# Chapter 140: Sexually Transmitted Infections

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## CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 47, Sexually Transmitted Infections.

## KEY CONCEPTS

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1. A single dose of ceftriaxone is recommended for uncomplicated gonococcal infections. Antimicrobial stewardship concerns over the impact on the microbiome, increasing rates of azithromycin resistance and continued low ceftriaxone resistance rates, led to the move away from dual drug therapy. If chlamydial infection cannot be excluded, doxycycline should be added.

2. Chlamydia genital tract infections represent the most frequently reported communicable disease in the United States. Females are frequently asymptomatic or minimally symptomatic and, if left untreated, may develop complications such as pelvic inflammatory disease (PID), ectopic pregnancy, or infertility. All sexually active females younger than 25 years and women with multiple sexual partners should be screened annually.

3. A 7-day course of metronidazole is the preferred treatment for trichomoniasis in women, with single dose tinidazole as an alternative. Single-dose metronidazole remains the recommended therapy for men.

4. PID treatment should target gonorrhea and chlamydia, with the addition of anaerobic coverage.

5. Parenteral penicillin is the treatment of choice for all syphilis infections. Alternative therapies for penicillin-allergic patients are usually suboptimal, have insufficient data, require prolonged oral courses, and/or are not recommended for specific populations. When allergies are reported, clarification of the type of reaction is critical to ensure optimal therapy. For true penicillin allergies, penicillin desensitization protocols are available when penicillin is required.

6. Oral acyclovir, famciclovir, and valacyclovir are effective in reducing viral shedding, duration of symptoms, and time to healing of first-episode genital herpes infections, with maximal benefits seen when therapy is initiated at the earliest stages of infection. Patient-initiated, episodic antiviral therapy started within 1 day of lesion onset or during the prodromal stage preceding an outbreak offers an alternative to continuous suppressive therapy of recurrent infection in some individuals.

7. Human papilloma virus (HPV) vaccination reduces complications associated with HPV infection, including development of genital warts and HPV-related cancers. Adolescent vaccination, prior to onset of sexual activity is recommended. Despite robust safety and efficacy data, vaccination rates remain below 80% in target populations.

## BEYOND THE BOOK

Obtaining a relevant and culturally sensitive sexual history is an important part of ensuring an individual's optimal health. Patient interviews should

include the five Ps: partners, practices, protection, past STIs, and prevention of pregnancy strategies.

Watch the following videos that focus on the importance of collecting a sexual history and understanding at-risk populations. These videos are useful to enhance student understanding regarding the Collect and Assess steps in the patient care process.

https://www.cdc.gov/std/be-smart-be-well/letstalk.htm

https://www.youtube.com/watch?v=WUsebbT39C4

## INTRODUCTION

Sexually transmitted infections (STIs) encompass a wide variety of pathogens (Table 140-1), diverse presentations, and continually evolving diagnosis, treatment and prevention strategies. STIs impact short- and long-term health of millions in the United States, yet continue to be underfunded, stigmatized, and devalued as a public health priority. Since 2000, rates continue to rise, with chlamydia doubling, gonorrhea increasing 40%, and primary and secondary syphilis cases soaring fivefold.[1,2] In 2018, one in five people in the United States had an STI.[2] Almost half of the 26 million new infections in 2018 were acquired by teens and young adults (15-24 years old).[1] Besides in youth, STIs rates are disproportionally higher in marginalized groups, specifically sexual and gender minorities (encompassing lesbian, gay, bisexual, and transgender communities), Black, Latinx, American Indian/Alaska Native, and Native Hawaiian/other Pacific Islander people.[1] Furthermore, the financial impact of STIs are substantial, costing the U.S. healthcare system an estimated $16 billion in direct lifetime medical costs.[3]

TABLE 140-1

**Sexually Transmitted Infections**

| Disease | Associated Pathogens |
|---|---|
| **Bacterial** | |
| Gonorrhea | *Neisseria gonorrhoeae* |
| Syphilis | *Treponema pallidum* |
| Chancroid | *Haemophilus ducreyi* |
| Granuloma inguinale | *Klebsiella granulomatis* |
| Enteric disease | *Salmonella* spp., *Shigella* spp., *Campylobacter* spp. |
| *Campylobacter* infection | *Campylobacter jejuni* |
| Bacterial vaginosis | *Gardnerella vaginalis, Mycoplasma hominis, Bacteroides* spp., *Mobiluncus* spp. |
| **Chlamydial** | |
| Nongonococcal urethritis | *Chlamydia trachomatis* |
| Lymphogranuloma venereum | *C. trachomatis*, type L |
| **Viral** | |
| Acquired immunodeficiency syndrome | Human immunodeficiency virus |
| Herpes genitalis | Herpes simplex virus, types 1 and 2 |
| Viral hepatitis | Hepatitis A, B, C, and D viruses |
| Condylomata acuminata | Human papillomavirus |
| **Mycoplasmal** | |
| Nongonococcal urethritis | *Mycoplasma genitalium* |
| **Protozoal** | |
| Trichomoniasis | *Trichomonas vaginalis* |
| **Fungal** | |
| Vaginal candidiasis | *Candida albicans* |

STI health consequences range from urogenital discomfort to encephalitis. Women are especially susceptible to complications, many of which center

around reproductive health. Pregnancy-related morbidity is often devastating, including stillbirth and fetal or newborn transmission. Men can also experience reproductive sequelae. Extragenital manifestations, such as neurosyphilis and septic arthritis, can be classic findings or present with non-specific symptoms.

While the terms sexually transmitted diseases (STDs) and STIs are often used interchangeably, there has been a global shift toward using the term STI. Many infections are asymptomatic, with some clearing spontaneously. An STD is a recognizable disease or condition that develops from an STI. Thus, the term STI is more accurate, more inclusive, and carries less stigma than STD.[4]

The risk of acquiring and transmitting an STI varies based on pathogen, host characteristics, local epidemiology, individual behavior, sexual networks, and broader social and structural factors. Age-specific STI rates are historically higher in men versus women; however, reported rates may not represent true gender differences and may reflect ease of detection in men. In recent years, male-to-female ratios for most STIs have declined or reversed, reflecting improved STI screening. Rates of some STIs, such as syphilis and HIV, are disproportionately greater in men who have sex with men (MSM).[1] The risks of acquiring select STIs are elevated among racial and ethnic minorities in the United States, particularly, chlamydia, gonorrhea, and (primary and secondary) syphilis rates among Black versus White Americans.[5] Multiple or anonymous sex partners, condomless sex, and sex while under the influence of drugs or alcohol can increase STI (and HIV) acquisition risks.[6] Limited access and reduced engagement with medical care, living in areas with high prevalence, high-risk sexual networks, and marginalized and/or stigmatized communities are broader factors that can increase STI risk.[7]

The national strategy toward addressing STIs has historically centered on screening, treating, and preventing infections based on individual risks and/or behaviors. These tactics, combined with the complexities of the US healthcare system, societal discomfort discussing sexuality and sexual health, and structural inequities, have led to some of the highest STI rates among higher income nations. Healthcare provider's implicit bias and systemic discriminatory policies have also hampered efforts to reduce STIs through suboptimal screening initiatives and limited engagement of affected individuals within the healthcare system.[8,9] The Committee on Prevention and Control of STIs in the United States encourages a new approach, centered around the understanding that sexual health is a "state of physical, emotional, mental, and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity," as stated by World Health Organization (WHO).[10] Efforts should be more holistic, addressing principal drivers of health inequities, such as social determinants of health and structural bias and acknowledging how social networks and prevalence variations impact STI risk. To expand the STI workforce, the Centers for Disease Control and Prevention (CDC) encourages primary care providers help close STI screening and treatment gaps.[9,11]

Other than complete abstinence, the most effective way to prevent STI transmission is by maintaining a mutually monogamous sexual relationship between uninfected partners. Short of this, use of barrier contraceptive methods provide varying degrees of protection. Post-exposure prophylaxis with doxycycline has been found to reduce risk of transmission of bacterial STIs in certain populations, and guidelines are under construction to outline the optimal use of this strategy.[107] Reducing the number of partners and increased testing can also lower risk. Obtaining a relevant and culturally sensitive sexual history is important to perform an accurate risk assessment. Even when providers ask about sexual and STI history, less often are number or gender of sex partners, or types of sexual practices collected. Patient interviews should include the five Ps: partners, practices, protection, past STIs, and prevention of pregnancy strategies.[11]

Treating STIs appropriately and early is important to curb transmission and prevent complications. Ensuring screening and/or treatment of sex partners is a critical facet of STI management. Partner referral can be initiated by the index patient or provider.[12] Expedited partner therapy (EPT) is another option when partners cannot receive a medical evaluation. In EPT, a partner's prescription is provided to the index patient for the dual benefit of treating the partner(s) and preventing reinfection of the index patient. Although legal status of EPT has not always been explicitly clear, the CDC and the Center for Law and the Public's Health have found that EPT is permissible or potentially allowable in all states and other US territories. Increased awareness and education are needed to remove barriers that continue to limit this practice.[12]

With the exception of human immunodeficiency virus (HIV) infection, reviewed in detail in Chapter 148, the most frequently occurring STIs in the United States are discussed in this chapter. The varied spectrum of clinical syndromes produced by common STIs is determined not only by the etiologic pathogen(s) but also by differences in anatomy and reproductive physiology. For many STIs, signs and symptoms overlap sufficiently to prevent accurate diagnosis without microbiologic confirmation. Frequently, symptoms are minimal or absent despite the presence of infection. Table 140-2 lists common clinical syndromes associated with STIs.[4]

TABLE 140-2

**Selected Syndromes Associated with Common Sexually Transmitted Pathogens**

| Syndrome | Commonly Implicated Pathogens | Common Clinical Manifestations[a] |
|---|---|---|
| Urethritis | *C. trachomatis*, herpes simplex virus, *N. gonorrhoeae*, *T. vaginalis*, *Ureaplasma spp.*, *M. genitalium* | Urethral discharge, dysuria |
| Epididymitis | *C. trachomatis*, *N. gonorrhoeae,* Enterobacterales | Scrotal pain, inguinal pain, flank pain, urethral discharge |
| Cervicitis/vulvovaginitis | *C. trachomatis, G. vaginalis*, herpes simplex virus, human papillomavirus, *N. gonorrhoeae, T. vaginalis* | Abnormal vaginal discharge, vulvar itching/irritation, dysuria, dyspareunia |
| Genital ulcers (painful) | *H. ducreyi*, herpes simplex virus | Usually multiple vesicular/pustular (herpes) or papular/pustular (*H. ducreyi*) lesions that can coalesce; painful, tender lymphadenopathy[b] |
| Genital ulcers (painless) | *T. pallidum* | Usually single papular lesion, usually painless |
| Genital/anal warts | Human papillomavirus | Multiple lesions ranging in size from small papular warts to large exophytic condylomas |
| Pharyngitis | *C. trachomatis*, herpes simplex virus, *N. gonorrhoeae* | Symptoms of acute pharyngitis, cervical lymphadenopathy, fever[c] |
| Proctitis | *C. trachomatis*, herpes simplex virus, *N. gonorrhoeae, T. pallidum* | Constipation, anorectal discomfort, tenesmus, mucopurulent rectal discharge |
| Salpingitis | *C. trachomatis, N. gonorrhoeae* | Lower abdominal pain, purulent cervical or vaginal discharge, adnexal swelling, fever[d] |

[a]For some syndromes, clinical manifestations can be minimal or absent.

[b]Recurrent herpes infection can manifest as a single lesion.

[c]Most cases of pharyngeal gonococcal infection are asymptomatic.

[d]Salpingitis increases the risk of subsequent ectopic pregnancy and infertility.

First, STIs commonly presenting with urethritis or vaginal discharge and associated complications are discussed, followed by STIs commonly associated with genital ulcers or lesions. Several STIs not included in this chapter warrant mention, including increased awareness of proctitis among MSM caused by gram-negative bacteria normally present in the gut microbiota, such as *Campylobacter* and *Shigella* species, as well as atypical organisms, such as herpes simplex virus (HSV). Outbreak concerns and growing viral hepatitis rates led to updates in screening recommendations. The most current information on the epidemiology, diagnosis, and treatment of these and other STIs can be obtained at the CDC Website (http://www.cdc.gov).

## GONORRHEA

## Epidemiology and Etiology

Gonorrhea is the second most commonly reported notifiable disease in the United States.[1,4] Since the mid-1990s through early 2000s, rates of reported cases in the United States remained relatively stable. However, since a historic low in 2009, rates of gonorrhea have increased 92% with 616,392 cases reported to the CDC in 2019 equating to 188.4 cases/100,000 persons compared to 98.1 cases/100,000 persons in 2009.[1] Of growing concern are substantial numbers of infections that remain undiagnosed and unreported, thereby perpetuating spread of disease. Reported cases among males increased 112% compared to 42% among females from 2012 to 2019. Higher rates in males may be representative of increased transmission, detection via extra-genital screening among MSM, or both.[1]

In 2013, the CDC identified drug-resistant *Neisseria gonorrhoeae* as a top three pathogen presenting an urgent level threat, posing an immediate health threat requiring urgent and aggressive action.[13] The 2019 update maintains the urgent threat level, showcasing increasing resistance over time and doubling of infections from 2013 to 2019.[14] Additionally, the WHO identified drug-resistant *N. gonorrhoeae* as a high priority organism for new antibiotic development.[15] Due to rising resistance, large numbers of asymptomatic infections, and ease of transmission, gonorrhea is difficult to control. Additionally, HIV infection is more easily transmitted in patients coinfected with gonorrhea.[4]

## Pathophysiology

*N. gonorrhoeae,* the causative agent of gonorrhea infections, a gram-negative diplococcus, does not have any animal or environmental reservoirs and humans are the only known host. *N. gonorrhoeae* infects mucosa of the urethra, endocervix, anorectum, pharynx, and conjunctiva. After mucosal damage is established, polymorphonuclear (PMN) leukocytes invade tissue and form submucosal abscesses, resulting in purulent exudates.[4,16]

Gonorrhea is highly transmissible via sexual contact. Female risk of acquisition after a single episode of vaginal intercourse with an infected male partner is 50% to 70%; however, risk of female-to-male transmission following a single act is 20%.[17,18] With repeated exposure, risk of female-to-male transmission increases to 60% to 80%.[17] Although transmission rates for other types of sexual contact are not quantified, anal intercourse is likely more efficient while oral sex is less efficient than penile-vaginal sex.[16]

## Clinical Presentation

Individuals infected with gonorrhea can be symptomatic or asymptomatic and have infections involving several anatomic sites. Interestingly, most untreated symptomatic patients become asymptomatic within 6 months, with only a few becoming asymptomatic carriers of disease.[4,16] In settings where sexually active women are routinely screened for subclinical infections, most diagnosed with gonorrhea are asymptomatic. Up to 50% of women experience nonspecific symptoms, including mucopurulent vaginal discharge or post-intercourse vaginal bleeding. In comparison, 90% of males experience symptoms within 2 to 6 days following exposure, most commonly mucopurulent penile discharge or dysuria.[1,19] The most common clinical features of gonococcal infections are presented in Table 140-3.

TABLE 140-3

**Presentation of Gonorrhea Infections**

| | Males | Females |
|---|---|---|
| General | Incubation period: 1-14 days | Incubation period: 1-14 days |
| | Symptom onset in 2-8 days | Symptom onset in 10 days |
| Site of infection | Most common: urethra | Most common: endocervical canal |
| | Others: rectum (usually caused by rectal intercourse in MSM), oropharynx, eye | Others: urethra, rectum (usually caused by perineal contamination), oropharynx, eye |
| Symptoms | Commonly symptomatic, may be asymptomatic | Can be asymptomatic or minimally symptomatic |
| | Urethral infection: dysuria and urinary frequency | Endocervical infection: usually asymptomatic or mildly symptomatic |
| | Anorectal infection: asymptomatic to severe rectal pain | Urethral infection: dysuria, urinary frequency |
| | Pharyngeal infection: asymptomatic to mild pharyngitis | Anorectal and pharyngeal infection; symptoms same as for men |
| Signs | Purulent urethral or rectal discharge can be scant to profuse<br>Anorectal: pruritus, mucopurulent discharge, bleeding | Abnormal vaginal discharge or uterine bleeding; purulent urethral or rectal discharge can be scant to profuse |
| Complications | Rare (epididymitis, prostatitis, inguinal lymphadenopathy, urethral stricture) | PID and associated complications (ie, ectopic pregnancy, infertility) |
| | Disseminated gonorrhea | Disseminated gonorrhea |

Complications associated with untreated gonorrhea appear more pronounced in women, likely a result of a high percentage who experience nonspecific or minimal symptoms. As a result, many women do not seek treatment until after development of serious complications, such as pelvic inflammatory disease (PID). Approximately 10% to 20% of women with gonorrhea develop PID.[1,6,20] Left untreated, PID can cause infertility and ectopic pregnancies. Previous reports indicate 0.5% to 3% of gonorrhea infections result in disseminated gonococcal infection (DGI), but the risk may be less given declining prevalence of strains prone to dissemination.[21–23] Usual clinical manifestations of DGI are tender necrotic skin lesions, tenosynovitis, and monoarticular arthritis, or rarely meningitis or endocarditis.[4,16]

## Diagnosis

Obtaining specific microbiologic diagnosis is recommended to reduce complications, reinfections, and transmission versus clinical diagnosis. Diagnosis of gonococcal infections can be made by Gram-stained smears, culture, or detection of cellular components (eg, enzymes, antigens, or DNA).[4]

Nucleic acid detection tests replaced culture or Gram stain in most settings as the primary diagnostic or screening test. These offer increased sensitivity and/or specificity over traditional diagnostic methods and provide more rapid results versus culture.[4,24]

Nucleic acid amplification tests (NAATs) are the most widely used and employ techniques and have high sensitivity for detecting *N. gonorrhoeae* using

noninvasive specimens (eg, self-collected urine specimens, vaginal swabs). A NAAT is recommended by the CDC for detection of gonorrhea[4,24] and are approved for endocervical (women), urethral (men), and urine specimens. Extragenital diagnostic NAAT testing is now available for pharyngeal and rectal samples, in combination with testing for *Chlamydia trachomatis*.[25] A major drawback of NAATs is their inability to provide resistance data. In cases of documented treatment failure, culture and antimicrobial susceptibility testing is recommended.[4,24]

While NAATs are most commonly used in clinical practice, Gram stains can be used to make a presumptive diagnosis of gonorrhea infections. A Gram stain performed on purulent male urethral discharge is diagnostic for infection when gram-negative diplococci are identified within PMN leukocytes. However, due to lower sensitivity, Gram-stained smears are not recommended for diagnosis of endocervical, rectal, pharyngeal, and asymptomatic male urethral infections. Because of the pharyngeal presence of nonpathogenic *Neisseria* spp., Gram stain is not useful in pharyngeal infection diagnosis.[4,16]

Bacterial cultures are highly sensitive and specific, provide opportunity for susceptibility testing, and can be performed on a variety of specimens. Prolonged turnaround times, decreased sensitivity compared to NAATS, and additional laboratory requirements preclude widespread usage. With the expansion of FDA-approval of NAATs on various specimen types, culture is primarily reserved for cases of suspected or documented treatment failures, as a test of cure (TOC) following use of alternative treatment regimens, or when evaluating for DGI.[4]

Routine screening for *N. gonorrhoeae* is recommended in certain populations to reduce burden of disease and morbidity associated with gonococcal infection. As females are more commonly asymptomatic, the CDC and US Preventative Services Task Force (USPSTF) recommend routine annual screening for gonococcal infection for all sexually active women younger than 25.[4,26] For those 25 years and older, annual screening is recommended for those at increased risk of gonococcal infection (eg, multiple or new sexual partners, partners with an STI, inconsistent condom use, transactional sex, or history of STI[s]). Pregnant women should be screened for gonorrhea at the first prenatal visit and again during the third trimester, for those at continued risk. The CDC also recommends that MSM should be screened at least annually, regardless of condom use, testing sites involved with sexual activity.[4]

## Treatment

1 *N. gonorrhoeae* has developed resistance to all antibiotics previously used for treatment, including sulfonamides, penicillins, tetracyclines, fluoroquinolones, and early generation macrolides and cephalosporins. In 2020, the CDC issued updated gonorrhea treatment recommendations.[27]

A single 500 mg ceftriaxone dose is recommended for treatment of uncomplicated gonococcal infections. Previously, dual antibiotic therapy with different mechanisms of action (ceftriaxone plus azithromycin or doxycycline) was recommended to delay further development of cephalosporin resistance. However, rising incidence of azithromycin resistance, antimicrobial stewardship concerns regarding microbiome harm, pharmacokinetic and pharmacodynamic considerations, and continued low ceftriaxone resistance, influenced the recommendation to current single-drug regimen. Single-dose intramuscular (IM) ceftriaxone remains the only recommended agent for treating gonorrhea as ceftriaxone-based regimens have well-documented efficacy in the treatment of urethral, cervical, rectal, and pharyngeal infections.[4,27,28] (Table 140-4). To optimize pharmacokinetic and pharmacodynamic properties of ceftriaxone, the dose of ceftriaxone was increased from previous recommendations. Additionally, patients weighing 150 kg or more should receive ceftriaxone 1 g.[4]

An 800 mg oral dose of cefixime may be substituted if ceftriaxone is unavailable or not feasible, but due to reduced bactericidal levels and efficacy, especially in pharyngeal infections, this regimen is not preferred. Note that based on pharmacokinetic and pharmacodynamic properties, the dose of cefixime was optimized to 800 mg compared to the previous dose of 400 mg.[4,27] Additionally, only ceftriaxone is effective in treating pharyngeal gonorrhea as oral cephalosporins do not reliably cure these infections.[27,28]

Because coexisting chlamydial infections are common, documented in up to 50% of women and 20% of men with gonorrhea, and symptoms may be similar to that of gonorrhea, for those where concurrent chlamydial infection has not been ruled out, chlamydia treatment should be added.[27,29] Doxycycline 100 mg orally twice daily for 7 days is preferred to azithromycin 1 g orally as a single dose.[27] Where previously azithromycin and doxycycline were both considered first-line therapy, this change was based on data suggesting lower efficacy rates when treating chlamydial with azithromycin compared with doxycycline, with increased concern regarding rectal chlamydia.[30–32]

Despite resistance concerns, to date, ceftriaxone treatment failure in the United States has not been reported. If cephalosporins cannot be used, due to allergy or concern for resistance, the recommended alternate regimen is a single dose of 240 mg IM gentamicin in combination with 2 g oral azithromycin. While azithromycin as a single 2 g dose appears highly effective in eradicating both gonorrhea and chlamydia, it is not recommended as a preferred alternative due to concerns regarding resistance. GI side effects are common with the 2 g dose of azithromycin.[27,33]

Parenteral ceftriaxone is the recommended therapy for DGI, including meningitis and endocarditis, and any type of gonococcal infection in children. In DGI, patients should be hospitalized and treated with ceftriaxone or an alternative parenteral cephalosporin (see Table 140-4). Although marked improvement is usually noted within 48 hours of initiating therapy, treatment should be continued for at least 7 days, with longer durations necessary for serious infections, such as meningitis and endocarditis.[4] Gonococcal ophthalmia is highly contagious in adults and neonates and requires ceftriaxone therapy. Single, but higher, dose therapy is adequate for gonococcal conjunctivitis, although some physicians recommend continuing therapy until cultures are negative at 48 to 72 hours. Topical antibiotics are not effective when used alone for ocular infections and are unnecessary with appropriate systemic therapy. Infants with any evidence of ocular infection should be evaluated for signs of DGI.[4,34]

TABLE 140-4

**Treatment of Gonorrhea**

| Type of Infection | Recommended Regimens[a] | Alternative Regimens[a] |
|---|---|---|
| Uncomplicated infections of the cervix, urethra, and rectum in adults | Ceftriaxone 500 mg IM once[b,c] | Gentamicin 240 mg IM[d]<br>*plus*<br>Azithromycin 2 g orally once<br>*or*<br>When ceftriaxone administration is not feasible, cefixime 800 mg orally once[c] |
| Uncomplicated infections of the pharynx | Ceftriaxone 500 mg IM once[b,c] | Consult with infectious disease expert |
| DGI in adults (>45 kg) | Ceftriaxone 1-2 g IM or IV every 12-24 hours[c,e] | Cefotaxime 1 g IV every 8 hours[c,e] or ceftizoxime 1 g IV every 8 hours[c,e] |
| Gonococcal conjunctivitis in adults | Ceftriaxone 1 g IM once[f] | |
| Ophthalmia neonatorum | Ceftriaxone 25-50 mg/kg IV or IM once (not to exceed 250 mg) | |
| Infants born to mothers with gonococcal infection (prophylaxis) | Erythromycin (0.5%) ophthalmic ointment in a single application[g]<br>Ceftriaxone 25-50 mg/kg IM or IV once (not to exceed 125 mg) | |

[a]Recommendations are those of the CDC.

[b]For patients weighing > 150 kg, a 1 g dose of ceftriaxone is recommended.

[c]If chlamydial infection cannot be ruled out, treatment for chlamydia should be administered. Preferred therapy is doxycycline 100 mg orally twice daily × 7 days. Azithromycin 1 g orally once may be used as an alternative. Tetracyclines are contraindicated during pregnancy. Pregnant women should be treated with recommended cephalosporin-based combination therapy. In severe cephalosporin allergy, consultation with an infectious diseases expert is recommended.

[d]For patients with severe cephalosporin allergy.

[e]Parenteral treatment duration should be determined in consultation with an infectious diseases expert. Gonococcal meningitis should be treated with ceftriaxone 2 g IV every 12 hours. Parenteral therapy for meningitis should be continued for at least 10 to 14 days and at least 4 weeks in endocarditis.

[f]A single lavage of the infected eye with normal saline should be considered; empiric therapy for *C. trachomatis* is recommended.

[g]Efficacy in preventing chlamydial ophthalmia is unclear.

Treatment of gonorrhea during pregnancy is essential to prevent ophthalmia neonatorum. Pregnant women infected with *N. gonorrhoeae* should be treated with a single intramuscular dose of ceftriaxone 500 mg, with the addition of 1 g of oral azithromycin if chlamydia has not been ruled out. Fluoroquinolones and tetracyclines are contraindicated in pregnancy. Gonococcal infection in newborns results primarily from passage through an infected birth canal, but may be transmitted in utero. Conjunctival involvement, characterized by intense, bilateral conjunctival inflammation with chemosis, usually develops within 7 days of delivery. If not treated promptly, corneal ulceration and blindness can develop. Because the law in most

states requires neonatal prophylaxis with topical ocular antimicrobials, gonococcal ophthalmia neonatorum is rare in the United States. The CDC recommends erythromycin (0.5%) ophthalmic ointment be instilled in each conjunctival sac immediately postpartum.[4,27,34]

### Patient Care Process for Genital Infection due to *Neisseria gonorrhoeae*


#### Collect

- Patient characteristics (eg, age, gender, pregnancy status)
- Patient medical history (personal and family)
- Social history, including sexual history
- Current medications
- Objective data
  - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight
  - Laboratory data including urine NAATs for gonorrhea and chlamydia, and/or urethral or vaginal cultures
  - Signs and symptoms consistent with gonorrhea (dysuria, mucopurulent urethral or vagina discharge)

#### Assess

- Presence of additional STIs (chlamydia, syphilis, HIV, etc.)
- Presence of extra-genital infection
- Ability/willingness to obtain follow-up testing as needed
- Ability/willingness to notify sexual partners
- Emotional status (eg, presence of anxiety, depression)

#### Plan

- Drug therapy regimen including, dose, route, frequency, and duration (Table 140-4)
- Monitoring parameters including efficacy (eg, retest 3 months after treatment) and safety, frequency and timing of follow-up
- Patient education (eg, purpose of treatment, notification of sexual partners, safe sexual practices, drug-specific information)
- Self-monitoring for resolution of gonorrhea symptoms, and seeking follow-up for a reevaluation if not resolved

- Referrals to other providers when appropriate (eg, HIV care, behavioral health)

**Implement***

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, retest 3 months after treatment)
- Offer expedited partner therapy for patient's sexual partner(s) and partner education

**Follow-up: Monitor and Evaluate**

- Resolution of symptoms (eg, dysuria, mucopurulent urinary or vaginal discharge); in absence of symptom resolution after treatment, assess for resistance by obtaining culture and susceptibilities Presence of adverse effects (eg, rash or gastrointestinal [GI] upset)
- Patient adherence to treatment plan
- Reevaluation of laboratory tests in specific time frames (eg, retest after 3 months for retest)

*Collaborate with patient, caregivers, and other healthcare professionals.*

### Evaluation of Therapeutic Outcomes

Persistent symptoms following treatment with a recommended regimen often indicate reinfection rather than treatment failure, reflecting the need for improved patient education and sex partner referral. If reinfection is most likely, retreatment with the initial regimen is recommended. However, reinfection can no longer be assumed due to increased rates of drug resistance and subsequent treatment failure. True treatment failure should be considered in persons whose symptoms do not resolve within 3 to 5 days after appropriate treatment or who failed a TOC (positive culture 72 hours after or positive NAAT at least 7 days after receiving treatment) and abstained from sexual contact during the posttreatment 7-day follow-up period. The CDC recommends all treatment failures receive culture and sensitivity testing. Persistent symptoms may also be due to other infectious causes, such as *C. trachomatis*.[4,16,27]

While the CDC does not recommend a TOC for patients with uncomplicated urogenital or rectal gonorrhea treated, any patient treated for pharyngeal gonorrhea should return 7 to 14 days after treatment for a TOC. The TOC test may be either culture or NAAT; however, if the NAAT is positive, confirmatory culture should be obtained prior to retreatment. Antimicrobial susceptibilities should be obtained for all TOC positive cultures. Patients who require retreatment should receive TOC 7 to 14 days following the second regimen. Additionally, as reinfection within 12 months occurs in 7% to 12% of persons treated for gonorrhea, all patients who receive treatment for gonorrhea should be retested 3 months after treatment or when the patient next presents for medical care in the following 12 months.[4,35,36]

Recent sex partners (within 60 days of preceding onset of symptoms or diagnosis) should be referred for evaluation and treatment. The recommended EPT regimen for uncomplicated gonorrhea infections is a single oral dose of cefixime 800 mg, with the addition of oral doxycycline 100 mg twice daily for 7 days if chlamydia cannot be ruled out.[27] Patients and sex partners should abstain from unprotected sexual intercourse for 7 days after both have completed treatment and symptoms have resolved.[4] EPT is contraindicated for females experiencing signs or symptoms of PID and should seek prompt medical care. EPT should be used with caution among MSM due to high rates of co-infection of HIV and syphilis, and inadequate data regarding the EPT efficacy due to concerns of cefixime resistance rates in this population.

## CHLAMYDIA TRACHOMATIS

### Epidemiology and Etiology

Over 1.8 million cases of chlamydia infection were reported in 2019, making it the most frequently reported notifiable condition in the United

States since 1994.[1] Since 2000, chlamydia has been a notifiable condition in all 50 states and infection rates have continued to rise. However, due to the silent nature of many infections, more than double the number of cases reported occur annually.[1,2] Left untreated, chlamydia infections can cause PID, infertility, ectopic pregnancy, and chronic pelvic pain.[4,37]

Chlamydia is more commonly reported in females, approximately 1.75 times the rate in males, reflective of increased screening. Rates among men have increased 32% from 2015 to 2019 and may be reflective of the increased number of male testing with increased urine and extragenital screening, increased transmission among MSM, or both.[1] Chlamydia is also a primary cause of nongonococcal urethritis (NGU), accounting for up to 40% of cases.[4,38,39]

Coinfection with chlamydia occurs in a substantial number of individuals with gonorrhea and all individuals diagnosed with *N. gonorrhoeae* should be assumed to have *C. trachomatis* present, until chlamydial infection has been ruled out.[4] Chlamydial infections, especially rectal infections, are associated with significantly increased risk of acquiring HIV infection.[40] In addition to genital infections, ocular infections in adults (via autoinoculation) and infants (via vaginal delivery through an infected birth canal) are reported. Pharyngeal and rectal infections may develop secondary to orogenital or receptive anal intercourse, respectively, with an infected individual.[4,37]

## Pathophysiology

*C. trachomatis* is an obligate intracellular bacterium that exclusively infects humans, via infection of mucosal epithelial cells. Like viruses, chlamydiae require cellular material from host cells for replication and eventually lead to host cell death. *C. trachomatis* shares a similar outer membrane and ribosomes to gram-negative bacteria, but lacks cell-wall peptidoglycan, and cannot be detected via Gram staining. Their complex two-stage lifecycle includes an infectious and noninfectious forms, and even after treatment, nonviable and noninfectious organisms may persist within cells for up to 3 weeks.[37]

Risk of chlamydia transmission after exposure is not well described, but is believed to be less than that of *N. gonorrhoeae*. The risk of male-to-female and female-to-male transmission is 39% and 32%, respectively.[41] The rate of transmission per-act is 10%, increasing to 55% with multiple encounters between sexual partners.[42]

## Clinical Presentation

Chlamydia causes a range of clinical syndromes, including urethritis, cervicitis, proctitis, and conjunctivitis. In comparison with gonorrhea, chlamydial genital tract infections are more frequently asymptomatic, and when present, symptoms tend to be less noticeable. Urethral discharge is usually less profuse and more mucoid or watery than that associated with gonorrhea.[4,37,38] Many cases of chlamydia in asymptomatic or minimally symptomatic women are diagnosed as a result of screening. Table 140-5 summarizes usual clinical presentations of chlamydial infections.

TABLE 140-5

**Presentation of Chlamydia Infections**

| | Males | Females |
|---|---|---|
| General | Incubation period: 7-35 days Symptom onset: 7-21 days | Incubation period: 7-35 days Symptom onset: 7-21 days |
| Site of infection | Most common: urethra<br>Others: rectum (receptive anal intercourse), oropharynx, eye | Most common: endocervical canal<br>Others: urethra, rectum (usually caused by perineal contamination), oropharynx, eye |
| Symptoms | More than 50% of urethral and rectal infections are asymptomatic<br>Urethral infection: mild dysuria, discharge<br>Pharyngeal infection: asymptomatic to mild pharyngitis | More than 66% of cervical infections are asymptomatic.<br>Urethral infection: usually subclinical; dysuria and frequency uncommon<br>Rectal and pharyngeal infection: symptoms same as for men |
| Signs | Scant to profuse, mucoid to purulent urethral or rectal discharge<br>Rectal infection: pain, discharge, bleeding | Abnormal vaginal discharge or uterine bleeding, purulent urethral or rectal discharge can be scant to profuse. |
| Complications | Epididymitis, Reiter's syndrome (rare) | PID and associated complications (ie, ectopic pregnancy, infertility)<br>Reiter's syndrome (rare) |

Chlamydia can be transmitted to an infant during contact with infected cervicovaginal secretions. Nearly two-thirds of infants acquire chlamydial infection after endocervical exposure, with primary morbidity associated with seeding of the infant's eyes, nasopharynx, rectum, or vagina. In exposed infants, neonatal conjunctivitis develops in as many as 50%, and pneumonia develops in up to 16%. Inclusion conjunctivitis in newborns is usually self-limited, but can result in scarring and micropannus of the cornea. Interstitial pneumonitis occurring secondary to carriage in the nasopharynx typically is mild, but it can be severe and require hospitalization.[4,37,43]

## Diagnosis

Laboratory confirmation of chlamydial infection is important because of the relative lack of symptom specificity when present.[4] Cell culture is the reference standard against which all other diagnostic tests are measured. Because chlamydiae are obligate intracellular organisms, specimens for culture must be obtained from endocervical (women) or urethral (men) epithelial cell scrapings rather than from urine or urethral discharges. Although tissue culture techniques have close to 100% specificity, the sensitivity is as low as 70%. Because of the technical demands of specimen collection, transport, processing, expense, and prolonged time until results (3-7 days), culture is not widely used for diagnostic purposes. However, culture remains the diagnostic standard in medicolegal cases, such as sexual assault and child abuse because of its high specificity and ability to detect only viable organisms.[4,37]

Similar to gonorrheal testing, NAATs can be used to detect small amounts of chlamydial DNA or RNA, and are highly sensitive and specific for detecting infection in urine, urogenital, and anal specimens. As such, they are recommended for detecting chlamydia infection.[4] In 2019, NAATs were approved for diagnosis of chlamydial infection in extragenital sites including the pharynx and rectum.[26] Use of self-collected vaginal or anal specimens or first-void urine samples offers greater patient acceptability. Because NAATs can detect as little as a single-gene copy in a specimen, whether it is live or a nonviable organism, nucleic acid residues that persist following successful antibiotic therapy can result in a false-positive test for several weeks following cure. Molecular tests that do not use nucleic amplification are no longer recommended for diagnosis of *C. trachomatis* because of their poor sensitivity in comparison to NAATs.[4,25]

Because of the high rate of asymptomatic disease and the high prevalence of chlamydial infection in sexually active females 25 years of age or younger and sexually active women with new sex partners or multiple sex partners, the CDC and USPSTF recommends routine annual screening in these

individuals.[4,27] Additionally, the CDC recommends routine, at least annual, chlamydia screening of genital and rectal sites in MSM populations. Screening for rectal chlamydia among MSMs may also be a cost-effective intervention for HIV prevention.[44] Pregnant women are recommended to be screened at the first prenatal visit and during the third trimester if at continued risk.[4]

## Treatment

Many antimicrobials, including tetracyclines, macrolides, and some fluoroquinolones, display good *in vitro* and *in vivo* activity against *C. trachomatis*. In most clinical trials, cure rates exceed 90% for these agents.[4,36,37] Treatment of *C. trachomatis* is limited based on the organism's unique life cycle. Antibiotics must target the intracellular active form, requiring medications with good intracellular penetration. Additionally, to maintain concentrations throughout the organisms life-cycle (up to 48 hours), selection of an antibiotic with long half-life or prolonged course of therapy is important.

Previously, single-dose azithromycin 1 g orally and doxycycline 100 mg orally twice daily for 7 days were equally considered regimens of choice for treatment of uncomplicated urogenital chlamydia infections (Table 140-6).[4] Because of its prolonged serum and tissue half-life, azithromycin is the only single-dose therapy effective in treating *C. trachomatis*. Both therapies clear over 97% of urogenital infections; however, there are concerns regarding azithromycin efficacy in rectal chlamydia.[30–32,45–47] As rectal chlamydia may occur by autoinoculation from the vaginal tract and cannot be predicted by sexual activity, doxycycline is now preferred as first line. Additionally, doxycycline demonstrates better *in vitro* activity against *C. trachomatis*.[48] For those patients with adherence concerns, azithromycin may be used, but TOC after treatment is recommended. Although some fluoroquinolones have activity against *C. trachomatis*, high dosages have not consistently eradicated chlamydial infections.[4,37,38]

TABLE 140-6

**Treatment of Chlamydia Infections**

| Infection | Recommended Regimens[a] | Alternative Regimens[a] |
|---|---|---|
| Uncomplicated urethral, endocervical, or rectal infection in adults | Doxycycline 100 mg orally twice daily for 7 days | Azithromycin 1 g orally once[b], *or* levofloxacin 500 mg orally once daily for 7 days |
| Urogenital infections during pregnancy | Azithromycin 1 g orally as a single dose | Amoxicillin 500 mg orally three times daily for 7 days |
| Conjunctivitis of the newborn or pneumonia in infants | Erythromycin base or ethylsuccinate 50 mg/kg/day orally in four divided doses for 14 days[c,d] | Azithromycin suspension 20 mg/kg/day orally once daily for 3 days[c] |

[a]Recommendations are those of the CDC.

[b]Azithromycin may be used if there are concerns for nonadherence. Test after treatment is recommended due to reduced efficacy in rectal chlamydia.

[c]An association between oral erythromycin and azithromycin and infantile hypertrophic pyloric stenosis (IHPS) has been reported in infants aged <6 weeks. Infants treated with either of these antimicrobials should be followed for signs and symptoms of IHPS.

[d]Topical therapy alone is inadequate for ophthalmia neonatorum and is unnecessary when systemic therapy is administered. Effectiveness of erythromycin treatment is approximately 80%; therefore, a second course of therapy may be required.

For pregnant women, treatment can significantly reduce the risk of pregnancy complications and newborn transmission. Because tetracyclines and fluoroquinolones are contraindicated during pregnancy, azithromycin is recommended (see Table 140-6). Due to concerns regarding persistence of chlamydia infections after exposure to penicillin-class antibiotics, amoxicillin is an alternative therapy only in pregnant women. When compliance with a multiday regimen is a concern, azithromycin is the preferred treatment in women, regardless of pregnancy status, and directly observed single-dose

administration ensures adherence. TOC 3 to 4 weeks after completion should be obtained for pregnant patients treated for chlamydial infections.[4]

*C. trachomatis* transmission during perinatal exposure can result in neonatal or infant infections of the eye, oropharynx, lungs, urogenital tract, and rectum. Despite efficacy in preventing gonococcal ophthalmia, topical erythromycin ointment (0.5%) appears less effective in preventing chlamydial ophthalmia and has no effect on nasal carriage or colonization, so the potential for other infections, including pneumonia, remains. Because of high percentage of treatment failures, topical therapy is not recommended to treat ophthalmia caused by *C. trachomatis*. Instead, an oral erythromycin regimen is recommended.[4]

### Evaluation of Therapeutic Outcomes

Treatment of chlamydial infections with recommended regimens is highly effective; therefore, posttreatment laboratory testing for therapeutic failure is not recommended unless symptoms persist or there are specific concerns (eg, regimen nonadherence or pregnancy). However, due to high risk of reinfection, all patients treated for chlamydia should be retested approximately 3 months after treatment. Posttreatment tests should not be performed for at least 3 weeks following completion of therapy due to false positives with continued presence of nonviable organisms.[4] When posttreatment tests are positive, suspect noncompliance, failure to treat sexual partners, or laboratory error rather than inadequate therapy or resistance. Infants with pneumonitis should receive follow-up testing, and sometimes subsequent courses of therapy, because erythromycin is only 80% effective.[4,37]

Sex partners of patients with *C. trachomatis* infections should be examined, tested for other STIs, and counseled on prevention. EPT may also be offered with either azithromycin or doxycycline-based regimens. Patients, and sex partners, should abstain from unprotected sexual intercourse for 7 days after both have completed treatment and symptoms have resolved.[4]

## TRICHOMONIASIS

### Epidemiology and Etiology

In 2018, 6.9 million people developed trichomoniasis in the United States, making it the most common nonviral STI. The prevalence is approximately 2.6 million, with 2.1% of US women aged 14 to 59 years infected at a given time.[2,5,49] The distribution of trichomoniasis is varied; women are six times more likely to be infected than men, with disproportionate infection among women 40 years of age or older (11%) and Black women (13%).[49] Men who have sex with women are at greater risk of trichomoniasis compared to MSM exclusively and are usually asymptomatic. The causative organism, *Trichomonas vaginalis*, is primarily transmitted through sexual contact although acquisition from inanimate objects is a theoretical possibility since the organism can survive for up to 3 hours in a wet environment.[50] Neonatal infections may also occur. Coinfection with other STIs is not unusual, and the inflammatory response produced by trichomoniasis increases the risk of acquiring HIV by at least 50%.[4,50–54]

### Pathophysiology

Trichomonads typically infect the squamous epithelium of the genital tract. Extragenital sites are epidemiologically important because infection can persist and result in reinfection. After attachment to vaginal or urethral mucosa, trichomonads elicit an inflammatory response that manifests as discharge containing large numbers of PMNs.[50]

### Clinical Presentation

Trichomonal infections are reported more commonly in women than in men. Most patients experience minimal or no symptoms, with untreated infections lasting years. The clinical presentation of trichomoniasis in males and females is presented in Table 140-7. Trichomoniasis is one of the principal infectious causes of vaginal discharge (in addition to bacterial vaginosis and vulvovaginal candidiasis). In both genders, trichomoniasis can manifest as urethral discharge and dysuria and should be considered in NGU. Rarely, *T. vaginalis* can lead to epididymitis, prostatitis, and/or infertility in men and PID in women. During pregnancy, it can cause preterm rupture of membranes, premature delivery, endometritis, and low-birth-weight neonates.[4,50]

TABLE 140-7

**Presentation of Trichomonas Infections**

| | Males | Females |
|---|---|---|
| **General** | Incubation period: 3-28 days Organism can be detectable within 48 hours after exposure to infected partner | Incubation period: 3-28 days |
| **Site of infection** | Most common: urethra<br>Others: rectum (usually caused by rectal intercourse in MSM), oropharynx, eye | Most common: endocervical canal<br>Others: urethra, rectum (usually caused by perineal contamination), oropharynx, eye |
| **Symptoms** | Can be asymptomatic (more common in males than females) or minimally symptomatic<br>Urethral discharge (clear to mucopurulent)<br>Dysuria, pruritus | Can be asymptomatic or minimally symptomatic<br>Scant to copious, typically malodorous vaginal discharge (50%-75%) and pruritus (worse during menses)<br>Dysuria, dyspareunia (pain with sexual intercourse) |
| **Signs** | Urethral discharge | Vaginal discharge Vaginal pH 4.5-6<br>Inflammation/erythema of vulva, vagina, and/or cervix<br>Urethritis |
| **Complications** | Epididymitis and chronic prostatitis (uncommon)<br>Male infertility (decreased sperm motility and viability) | PID and associated complications (ie, ectopic pregnancy, infertility)<br>Premature labor, premature rupture of membranes, and low-birth-weight neonates (neonatal infection risk is low)<br>Cervical neoplasia |

## Diagnosis

Testing for *T. vaginalis* should be performed on all women presenting with vaginal discharge and at least annually in women with HIV. Screening may be considered in settings of high prevalence (eg, STI clinic, correctional facilities) and for persons at increased risk for infection (eg, recent STI diagnosis, multiple sexual partners, transactional sex). *T. vaginalis* produces nonspecific symptoms that may be indistinguishable from bacterial vaginosis, which can be concomitantly present. Because *T. vaginalis* requires a pH range of 4.9 to 7.5 for survival, a vaginal discharge pH of greater than 5 usually indicates the presence of either *T. vaginalis* or *Gardnerella vaginalis*, a common cause of bacterial vaginosis. The simplest means of diagnosis is a wet mount of vaginal discharge where *T. vaginalis* is visualized via bright-field microscopy. Trichomoniasis is confirmed if characteristic pear-shaped, flagellated, motile organisms are observed. This technique is still readily used given its relative convenience for experienced personnel and low cost. However, the wet mount is only 51% to 65% sensitive, with lower sensitivities in men and women with low-grade, subacute, or chronic infections. Culture was the gold standard for trichomoniasis and is highly specific; however, these tests are labor intensive, expensive, not widely available, and have a long turnaround.[4,50,52–54]

Newer diagnostic tests are now widely available, with the sensitivities approaching those of culture techniques. NAAT are FDA-approved for *T. vaginalis* detection in vaginal, endocervical or urine specimens in women and is three to five times more sensitive than wet mount microscopy (95%-100%). In men, urethral swab specimens may yield a higher sensitivity than urine.[50,55] Rapid point of care tests are also readily available, allowing for office-based testing. Sensitivity among these tests can vary and might be higher in symptomatic women.[4,52–55]

## Treatment

Recommended and alternative treatment regimens for *T. vaginalis* include either metronidazole or tinidazole (Table 140-8).[4] Metronidazole 500 mg twice daily for 7 days was more effective than 2 g single-dose regimen.[56] Increasing the dose for either agent to 2 g once daily for 7 days cures persistent

infections. Adding topical metronidazole or tinidazole may improve efficacy during persistent infection. Tinidazole 2 g orally as a single dose is an alternative for women. Single-dose therapy with 2 g of metronidazole or tinidazole are recommended for men with trichomoniasis. To achieve maximal cure rates and prevent relapse, simultaneous treatment of infected sexual partners for presumed infection is recommended.[4,52–54]

TABLE 140-8

**Treatment of Trichomoniasis**

| Type | Recommended Regimens[a] | Alternative Regimens[d] |
|---|---|---|
| Symptomatic and asymptomatic infections | Women<br>Metronidazole 500 mg orally twice daily for 7 days[a,b,c]<br>Men<br>Metronidazole 2 g orally in a single dose[b,c] | Tinidazole 2 g orally in a single dose |
| Persistent or recurrent infections | Metronidazole 2 g orally once daily for 7 days<br>or<br>timidazole 2 g orally once daily for 7 days | |
| Treatment in pregnancy | Metronidazole 500 mg<br>orally twice daily for 7 days | |

[a]Recommendations are those of the CDC.

[b]Randomized controlled trial comparing metronidazole 500 mg twice daily for 7 days and a single 2 g dose in women found fewer treatment failures in the 7-day regimen.

[c]Metronidazole labeling approved by the FDA does not include this regimen. Dosage regimens for treatment of trichomoniasis included in the product labeling are the single 2 g dose; 250 mg three times daily for 7 days; and 375 mg twice daily for 7 days. The 250-mg and 375-mg dosage regimens are currently not included in the CDC recommendations.

[d]For men, data are lacking for alternative treatment regimens and regimens for persistent infection. Consult an infectious diseases specialist.

[e]Symptomatic pregnant women can be treated with this regimen at any stage of pregnancy.

In patients who fail to respond to an initial course of metronidazole therapy, a second course of therapy with metronidazole 500 mg twice daily for 7 days is recommended. Infections refractory to a second course of treatment often respond to a 2 g daily 7-day regimen of either agent.[4,57] Tinidazole should be considered after failure to a 7-day metronidazole regimen given its longer half-life, greater serum concentrations, and a lower minimum lethal concentration demonstrated in 60% of *T. vaginalis* isolates compared to metronidazole.[58] The combination of oral and intravaginal administration improves cure rates in refractory cases. There are higher rates of resistance with metronidazole (4%-10%) versus tinidazole (1%); however, resistance testing is not routinely performed by most laboratories. In persistent cases, consultation with the CDC is recommended for treatment and resistance testing.[53,59]

Metronidazole is associated with a risk of a disulfiram-like reaction, although published data have not supported this claim. *In vitro* and animal data described a possible inhibition of aldehyde dehydrogenase and subsequent increase in acetaldehyde levels, which can cause facial flushing, nausea, vomiting, and other symptoms. Although there are considerable human data describing disulfiram-like reactions after concomitant metronidazole and alcohol use, these manifestations may be attributed directly to alcohol. Most controlled studies failed to find an association between metronidazole with alcohol use and disulfiram-like reactions.[60] The updated CDC guidelines do not link metronidazole use with the potential for a disulfiram-like reaction in those that consume alcohol concurrently.[4]

The CDC recommends testing all symptomatic pregnant women for *T. vaginalis*, regardless of pregnancy stage, and to consider treatment. Concerns regarding the use of metronidazole in pregnant women and breastfeeding have been raised. Some clinicians prefer to delay treatment in women in the first trimester; however, metronidazole is pregnancy category B and may be used for treatment in any trimester. Tinidazole is pregnancy category C and should be avoided. Both agents are secreted in breast milk, although metronidazole is indicated for use in neonates and infants. Metronidazole concentrations in breast milk were deemed compatible with breastfeeding when the mother was given 500 mg three times daily, while 2-g dose warrants a 12 to 24 hour breastfeeding pause. Careful monitoring of breastfed child is recommended with metronidazole treatment of the mother. Breastfeeding should be deferred for 72 hours after a 2-g dose of tinidazole.[4,52]

### Evaluation of Therapeutic Outcomes

Retesting for *T. vaginalis* is recommended for all sexually active women within 3 months following initial treatment due to high rates of reinfection. If retesting with NAAT is clinically warranted without reexposure (eg, third trimester), the optimal timing to prevent a false-positive is 3 weeks. Concurrent treatment of all sex partners is critical to ensure relief of symptoms and prevent reinfection and transmission. When patients remain symptomatic, it is important to ensure patient adherence and to determine if reinfection has occurred. In these cases, a repeat course of therapy, including sexual partner(s) is indicated. In situations where reinfection can be excluded, a relative resistance to metronidazole or tinidazole should be assumed, and an alternative regimen prescribed. Culture and sensitivity are warranted for infections unresponsive to alternative regimens.[4]

## ASSOCIATED COMPLICATIONS

### Mycoplasma Genitalium

Of notable importance is *Mycoplasma genitalium* infection, a common cause of NGU. The CDC has identified *M. genitalium* infections as an emerging issue due to the increasing rates of resistance and lack of diagnostic assays.[4,19,61,62]

*M. genitalium* is a known colonizer of the genital tract in both males and females; however, it is an emerging cause of urogenital infections.[4,19,61,62] While *C. trachomatis* accounts for a majority of NGU cases, *M. genitalium* is the causative pathogen in up to 20% of NGU cases and 25% of nonchlamydial NGU. Rates are even higher in persistent or recurrent NGU, constituting approximately 30% of cases.[4] The relationship between *M. genitalium* and other male anogenital tract infections, like epididymitis or clinical proctitis, is not well defined. The pathogenic role is even less defined in women, as infections are commonly asymptomatic, but has been isolated in up to 30% of cervical infections. However, women infected with *M. genitalium* are at a 2 to 2.5-fold increased risk of cervicitis, PID, infertility, and preterm delivery.[61] Many infections go undiagnosed, but *M. genitalium* should be suspected in persistent or recurrent urethritis or proctitis and considered in persistent or recurrent cervicitis or PID.[4,19,61,62] There are no current recommendations for routine screening in asymptomatic individuals.

*M. genitalium* lacks a cell wall and is a slow growing, fastidious organism. It is not readily cultured in a laboratory and, when able to grow, may take up to 6 months to isolate. NAATs are the preferred method to detect *M. genitalium*.[19,63]

The 7-day doxycycline regimen, a primary treatment option for NGU, is largely ineffective for treatment of *M. genitalium* urethritis, with a median cure rate of 31%.[4] A 1 g single dose of azithromycin was significantly more effective than doxycycline, and has been the mainstay of therapy for *M. genitalium* infections.[4,19,61,62] Unfortunately, resistance to azithromycin is rapidly emerging, with 50% of all *M. genitalium* infections caused by organisms already resistant to azithromycin. The overuse of macrolides to treat respiratory tract infections, like community acquired pneumonia, may play a role in azithromycin resistance seen in *M. genitalium*. Moxifloxacin, 400 mg daily for 7, 14, or 21 days, has been successfully used to eradicate *M. genitalium* infections.[61,62] To optimize chance of treatment success, CDC STI guidelines recommend doxycycline 100 mg twice daily for 7 days followed by moxifloxacin 400 mg daily for 7 days.[4,64] Macrolide susceptibility testing is unavailable in the United States. If macrolide susceptibility is known, a regimen of doxycycline 100 mg twice daily for 7 days followed by azithromycin 1 g and then 500 mg daily for 3 days is an alternative option. For those with unknown or known macrolide resistance, the doxycycline-moxifloxacin regimen is preferred.

As with all STIs, patients are recommended to abstain from unprotected sexual activity until both partners have completed treatment and are asymptomatic. Additionally, patients and their sexual partners should be screened for other STIs and counseled on risk of transmission and consequences of untreated infections. If a patient's sexual partner is not tested, the same treatment may be offered to both.[62]

### Pelvic Inflammatory Disease

PID is an inflammatory disorder of the upper female genital tract and can include any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis that may result in long-term reproductive damage, including infertility, ectopic pregnancy, and chronic pelvic pain. It is most often caused by ascending infection of the vagina and cervix, most commonly with STI pathogens. Microorganisms that colonize the vaginal canal may also play a role, including anaerobes or causes of bacterial vaginitis, as well as enteric gram-negative rods. The microbiologic etiology of acute PID is not well known. Where gonorrhea or chlamydia were once thought to be the primary cause, <50% of women with acute PID test positive for one of these organisms. The role of *M. genitalium* is unclear, but testing was unavailable for this organism until recently and may be considered in persistent cases.[4,20]

Acute PID is difficult to diagnose as many patients may be asymptomatic or have subtle, nonspecific symptoms. PID is often diagnosed based on clinical findings and confirmed with more invasive testing. Delays in diagnosis and treatment likely contribute to inflammatory sequelae and long-term reproductive damage. The hallmark sign of PID is sudden onset pelvic and lower abdominal pain, notably after menses. Additional signs may include abnormal vaginal discharge, intermenstrual or postcoital bleeding, dyspareunia, and dysuria. All patients with suspected PID should undergo cervical or vaginal NAAT testing for gonorrhea or chlamydia. Vaginal fluid may also be evaluated for signs of bacterial vaginosis. Negative endocervical screening does not rule out upper reproductive tract infections, but positive results may help guide therapy.[4,20]

4 Treatment for PID is targeted toward empiric coverage for *N. gonorrhoeae* and *C. trachomatis* and anaerobic bacteria. Patients with suspected PID should be initiated on treatment with ceftriaxone 1 g IV daily (or cefotetan 2 g IV every 12 hours or cefoxitin 2 g IV every 6 hours) plus doxycycline 100 mg orally twice daily for 14 days and metronidazole 500 mg orally twice daily for 14 days.[65] The addition of metronidazole resulted in reduced pelvic pain and was associated with higher clinical improvement compared to ceftriaxone and doxycycline alone. This is an update from the previous guideline recommendations and aligns with current gonorrhea and chlamydia treatment recommendations.[4] Patients who require hospitalization for PID should be initiated on a parenteral regimen. Once the patient is clinically stable and can tolerate oral medications, they can be switched to oral formulations to complete two weeks of therapy. Ampicillin-sulbactam 3 g IV every 6 hours plus doxycycline can be used as an alternative. Clindamycin 900 mg IV every 8 hours plus gentamicin IV is another alternative treatment regimen, but provides suboptimal coverage for anaerobic organisms.[4,66,67]

Clinical improvement (defervescence, reduction in abdominal/pelvic pain) should occur within 3 days of initiation of therapy. Intrauterine contraceptive devices (IUD) have not been associated with PID, outside of the initial 3 months after insertion. If an IUD user is diagnosed with PID, the IUD does not need to be removed, but may be considered if the patient does not show clinical improvement within 72 hours.[4] All patients with confirmed gonorrheal or chlamydial PID should be retested 3 months after treatment. Recent sex partners should also be evaluated and presumptively treated for chlamydia and gonorrhea, regardless of the etiology of PID. EPT may be offered and partners should be instructed to abstain from sexual intercourse until both partners have been treated and symptoms have resolved. Approximately one-third of women report chronic pelvic pain after treatment and resolution of PID. Infertility may occur in up to 20% of patients and ectopic pregnancy in <1%.[68] Routine screening for gonorrhea and chlamydia as recommended by the USPSTF and CDC, and early recognition of symptoms may help reduce the burden of disease.[4,27]

## SYPHILIS

### Epidemiology and Etiology

Syphilis is a chronic bacterial infection that presents through various stages. Although nearly eradicated in 2000, cases of syphilis have increased 400% in the United States from 2000 to 2019, with an annual total of primary and secondary syphilis diagnoses of around 39,000. While the rise of newly diagnosed cases are primarily attributed to males, a majority of whom identify as MSM, a 179% increase was observed in women during the years 2015 to 2019.[1] This increase among women has been accompanied by a threefold rise in congenital syphilis during the same period.[69] In 2018, one-third of congenital syphilis cases in live-born infants were symptomatic, while 6% of maternal syphilis cases resulted in stillbirth.[69]

Rates of coinfection with HIV have remained high, particularly among MSM. Similar to other STIs, syphilis can increase the risk of acquiring HIV in exposed individuals. In addition, immunologic defects in HIV-infected individuals can produce an atypical serologic response to syphilis. In particular, the possibility of delayed seroreactivity, markedly elevated serologic titers, and increased false-positive results could complicate the diagnosis, as well

as assessment of treatment efficacy in HIV-positive individuals infected with syphilis. As a result of this association, the CDC recommends that all patients diagnosed with syphilis be tested for HIV infection.[4,70]

## Pathophysiology

The causative organism is *Treponema pallidum* subspecies *pallidum*, a spirochete. The primary mode of transmission is through sexual contact, with the organism penetrating through intact mucous membrane or a break in the cornified epithelium. The spirochetes replicate locally, followed by widespread dissemination through the lymphatic and intravascular systems. Transmissibility varies based on the stage of the infection, with the highest rates early in the course of disease. *T. pallidum* can also cross the placenta during any time of the pregnancy and during any stage of infection. Despite the limited risk of transmission after the first few years, approximately one-third of those are untreated will develop further clinical manifestations and irreversible complications, such as neurological and cardiovascular complications.[70]

## Clinical Presentation

The clinical presentation of syphilis is varied with progression through multiple stages possible in untreated or inadequately treated patients (Table 140-9).

TABLE 140-9

**Presentation of Syphilis Infections**

| | |
|---|---|
| **General** | |
| Primary | Incubation period: 10-90 days (mean, 21 days) |
| Secondary | Develops 2-8 weeks after initial infection in untreated or inadequately treated individuals |
| Latent | Develops 4-10 weeks after secondary stage in untreated or inadequately treated individuals; risk of secondary stage relapse within the first year |
| Neurosyphilis | Neuroinvasion can occur at any stage (weeks to years) |
| Tertiary | Develops in approximately 28% of untreated or inadequately treated individuals 10-30 years after initial infection |
| **Site of Infection** | |
| Primary | Genital or external genitalia area (perineum, mouth, throat) |
| Secondary | Multisystem involvement secondary to hematogenous and lymphatic spread |
| Neurosyphilis | Meninges, cerebral vasculature, brain parenchyma, eyes, ears |
| Tertiary | CNS, heart, bones, and joints |
| **Signs and Symptoms** | |
| Primary | Single, painless, indurated lesion (chancre) that erodes, ulcerates, and eventually heals (typical); regional lymphadenopathy is common; multiple, painful, purulent and/or multiple lesions possible |
| Secondary | Pruritic or nonpruritic rash (may involve the palms and soles), mucocutaneous lesions, flu-like symptoms, lymphadenopathy |
| Latent | Asymptomatic |
| Neurosyphilis | Meningitis (headache, photophobia, stiff neck), general paresis, stroke, dementia, ocular (blindness, blurred vision, eye pain) and otic (deafness, imbalance) complications |
| Tertiary | Cardiovascular syphilis (aortitis or aortic insufficiency), gummatous lesions involving any organ or tissue |

CNS, central nervous system.

## Primary Syphilis

The primary stage, characterized by a chancre on cutaneous or mucocutaneous tissue exposed to the organism, is highly infectious. Lesions are usually painless, solitary and indurated, although they may be painful and/or present as multiple lesions. Regional lymphadenopathy may accompany the chancre. Syphilis should be considered with atypical presentations as lesions can mimic other infectious or noninfectious etiologies. As such, appropriate diagnostic testing is important. Chancres heal within 4 to 6 weeks, while lymphadenopathy may persist longer.[70–72]

## Secondary Syphilis

Often referred to as the "great imitator" due to its florid and diverse differential diagnosis, the secondary stage of syphilis is characterized by a variety of mucocutaneous eruptions resulting from widespread hematogenous and lymphatic spread of *T. pallidum*. Skin lesions are often maculopapular and are usually nonpruritic, developing first on trunk and proximal arms and disseminating bilaterally. Secondary syphilis lesions typically involve the palms and soles, can present as mucous patches, and/or can have a wart-like appearance (condylomata lata). Patchy alopecia is another finding periodically seen.

Constitutional symptoms often accompany secondary syphilis, such as malaise, low-grade fever, pharyngitis, headache, anorexia, and generalized lymphadenopathy. Subclinical hepatitis, renal dysfunction, and neurologic findings may also be present. If untreated, secondary syphilis disappears spontaneously within 1 to 6 months.[70–72]

## Latent Syphilis

Persons with an absence of mucocutaneous lesions or other evidence of disease are in a latency period, which can only be diagnosed with positive serologic tests for syphilis. Prior to the availability of effective treatment, 25% of those infected developed secondary syphilis relapses, 90% of which occurred within the first year.[73] These individuals are thus deemed potentially infectious during this early period. By CDC terminology for the latent infection, the first year after acquisition is designated as early latent (or nonprimary, nonsecondary) syphilis.[74] Those with asymptomatic infection established to be over 12 months from exposure, or when a duration cannot be determined, are classified as late latent syphilis (or late or unknown duration syphilis). If left untreated, syphilis can slowly produce an inflammatory reaction in virtually any organ in the body. Most patients with late syphilis will have no further sequelae. However, approximately 28% will develop further disease years after the initial infection.[70–72]

## Neurosyphilis

Neurologic manifestations, including ocular and otic, may present at any stage of syphilis. Central nervous system (CNS) invasion by treponemes can lead to cerebrospinal fluid (CSF) abnormalities (eg, pleocytosis, elevated protein levels) in up to half of the individuals with early infections, with the majority being devoid of symptoms (asymptomatic neurosyphilis). Some patients will have meningeal symptoms (eg, headache, photophobia, stiff neck) present in early infection. Meningovascular (eg, stroke, seizures) or parenchymal (eg, dementia, aphasia) are other complications of neuroinvasion, which at times may overlap. The latter manifestations are more apt to occur years after infection, although strokes have been described early in disease. Ocular findings, especially uveitis, can be part of the neurological presentation. Hearing loss and/or vestibular dysfunction (eg, dizziness, vertigo) are rare, although syphilis should be considered for patients presenting with these complaints.[70,71]

## Tertiary Syphilis

Nonneurologic manifestations of late syphilis include benign gumma formation and cardiovascular syphilis. Gummas, nonspecific granulomatous lesions, are the classic lesions of late syphilis and can infiltrate any organ or tissue. Gummas of critical organs, such as the heart or brain, can be fatal. Cardiovascular disease often manifests as aortic insufficiency, ascending aortic aneurysm or myocarditis. Treatment of all patients with latent syphilis is essential, as there is no way to predict which patients will experience disease progression.[70]

## Congenital Syphilis

In pregnant women with syphilis, *T. pallidum* can cross the placenta at any time during pregnancy. The risk of fetal infection is greatest in pregnant women with primary and secondary syphilis and declines in pregnant women with late disease. Transmission of syphilis during pregnancy occurs primarily transplacentally and can result in fetal death, prematurity, or congenital syphilis. Symptoms vary based on onset, with early congenital manifestations appearing from 2 weeks to 2 years, and late syphilis symptoms appearing after 2 years throughout adolescence. Manifestations of early congenital syphilis resemble those of secondary syphilis, in addition to other findings, notably hemolytic anemia, hepatic dysfunction, intrauterine growth retardation, bone deformities, or nephrotic syndrome. Deformities of the nose (saddle nose) and lower extremities (anterior bowing) are examples of untreated late syphilis complications.[70,72]

## Diagnosis

Syphilis is diagnosed through a combination of clinical and/or laboratory criteria and is stage-dependent. Techniques used to directly visualize *T. pallidum*, such as darkfield microscopy, are now only performed by select facilities (eg, STI specialty clinics). Polymerase chain reaction (PCR)–based tests are used by some institutions despite not being commercially available in the United States. Unlike other methods, PCR does not require specimens from fresh lesions or tissue samples. Real-time PCR can detect *T. pallidum* DNA when primary syphilis is highly suspected, even when darkfield microscopy is negative.[75] PCR is also useful for detection in other bodily fluids and tissues.[70,71]

Serologic tests are the mainstay in the diagnosis and are based on two distinct antibody responses elicited by syphilis. Tests are categorized as nontreponemal or treponemal based on the type of antibodies they detect. Nontreponemal tests identify immunoglobulin released by inflamed tissues and/or *T. pallidum* by forming immune complexes with the reagent. Rapid plasma reagin (RPR) card test is the most common nontreponemal test. The Venereal Disease Research Laboratory (VDRL) slide test, another nontreponemal test, is almost exclusively used for CSF specimens. A positive RPR test can indicate the presence of any stage of syphilis or congenital syphilis if taken at least 3 weeks after exposure. RPR tests are simple and inexpensive, but require manual manipulation and interpretation.[70]

Beyond their screening role, RPR tests help monitor syphilis progression, treatment success, and identify reinfection as they measure *T. pallidum* antibody titers. Higher titers (eg, 1:512) correlate with a greater spirochetal burden and stage of infection. In 1% to 2% of secondary syphilis cases, the high concentrations of antibodies prevent the antigen–antibody complex from forming, leading to a false-negative. This phenomenon is called the "prozone" effect. Titers generally decline by at least fourfold after effective treatment (eg, 1:64 → 1:16), with only 20% of individuals failing to serorevert to a nonreactive test. Thus, strategic sequential RPR tests are an integral part of syphilis management. Access to previous diagnosis and treatment history is often necessary to determine if reinfection has occurred.[4,70,71,75]

In diagnosing all stages of syphilis, treponemal tests are more sensitive and specific than nontreponemal tests. Cost has contributed to their role as confirmatory tests rather than screening tools. Treponemal tests detect antibodies specific against *T. pallidum* antigens, which persist throughout a person's lifetime after infection. This test cannot distinguish between a new or past infection, nor treatment status. They can identify syphilis 6 to 14 days after a chancre develops, earlier than RPR tests (10-15 days). For many years, the fluorescent treponemal antibody absorption (FTA-ABS) test or the *T. pallidum* particle agglutination assay (TPPA) were the most frequently used treponemal tests. However, enzyme-linked immunoassays (EIAs) and chemiluminescent immunoassays (CIAs) are increasingly utilized as these processes are cheaper and allow for automated testing and interpretation. Advances in point of care could further remove challenges for screening and diagnosing syphilis, especially in rural and resource-limited areas.[4,70,71,75]

The traditional algorithm for diagnosing syphilis involves an initial RPR test, followed by a treponemal test for confirmation if the RPR was reactive. For individuals with a previously treated infection, presenting with new clinical suspicion of syphilis (or being screened due to high risk of re-exposure), a new RPR test should be collected. RPR results should be compared to their last titer. A fourfold or greater increase would suggest reinfection.[4,70,72,76]

For many laboratories with high volumes and programs screening large numbers (eg, prenatal screening), a reverse sequence algorithm is now a viable option. This strategy uses a treponemal test for the initial screen, with a positive test reflexively followed by an RPR test. If there is discordance with the RPR test, a second treponemal test distinct from the initial product would resolve the discrepancy. The availability of EIAs/CIAs for high throughput at increasingly lower costs have made this algorithm more attractive economically and logistically. Products testing for multiple pathogens, such as a point of care dual syphilis and HIV-1 test, have been approved and are in development.

False-positive tests occur more commonly with nontreponemal tests than treponemal ones, and can cause anxiety, stigmatization and unnecessary treatment. Acute febrile illnesses, after immunizations, pregnancy, injection drug use, hepatitis C infection, HIV, and autoimmune disease (particularly lupus erythematosus) can induce these false-positives. Regardless of which test is used initially, confirmation with the other type is necessary for the diagnosis. If the nontreponemal test is negative after a positive treponemal test during a reverse algorithm screening, a second treponemal test based on a different antigen than the original test should be performed to adjudicate the results.[4,70,72,76]

Taking an accurate and careful history is important when considering a syphilis diagnosis, particularly when lesions are not present or missed early in disease. Missed identification of primary lesions delay diagnosis and may lead to uncertainty when patients present in later stages, particularly given the wide range of syphilis manifestations. In latent disease, early nonprimary, nonsecondary syphilis can be differentiated from late or unknown duration syphilis if within the past 12 months an individual: had a negative RPR result, recent primary or secondary syphilis without current symptoms, a sex partner diagnosed with primary or secondary syphilis or a fourfold increase in RPR titers from a previously treated infection.[4,70]

A lumbar puncture is recommended for those with neurologic findings at any stage. A confirmatory diagnosis in those with a reactive VDRL from a CSF specimen of a patient with consistent clinical picture. However, a probable diagnosis can be made if there are neurologic symptoms, a positive serum RPR test and CSF abnormalities. A lumbar puncture is not required for diagnosis of ocular and otic syphilis as it yields an unremarkable CSF result in 30% and 90% of ocular and otic syphilis, respectively. For tertiary syphilis, diagnosis requires a clinically compatible case with microbiologic identification or a positive treponemal test.[4,70]

Maternal and congenital screening recommendations vary by state, with most requiring testing at the first prenatal visit. Some states mandate testing at the third trimester and/or delivery, whereas others recommend testing only for women at increased risk (eg, recreational drug use, STI diagnosis during pregnancy, high prevalence areas, or partner(s) with HIV). Additional maternal risk factors include multiple partners (regardless of HIV status), engaging in transactional sex, late or no prenatal care, incarceration, and unstable housing or homelessness. A congenital syphilis diagnosis can be made if the mother has untreated or inadequately treated syphilis at delivery or a reactive treponemal result of the infant/child with clinical findings or a positive RPR test.[4,69,70]

## Treatment

Table 140-10 presents the CDC's treatment recommendations.[3] Parenteral penicillin G is the treatment of choice for all stages of syphilis. Because *T. pallidum* multiplies slowly, single doses of short- or intermediate-acting penicillins do not provide the prolonged, low-level exposure to penicillin required for treponeme eradication. As a result, benzathine penicillin G is the only penicillin effective for single-dose therapy.[4,70]

TABLE 140-10

**Drug Therapy and Follow-up of Syphilis**

| Stage/Type of Syphilis | Recommended Regimens[a,b] | Follow-up Serology |
|---|---|---|
| Primary, secondary, or early latent syphilis (<1 year's duration) | Adults: Benzathine penicillin G 2.4 million units IM in a single dose<br>Children: Benzathine penicillin G 50,000 units/kg IM in a single dose, up to 2.4 million units | Quantitative nontreponemal tests at 6 and 12 months, with failure if titer does not decrease at least fourfold in 12 months[c] |
| Late latent syphilis (>1 year's duration), syphilis of unknown duration, tertiary syphilis or retreatment after failure | Adults: Benzathine penicillin G 2.4 million units IM once a week for 3 successive weeks (7.2 million units total)<br>Children: Benzathine penicillin G 50,000 units/kg IM once a week for 3 successive weeks, up to 7.2 million units total | Quantitative nontreponemal tests at 6, 12, and 24 months, with failure if titer does not decrease at least fourfold in 24 months[c] |
| Neurosyphilis, including ocular or otic involvement | Aqueous crystalline penicillin G 18-24 million units IV (3-4 million units every 4 hours or by continuo us infusion) for 10-14 days[d,f]<br>*or*<br>Aqueous procaine penicillin G 2.4 million units IM daily plus probenecid 500 mg orally four times daily, both for 10-14 days | Repeat CSF examination is no longer required at 6 months if adequate RPR response (decrease by fourfold or greater) |
| Congenital syphilis (infants with proven or highly probable disease) | Aqueous crystalline penicillin G 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days<br>*or*<br>Procaine penicillin G 50,000 units/kg IM daily for 10 days[d] | Serologic follow-up only recommended if antimicrobials other than penicillin are used |
| **Penicillin-Allergic Patients[e,f]** | | |
| Primary, secondary, or early latent syphilis | Doxycycline 100 mg orally two times daily for 14 days<br>*or*<br>Tetracycline 500 mg orally four times daily for 14 days<br>*or*<br>Ceftriaxone 1-2 g IM or IV daily for 10-14 days | Same as for non–penicillin-allergic patients |
| Late latent syphilis (>1 year's duration) or syphilis of unknown duration | Doxycycline 100 mg orally twice a day for 28 days<br>*or*<br>Tetracycline 500 mg orally four times daily for 28 days | Same as for non–penicillin-allergic patients |

[a]Recommendations are those of the CDC.

[b]The CDC recommends that all patients diagnosed with syphilis be tested for HIV infection.

[c]No specific recommendations exist for tertiary syphilis because of the lack of available data.

[d]Some experts administer benzathine penicillin G 2.4 million units IM once per week for up to 3 weeks after completion of the neurosyphilis regimens to provide a total duration of therapy comparable to that used for late syphilis in the absence of neurosyphilis.

[e]For nonpregnant patients; pregnant patients should be treated with penicillin after desensitization.

[f]Growing data support ceftriaxone efficacy, although the optimal dosage and treatment duration are unclear; in neurosyphilis, 2 g IV daily for at least 10 days found to be as effective as intravenous penicillin G in a recent study.

CSF, cerebrospinal fluid.

The recommended treatment for syphilis of less than 1 year's duration is benzathine penicillin G 2.4 million units as a single IM dose. In patients with late syphilis (including those with tertiary syphilis) or of unknown duration, benzathine penicillin G is administered weekly for three successive doses.[4] There is limited data regarding the questionable benefit of additional doses of benzathine penicillin G (or any other antibiotics) for later stages of syphilis.

Neurosyphilis requires more intensive therapy. The preferred regimen is 18 to 24 million units of IV penicillin G per day, administered as 3 to 4 million units every 4 hours or by continuous infusion, for 10 to 14 days. Intramuscular procaine penicillin G 2.4 million units once daily plus probenecid 500 mg orally four times daily is another option when IV administration is not feasible, such as outpatient treatment requiring a peripherally inserted central catheter (PICC) placement. Benzathine penicillin G alone in standard weekly doses does not consistently provide treponemicidal levels in the CSF, resulting in treatment failures. Because *T. pallidum* penicillin resistance has not emerged, the primary need for alternative drugs in treating syphilis is for penicillin-allergic patients.[4]

Alternative regimens recommended for penicillin-allergic patients are doxycycline 100 mg orally twice daily or tetracycline 500 mg orally four times daily for 2 to 4 weeks depending on the duration of syphilis infection. Parenteral ceftriaxone is another option, particularly because there is a low propensity of cross-reactivity between penicillin and cephalosporins. Ceftriaxone 1 g IV for 10 days was superior to two weekly doses of benzathine penicillin G.[77] In neurosyphilis, ceftriaxone 2 g daily for at least 10 days was as effective as IV penicillin G.[78] Clinicians may avoid ceftriaxone if the penicillin reaction was IgE-mediated or life-threatening (eg, Stevens Johnson Syndrome). Various other beta-lactams have been successfully used to treat syphilis; however, none offer significant advantage over benzathine penicillin G. Azithromycin 2 g as a single dose is no longer recommended due to increasing and unpredictable rates of resistance. Tetracyclines and ceftriaxone should be reserved for cases of documented penicillin allergy and, given concerns regarding patient compliance with these regimens, follow-up serologic testing is particularly important.[4]

For pregnant patients, penicillin is the treatment of choice at the dosage recommended for adults with that particular stage of syphilis. Some clinicians administer an additional IM dose of benzathine penicillin G 2.4 million units 1 week after completion of the recommended regimen, although there is no literature supporting this practice. In women allergic to penicillin, safe and effective alternatives are not available; therefore, skin testing should be performed to confirm a penicillin allergy. Women with positive penicillin skin tests may undergo penicillin desensitization and receive the appropriate treatment regimen for their stage of disease.[4]

Patients treated for primary and secondary syphilis may experience an acute reaction characterized by flu-like symptoms, such as transient headache, fever, chills, malaise, arthralgia, myalgia, tachypnea, peripheral vasodilation, and aggravation of syphilitic lesions, called the Jarisch-Herxheimer reaction. It usually begins within 6 to 8 hours of initiating therapy and lasts 12 to 24 hours. The exact mechanism of the reaction is unknown, although proposed etiologies, including immunologic mechanisms and release of endotoxin or other toxic treponemal products, are not substantiated. The Jarisch-Herxheimer reaction is independent of the drug and dose used and should not be confused with penicillin allergy. Most reactions can be managed symptomatically with analgesics, antipyretics, and rest. Steroids and antihistamines have been administered prior to initiation of syphilitic therapy, but are of limited value.[4,70]

### Evaluation of Therapeutic Outcomes

Table 140-10 lists the CDC recommendations for serologic follow-up of patients treated for syphilis.[4] Quantitative nontreponemal tests (eg, RPR) should be performed at 6 and 12 months in all patients treated for primary, secondary, and early non-primary, non-secondary syphilis and at 6, 12, and 24 months for late disease or when duration is unknown. In general, the time to reach seronegativity is proportional to the duration of the disease. Serologic cure is defined by a drop in nontreponemal titers by at least fourfold by 12 months in those treated within a year of infection and by 24 months if the time of exposure cannot be determined or treatment 12 months after infection. Table 140-10 also includes specific testing recommendations for other stages of syphilis. Despite appropriate therapy, about 15% to 20% of patients fail to mount a sufficient antibody titer

response. There is limited guidance on the best course of action when this occurs. If the titers were initially low at the time of treatment (eg, 1:2, 1:4), a twofold decline or no change may dictate additional serologic follow-up without retreatment.[4,70,72]

When retreatment is indicated, individuals should receive three weekly treatments of 2.4 million units of IM benzathine penicillin G, excluding neurosyphilis. Retreatment may be indicated when an alternate treatment was used initially, such as doxycycline in a patient without a penicillin-allergy. This differs from treatment of a repeat infection diagnosed within 1 year of exposure, which warrants a single IM dose of benzathine penicillin 2.4 million units. For women treated during pregnancy, monthly quantitative nontreponemal tests are recommended in those at high risk of reinfection. Recent sex partners (within 90 days) of anyone diagnosed should be treated presumptively if serologic tests are not immediately available.[4]

# GENITAL HERPES

## Epidemiology and Etiology

Genital herpes infections are the predominate cause of genital ulceration in the United States and globally. These infections are primarily attributed to HSV-2, with a prevalence of 11.9% among 14- to 49-year-olds and approximately 572,000 new infections annually.[2,79] The number of individuals with genital herpes is magnified by rising infections caused by HSV-1, usually associated with oropharyngeal disease (eg, “cold sores”).[80] Most persons with HSV-2 are unaware of their infection.[81] Only 30% of those with HSV-1 infection experience clinically recognized outbreaks. HSV-2 rates among women are almost twice that of men. The incidence of HSV-2 is strongly correlated with the start of sexual activity, with rates decreasing gradually in subsequent age groups. Alternatively, HSV-1 is usually acquired earlier in childhood and is inversely proportional to socioeconomic status. Although the number of lifetime sexual partners, age of sexual debut, and STI history correlate with HSV-2 infection, it is commonly transmitted through long-term relationships rather than casual sexual relationships.[82,83]

Genital herpes is of major public health importance, despite most individuals having limited or no manifestations of disease. Although the risk of HSV is higher during clinical outbreaks, most transmission occurs during periods of asymptomatic shedding, hampering prevention efforts. Serious complications, particularly among those with immunosuppression, during pregnancy, and neonates born to mothers with HSV, may occur. For people who experience symptoms, episodes are often recurrent, causing painful ulcers and generalized discomfort for days at a time. A diagnosis of genital herpes may impact sexual relationships, cause social stigma, and lead to psychological distress. For various reasons, the CDC does not recommend screening for HSV in the general population.[3] Similar to syphilis and other STDs, the presence of genital herpes lesions is associated with an increased risk of acquiring HIV following exposure.[4,83–85]

## Pathophysiology

HSV-1 and 2 are two members of the Herpesvirus family. Humans are the sole known reservoir for HSV. Each virus is capable of causing clinically indistinguishable infections, although the likelihood of causing disease in a specific anatomic area differs. Infection is transmitted via inoculation of virus from infected secretions onto mucosal surfaces (eg, urethra, oropharynx, cervix, and conjunctivae) or through abraded skin.[4,83–85]

The cycle of HSV infection occurs in five stages: initial mucosal or dermal infection, ganglia infection, establishment of latency, reactivation, and recurrent infection. After cell entry, transportation and replication occurs via viral spread from peripheral sensory nerves to contiguous cells and ganglia, most commonly the sacral nerve root ganglia if genital entry and the trigeminal ganglia if oropharyngeal entry. Chronic infection is established at this time, with clinical latency occurring for the majority of the person’s life. Latency does not mean dormancy, as viral replication occurs in infected neurons and peripheral nerve endings, despite lack of symptoms. These reactivation periods are highly variable among patients. Stress, illness, and sun exposure (UV light) are identified as precipitating factors.[83,84]

## Clinical Presentation

The signs and symptoms of genital herpes infection are influenced by many factors, including previous exposure to HSV, viral type, and host factors, such as age and site of infection. Because a high percentage of initial and recurrent infections are asymptomatic, and viral shedding can occur in the absence of apparent lesions or symptoms, identification and education of individuals with genital herpes is essential in controlling transmission. A summary of the clinical presentation of genital herpes is provided in Table 140-11. Those who experience symptoms usually develop multiple painful ulcers, at times accompanied by itching, discomfort, paresthesias, and local lymphadenopathy. These symptoms are typically more severe, involve

neurologic complaints (fever, headache, malaise, myalgias), and persist longer in the first episode, especially if they occur during primary infection. Lesions may present at various stages in addition to ulcers, such as vesicles, pustules, and crusting. Frequency of genital herpetic recurrences differ among the HSV types after the first episode, with 90% of those infected with HSV-2 experiencing within the first year in comparison to 55% of HSV-1-infected individuals.[4,83–85]

TABLE 140-11

**Presentation of Genital Herpes Infections**

| | |
|---|---|
| **General** | Incubation period: 2-14 days (mean, 4 days) Can be caused by either HSV-1 or HSV-2 |
| **Classification of infection** | |
| First-episode primary<br>First-episode nonprimary<br>Recurrent | Initial genital infection in individuals lacking antibody to either HSV-1 or HSV-2<br>Initial genital infection in individuals with clinical or serologic evidence of prior HSV (usually HSV-1) infection<br>Appearance of genital lesions at some time following healing of first-episode infection |
| **Signs and symptoms** | |
| First-episode infections | Most primary infections are asymptomatic or minimally symptomatic<br>Multiple painful pustular or ulcerative lesions on external genitalia developing over a period of 7-10 days; lesions heal in 2-4 weeks (mean, 21 days)<br>Flu-like symptoms (eg, fever, headache, malaise) during first few days after appearance of lesions<br>Others—local itching, pain, or discomfort; vaginal or urethral discharge, tender inguinal adenopathy, paresthesias, urinary retention<br>Severity of symptoms greater in females than in males<br>Symptoms are less severe (eg, fewer lesions, more rapid lesion healing, fewer or milder systemic symptoms) with nonprimary infections<br>Symptoms more severe and prolonged in the immunocompromised<br>On average viral shedding lasts approximately 11-12 days for primary infections and 7 days for non-primary infections |
| Recurrent | Prodrome seen in approximately 50% of patients prior to appearance of recurrent lesions; mild burning, itching, or tingling are typical prodromal symptoms<br>Compared to primary infections, recurrent infections associated with (1) fewer lesions that are more localized, (2) shorter duration of active infection (lesions heal within 7 days), and (3) milder symptoms<br>Severity of symptoms greater in females than in males<br>Symptoms more severe and prolonged in the immunocompromised<br>On average viral shedding lasts approximately 4 days<br>Asymptomatic viral shedding is more frequent during the first year after infection with HSV |
| **Therapeutic implications of HSV-1 vs HSV-2 genital infection** | Primary infections caused by HSV-1 and HSV-2 virtually indistinguishable<br>Recurrent infections and subclinical viral shedding are less frequent with HSV-1<br>Recurrent infections with HSV-2 tend to be more severe |
| **Complications** | Secondary infection of lesions; extragenital infection because of autoinoculation; disseminated infection (primarily in immunocompromised patients); meningitis or encephalitis; neonatal transmission |

HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2.

Recurrent episodes are usually more localized, have fewer lesions, are shorter in duration, and present with milder symptoms. About half of recurrent ulcers are preceded by prodomal symptoms (mild burning, itching, tingling, or shooting pains), which could extend to the buttocks or leg. Prodromal symptoms may also occur in the absence of genital lesions. Mucocutaneous HSV is detected in these prodromal states, solidifying the evidence that viral reactivation is linked to the symptom presentation. HSV as the cause of atypical presentations can be missed and warrant HSV testing when the clinical picture is uncertain. Education on signs and symptoms of genital herpes to those who were unaware of their seropositivity have resulted in a 48% to 62% observation of classic lesions within the following months, highlighting the knowledge gap among the general public. HSV-1 is associated with a lower rate of asymptomatic and symptomatic recurrence, while HSV-2 is characterized by more frequent recurrences and subclinical shedding.[4,83–85]

## Complications

Complications from genital herpes infections resulting from both local autoinoculation and extragenital spread commonly to the eye, rectum, pharynx, and fingers. CNS involvement is seen occasionally and can take several forms, including encephalitis, aseptic meningitis, and transverse myelitis. HSV-2 is more likely to cause aseptic meningitis than HSV-1, while HSV-1 is the most commonly identified cause of acute viral encephalitis.

A major concern is the effect of genital herpes on neonates exposed during pregnancy. Neonatal herpes is associated with a high mortality and significant morbidity. It is transmitted to the newborn primarily through exposure in the birth canal but, in rare cases, transplacentally. The risk of transmission during birth appears much greater for first-episode primary infections than for recurrent infections. Neonatal herpes infection has a case-fatality rate of approximately 50%, with a large proportion of surviving infants experiencing significant morbidity, including permanent neurologic damage. Morbidity and mortality caused by HSV in immunocompromised transplant recipients or those receiving cancer chemotherapy has dramatically reduced by the inclusion of antiviral prophylaxis into most therapeutic plans.[4,83,84]

## Diagnosis

Confirmation of genital herpes infection can be made only with laboratory testing. Viral culture and HSV DNA detection with PCR assays are primary modalities used to confirm the diagnosis of first-episode genital herpes as the antibodies produced early in infection may not be detected (complete seroconversion can take months). These tests can also be used when recurrent lesions are present. Although viral culture is highly specific, it is relatively insensitive in detecting HSV in ulcers in the latter stages of healing and in recurrent infections, in part due to reduced viral load. Viral culture is expensive, time-consuming, and improper collection or transport of specimens can result in false-negative results, but may be helpful when acyclovir resistance is suspected. In most situations, HSV isolation from culture takes 48 to 96 hours.[4,83]

PCR assays are the preferred diagnostic tests due to greater sensitivity (in active lesions or asymptomatic viral shedding), significantly faster turnaround, and wider availability. Subtyping should be sought once HSV is detected. Although some PCR tests can differentiate serotype, not all have that capability. Serologic testing plays a role in diagnosing HSV infection in select scenarios: (1) recurrent genital symptoms present with negative PCR/culture; (2) patients with clinical signs of HSV infection without laboratory confirmation; (3) when the partner has documented genital herpes. Type-specific serology can distinguish between HSV-1 and HSV-2 based on HSV-specific glycoprotein G-1 and glycoprotein G-2, respectively. The sensitivity of these tests can vary from 80% to 98%, with false-negatives more likely to occur early in disease. EIAs are the most commonly used tests, which at low index values (1.1-3.0) have high rates of false-positivity. A confirmatory test with another method, such as the Biokit or a western blot, should be performed before interpretation of an EIA, particularly when with low index values.[4,83,84]

## Treatment

Management goals for genital herpes include symptom relief, reducing the clinical course to prevent complications and recurrences, and minimizing disease transmission. The CDC recommended genital herpes treatments include the antiviral agents acyclovir, valacyclovir, and famciclovir (Table 140-12). The overall efficacy of these agents is comparable, although patient compliance can be improved with less frequent dosing regimens.[4]

TABLE 140-12

**Treatment of Genital Herpes**

| Type of Infection | Recommended Regimens[a,b] | Alternative Regimens |
|---|---|---|
| First clinical episode of genital herpes[c] | Acyclovir 400 mg orally three times daily for 7-10 days,[d] *or* Famciclovir 250 mg orally three times daily for 7-10 days,[d] *or* Valacyclovir 1 g orally twice daily for 7-10 days[d] | Acyclovir 5-10 mg/kg IV every 8 hours for 2 -7 days or until clinical improvement occurs, followed by high-dose oral therapy (valcyclovir 1 g thrice daily) to complete 10-14 days of total therapy[e] |
| **Recurrent infection** | | |
| Episodic therapy[f] | Acyclovir 800 mg orally twice daily for 5 days, *or* Acyclovir 800 mg orally three times daily for 2 days, *or* Famciclovir 125 mg orally twice daily for 5 days, *or* Famciclovir 1 g orally twice daily for 1 day, *or* Famciclovir 500 mg orally once, followed by 250 mg orally twice daily for 2 days, *or* Valacyclovir 500 mg orally twice daily for 3 days, *or* Valacyclovir 1 g orally once daily for 5 days | |
| Suppressive therapy[g] | Acyclovir 400 mg orally twice daily, *or* Famciclovir 250 mg orally twice daily,[h] *or* Valacyclovir 500 mg or 1 g orally once daily[i] | |

[a]Recommendations are those of the CDC.

[b]HIV-infected patients can require more aggressive therapy.

[c]Primary or nonprimary first episode.

[d]Treatment duration can be extended if healing is incomplete after 10 days.

[e]Only for patients with severe symptoms or complications that necessitate hospitalization. HSV encephalitis requires 14-21 days of IV therapy.

[f]Requires initiation of therapy within 24 hours of lesion onset or during the prodrome that precedes some outbreaks.

[g]Consider discontinuation of treatment after one year to assess frequency of recurrence.

[h]Famciclovir appears less effective for suppression of viral shedding.

[i]Valacyclovir 500 mg appears less effective than other valacyclovir and acyclovir regimens in patients with 10 or more recurrences per year.

IV, intravenous.

### First-Episode Infections

6 Oral formulations of acyclovir, famciclovir, and valacyclovir have demonstrated efficacy in reducing viral shedding, duration of symptoms, and time to healing of first-episode genital herpes infections, with maximal benefits seen when therapy is initiated at the earliest stages of infection. Table 140-12 lists the recommended regimens for first-episode infections. The CDC recommends all patients with first episodes genital herpes receive systemic antiviral therapy to prevent severe or prolonged symptoms associated with newly acquired infections. Additionally, topical antiviral therapy offers minimal clinical benefit and is not recommended. In immunocompromised patients, or those with severe symptoms or complications necessitating hospitalization, parenteral acyclovir is recommended, but has been associated with renal, GI, bone marrow, and CNS toxicity, particularly in patients with renal dysfunction receiving high doses. No antiviral regimen is known to prevent latency or alter the subsequent frequency and severity of recurrences in humans.[4,83–85]

### Recurrent Infections

Mild and infrequent recurrences can be managed without pharmacologic therapy. When therapy is warranted or desired, there are two approaches: episodic or chronic suppressive therapy. Episodic therapy is initiated early during the course of the recurrence, preferably within 6 to 12 hours of the onset of prodromal symptoms, but within 24 hours after lesions first appear. Timely episodic therapy can decrease the duration of lesions by 1 to 2 days. Valacyclovir and famciclovir have improved pharmacokinetic profiles versus acyclovir, allowing for reduced dosing frequency and shorter courses. For optimal therapy, providers should prescribe the regimen of choice ahead of recurrences to allow the patient to initiate treatment at home at the first sign of symptoms.[4,83–85]

Table 140-12 lists the recommended suppressive regimens. Daily suppressive therapy may yield a benefit for patients with frequent episodes (≥6 per year), severe recurrences, those who wish to reduce transmission risk to a partner, and to ease anxiety over unpredictable recurrences. Suppressive therapy reduces the frequency and severity of clinical episodes and asymptomatic shedding in 70% to 80% of patients experiencing frequent recurrences. The extent to which suppressive therapy decreases disease transmission to sexual partners remains to be determined. Because the frequency of recurrences tends to diminish over time, periodic “drug holidays” are advocated to assess changes in the underlying recurrence rate and determine if continued suppressive therapy is warranted.[4,83,84]

### Selected Populations

Immunocompromised patients are at greatest risk for severe and recurrent HSV infections. Acyclovir, valacyclovir, and famciclovir have been used to prevent reactivation of infection in patients seropositive for HSV who undergo transplantation procedures or induction chemotherapy. Immunocompromised individuals, such as patients with acquired immunodeficiency syndrome (AIDS), who fail treatment or prophylaxis with recommended antiviral doses frequently demonstrate improved response with higher doses. Resistant isolates are a concern in this immunocompromised population, mediated by alterations in viral thymidine kinase. Resistance is conferred to acyclovir, valacyclovir, and, commonly, famciclovir. If resistance is suspected or confirmed with recommended first-line antivirals, foscarnet is usually effective. However, foscarnet is associated with a greater risk of serious adverse effects. Intravenous cidofovir or topical imiquimod may be effective alternatives to forscarnet. Lesional application of an extemporaneous compounded cidofovir (1%) gel or trifluridine ophthalmic solution appears to offer some benefits.[4,83–85]

The safety of famciclovir and valacyclovir during pregnancy is not well established. Acyclovir has been used in pregnant patients and has produced no evidence of teratogenicity. However, levels in amniotic fluid are similar to infants treated with acyclovir, of which 20% develop neutropenia. Because of the high maternal and infant morbidity associated with first-episode primary genital infections or severe recurrent infections at or near term, many clinicians advocate the use of systemic acyclovir as the standard of care in such cases.[4,85,86]

### Evaluation of Therapeutic Outcomes

Antivirals can reduce morbidity and improve patient quality of life. Outside of serious conditions, like encephalitis and neonatal infection, these agents are palliative. CDC guidelines suggest discontinuation of suppressive therapy after 1 year should be considered to assess for possible changes in the patient’s intrinsic pattern of recurrence. In most patients, decreases in recurrence rates and severity of symptoms occur over time. However, some clinicians prefer to continue suppressive therapy indefinitely because it significantly reduces asymptomatic viral shedding, reducing the risk of disease

transmission to uninfected sexual partners.[4]

Education on the natural course of the infection, reinforcing accurate information, and dispelling misconceptions can significantly improve a patient's experience with HSV. Descriptions of typical and atypical presentations can empower patients to initiate therapy early and minimize anxiety. Prevention strategies should be emphasized, highlighting disclosure to partner(s), abstaining from sexual activity when active lesions are present, condom use, and antiviral therapy.[83,84]

## HUMAN PAPILLOMAVIRUS INFECTIONS

### Epidemiology and Etiology

In 2018, the CDC estimated there were 43 million HPV infections in the United States, 13 million of which were new infections.[5] However, as HPV is not a reportable condition, the incidence is likely much higher. HPV accounts for approximately 50% of new STIs each year.[2] Over 40% of women have evidence of HPV infection, with incidence peaking in teens and early twenties, aligning with initiation of sexual activity.[5] Additionally, lifetime risk of acquiring an HPV infection is over 80%, and risk increases with number of sexual partners.[86] Since the introduction of the HPV vaccine, incidence of HPV infections in teen girls and women in their early twenties have decreased.[87] Persistent infection with some HPV types can cause genital warts and cancer, and reinfection is common, especially in young, sexually active populations.

More than 125 HPV types have been characterized and over 40 are associated with genital tract lesions. Of these, infection with types 6 and 11 most commonly develop low-grade dysplasia manifested as genital warts. Infection with several HPV types, particularly HPV-16 and HPV-18, is associated with cervical neoplasma, the second most common cancer in women worldwide and accounts for approximately 66% cervical cancers in the United States.[4,5,88] The WHO estimates that 84% of HPV lesions are represented as cervical cancers worldwide.[89] Persistent carriers of oncogenic HPV strains, in combination with a variety of other factors including immunosuppression, smoking, chlamydial infection, may all play a role in promotion of viral persistence and cancer.[88] Additionally, women living with HIV are six times more likely to develop cervical cancer compared to women without HIV.[90,91]

### Pathophysiology

HPV is a double-stranded DNA virus that targets basal epithelial cells. It enters cells through a break in the epithelium, and replicates within basal cells as it differentiates and progresses to the epithelial surface. Virus is shed with dead keratinocytes and infection is transmitted via contact dead keratinocyte or free virions. In a wart, viral replication is associated with excessive proliferation of all epidermal layers, except the basal layer, whereas malignant HPV disease is associated with proliferation of basal cells. HPV is transmitted by sexual intercourse, including oral sex, and may also be spread by touching an infected partner's genitalia.[88,89]

### Clinical Presentation

In most individuals, genital infection with HPV is subclinical and self-limited, clearing within 6 to 9 months. HPV can infect genitalia of both women and men, as well as perianal, anal, and oropharynx regions in both genders. Approximately 1% of all infected individuals develop genital warts. When present, genital warts can be large and multifocal, producing variable degrees of discomfort. Appearance of genital warts may differ based on gender and anatomic site. For example, penile warts may be slightly raised with a rough pigmented surface, while vulvar warts are usually soft and whitish. Based on HPV DNA detection methods, most warts will regress spontaneously within 1 to 2 years of their initial appearance. HPV, while known for links to cervical cancer, can also cause cancer of the anus, penis, vulva, vagina, and oropharynx, but are less common.[4,88,89]

### Diagnosis

Anogenital warts are diagnosed clinically and confirmed by biopsy in cases where the diagnosis is uncertain, when warts do not respond to standard treatment, or the patient is immunocompromised. The Papanicolaou smear (Pap smear) is the most frequently used and cost-effective diagnostic test for detecting clinical and subclinical HPV in women. However, Pap smears are neither specific for HPV nor useful in detecting latent infections. Various tests for detecting HPV DNA, RNA, or capsid protein also are available, and unlike the Pap smear do not require subjective interpretation of the results. The HPV-specific tests are only approved in women with abnormal Pap smears or women older than 30 years. However, use of HPV DNA testing as a routine screening test in lieu of Pap smears is expected in the near future. In women identified to have high-risk HPV strain infections, follow-up

cytology is performed. HPV tests are not approved for use in men and are not indicated as a screening tool for STIs.[4,88,89]

Routine screening for cervical cancer is recommended for all persons with a cervix, regardless of gender identity or partner preference. Age recommendations vary by organization. The USPSTF and the American College of Obstetricians and Gynecologists (ACOG) recommend routine cervical cancer screening every 3 years for all persons with a cervix ages 21 to 65 regardless of vaccination status. For women 30 to 65, screening can also include one of several FDA-approved oncogenic or high-risk HPV tests. The American Cancer Society recommends cervical screening of any persons with a cervix, regardless of gender identity, ages 25 to 65 by combining a Pap test with an HPV test or a Pap test alone every 3 years.[91–93] Data are insufficient to recommend routine anal cancer screening. An annual digital anorectal exams (DARE) may be useful in high-risk patient populations for early detection of HPV. The updated CDC STI Guidelines provide a table detailing the screening recommendations from various organizations.[4]

## Treatment

No consensus exists regarding the best treatment approach for patients with genital HPV infection, particularly because most cases appear to be transient with spontaneous regression of lesions. A number of treatments are recommended (see Table 140-13), but none are clearly superior. Treatment is directed toward patients with manifestations of genital warts, with the goal of removing or destroying lesions and grossly infected surrounding tissue. Shared decision making between patient and provider determine the decision to treat and utilization of patient or provider applied therapy. Type of therapy is depended upon lesion location, provider experience, patient preference, and availability. Provider-applied therapies, cryotherapy and surgical removal, are options for any site, while acid treatments are options for vaginal, cervical, and intra-anal warts. Many patients will require multiple courses of therapy. Because such treatments neither stop viral expression in surrounding tissue nor eliminate viral latency, recurrence of lesions is common.[4]

TABLE 140-13

**Treatment Regimens for Miscellaneous STIs**

| Infection | Recommended Regimens[a] | Alternative Regimens |
|---|---|---|
| Cervicitis[b] | Doxycycline 100 mg orally twice daily for 7 days | Azithromycin 1 g orally in a single dose |
| Epididymitis | | |
| Acute infection most likely caused by *C. trachomatis* or *N. gonorrhoeae*<br>Acute infection most likely caused by *C. trachomatis, N. gonorrhoeae,* or enteric organisms (men who practice insertive anal sex)<br>Acute infection most likely caused by enteric organisms only | Ceftriaxone 500 mg IM in a single dose PLUS doxycycline 100 mg orally twice daily for 7 days<br>Ceftriaxone 500 mg IM in a single dose PLUS levofloxacin 500 mg orally daily for 10 days<br>Levofloxacin 500 mg orally daily for 10 days | |
| Lymphogranuloma venereum | Doxycycline 100 mg orally twice daily for 21 days[c] | Azithromycin 1 g weekly for 3 weeks or erythromycin base 500 mg orally four times daily for 21 days[c,d] |
| Nongonococcal urethritis (NGU) | Doxycycline 100 mg orally twice daily for 7 days | Azithromycin 1 g orally in a single dose or 500 mg orally in a single dose followed by 250 mg daily for 4 days |
| NGU (persistent or recurrent or due to *M. genitalium*) | Doxycycline 100 mg orally twice daily for 7 days followed by moxifloxacin 400 mg orally daily for 7 days | If azithromycin resistance can be ruled out, moxifloxacin may be substituted with oral |

| | | |
|---|---|---|
| | | azithromycin 1 g and then 500 mg daily for 3 days |
| **HPV infection** | | |
| External genital/perianal warts | *Provider-Administered Therapies:*<br>Cryotherapy (eg, liquid nitrogen or cryoprobe); repeat weekly as necessary, *or*<br>TCA 80%-90% *or* BCA 80%-90% applied to warts; repeat weekly as necessary, *or*<br>Surgical removal (tangential scissor excision, tangential shave excision, curettage, or electrosurgery)<br>*Patient-Applied Therapies:*<br>Podofilox 0.5% solution or gel applied twice daily for 3 days, followed by 4 days of no therapy; cycle is repeated as necessary for up to four cycles.<br>Imiquimod 3.75% or 5% cream applied at bedtime three times weekly for up to 16 weeks,[e,f] *or*<br>Sinecatechins 15% ointment applied three times daily for up to 16 weeks | |
| Vaginal and anal warts | Cryotherapy with liquid nitrogen, or TCA or BCA 80%-90% as for external HPV warts; repeat weekly as necessary<br>Surgical removal (not for vaginal or urethral meatus warts) | |
| Urethral meatus warts | Cryotherapy with liquid nitrogen, or surgical removal | |
| Prevention (ages 9-14 years)[f] | Gardasil9® (HPV 9-valent [type s 6, 11, 16, 18, 31, 33, 45, 52, 58]) recombinant vaccine 0.5 mL IM on day 1; a second dose administered 6-12 months following the first dose | |
| Prevention (age ≥15-26 years)[f] | Gardasil (HPV 9-valent [types 6, 11, 16, 18, 31, 33, 45, 52, 58]) recombinant vaccine 0.5 mL IM on day 1; a second and third dose are administered 1 and 6 months following the first dose | |

[a]Recommendations are those of the CDC.

[b]Consider concurrent treatment for gonorrhea infection if the patient is at risk for gonorrhea.

[c]Pregnant patients should be treated with erythromycin.

[d]If NGU is due to *C. trachomatis*, refer to treatment in Table 140-6. If NGU not due to *C. trachomatis*, consider HSV, trichomoniasis, *M. genitalium*, or HPV as potential causes of NGU and perform testing when appropriate.

[e]Safety during pregnancy is not established.

[f]CDC recommendations: vaccination is recommended in adolescents 11-12 years of age, and can be given as early as age 9. Catch up vaccination is recommended through age 26 years for those who either were not previously vaccinated, or who did not complete the vaccination series. Vaccination for adults ages 27-45 can be considered.

BCA, bichloracetic acid; HPV, human papillomavirus; TCA, trichloroacetic acid.

### Vaccination

7 As lesions are difficult to successfully treat, high incidence of reinfection, and concern for malignancy with persistent infections, the focus of HPV treatment is primarily on prevention. The only way to avoid acquiring HPV is to abstain from any type of sexual activity; however, barrier contraceptive methods may help decrease the risk of HPV transmission. Therefore, three HPV vaccines are licensed in the United States and endorsed by the CDC and Advisory Committee on Immunization Practices (ACIP).[94] The vaccines cover the most common and virulent HPV strains. Cervarix (a bivalent vaccine for HPV-16 and 18), Gardasil (a quadrivalent vaccine (4vHPV) for HPV-6, 11, 16, and 18), and Gardasil 9 (a 9-valent (9vHPV) vaccine for HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58) are all indicated for preventing cervical precancers and cervical cancer in females 9 to 26 years of age. The 9vHPV vaccine offers protection against seven oncogenic strains of HPV, which accounts for approximately 80% of cervical cancers.[95] In addition, 4vHPV and 9vHPV are indicated in unvaccinated males 9 to 26 years of age.[94]The FDA extended approval for use of the 9vHPV for women and men ages 27 to 45 years and in 2019 ACIP recommended that adults in that age group discuss receiving the HPV vaccine with their provider through shared decision making.[94] For women and men ages 30 to 45 years, the cost-effectiveness of HPV vaccination should be considered as vaccination may provide limited health benefit at the population level.[96] All three vaccines are equally recommended by the ACIP; however, only 9vHPV vaccine is available for sale within the United States.[94,95]

Although it is ideal to vaccinate patients prior to the onset of sexual activity, those infected with one or more HPV types may still receive protection from vaccination.[4] Additionally, while the vaccine indication is cervical cancer prevention, males are included in the recommendations to reduce spread of asymptomatic disease and reduce risk of HPV-related malignancies.

Previously, all vaccines were administered as a three-dose series over 6 months, but in 2016 ACIP recommendation changed for patients less than 15 years to a two-dose schedule at 0 and 6 to 12 months. Data in women aged 16 to 26 years support the use of a two-dose schedule in those 9 to 14 years old, instead of the three-dose schedule, as antibody response with two doses was noninferior to three doses. All other age groups are recommended to receive the three-dose series at 0, 2, and 6 months.[94,96–99]

The safety profile of the HPV vaccines has been well established over the past decade.[99–102] The CDC and FDA continuously monitor the safety of vaccines via program such as Vaccine Adverse Event Reporting System (VAERS), Vaccine Safety Data link, and Clinical Immunization Safety Assessment Project.[100] The most common adverse events are related to injection site reactions, including pain, redness, or swelling. Additionally, patients may also report fever, headache, asthenia, nausea, or muscle or joint pain. Early VAERS data showed high rates of syncope. Syncope is a known adverse event after any injectable vaccination, and adolescents are also more likely to experience syncope after a medical procedure, including vaccination. In response, the FDA, CDC, and ACIP recommend to observe all patients for 15 minutes after administration of the vaccine to monitor for syncope, taking appropriate precautions to prevent falls and injuries from fainting. Over 90% of health events reported to VAERS were classified as nonserious.[1,100] HPV vaccination has not been linked to new autoimmune diseases or neurologic disorders.[99–101]

The main goal of HPV vaccination is to prevent HPV-associated malignancies; however, time from HPV infection to cervical cancer may exceed 20 years, so effects of the vaccine may not be seen for some time.[88,100] Although the ability to measure effect of the vaccine on malignancies is limited, introduction of the vaccines has substantially reduced HPV prevalence and HPV-related diseases.[5,103] There was substantially reduced risk of cervical cancer among Swedish girls ages 10 to 30 vaccinated with the quadrivalent HPV vaccine.[103] There have also been concerns regarding the long-term effect of the vaccine given the young age at which it is recommended to be administered. Antibody titers maintain appropriate levels for approximately 10 years and there is no evidence to suggest that protection decreases with time.[86] Patients should be vaccinated prior to onset of sexual activity to gain the greatest protection from the vaccine for the duration of time when they are at highest risk. As mentioned, the vaccine may still be protective even after patients have become sexually active.

Despite CDC and ACIP recommendations, the number of adolescents receiving the vaccine is below the desired threshold of 80%.[7,102,104,105] However, numbers are increasing. In girls aged 13 to 17, 70% received at least one dose of the vaccine and 54% received the entire series. The numbers are lower for boys, with 66% receiving at least one dose and 49% receiving all three.[102] Rates of vaccine implementation may increase with interventions, such as

patient education and reminders, but a barrier still exists introducing this vaccine into a nontraditional target population.[105,106]

### Other STIs

Several STIs other than those just discussed occur with varying frequency in the United States and throughout the world. Although an in-depth discussion of these diseases is beyond the scope of this chapter, Table 135-13 lists recommended treatment regimens.[4]

## ABBREVIATIONS

| | |
|---|---|
| ACIP | Advisory Committee on Immunization Practices |
| BCA | bichloracetic acid |
| CDC | Centers for Disease Control and Prevention |
| CNS | central nervous system |
| CSF | cerebrospinal fluid |
| DGI | disseminated gonococcal infection |
| DNA | deoxyribonucleic acid |
| EIA | enzyme immunoassay |
| EPT | expedited partner therapy |
| FDA | Food and Drug Administration |
| GI | gastrointestinal |
| HIV | human immunodeficiency virus |
| HPV | human papillomavirus |
| HSV | herpes simplex virus |
| HSV-1 | herpes simplex virus type 1 |
| HSV-2 | herpes simplex virus type 2 |
| IM | intramuscular |
| IUD | intrauterine contraceptive devices |
| IV | intravenous |
| MSM | men who have sex with men |
| NAATs | nucleic acid amplification tests |

| | |
|---|---|
| NGU | nongonococcal urethritis |
| Pap | Papanicolaou smear |
| PCR | polymerase chain reaction |
| PID | pelvic inflammatory disease |
| RPR | rapid plasma reagin |
| STD | sexually transmitted disease |
| STI | sexually transmitted infection |
| TCA | Trichloroacetic acid |
| TOC | test of cure |
| USPSTF | US Preventative Services Task Force |
| VAERS | Vaccine Adverse Event Reporting System |

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## SELF-ASSESSMENT QUESTIONS

1. Which of the following age groups represent the highest proportion of new STIs?

   A. 15 to 24 years old

   B. 25 to 34 years old

   C. 35 to 54 years old

   D. ≥ 55 years old

2. When taking a sexual history, it is important to consider the five Ps. Which of the following are not included in the five Ps patient assessment?

   A. Partners

   B. Practices

C. Providers

D. Protection

3. Which of the following is the recommended treatment for a 22-year-old 65 kg female diagnosed with a cervical gonococcal infection? The patient tested negative for chlamydia and has no known drug allergies.

   A. Ceftriaxone 500 mg IM × 1 dose

   B. Cefixime 800 mg PO × 1 dose and doxycycline 100 mg orally twice daily × 7 days

   C. Ceftriaxone 500 mg IM × 1 dose and azithromycin 1,000 mg orally × 1 dose

   D. Ciprofloxacin 500 mg orally twice daily × 7 days

4. A 20-year-old male presents to the clinic with purulent urethral discharge and a positive urine NAAT for gonorrhea and chlamydia. When taking a sexual history, the patient discloses two sexual partners in the past 60 days, one male and one female. To the patient's knowledge, neither partner is experiencing symptoms. The patient is provided first-line therapy for gonorrhea and chlamydia in the clinic. In addition to referral for medical care, which of the following strategies are most appropriate for partner management?

   A. Offer expedited partner therapy for both partners.

   B. Offer expedited partner therapy only for the female partner as use is cautioned for the male patient.

   C. Offer expedited partner therapy only for the male partner as use is cautioned for the female patient.

   D. Expedited partner therapy is inappropriate for both patients.

5. After successful treatment for uncomplicated genital chlamydia infection, which of the following are recommended for patients without persistent or recurrent symptoms?

   A. Retest 3 months after completion of therapy

   B. Test of cure NAAT at conclusion of therapy

   C. Culture and sensitivity testing in combination with test of cure NAAT at conclusion of therapy

   D. No follow-up testing necessary

6. Which of the following regimens is recommended for treatment of *C. trachomatis* rectal infections?

   A. Ciprofloxacin 500 mg orally twice a day for 7 days

   B. Azithromycin 1 g orally as a single dose

   C. Doxycycline 100 mg orally twice a day for 7 days

   D. Erythromycin base 500 mg orally four times a day for 7 days

7. Which of the following statements regarding trichomoniasis is true?

   A. Only sexual transmission of trichomoniasis is possible.

   B. The majority of infected men are symptomatic.

   C. Vaginal discharge is rare among symptomatic women.

   D. NAAT testing for trichomoniasis is preferred to wet-mount specimen examination.

8. Of the following treatment regimens, which is (are) recommended by the CDC for treating a patient with trichomoniasis who fails initial treatment with metronidazole 500 mg orally twice daily for 7 days and reinfection has been excluded?

   A. Tinidazole 2 g orally as a single dose

   B. Metronidazole 500 mg orally twice a day for 7 days

   C. Metronidazole 2 g orally for 3 to 5 days

   D. Tinidazole 2 g orally for 7 days

9. Which of the following organisms may be suspected in patients with persistent symptoms of pelvic inflammatory disease who have received treatment with ceftriaxone, doxycycline, and metronidazole?

   A. *Treponema pallidum*

   B. *Mycoplasma genitalium*

   C. *Group B streptococcus*

   D. *Chlamydia trachomatis*

10. Which of the following are a complication of pelvic inflammatory disease?

    A. Persistent pelvic pain

    B. Ectopic pregnancy

    C. Infertility

    D. All of the above

11. The CDC recommends that a penicillin-allergic pregnant patient with a diagnosis of primary syphilis should be treated with

    A. Azithromycin

    B. Doxycycline

    C. Erythromycin

    D. Penicillin desensitization

12. A 21-year-old man with no known drug allergies who is receiving HIV preexposure prophylaxis (PrEP) is seen for routine follow-up visit. Screening laboratory tests show a positive treponemal enzyme immunoassay (EIA) and a positive RPR with a titer of 1:16. He does not have any symptoms and does not recall any symptoms over the past year and states he has never been diagnosed with syphilis. His screening tests 6 months ago were negative. What is the most appropriate management of syphilis for this patient?

    A. No treatment is necessary since he is asymptomatic.

    B. Benzathine penicillin G 2.4 million unites intramuscular as a single dose.

    C. Benzathine penicillin G 2.4 million unites intramuscular weekly for 3 weeks.

    D. Ceftriaxone 1 g intramuscular daily for 10 days.

13. Which of the following statements regarding genital herpes infection is false?

A. Most genital infections are caused by HSV-2.

B. Clinical manifestations of infection can occur within 2 days following exposure.

C. Asymptomatic viral shedding is considered the most important source of transmission.

D. Routine screening for HSV-1 and HSV-2 infections is recommended for asymptomatic patients ages 15 to 24.

14. A 32-year-old woman presents for counseling regarding management of recurrent genital herpes. She has had three episodes in the past 11 months and is interested in reducing her risk of recurrence as well as reducing her risk of transmisison to her new partner. Which of the following regimen is most appropriate to reduce genital HSV recurrence?

A. Episodic therapy with famciclovir 125 mg orally two times a day × 5 days

B. Episodic therapy with acyclovir 400 mg orally three times a day for 5 days

C. Suppressive therapy with valacyclovir 500 mg orally once daily

D. Suppressive therapy with valacyclovir 1000 mg orally three times weekly

15. Which of the following statements regarding human papillomavirus (HPV) vaccination is false?

A. HPV vaccination has not been shown to decrease cervical cancer rates

B. HPV vaccination is indicated for anyone who has not completed the HPV vaccination series through age 26

C. Adults ages 27 to 45 may decide to receive HPV vaccination based on discussion with their clinician if they were not previously vaccinated

D. HPV vaccination is indicated, even if someone has tested positive for HPV

## SELF-ASSESSMENT QUESTIONS-ANSWERS

1. **A.** In 2018, the highest rates of new STIs were acquired by teens and young adults aged 15-24 years old.

2. **C.** The five Ps include: partners, practices, protection, past STIs, and prevention of pregnancy strategies.

3. **A.** First-line recommended therapy for uncomplicated cervical gonorrhea is now 500 mg of ceftriaxone given intramuscularly once. This increased dose of ceftriaxone better attains pharmacokinetic and pharmacodynamic targets for *N. gonorrhoeae*. Additionally, single- drug therapy is now recommended versus dual therapy to address rising azithromycin resistance and reduce collateral damage to the human microbiome. If chlamydial infection cannot be ruled out, however, dual therapy is recommended with the addition of doxycycline. Intramuscular ceftriaxone is preferred over oral cefixime. Due to fluoroquinolone resistance rates, ciprofloxacin is no longer recommended for treatment of gonorrhea.

4. **B.** Expedited partner therapy (EPT) with oral cefixime 800 mg once and doxycycline 100 mg twice daily × 7 days is appropriate for uncomplicated gonococcal infections (see section "Evaluation of Therapeutic Outcomes" under "Gonorrhea"). Females with symptoms of pelvic inflammatory disease are contraindicated for EPT, but this patient's female partner dose not describe symptoms. EPT should be used with caution in men who have sex with men due to high rates of HIV and syphilis co-infection and inadequate data in this patient population. Both partners should be referred for medical evaluation.

5. **A.** Posttreatment laboratory testing (ie, NAAT or culture and sensitivity) for therapeutic failure is not recommended unless symptoms persist, concern for non-adherence, or in pregnancy. Due to high risk of reinfection, all patients who have been treated for chlamydia should be retested approximately 3 months after treatment. Posttreatment tests should be performed 3 weeks after completion of therapy due to false positives with continued presence of nonviable organisms.

6. **C.** Oral doxycycline 100 mg twice daily × 7 days and azithromycin 1 g as a single dose are both recommended treatments for uncomplicated chlamydia infections. However, there are efficacy concerns with the azithromycin regimen in rectal chlamydia. Therefore, doxycycline is now the

preferred regimen. Ciprofloxacin and erythromycin are alternative options.

7. **D.** Non-sexual transmission of trichomoniasis is possible, but the overwhelming majority of cases are transmitted via sexual contact. Men rarely present with symptoms of trichomoniasis, compared to women who the majority are symptomatic most commonly with vaginal discharge. NAAT testing is now preferred to wet-mount examination as it is more sensitive versus wet-mount examinations.

8. **B.** Metronidazole 500 mg orally twice daily for 7 days is now the recommended first-line regimen for female patients with trichomoniasis. A second 7-day course of metronidazole is recommended if initial therapy fails. Metronidazole 2 g orally for 7 days or tinidazole 2 g orally for 7 days are options if infection persists and reinfection is ruled out.

9. **B.** Mycoplasma genitalium is an emerging cause of urogenital infections and should be considered in symptomatic patients who do not respond to therapy targeted at gonorrhea, chlamydia, or anaerobes. Untreated M. genitalium infection increases risk of complications, including pelvic inflammatory disease.

10. **D.** PID is an inflammatory disorder of the upper female genital tract and can include any combination of complications that may result in long-term reproductive damage (see section "Pelvic Inflammatory Disease" under "Associated Complications").

11. **D.** Doxycycline in non-pregnant patients is an acceptable alternative to penicillin for the treatment of primary syphilis. Macrolides are no longer recommended as alternatives due to increasing concerns for resistance. For pregnant patients, penicillin is the only recommended therapy and penicillin desensitization is appropriate.

12. **B.** The patient in this case has early non-primary, non-secondary syphilis (formerly early latent syphilis) since he has positive serologic tests without clinical symptoms and a negative test in the past 6 months (<1 year). Even if patients are asymptomatic, treatment is recommended. Benzathine penicillin G 2.4 million units intramuscularly.

13. **D.** Routine screening is not indicated for the general population. However, patients with no history of genital herpes, but whose partner has genital herpes may benefit from screening to determine risk of infection and to guide counseling. Additionally, patients who present for an STD evaluation, especially those with multiple sex partners, patients with HIV infection, and MSM may benefit from HSV screening as they may be at increased risk of HIV acquisition and other STIs.

14. **C.** Daily suppressive therapy can provide symptomatic relief by reducing frequency of recurrence and may be effective at reducing subclinical viral shedding. Suppressive therapy is preferred for those with frequent recurrences and in serodiscordant partners. Valacyclovir 500 mg or 1000 mg daily, famciclovir 250 mg twice daily, or acyclovir 400 mg twice daily are the recommended suppressive regimens (see sections "Treatment," "Recurrent Infections" under "Genital Herpes").

15. **A.** HPV vaccination has been shown to decrease rates of cervical cancer and genital warts. HPV vaccination is indicated in patients ages 9 to 26, and may be considered in those ages 27 to 45 based on shared clinical decision making. Regardless of a patient's previous HPV infection history, vaccination may still prevent against additional strains.