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Review

2021 CDC Update: Treatment and Complications of Sexually Transmitted Infections (STIs)

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Abstract: The Centers for Disease Control and Prevention (CDC) recently updated their Sexually-Transmitted Infection (STI) Treatment Guidelines with a revision to the approach to gonococcal infections in December 2020 and other STIs in July 2021. This article reviews the new recommendations and highlights important updates from the 2015 iteration that are crucial for primary care and community health practice.

Keywords: sexual health; minority populations; asymptomatic infection; risk; sexually-transmitted infections (diseases); complications; update

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1. Introduction

Recent estimates of eight common bacterial, viral, and parasitic sexually transmitted infections in the United States (chlamydia, gonorrhea, trichomoniasis, syphilis, herpes simplex virus type 2, human papillomavirus, hepatitis B virus, and human immunodeficiency virus) found them to have a combined prevalence of 67.6 million and incidence of 26.2 million [1]. Although preventative health guidelines have clarified screening recommendations for some populations, many bacterial sexually transmitted infections (STIs) are asymptomatic, leading to missed opportunities for diagnosis and underreporting of disease prevalence and incidence. The best available estimates, published in early 2021, are from 2018. Overall, it is thought that 1 in 5 people in the United States (U.S.) has an STI [2], with 45.5% of all new STIs occurring in adolescents and young adults [3]. New infections in the U.S. amount to $16 billion in direct medical costs [2].

Disease-associated types of human papilloma virus (HPV) account for the greatest number of infections, with herpes simplex virus type 2 (HSV-2), trichomonas, and chlamydia also contributing heavily to the disease burden. Among individuals age 15–59, HPV has a prevalence of 42.5 million and incidence of 13 million. Genital herpes caused by HSV-2 has a prevalence of approximately 18.6 million in individuals age 15–49, with an incidence of 572,000. Prevalent infections with trichomonas are disproportionately female and amount to 2.6 million individuals age 15–59. The incidence of trichomoniasis is 6.9 million and is more evenly distributed between the sexes [1].

Urogenital chlamydial infections among individuals age 15–39 have a prevalence of approximately 2.4 million, with an incidence of 4 million. It is estimated that the prevalence of urogenital gonorrheal infections in this same demographic is 209,000 cases, with 107,000 demonstrating resistance or elevated minimum inhibitory concentrations (MICs) to

antibiotics. The incident of gonococcal infections is 1.6 million. Females are disproportionately affected by gonorrhea [1]. Males, on the other hand, are disproportionately affected by syphilis, with an estimated total prevalence of 156,000 and incidence of 146,000 among individuals age 14–49 [1].

Although treatment of human immunodeficiency virus (HIV) itself is beyond the scope of this review, an estimated 984,000 people aged 13 and older in the United States are living with a sexually transmitted HIV infection, and 32,600 are infected through sexual contact annually. Both the prevalence and incidence of these sexually transmitted HIV infections are disproportionately male [1]. HIV alone costs the U.S. healthcare system $13.7 billion annually [2]. The Centers for Disease Control and Prevention (CDC) also just updated their HIV pre-exposure prophylaxis (PrEP) guidelines in December 2021 [4].

Prevalence data for these infections are listed in Table 1. Unsurprisingly, the incidence and prevalence of STIs varies by geographic location and population demographics. Table 2 attempts to summarize the limited available, heterogeneous information about other infections and sequelae in the global context.

Table 1. Estimated point prevalence of STIs in the United States [1].

	Men, Median	Women, Median	Demographic *
Chlamydia	1,050,000	1,306,000	15–39 years-old
Gonorrhea	50,000	155,000	15–39 years-old
Trichomoniasis	470,000	2,103,000	15–59 years-old
Syphilis	112,000	38,000	14–49 years-old
Genital herpes (due to HSV-2)	6,354,000	12,203,000	15–49 years-old
HPV	23,411,000	19,210,000	15–59 years-old
HBV	51,000	52,000	≥15 years-old
HIV	775,600	208,400	≥13 years-old

* Prevalence estimates based on availability of data.

Table 2. Worldwide epidemiology of selected STIs and sequelae [5–31].

	Incidence	Prevalence
Primary infections		
Chancroid *	6–7 million	23–56% of genital ulcerative disease in endemic areas
Donovanosis **	Not well-defined ***	Not well-defined
Scabies	527.5 million	175.4 million
Public lice	1.3–4.6% (average 2%)	Not well-defined
Secondary syndromes		
Balanoposthitis	3–6% †	Not well-defined
Epididymitis	0.1% ‡	Not well-defined
Prostatitis	4.9 physician-diagnosed cases per 1000 person-years	2.2–9.7% (overall 8.2%)
Proctitis	Not well-defined ^	5% secondary to rectal gonorrhea among MSM; 9% secondary to rectal chlamydia among MSM
Cervicitis	Not well-defined	30–40% of patients seen in STI clinics; 7.4% of women with HIV
PID	1.4%	4.4% (self-reported)
LGV *	Not well-defined ^^	Not well-defined

* Poor data given lack of (high quality) testing. ** Poor data given limited geographic distribution and lack of political will to report infections. *** Approximately 100 cases are reported annually in the United States, most typically in travelers to endemic regions. † Of uncircumcised males; balanitis alone affects 3–11% of all males. ‡ Approximately 600,000 cases occur annually in the United States. ^ Greater incidence in males than females. ^^ More commonly reported in men and, separately, is associated with HIV-positivity.

2. Bacterial Infections

2.1. Chlamydia Trachomatis

Most people affected by *C. trachomatis* are asymptomatic, which precipitates further spread of the infection. When symptoms do occur, they may include vaginal discharge, vaginal bleeding, dysuria, and/or lower abdominal pain in females, and penile discharge/itch, dysuria, and testicular pain in males [32]. Screening recommendations for females, males, transgender and gender-diverse individuals, and persons living with HIV are listed in Table 3.

Table 3. Screening recommendations for chlamydia (CT) and gonorrhea (GC) [32–34].

Women	• Sexually active women <25 years old • Sexually active women ≥25 years old if at increased risk * • Retest ~3 months after treatment • Pregnant individuals <25 years-old or at increased risk should be retested during 3rd trimester; pregnant patients with CT should have a test of cure 4 weeks after treatment and repeat testing within 3 months; pregnant patients with GC should be retested within 3 months • In addition to urogenital GC/CT, consider pharyngeal GC and rectal GC/CT testing based on reported sexual behaviors and exposure
Men	• Insufficient evidence for routine screening of men who have sex with women (MSW) at low risk of infection; consider screening young men for CT in high prevalence settings ** • Men who have sex with men (MSM) should be screened for GC/CT at least annually at sites of contact (urethra, rectum) irrespective of reported condom use; consider also screening for pharyngeal GC; if at increased risk, screening every 3–6 months may be appropriate
Transgender	• Screening should be based on anatomy and reported sexual behaviors and exposure
HIV-positive	• Sexually active HIV-positive individuals at their first HIV evaluation and at least annually thereafter; more frequent testing may be considered based on individual risk behaviors and local epidemiology

* e.g., new sexual partner, >1 partner. ** e.g., correctional facilities, adolescent clinics, sexual health clinics.

Table 4 summarizes the current treatment guidelines for chlamydia infection. In adolescents and adults, doxycycline 100 mg PO BID × 7 days is now the preferred treatment—one of the most notable updates from the 2015 CDC STI treatment guidelines and reflective of increasing rates of antibiotic resistance. Alternative regimens include azithromycin 1 g PO × 1 or levofloxacin 500 mg PO daily × 7. Although rates of adherence to doxycycline's longer course, compared to azithromycin's single dose, have perennially been called into question [35,36], doxycycline appears to have a higher efficacy rate, even with suboptimal compliance to treatment [37,38]. Indeed, doxycycline is effective against urogenital, rectal, and oropharyngeal infections. Azithromycin, on the other hand, may be less effective against rectal infection [32]. Levofloxacin is still considered to be effective but its use is limited by cost. Erythromycin is no longer recommended due to side effects [32].

Table 4. Treatment of chlamydia [32].

Adolescents and Adults	
First-line therapy	Doxycycline 100 mg PO BID × 7 days
Alternative therapies	Azithromycin 1 g PO × 1 Levofloxacin 500 mg PO daily × 7 days
During Pregnancy	
First-line therapy	Azithromycin 1 g PO × 1
Alternative therapy	Amoxicillin 500 mg PO TID × 7 days
Neonates (ophthalmia, pneumonia) Erythromycin (base *or* ethyl succinate) 50 mg/kg/day PO divided QID × 14 days	
Infants and Children (nasopharynx, urogenital, rectal) If <45 kg: Erythromycin (base *or* ethyl succinate) 50 mg/kg/day PO divided QID × 14 days * If ≥45 kg but <8 years old: Azithromycin 1 g PO × 1 If ≥8 years old: Azithromycin 1g PO × 1 *or* Doxycycline 100 mg PO BID × 7 days	

* An alternative regimen for chlamydial pneumonia in infants is azithromycin 20 mg/kg/day PO daily × 3 days.

Test of cure (i.e., repeat testing 4 weeks after treatment) is not recommended for most patients, but repeat testing 3 months (up to 12 months) after diagnosis and treatment should be performed [32,34].

Patients who are pregnant and found to have chlamydia infection should be treated with azithromycin 1 g PO × 1, although amoxicillin 500 mg PO TID × 7 days is an alternative regimen. Again, erythromycin is not recommended [32].

Chlamydial infection in neonates is treated with erythromycin base or ethyl succinate 50 mg/kg/day divided QID × 14 days. Infants younger than 6 weeks old who have been treated with oral erythromycin or azithromycin should be monitored for infantile hypertrophic pyloric stenosis. Subacute pneumonia in infants, caused by *C. trachomatis*, is treated with erythromycin base or ethyl succinate 50 mg/kg/day divided QID × 14 days; the alternative regimen is azithromycin suspension 20 mg/kg/day once daily × 3 [32].

2.2. Neisseria gonorrhoeae (Gonorrhea)

In females, the most common site of infection with *N. gonorrhoeae* is the cervix. Most affected individuals are asymptomatic, but patients may present with nonspecific symptoms such as pruritis, mucopurulent vaginal discharge, intermenstrual bleeding (metrorrhagia), and/or menorrhagia [32]. Exam findings may range from a normal-appearing cervix to one exhibiting mucosal friability and exuding fluid [32].

Since these signs and symptoms are not specific to *N. gonorrhea*, testing to confirm the diagnosis is recommended [7]. Co-infection with chlamydia is not uncommon [39,40]. Additionally, like chlamydia, infection with gonorrhea can also increase one's risk of acquiring or transmitting HIV. Screening recommendations are listed in Table 3.

Current recommendations for the treatment of gonococcal infections in adults, children, and neonates are listed in Tables 5–7, respectively. In short, the dosage of ceftriaxone has doubled since the 2015 guidelines, with further consideration of the patient's weight. *N. gonorrhoeae* isolates have shown increasing resistance to azithromycin over the last few years, but not to ceftriaxone [33]. Test of cure (culture or nucleic acid amplification test (NAAT)) is not necessary for uncomplicated urogenital or rectal infections but is recommended 7–14 days after treatment of pharyngeal gonorrhea [33].

Table 5. Treatment of gonorrhea in adolescents and adults [32,41].

Urethra, Cervix, and Rectum *	
First-line therapy	If <150 kg: Ceftriaxone 500 mg IM × 1 If ≥150 kg: Ceftriaxone 1 g IM × 1
Alternative therapies **	Gentamicin 240 mg IM × 1 + azithromycin 2 g PO × 1 Cefixime 800 mg PO × 1
Pharynx	
If <150 kg: Ceftriaxone 500 mg IM × 1 If ≥150 kg: Ceftriaxone 1 g IM × 1	
Conjunctivitis † Ceftriaxone 1 g IM × 1	
Gonococcal-related Arthritis and Arthritis-dermatitis Syndrome *,‡	
First-line therapy	Ceftriaxone 1 g IM/IV q 24 h
Alternative therapies	Cefotaxime 1 g IV q 8 h Ceftizoxime 1 g IV q 8 h
Gonococcal Meningitis * Ceftriaxone 1–2 g IV q 24 h × 10–14 days	
Gonococcal Endocarditis * Ceftriaxone 1–2 g IV q 24 h × 4 + weeks	

* If chlamydial infection has not been excluded, add doxycycline 100 mg PO BID × 7 days. ** Pregnant patients should be treated with ceftriaxone; specialist consult is recommended if this is not possible. † Additionally, consider one-time lavage of the affected eye with saline solution. ‡ 24–48 h after substantial clinical improvement, can switch to an appropriate oral agent, with total treatment course of at least 7 days.

Table 6. Treatment of gonorrhea in infants and children [32].

Urethritis, Vulvovaginitis, Cervicitis, Proctitis, and Pharyngitis	If ≤45 kg: Ceftriaxone 25–50 mg/kg IM/IV × 1 (not to exceed 250 mg) If >45 kg: Follow adult treatment guidelines
Bacteremia and Arthritis	If ≤45 kg: Ceftriaxone 50 mg/kg IM/IV (not to exceed 2 g) q 24 h × 7 days If >45 kg: Ceftriaxone 1 g IM/IV q 24 h × 7 days

Table 7. Treatment of gonorrhea in neonates [32].

Gonococcal Ophthalmia Neonatorum	Prophylaxis: Erythromycin 0.5% ophthalmic ointment OU × 1 at birth Treatment: Ceftriaxone 25–50 mg/kg IM/IV × 1 (not to exceed 250 mg) *
Disseminated Gonococcal Infection (DGI) **	Ceftriaxone 25–50 mg/kg IM/IV daily × 7 days Cefotaxime 25 mg/kg IM/IV q 12 h × 7 days

* If unable to give ceftriaxone due to simultaneous IV calcium, use cefotaxime 100 mg/kg IM/IV × 1. ** Course of antibiotics should be 10–14 days if meningitis is documented.

2.3. Syphilis

Caused by the spirochete bacterium *Treponema pallidum*, syphilis is unique in that it goes through three clinical stages if it is not treated. Primary syphilis occurs after infection at the site of inoculation and is characterized by a painless skin ulcer ("chancre") lasting 3–6 weeks. If the infection is not appropriately addressed, syphilis progresses to its second stage, in which a diffuse, nonpruritic macular or papular rash on the extremities and trunk is the most classic symptom [42,43]. Other symptoms in this stage are nonspecific and may include fever, headache, fatigue/malaise, myalgias, and weight loss. Femoral, inguinal, axillary, epitrochlear, and posterior cervical adenopathy are also likely. The dermatologic findings of secondary syphilis are varied, but in addition to the classic rash that is typically seen, "moth-eaten" alopecia may be present [42–45]. Secondary syphilis may also affect

other organs/systems, such as the liver (hepatitis), gastrointestinal system, musculoskeletal system (synovitis, osteitis, periostitis), kidneys (nephrotic syndrome, acute renal failure, acute nephritis), neurological system (headache, cranial nerve deficits, stroke), and eyes (anterior and posterior uveitis, optic neuritis, retinal necrosis) [42]. Latent syphilis is defined as infection with *T. pallidum* shown on serologic testing but without symptoms or clinical manifestations. If the infection occurred within the preceding 12 months (24 months by the World Health Organization's definition), it is considered early latent syphilis. Infection greater than 12 (or 24) months prior defines late latent syphilis, and latent syphilis of unknown duration, although seemingly aptly named, draws ire from some clinicians given its implicit ambiguity [46]. Tertiary syphilis is the symptomatic form of late syphilis and can occur in up to 40% of patients who do not receive appropriate treatment [47]. Symptoms are variable but the most classic symptoms involve the cardiovascular system (aortitis), the central nervous system (general paresis, tabes dorsalis), and the formation of gummas (granulomatous, nodular lesions of any organ) [48].

Tables 8 and 9 list appropriate treatments for syphilis by stage. Alternative regimens should only be used when penicillin desensitization is not possible; however, there are no proven alternatives to penicillin for the treatment of syphilis during pregnancy (including erythromycin). Consequently, pregnant persons with syphilis and an allergy to penicillin should be desensitized and treated with parenteral Penicillin G (PCN G) appropriate to their stage of infection [34]. Note that treatment for neurosyphilis only halts progression—it does not reverse the damage that has already been done.

Table 8. Treatment of syphilis with penicillin [32,49,50].

Primary, Secondary, and Early Latent Syphilis *,†	Benzathine PCN G 2.4 M units IM × 1
Late Latent Syphilis (or Latent Syphilis of Unknown Duration) and Tertiary Syphilis **,†	Benzathine PCN G 2.4 M units IM weekly × 3 doses (7.2 M units total)
Neurosyphilis, Ocular Syphilis, and Otosyphilis	*First-line:* Aqueous crystalline PCN G 18–24 M units IV daily × 10–14 days (this can be given either as a continuous infusion or 3–4 M units IV q 4 h) *Alternative:* Procaine PCN G 2.4 M units IM daily + probenecid 500 mg PO QID, both × 10–14 days ‡

* Infants and children diagnosed with syphilis should be evaluated for congenital versus acquired syphilis, and also potentially evaluated for sexual abuse; medical management should be per specialist consult, typically benzathine PCN G 50,000 units/kg (not to exceed 2.4 M units) IM × 1 for primary and secondary syphilis. ** If tertiary syphilis with normal CSF examination. † This regimen is also recommended for HIV-positive and pregnant individuals. ‡ If compliance can be ensured.

Table 9. Treatment of syphilis for patients allergic to penicillin [32,49,50].

Primary and Secondary Syphilis	Doxycycline 100 mg PO BID × 14 days Tetracycline 500 mg PO QID × 14 days Ceftriaxone 1 g IM/IV daily × 10 days *
Latent Syphilis	Doxycycline 100 mg PO BID × 28 days Tetracycline 500 mg PO QID × 28 days **
Tertiary Syphilis	Seek specialist consult
Neurosyphilis	Ceftriaxone 1–2 g IM/IV daily × 10–14 days ***

* Compliance better with doxycycline compared to tetracycline; optimal dose/duration of ceftriaxone unclear. ** Effectiveness not established. *** Limited data; low risk of cross-reactivity but skin testing could be performed.

2.4. Mycoplasma genitalium

Infection with *Mycoplasma genitalium* does not always cause overt symptoms. However, when it does, *M. genitalium* can cause cervicitis, pelvic inflammatory disease (PID), preterm delivery, spontaneous abortion, and infertility in females and urethritis (particularly persistent or recurrent urethritis) in males [32]. It is unclear if *M. genitalium* is associated with epididymitis, prostatitis, or male infertility [32]. As a bacterial culture of *M. genitalium* can take months to grow, NAAT of urine or vaginal/endocervical samples is recommended

in symptomatic individuals. The U.S. Food and Drug Administration (FDA) approved such testing in early 2019 [51–53]. Unfortunately, recent research has identified various genetic mutations in *M. genitalium* that result in antimicrobial resistance (AMR) [54–57]. The prevalence of mutations in the 23S rRNA gene (which allow for macrolide resistance) seems to be increasing worldwide, and more rapidly than topoisomerase/gyrase mutations (parC/gyrA) (which provide fluoroquinolone resistance) [58,59]. Although molecular testing for resistance markers is not yet available in the U.S. [32], increasing resistance to azithromycin has shaped the CDC's treatment recommendations, as listed in Table 10. Since macrolide resistance detection became commercially available in Europe in late 2019 [60], it stands to reason that American clinicians should have access to this testing soon.

Table 10. Treatment of *M. genitalium* [32].

If resistance testing shows:	
Macrolide resistance *	Doxycycline 100 mg PO BID × 7 days *then* moxifloxacin 400 mg PO daily × 7 days
Macrolide sensitivity **	Doxycycline 100 mg PO BID × 7 days *then* azithromycin 1 g PO × 1 followed by 500 mg PO daily × 3 days (i.e., 2.5 g total)

* This is also the treatment regimen if *M. genitalium* resistance testing is not available but *M. genitalium* is detected by an FDA-cleared NAAT. ** This regimen is also used if resistance testing is not available but moxifloxacin cannot be used.

Note that the recommended antimicrobial regimens for PID (see Section 6.7) do not cover *M. genitalium*. When PID is diagnosed, empiric treatment should be offered at time of presentation, and, if infection with *M. genitalium* is subsequently discovered, the patient should then receive moxifloxacin 400 mg PO daily × 14 days [34].

2.5. Chancroid

Chancroid, which is caused by the fastidious, gram-negative rod *Haemophilus ducreyi*, is a rare disease. Fewer than 10 cases have been reported annually across the whole United States in recent years [61,62], but its true incidence is difficult to ascertain due to the difficulty with isolation [61]. The pathogenesis of chancroid is poorly understood; however, it is believed to only infect skin that is not intact [63]. Clinical presentations include genital ulcers that will appear approximately 4–10 days after infection [15,61]. The ulcer is preceded by an erythematous papule that rapidly evolves into a pustule, then to the ulcer. Inguinal lymphadenopathy is also present in many cases and is more common in males that are infected compared to females [61].

Given the low incidence of infection, there are no routine screening recommendations for chancroid. Diagnosis of a suspected infection is made using clinical criteria. A probable diagnosis is made if all four of the following clinical criteria are met: one or more painful genital ulcers, no evidence of *T. pallidum* infection, a typical clinical presentation for chancroid (i.e., ulcers and lymphadenopathy), and a negative test (polymerase chain reaction (PCR) or culture) for herpes simplex virus (HSV) [32]. Although a confirmatory culture and PCR testing exist, they are not rapid and often not widely available [64].

Recommended treatment regimens for chancroid are listed in Table 11. Azithromycin and ceftriaxone are preferable, as they are given as a single dose, and, further, there may be some resistance worldwide to ciprofloxacin and erythromycin [32].

Table 11. Treatment of chancroid [32].

Azithromycin 1 g PO × 1
Ceftriaxone 250 mg IM × 1
Ciprofloxacin 500 mg PO BID × 3 days *
Erythromycin base 500 mg PO TID × 7 days

* Should be avoided while pregnant (low risk) or breastfeeding (potentially toxic).

2.6. Donovanosis (Granuloma Inguinale)

Formerly known as *Calymmatobacterium granulomatis*, the gram-negative bacterium *Klebsiella granulomatis* is responsible for the genital ulcerative disease donovanosis. Ever since the discovery and widespread utilization of antibiotics, the overall incidence of donovanosis has been decreasing [15,20]. However, because infections are largely limited to a handful of developing countries (e.g., Papua New Guinea, India, Zimbabwe, Brazil), its epidemiology is unclear [15].

Donovanosis typically has an incubation period of 3–40 days, but this period has been reported to be anywhere from 1 to 360 days [20]. A small papule ruptures to form a painless granulomatous lesion, which bleeds easily. Ulcers then extend along skin folds, usually affecting the genital region [15].

Treatment for donovanosis is listed in Table 12. Affected pregnant or breastfeeding patients should receive one of the macrolide regimens (azithromycin and erythromycin) [32].

Table 12. Treatment of donovanosis [32].

First-line therapies *	Azithromycin 1 g PO weekly Azithromycin 500 mg PO daily
Alternative therapies *	Doxycycline 100 mg PO BID Erythromycin base 500 mg PO QID Trimethoprim-sulfamethoxazole 160/800 mg (1 DS tablet) PO BID **

* All treatments given for at least 3 weeks and continued until all lesions have completely healed. ** Avoid in patients with G6PD deficiency and during the third trimester of pregnancy or while breastfeeding.

2.7. Bacterial Vaginosis (BV)

Bacterial vaginosis (BV) is a common clinical condition in females that is caused by a change in the vaginal flora from the natural *Lactobacillus* species towards more diverse species. Though not always symptomatic, this imbalance in the flora causes a rise in the vaginal pH and, generally, a tacky white/grey vaginal discharge and fishy vaginal odor [65,66]. The characteristic odor can be amplified by mixing a sample of the discharge with potassium hydroxide (KOH); this so-called "whiff test" seems to be fairly reliable [65,67]. Clue cells on microscopy (saline wet mount preparation or gram stain) represent the fourth Amsel criterion, though only 3 of 4 criteria are necessary to confirm the diagnosis of BV [68]. Commercially available molecular diagnostic assays such as direct DNA probes and NAATs can also be used [69].

While BV is not currently classified an STI, there is evidence that it could be an STI and sexual activity increases the risk of the development of BV [70,71]. Further, females who have BV are more at risk for acquiring other STIs such as HIV, HSV-2, trichomonas, gonorrhea, and chlamydia, and it increases the risk of pre-term delivery in pregnant individuals [70,72].

BV is common in women who have sex with women (WSW) with a prevalence of up to 50% that increases with increasing numbers of sexual partners [73]. BV also tends to be higher in the African-American and Mexican-American ethnicities as compared to females of European descent [69,73].

Symptomatic females should be treated as shown in Table 13. Pregnant patients should avoid tinidazole. Since data on secnidazole use in pregnancy are limited, metronidazole may be a safer choice [74,75]. Note that although the CDC no longer advises against drinking alcohol while taking these medications, the risk of a disulfiram-like reaction is still listed on the package inserts as well as with other advisory bodies such as the United Kingdom's National Health Service (NHS) [76].

Table 13. Treatment of bacterial vaginosis [32].

First-line therapies	Metronidazole 500 mg PO BID × 7 days Metronidazole 0.75% gel, 5 g (one applicator-full) PV qhs × 5 days Clindamycin 2% cream, 5 g (one applicator-full) PV qhs × 7 days *
Alternative therapies	Tinidazole 2 g PO daily × 2 days Tinidazole 1 g PO daily × 5 days Clindamycin 300 mg PO BID × 7 days Clindamycin ovules 100 mg PV qhs × 3 days * Secnidazole 2 g PO × 1 **

* This substance can damage latex/rubber; do not use latex condoms or vaginal diaphragms for 72 h after use. ** Oral granules should be sprinkled onto unsweetened applesauce or yogurt prior to ingestion; this can be followed with a glass of water.

3. Viral Infections

3.1. Herpes Simplex Virus (HSV)

Genital herpes is a chronic, lifelong infection with one of two serotypes of herpes simplex virus. Compared to HSV-2, infection with HSV-1 has a milder course and fewer recurrences. HSV-1 (which was previously thought to cause only oral lesions) actually causes up to 50% of genital herpes infections [32,77,78], although it is often neglected in prevalence estimates [1]. HSV-1 may be spread to the genitals through oral sex, and both serotypes may be present in anogenital lesions. Transmission occurs via skin-to-skin contact or direct contact with mucous membranes. Asymptomatic viral shedding (i.e., transmission of the virus from an infected person with no visible lesions) is possible, and many people remain asymptomatic once infected. However, a symptomatic outbreak is usually evidenced by clusters of painful or itchy blisters and ulcers, vaginal or penile discharge, inguinal lymphadenopathy, and/or flu-like symptoms [79]. The first episode is usually the most severe and tends to occur within 3 weeks of infection.

Serologic screening for HSV-1 and HSV-2 is not generally recommended; however, testing via type-specific IgG antibodies could be considered for patients with multiple sexual partners, HIV infection, a known partner with genital herpes, or negative HSV cultures with recurrent symptoms or genital lesions. A positive test does not belie the location of the herpetic infection nor reveal when the patient was infected. Testing in patients with active lesions may be performed via viral culture (the current gold standard for urogenital infection) or PCR (the preferred mode of testing if there is concern for HSV infection of spinal fluid) [49,80]. As skin lesions heal, shedding of the virus is reduced, making the viral culture less sensitive and serum testing for type-specific antibodies more helpful in diagnosis and management [79].

Treatment options for genital herpes, as recommended by the CDC, are listed in Table 14. Dosing and duration are slightly different for pregnant patients and immunocompromised or HIV-positive individuals, as shown in Table 15. Additionally, different countries/professional bodies may suggest different regimens, in part due to the availability of the drugs and unequal comparisons.

Table 14. Treatment for genital herpes [32].

Antiviral Agent	First Episode *	Recurrence (Episodic Outbreaks)	Suppressive Therapy
Acyclovir	400 mg PO TID × 7–10 days 200 mg PO 5x/day × 7–10 days **	800 mg PO BID × 5 days 800 mg PO TID × 2 days 400 mg PO TID × 5 days **	400 mg PO BID
Famciclovir	250 mg PO TID × 7–10 days	1 g PO BID × 1 day 500 mg PO once, then 250 mg PO BID × 2 days 125 mg PO BID × 5 days	250 mg PO BID
Valacyclovir	1 g PO BID × 7–10 days	1 g PO daily × 5 days 500 mg PO BID × 3 days	1 g PO daily 500 mg PO daily ***

* Treatment may be extended if healing incomplete after 10 days. ** Regimen effective but not recommended due to dosing schedule. *** Less effective than other regimens for patients experiencing ≥10 episodes per year.

Table 15. Treatment of genital herpes in special populations [32].

HIV-positive (episodic)	Acyclovir 400 mg PO TID × 5–10 days Famciclovir 500 mg PO BID × 5–10 days Valacyclovir 1 g PO BID × 5–10 days
HIV-positive (suppression)	Acyclovir 400–800 mg PO BID-TID Famciclovir 500 mg PO BID Valacyclovir 500 mg PO BID
Pregnant patients starting at 36 weeks' gestation (suppression)	Acyclovir 400 mg PO TID Valacyclovir 500 mg PO BID

Once-daily dosing increases adherence, particularly among adolescents [49]. It is important to note that while treatment decreases clinical symptoms, it does not decrease frequency of recurrence or transmission risk to an uninfected partner (while lesions remain open and uncrusted) [81]. Effective episodic treatment should begin within 24 h of the appearance of lesions during the prodromal phase (30 min to 48 h prior to eruption of a lesion) [79]. Patients with a first episode of genital herpes caused by the HSV-2 serotype are at risk for increased frequency of recurrence; consequently, suppressive therapy may be the preferred initial treatment for HSV-2 infections [49]. Suppressive therapy may also be warranted for those who endure more than 4–6 outbreaks per year or have severe symptoms. Chronic suppressive therapy should be evaluated annually, as frequency of recurrence declines over time [81].

3.2. Human Papilloma Virus (HPV)

Most HPV infections are self-limited; however, persistent infection can lead to warts, cervical cancer in females, and anogenital or oropharyngeal cancer in males, females, or children [81]. There are over 100 subtypes of HPV, of which more than 30 infect the genital tract through skin-to-skin contact between mucous membranes and epithelial tissues [82,83]. Oncogenic (high-risk) strains such as 16 and 18 are associated with cancers whereas low-risk strains such as 6 and 11 are associated with genital warts (condyloma acuminata). Although high-risk strains often infect adolescents, these infections typically resolve within 24 months without symptoms or treatment. Genital warts present as raised, fleshy, painless lesions in moist areas of the body. Cervical neoplasia will often present with abnormal vaginal bleeding or be discovered on routine screening [49].

Universal screening is recommended for the prevention of cervical cancer in young women. This is performed through cytology—the Papanicolaou or "Pap" smear. The U.S. Preventative Services Task Force (USPSTF) and American College of Obstetricians and Gynecologists (ACOG) recommend obtaining Pap smears starting at age 21, regardless of sexual debut [34,84,85]. Unless there is a concerning finding, screening by cytology is continued every 3 years afterwards until age 29. High-risk HPV infections are less likely to spontaneously resolve in women 30 years of age and older. As such, co-testing with HPV

DNA is recommended along with cytology every 5 years if results again remain normal for both [34,49]. By comparison, in mid-2020, however, the American Cancer Society (ACS) recommended that Pap smears be performed starting at age 25 and then every 5 years thereafter [86,87]. Abnormal cervical cytology on Pap smear that may progress to cervical intraepithelial neoplasia (CIN), and eventually cervical cancer, should be managed per the American Society for Colposcopy and Cervical Cytology guidelines, which outline subsequent monitoring, colposcope evaluation, and excisional therapy as appropriate [49].

Interestingly, anal Pap smears may also be useful for detecting HPV-associated cytologic changes in the anal tissue of individuals engaging in anal receptive intercourse [88,89].

Over time, genital warts may resolve spontaneously, remain unchanged, or increase in size and number, making the treatment goal simply to remove these growths. Treatment does not eradicate HPV. Neither condoms nor treatment eliminate infectivity, either. However, strains that lead to genital warts should not lead to cervical cancer [82]. Symptomatic external warts on the penis, scrotum, groin, vulva, perineum, external anus, or perianus can be treated by the healthcare provider or the patient, as shown in Table 16. All treatments may cause discomfort, erythema, ulceration, depigmentation, or scarring [49,79].

Table 16. Treatment of external condyloma acuminata [34].

Provider-Administered	Patient-Administered
Trichloracetic acid (TCA) or bichloracetic acid (BCA) 80–90% solution applied weekly	Imiquimod 3.75–5% cream applied topically 3×/week at bedtime for up to 16 weeks *
Cryotherapy (liquid nitrogen or cryoprobe)q1–2 weeks	Podofilox 0.5% solution (or gel) applied topically q 12 h × 3 days, followed by 4 days off; this can be performed weekly for up to 4 weeks
Surgical removal (scissor or shave excision, curettage, laser, electrosurgery)	Sinecatechins 15% ointment applied topically TID for up to 16 weeks *

* May weaken latex/rubber products like condoms or vaginal contraceptive diaphragms.

Individuals with external anal or perianal warts should be evaluated for intra-anal warts. Vaginal, cervical, intra-anal, and urethral meatus warts should only be treated by a clinician with the following additional recommendations: A cryoprobe should not be used in these areas, cervical and intra-anal warts warrant specialist consultation, and TCA/BCA should not be used at the urethral meatus [32,90].

3.3. Molluscum Contagiosum (MC)

Though not specifically mentioned in the CDC guidelines, MC can be transmitted by any form of skin-to-skin contact. Caused by a poxvirus, MC is characterized by clusters of smooth, flesh-colored papules, usually featuring a central umbilication (divot), and found on the trunk, axillae, or groin. This benign condition is common in adolescents and is typically self-limited. Diagnosis is made based on clinical appearance; however, excisional biopsy may also lead to a diagnosis in atypical cases [91].

MC is frequently seen in immunocompromised individuals, for whom it has increased presence on the face compared to immunocompetent patients. MC has the potential to become disseminated in HIV-positive individuals and even poses risk for disfigurement in patients with AIDS, as lesions can be greater than 1 cm in size [91].

Providers may offer a wide range of topical treatments, including salicylic acid, imiquimod, retinoids, cryotherapy, or curettage for symptomatic or large lesions. Patients with HIV-associated MC infection improve with anti-retroviral (ART) treatment, as these infections are typically resistant to topical therapies [91].

3.4. Hepatitis

The hepatitis A virus (HAV) is primarily transmitted via fecal–oral routes and may arise from oral–anal sexual contact. Infection with hepatitis A is typically self-limited;

however, acute illness may include fever, jaundice, and gastrointestinal upset. The hepatitis B virus (HBV) is transmitted through seminal fluid, vaginal fluid, or blood and may present as an acute, self-limited illness or a chronic infection [92]. The current adolescent population in the United States has increased immunity secondary to routine immunization against HBV during infancy. People who remain at risk include men who have sex with men (MSM), injection drug users, the unimmunized, and those whose immunity has waned. The hepatitis C virus (HCV) is typically a blood-borne infection and is uncommon among adolescents in the United States [93]. Acute hepatitis C infection progresses to liver disease in approximately 60–70% of patients; the remainder experience spontaneous cure within 6–12 months, with patients having either had symptoms of a mild viral syndrome or no symptoms at all [93].

Routine screening for HAV is not recommended; however, routine vaccination starting at age 2 (or age 1 if HIV-positive or other risks for infection are present) is advised [94]. Initiation of the hepatitis B vaccination series is universally recommended for medically stable infants within 24 h of birth [92]. Individuals not previously immunized should be vaccinated, especially those at high risk. Serologic screening (antibody titers) and revaccination (boosters) are generally not necessary, although healthcare personnel and hemodialysis patients may need such testing and repeat inoculation [92]. All patients seeking initiation of HIV Pre-Exposure Prophylaxis (PrEP) should be screened for hepatitis B by hepatitis B surface antigen (HBsAg), and any patient entering care for HIV should be screened for hepatitis B with HbsAg as well as hepatitis B surface antibody (HbsAb) and hepatitis B core antibody (HbcAb). In general, all adults should be screened for HCV at least once in their lifetime, and pregnant individuals should be screened with each pregnancy. Routine periodic testing is recommended for current injection drug users and individuals receiving maintenance hemodialysis. Further, the CDC recommends that anyone who requests testing for Hepatitis C infection should receive it, as many risk factors (e.g., HIV-positive serostatus) can be stigmatizing [95].

Hepatitis A is treated with supportive care; Hepatitis B and C should be treated by healthcare providers with expertise in the treatment of hepatitis, such as infectious disease and/or gastrointestinal physicians [93].

4. Parasitic Infections

4.1. Scabies

Scabies infection is caused by the *Sacroptes scabiei* mite, and sexual contact is one mode of transmission. After mating, the male mite dies and the female mite burrows under the skin, where she remains for the rest of her lifespan (1–2 months) laying eggs. Larvae emerge 2–3 days after the eggs are laid and will cut through the burrows to the skin surface to mate and multiply [13,96]. Symptoms may not develop until six weeks later, when a hypersensitivity reaction develops to the mites' feces. During this asymptomatic period, others may become unknowingly infected through direct sexual or non-sexual contact. Mites can be transferred after about 15–30 min of close contact with an infected person or fomite (e.g., clothing, linens, or towels) [13]. Symptomatic dermatologic manifestations of infection include small linear groupings of erythematous, pruritic papules and are commonly seen between the fingers and on the anterior wrists, elbows, axillae, buttocks, genitalia, and breasts. Due to the hypersensitivity reaction, patients may also have excoriations, eczema, and pyoderma. Diagnosis is confirmed by identification of mites, their eggs, and/or fecal pellets in microscopic evaluation of a skin scraping suspended in oil or through dermoscopy [13].

No universal screening recommendations for scabies exist; however, patients living in overcrowded conditions, tropical regions, or those who have poor hygiene, poor nutritional status, homelessness, or dementia are at increased risk for scabies [13].

Treatment is described in Table 17. Though there are over-the-counter (OTC) formulations of permethrin, these are not approved as scabicides [96]. Prescription-strength topical permethrin cream (5%) or ivermectin 1% lotion are applied to all areas of the body from

the neck down and washed off after 8–14 h. Permethrin should be efficacious after a single course; ivermectin may require a second treatment 1 week later if symptoms persist. Even after effective treatment, pruritis may last for up to 2 weeks. Sexual partners from the past 1–2 months should also undergo treatment [13,96]. Oral ivermectin has limited ovicidal activity and typically requires 2 doses. Lindane 1%, an alternative treatment, is not for use in infants, children, and pregnant or breastfeeding individuals, and may be banned/restricted in some areas due to toxicity. In addition to these medications, "environmental treatment" should also occur by washing clothing and linens in hot water and drying them at a high temperature. If items are unable to be washed, they should be sealed in a plastic bag for at least one week [13,96].

Table 17. Treatment of scabies [32].

First-line therapies	Permethrin 5% cream applied from the neck down and washed off after 8–14 h Ivermectin 1% lotion applied from the neck down and washed off after 8–14 h * Ivermectin 200 μg/kg PO × 1 and repeated after 2 weeks
Alternative therapy	Lindane 1% cream (1 ounce or 30 g) applied in a thin layer from the neck down and thoroughly washed off after 8 h **

* Repeat treatment after 1 week if symptoms persist. ** Contraindicated in some populations (e.g., children < 10 years old).

4.2. Pubic Lice

Lice are parasites that can infest hair-bearing areas, such as the pubic region (*Phthirus pubis*). They have a low profile and cannot fly or jump, thus requiring close contact for transmission. The female louse survives for up to one month and lays 8–10 eggs per day at the junction of the skin and hair. The eggs mature into adults within 20 days and are found at the base of the hair shaft [13]. Pediculosis (infection with lice) also often causes a delayed hypersensitivity reaction leading to intense pruritus 4–6 weeks after first exposure. This intense pruritus leads to scratching, excoriation, and potentially cellulitis. Body lice should be expected in patients who have poor hygiene and/or live in crowded conditions and present with genital pruritus [13]. Diagnosis may be made by identification of body lice or nits on the person or in the seams of their clothing. If pubic lice are identified, those patients should be evaluated for other STIs [13].

Treatment is described in Table 18. First-line topical treatments for pubic lice include permethrin 1% lotion (trade name Nix) and pyrethrins 0.3%/piperonyl butoxide 4% shampoo (trade name Rid), both of which are available OTC. Compared to scabies infection, treatment of pubic lice uses a less potent formulation of permethrin, and the chemical is only applied to affected areas and washed off after 10 min. Alternative treatments for pubic lice are available by prescription and include malathion 0.5% lotion and oral ivermectin. Limited data on ivermectin use in pregnant and breastfeeding patients disfavor its use in those populations [32]. Note, too, that dosing of oral ivermectin differs for pediculosis capitis and pediculosis corporis. Sexual partners from the previous 1–3 months should also be treated. In addition to topical or oral medications, clothing and bedding should be laundered in hot water and patients should be instructed to bathe regularly for treatment to be effective and lasting [13].

Table 18. Treatment of pediculosis pubis [32].

First-line therapies	Permethrin 1% cream applied to the affected areas and washed off after 10 min Pyrethrin with piperonyl butoxide applied to the affected areas and washed off after 10 min
Alternative therapies	Malathion 0.5% lotion applied to affected areas and washed off after 8–12 h Ivermectin 250 μg/kg PO and repeated after 1–2 weeks *

* May not be appropriate in all populations.

4.3. Trichomonas vaginalis

Trichomonas vaginalis is a protozoan transmitted through unprotected oral, vaginal, or anal sex. It is the third most common cause of vaginitis and often associated with other infections. Distinguishing characteristics of vaginitis due to trichomoniasis are yellow-green, malodorous, frothy vaginal discharge with an elevated pH > 4.5. Females may also have urethritis and irritation of the vulva along with a "strawberry cervix" due to punctate hemorrhages and tiny ulcerations of the cervix. Males are typically asymptomatic; however, they may present with urethritis [49,79].

All symptomatic individuals—and especially those with high-risk behaviors—should be tested for *T. vaginalis*. In contrast to a wet mount, NAAT has very high sensitivity and high specificity for female vaginal, endocervical, or urine specimens. TMA (transcription-mediated amplification) assays are acceptable testing modalities for male urine or urethral swabs [97,98]. However, as these tests are often expensive and can take several days to result [99], microscopic evaluation through wet mount preparations is the most common method for diagnosis despite requiring immediate evaluation (less than 1 h) of the specimen for optimal results [49].

Treatment guidelines are listed in Table 19. The preferred treatment for *T. vaginalis* infection is metronidazole, with the exact dosage/regimen depending on the patient's sex. Sexual partners of those diagnosed with trichomoniasis are recommended to undergo treatment [49,79]. Persistent or recurrent infections may reflect reinfection or drug resistance and warrant adjustment in pharmacotherapy. As with BV, pregnant patients should avoid tinidazole, and breastfeeding is not advised for 72 h after single-dose tinidazole treatment [32].

Table 19. Treatment of trichomoniasis [32].

First-line therapy (females)	Metronidazole 500 mg PO BID × 7 days *
First-line therapy (males)	Metronidazole 2 g PO × 1
Alternative regimen (males and females)	Tinidazole 2 g PO × 1 **

* This is also the recommended regimen for trichomoniasis in HIV+ women. ** Either single-dose metronidazole or tinidazole are first line therapies for NGU in heterosexual men where prevalence of *T. vaginalis* is high.

5. Fungal Infections

5.1. Vulvovaginal Candidiasis (VVC)

VVC is common in females, with 75% of women experiencing at least one episode in her lifetime. Typically caused by the opportunistic pathogenic yeast *Candida albicans*, VVC presents as vaginal pruritis with a thick, white vaginal discharge of normal pH and associated vulvar burning, dyspareunia, and dysuria. Diagnosis can be made through visual examination or upon discovery of budding yeast and/or pseudohyphae on microscopic evaluation of the vaginal discharge [32,79]. although there may be a role for their use (especially in complicated cases), per the CDC's most recent guidance, most molecular assays for VVC are not yet FDA-approved [32].

Treatment options for VVC are listed in Table 20. Most OTC treatments use 1–14 doses of intravaginal azoles (e.g., miconazole). Oral fluconazole (150 mg, given once and then repeated in 72 h if needed) is available by prescription and can be used depending on infection severity, recurrence, and associated co-morbidities [79]. It should be avoided during pregnancy but can be used while breastfeeding.

Table 20. Treatment of vulvovaginal candidiasis [32].

Over-the-counter (OTC) treatments	Clotrimazole 1% cream 5 g PV daily × 7–14 days Clotrimazole 2% cream 5 g PV daily × 3 days Miconazole 2% cream 5 g PV daily × 7 days Miconazole 4% cream 5 g PV daily × 3 days Miconazole 100 mg suppository PV daily × 7 days Miconazole 200 mg suppository PV daily × 3 days Miconazole 1200 mg suppository PV × 1 Tioconazole 6.5% ointment 5 g PV × 1
Prescription intravaginal agents	Butoconazole 2% cream 5 g PV × 1 Terconazole 0.4% cream 5 g daily × 7 days Terconazole 0.8% cream 5 g daily × 3 days Terconazole 80 mg suppository PV daily × 3 days
Prescription oral agent	Fluconazole 150 mg PO × 1 *

* Avoid use during the first trimester of pregnancy; weigh risk-benefit thereafter.

5.2. Tinea Cruris

Also not specifically mentioned in the CDC guidelines, tinea cruris (commonly known as "jock itch") often affects adolescent males and leads some to worry they have contracted a more severe infection. The term "tinea" refers to a fungal infection and may be caused by dermatophytes such as *Trichophyton, Microsporum,* or *Epidermophyton* [100]. In young males, infection commonly presents as a pruritic, erythematous rash on the upper thigh opposite the scrotum, brought about by heat and friction in a moist area. Diagnosis is often made through appearance; however, a KOH preparation may be used for detection in atypical presentations [100].

Twice-daily topical treatment with OTC or prescription creams such as terbinafine (trade name Lamisil) or butenafine (trade name Lotrimin) for 10–14 days is preferred. It is important to note that nystatin is effective for candidiasis but most tinea infections are resistant to it. Oral antifungals (itraconazole 200 mg PO daily or terbinafine 250 mg PO daily × 3–6 weeks) may be used for severe or refractory cases, or in immunocompromised patients [101].

6. Complications

6.1. Urethritis

Bacterial, viral, and parasitic etiologies can all cause inflammation of the urethra. Urethritis is currently categorized based on etiology, with gonorrheal infection being distinguished from all other types. Indeed, the causative agent for nongonococcal urethritis (NGU) is not always identified [32]. *Chlamydia trachomatis*, *Mycoplasma genitalium*, and *Trichomonas vaginalis* are the most common etiologies, though *Haemophilus* species, *Neiserria meningitidis*, HSV, and adenovirus have also been implicated [32]. Symptoms include urethral discharge and irritation, dysuria, and pruritis at the meatus. If urethral discharge cannot be expressed and tested directly, a swab can be inserted into the urethral meatus and brought into contact with the urethral wall. First-void urine may show leukocyte esterase on urinalysis. The recommended treatment for NGU—as well as rectal chlamydia—is doxycycline 100 mg PO BID × 7 days, as noted in Table 21. Although azithromycin is still listed as an alternative regimen, reports of treatment failures for chlamydia infection and increasing drug resistance by *M. genitalium* have deprioritized this antibiotic choice. If used, a multiday regimen (azithromycin 500 mg PO once, followed by 250 mg PO daily × 4 days) may avoid inspiring resistance in *M. genitalium* infections, compared to a single dose (azithromycin 1 g PO × 1). Levofloxacin and erythromycin are no longer recommended [32].

Table 21. Treatment of nongonoccal urethritis [32].

First-line therapy	Doxycycline 100 mg PO BID × 7 days
Alternative therapies	Azithromycin 1 g PO × 1 Azithromycin 500 mg PO × 1 then 250 mg PO daily × 4 days

If infection with chlamydia, gonorrhea, or trichomonas is confirmed and treated, repeat testing should be performed 3 months thereafter. Persistent or recurrent symptoms warrant testing for *M. genitalium* and *T. vaginalis* as well. *T. vaginalis* is treated with metronidazole 2 g PO × 1 or tinidazole 2 g PO × 1. *M. genitalium* should be treated based on resistance testing; if that is not possible, doxycycline 100 mg PO BID × 7 days should be followed with moxifloxacin 400 mg PO daily × 7 days. See Tables 10 and 19.

Untreated *C. trachomatis*-associated NGU can lead to epididymitis, prostatitis, and reactive arthritis [32].

6.2. Balanoposthitis

Balanoposthitis, a portmanteau of balanitis and posthitis, is inflammation of the glans penis and foreskin in an uncircumcised male [30]. Presenting symptoms may include itching, pain, irritation, discharge, and/or dysuria [100]. If the symptoms are severe, it may prevent retraction of the foreskin of the penis. While balanoposthitis is most commonly caused by yeast, especially in younger uncircumcised males with poor hygiene, *C. trachomatis* and *N. gonorrhoeae* are also possible causes in sexually active uncircumcised males [100]. If detected, chlamydia and/or gonorrhea should be treated as previously described.

6.3. Epididymitis

Epididymitis is typically a complication of *C. trachomatis* infection in younger, sexually active males but can be caused by other STIs and enteric organisms [32]. Affected individuals often present with testicular pain and tenderness, development of a hydrocele, and even swelling of the epididymis [32]. Epididymal infection from *C. trachomatis* can be misdiagnosed as a malignancy of the testicle; however, an ultrasound can typically rule this out [102].

Infection with *N. gonorrhoeae* alone is a less common cause of epididymitis than either *C. trachomatis* alone or co-infection with both *C. trachomatis* and *N. gonorrhoeae*. Like epididymitis from *C. trachomatis*, gonorrheal epididymitis will typically present with testicular pain and tenderness, possible swelling of the epididymis, and urethritis [103].

Treatment guidelines are based on the suspected microbial etiology, as described in Table 22.

Table 22. Treatment of acute epididymitis [32].

If most likely caused by chlamydia or gonorrhea	Ceftriaxone 500 mg IM × 1 * + doxycycline 100 mg PO BID × 10 days
If most likely caused by enteric organisms	Levofloxacin 500 mg PO daily × 10 days
If in the context of insertive anal intercourse (likely chlamydia, gonorrhea, or enteric organisms)	Ceftriaxone 500 mg IM × 1 * + levofloxacin 500 mg PO daily × 10 days

* If patient weighs ≥ 150 kg, ceftriaxone 1 g IM × 1.

6.4. Prostatitis

There are four clinical categories of inflammation or infection of the prostate: (1) acute bacterial prostatitis, (2) chronic bacterial prostatitis, (3) chronic abacterial prostatitis and chronic pelvic pain syndrome, and (4) asymptomatic inflammatory prostatitis. Only 5–10% of cases of prostatitis are thought to be caused by bacteria (e.g., *Escherichia coli*, *C. trachomatis*) [104].

Acute bacterial prostatitis usually presents with an acute febrile illness as well as dysuria, urinary dysfunction or obstruction, pain with ejaculation, or pelvic pain/pressure. Chronic bacterial prostatitis, on the other hand, tends to occur as an afebrile, relapsing disease with acute exacerbations [104,105]. Males with chlamydial prostatitis will routinely have an elevated number of leukocytes on microscopy of their prostatic secretions [106].

Treatment typically involves a prolonged course of fluoroquinolones or doxycycline but depends on the etiology [32]. For acute bacterial prostatitis, treatment for 4–6 weeks is needed to avoid chronic prostatitis or other sequelae (e.g., abscesses); for chronic bacterial prostatitis, treatment for 3 months is usually needed, given the poor penetration of antibiotics into an uninflamed prostate [104,105].

6.5. Proctitis

Proctitis from infection with *C. trachomatis* and/or *N. gonorrhoeae* can occur in sexually active individuals regardless of sexual orientation or practices but is most common among those who engage in receptive anal contact [32]. Patients affected by anorectal chlamydia usually present with inflammation of the distal rectum and surrounding mucosal surfaces [107]. Gonorrheal proctitis, on the other hand, is typically asymptomatic, but when symptoms present, they include rectal pain and fullness, tenesmus, constipation, bleeding, and mucopurulent discharge [108].

Treatment guidelines are listed in Table 23.

Table 23. Treatment of acute proctitis [32].

Acute proctitis	Ceftriaxone 500 mg IM × 1 * + doxycycline 100 mg PO BID × 7 days **

* If patient weighs ≥ 150 kg, ceftriaxone 1 g IM × 1. ** If bloody rectal discharge, perianal or mucosal ulcers, or tenesmus and positive rectal chlamydia testing, extend course of doxycycline to 21 days.

6.6. Cervicitis

Cervicitis is most often asymptomatic. If symptoms do occur, they are typically nonspecific and can mimic other vaginal or endometrial pathology (e.g., discharge, metorrhagia, and post-coital bleeding) [109].

Cervicitis is most commonly caused by *C. trachomatis* and/or *N. gonorrhoeae*, though trichomoniasis, genital herpes (particularly primary HSV-2 infection), and *M. genitalium* have also been implicated, and, as with NGU, a causative microbe is not always identified [110]. Patients should be evaluated for pelvic inflammatory disease (PID). Testing should include vaginal/cervical swabs or urine sample for *C. trachomatis* and *N. gonorrhoeae*, *T. vaginalis*, and bacterial vaginosis (BV) [32]. Testing for *M. genitalium* can be considered, though the utility of testing for HSV-2 is unclear. Recommended treatment regimens for cervicitis are shown in Table 24. Remember that patients with cervicitis should also receive treatment for gonococcal infection if this cannot be ruled out.

Table 24. Treatment of cervicitis [32].

First-line therapy	Doxycycline 100 mg PO BID × 7 days
Alternative therapy	Azithromycin 1 g PO × 1

As with NGU, repeat testing should be performed 3 months after diagnosis and treatment of chlamydia, gonorrhea, or trichomoniasis. Persistent or recurrent symptoms may suggest reinfection, BV, or, potentially, infection with *M. genitalium* [32,33].

6.7. Pelvic Inflammatory Disease (PID)

PID is a common complication of *C. trachomatis* infection due to its ability to ascend into the upper reproductive tract. In fact, approximately 15% of untreated chlamydia infections result in PID [8]. Affected patients typically present with pain of the lower abdomen or pelvic areas; clinical signs include cervical motion tenderness (CMT) and uterine or adnexal

tenderness [111]. Compared with PID caused by *N. gonorrhoeae*, PID associated with *C. trachomatis* infection is more likely to lead to subsequent infertility, ectopic pregnancy, and chronic pelvic pain because it typically presents with a more asymptomatic course [111].

PID is also a common complication of *N. gonorrhoeae* infection in up to 10–20% of infected females. While several other bacterial pathogens can cause PID, *N. gonorrhoeae* is felt to be the causal organism in up to 40% of cases. Signs and symptoms are similar to PID caused by *C. trachomatis* but may also include abnormal vaginal bleeding and dyspareunia. Additionally, persons with a gonorrheal etiology typically appear more acutely ill and have a fever [112,113].

Treatment options for PID are listed in Table 25.

Table 25. Treatment of PID [32].

Parenteral (first line)	Doxycycline 100 mg PO/IV q12 h + one of the following 3 options: Ceftriaxone 1 g IV q24 h + metronidazole 500 mg PO/IV q12 h Cefotetan 2 g IV q12 h Cefoxitin 2 g IV q6 h
Parenteral (alternatives)	Doxycycline 100 mg PO/IV q12 h + ampicillin-sulbactam 3 g IV q6 h Clindamycin 900 mg IV q8 h + gentamicin 2 mg/kg loading dose IV/IM × 1 followed by 1.5 mg/kg maintenance dose IV/IM q8 h *
Combination (oral/Intramuscular)	Doxycycline 100 mg PO BID + metronidazole 500 mg PO BID × 14 + one of the following 3 options: Ceftriaxone 500 mg IM × 1 ** Cefoxitin 2 g IM × 1 + probenecid 1 g PO administered concurrently × 1 Parenteral third-generation cephalosporin (e.g., ceftizoxime, cefotaxime)

* Single daily dosing of gentamicin, 3–5 mg/kg, can also be used. ** If patient ≥ 150 kg, use 1 g of ceftriaxone.

6.8. Lymphogranuloma Venereum (LGV)

LGV is a disease of the lymphatic tissue caused by the L1-3 serovars of *C. trachomatis* which induce a lymphoproliferative reaction from direct spread from the primary inoculation site to the draining lymphatic tissue. LGV has classically been a disease of tropical and subtropical climates, but in recent years, it has become more common in temperate climates, especially in MSM populations, where it typically presents as an anogenital disease [32,107]. Most cases of LGV are symptomatic and may present with a wide variety of anorectal symptoms including pain, tenesmus, constipation, bleeding, and discharge. LGV also commonly presents with fever, malaise, papules or ulcers of the genitals, and inguinal lymphadenopathy. If not treated appropriately (e.g., with doxycycline 100 mg PO BID × 21 days), LGV can lead to more serious complications such as strictures or fistulae of the rectum [107].

Treatment guidelines are listed in Table 26. Patients who are pregnant and diagnosed with LGV should have a test of cure 4 weeks after treatment [32].

Table 26. Treatment of lymphogranuloma venereum [32].

First-line therapy	Doxycycline 100 mg PO BID × 21 days *
Alternative therapies	Azithromycin 1 g PO weekly × 3 weeks ** Erythromycin base 500 mg PO QID × 21 days ***

* Risk is poorly-defined during pregnancy but the drug is safe to use while breastfeeding. ** Consider test of cure (*C. trachomatis* NAAT) 4 weeks after completion of treatment. *** Use may be limited by gastrointestinal side effects.

6.9. Disseminated Gonococcal Infection (DGI)

DGI, or the spread of *N. gonorrhoeae* from the original site of inoculation through the blood, can affect both males and females [114], and is estimated to occur in up to 3% of infected patients. Dissemination most commonly occurs in those with predisposing factors such as immune compromise [115]. DGI typically presents as one of two different clinical syndromes: either purulent arthritis, or a triad of tenosynovitis, polyarthralgia, and dermatitis (which is not the same as reactive arthritis) [116]. Rarely, disseminated disease

can present as endocarditis, osteomyelitis, or meningitis [32]. Tables 5–7 list treatment options for various complications.

7. Special Situations

7.1. Expedited Partner Therapy (EPT)

Although cases of gonorrhea, chlamydia, syphilis, chancroid, and HIV must be reported to the relevant health department in every state [32], partners of infected individuals are often only notified formally of exposure to syphilis or HIV, putting the onus of communication on the original patient, or, in some states, the treating clinician [32]. Increasing technologic interconnectedness has, ironically, allowed for the anonymous notification of potentially affected partners, which sometimes drives them to seek medical care. In another effort to mitigate risk and reduce barriers to treatment, EPT—the provision of appropriate antimicrobials and education to sexual partners after exposure to an STI, without them having been clinically assessed—has become permissible in 46 states and "potentially allowable" in the remaining 4 (as well as Guam and Puerto Rico) [32,117]. Originally utilized to stanch spread of syphilis, EPT is now used to combat gonorrhea, chlamydia, and potentially even HIV [32].

7.2. Sexual Assault

Survivors of sexual assault should be empirically treated for bacterial STIs. Treatment recommendations are listed in Table 27. HIV post-exposure prophylaxis (PEP) should be considered for patients who had substantial exposure risk and present for medical consultation within 72 h of exposure [32].

Table 27. Treatment of adolescent and adult sexual assault survivors [32].

Females: Ceftriaxone 500 mg IM × 1 * + doxycycline 100 mg PO BID × 7 days + metronidazole 500 mg PO BID × 7 days
Males: Ceftriaxone 500 mg IM × 1 * + doxycycline 100 mg PO BID × 7 days

* If patient weighs ≥150 kg, ceftriaxone 1 g IM × 1.

8. Summary

Compared to the 2015 recommendations, the 2021 CDC update on STI treatment guidelines includes the following key changes:

- Chlamydia—doxycycline is the preferred treatment (over azithromycin) for adolescents and adults who are not pregnant; erythromycin and ofloxacin have been dropped as alternative regimens for this population.
- Gonorrhea—the dose of ceftriaxone for adults has increased and, like the previous guidelines for the treatment of children, gives additional consideration to the patient's weight.
- *M. genitalium*—the treatment guidelines were clarified.
- Bacterial vaginosis—the concern for disulfiram-like reaction due to drinking alcohol within 24–72 h of metronidazole use has been removed.
- *T. vaginalis*—the disulfiram-like reaction warning has been removed, and the first-line treatment for women was adjusted to have a longer course.
- Scabies—the treatment options have been broadened.

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