation cephalosporins are not efficient in their coverage of anaerobes. More data are needed to determine if treatment regimens that do not cover anaerobic bacteria prevent long-term sequelae (eg, infertility, ectopic pregnancy) as successfully as regimens that are effective against these bacteria. The 2021 guidelines present the same rationale for consideration of the addition of metronidazole but the word without has been removed, making the recommendation more definitive. The current recommended outpatient treatment for PID includes a cephalosporin (ie, ceftriaxone, cefoxitin, ceftizoxime, cefotaxime) intramuscular injection followed by doxycycline and metronidazole for 14 days.

Mycoplasma genitalium management

The role of *M. genitalium* as a causative organism in nongonococcal urethritis among men is recognized, although data are not sufficient to implicate *M. genitalium* infection with epididymitis, prostatitis, or infertility.[7] *M. genitalium* has been associated with cervicitis, PID, preterm delivery, spontaneous abortion, and infertility, with an approximate twofold increase in the risk for these outcomes among women infected with *M. genitalium*.[8] The consequences of asymptomatic *M. genitalium* infection in men and women are unknown.

A nucleic acid amplification test (NAAT) approved by the US Food and Drug Administration for *M. genitalium* is now available for use with urine, urethral, endocervical, and vaginal swab samples. The 2021 CDC guidelines recommend that men with recurrent nongonococcal urethritis be tested for *M. genitalium*. Women with recurrent cervicitis should be tested, and testing should be considered among women with PID. If NAAT testing is not available, *M. genitalium* should be suspected in cases of persistent or recurrent urethritis or cervicitis.

Because of concerns about rapidly increasing resistance to azithromycin and possible although less prevalent resistance to quinolones, treatment for *M. genitalium* should be guided by antimicrobial resistance testing when available.[7,9] Beta-lactams including penicillins and cephalosporins are ineffective against *M. genitalium*. Because of the high rates of resistance, a 1-g dose of azithromycin should not be used.

Two-stage therapy approaches, ideally using resistance-guided therapy, are recommended for treatment. As part of this approach, doxycycline is provided as initial empiric therapy, which reduces the organism load and facilitates organism clearance, followed by high-dose azithromycin for macrolide-sensitive *M. genitalium* infections and moxifloxacin for macrolide-resistant infections.[1] See *Box 4* for recommended treatment regimens.

In settings without access to resistance testing, the macrolide-resistant regimen should be used. Based on limited data, if moxifloxacin cannot be used, an alternative is to use the macrolide-sensitive regimen followed by a test of cure 21 days after completion of therapy. This regimen should only be used when a test of cure is possible and no other alternatives exist. If symptomatic treatment failure or a positive test of cure occurs after this regimen, expert consultation is recommended.[1]

Sex partners of patients with symptomatic *M. genitalium* infection can be tested, and those with a positive test can be treated to possibly reduce the risk for reinfection. If antimicrobial testing for the partner is not possible, the antimicrobial regimen provided to the patient can be used.[1]

Box 4. Recommended regimens if *M. genitalium* resistance testing is available[1]

If macrolide sensitive:
Doxycycline 100 mg orally 2 times/day for 7 days, followed by azithromycin 1 g orally initial dose, followed by 500 mg orally for 3 additional days (2.5 g total)

If macrolide resistant:
Doxycycline 100 mg orally 2 times/day for 7 days, followed by moxifloxacin 400 mg orally once daily for 7 days

Expanded risk factors for syphilis testing among pregnant individuals

The 2021 CDC guidelines continue to recommend that all pregnant individuals should be screened for syphilis at the first prenatal visit, even if they have been tested previously. Testing again in the third trimester and at delivery with treatment if needed can prevent congenital syphilis cases. This is particularly relevant because the congenital syphilis rates in the United States have increased from 8.4 to 48.5 cases per 100,000 births from 2012 to 2019.[10] Given this alarming rise, the current CDC guidelines recommend that all pregnant individuals be retested for syphilis at 28 weeks' gestation and at delivery if the individual lives in a community with high syphilis rates or is at risk for syphilis acquisition during pregnancy (eg, has another STI, multiple sex partners, a new sex partner, or a sex partner with an STI).

One-time testing for hepatitis C infection

In the 2015 edition of the CDC guidelines, hepatitis C virus (HCV) was described as an emerging issue. The CDC and US Preventive Services Task Force recommended HCV screening for all persons born between 1945 and 1965 and others based on their risk for infection or on a recognized exposure, including past or current injection drug use, receiving a blood transfusion before 1992, long-term hemodialysis, being born to a mother with HCV infection, intranasal drug use, receipt of an unregulated tattoo, and other percutaneous exposures.[2]

In the 2021 edition, the CDC recommends HCV screening at least once in a lifetime for all adults and for all pregnant women during each pregnancy unless community prevalence of HCV infection is less than 0.1%.[11] Routine periodic HCV screening is recommended for persons with ongoing risk factors.

Two-step testing for serologic diagnosis of genital herpes simplex virus

The description of when type-specific serologic assays may be useful remains the same as in the 2015 guidelines and is not recommended for routine screening purposes. The only change has been in the qualifications of the recommendation to confirm positive HerpeSelect HSV-2 enzyme immunoassay (EIA) test results. The 2015 CDC guidelines provided information on the low specificity of this commercial EIA with the possibility of false-positive results especially when there are low index values. The recommendation was that a positive result with an index value of 1.1 to 3.5 should be confirmed with another test such as the commercially available Biokit or the Western blot but not with the HerpeSelect HSV-2 immunoblot because it uses the same antigen as the HSV-2 EIA.[2]

The 2021 CDC guidelines recommend that any positive result when using the HerpeSelect HSV-2 EIA be confirmed with another test (Biokit or Western blot) before test interpretation. Although false positives are more likely with low index values , one study reported an overall specificity of 57.4%.[12] Use of confirmatory testing with the Biokit or the Western blot assays has been reported to improve accuracy of HSV-2 serologic testing.[12] If confirmatory tests are unavailable, patients should be counseled about the limitations of available testing before obtaining serologic tests and clinicians should be aware that false-positive results occur.

Implications for practice

This article does not cover aspects of testing and treatment that have not changed. The clinician should have access to and consult the guidelines as needed. Sometimes recommendations change before a new edition of the guidelines is published because of emerging data. It is important to keep up to date through use of electronic resources, journals, and workshops. ■

Beth Kelsey is the Director of Publications for the National Association of Nurse Practitioners in Women's Health in Washington, DC, and the Editor-in-Chief of this journal. The author has no actual or potential conflicts of interest in relation to the contents of this article.

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