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Diagnosis and Treatment of Sexually Transmitted Infections
A Review

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IMPORTANCE Approximately 1 in 5 adults in the US had a sexually transmitted infection (STI) in 2018. This review provides an update on the epidemiology, diagnosis, and treatment of gonorrhea, chlamydia, syphilis, *Mycoplasma genitalium*, trichomoniasis, and genital herpes.

OBSERVATIONS From 2015 to 2019, the rates of gonorrhea, chlamydia, and syphilis increased in the US; from 1999 to 2016, while the rates of herpes simplex virus type 1 (HSV-1) and HSV-2 declined. Populations with higher rates of STIs include people younger than 25 years, sexual and gender minorities such as men and transgender women who have sex with men, and racial and ethnic minorities such as Black and Latinx people. Approximately 70% of infections with HSV and trichomoniasis and 53% to 100% of extragenital gonorrhea and chlamydia infections are asymptomatic or associated with few symptoms. STIs are associated with HIV acquisition and transmission and are the leading cause of tubal factor infertility in women. Nucleic acid amplification tests have high sensitivities (86.1%-100%) and specificities (97.1%-100%) for the diagnosis of gonorrhea, chlamydia, *M genitalium*, trichomoniasis, and symptomatic HSV-1 and HSV-2. Serology remains the recommended method to diagnose syphilis, typically using sequential testing to detect treponemal and nontreponemal (antiphospholipid) antibodies. Ceftriaxone, doxycycline, penicillin, moxifloxacin, and the nitroimidazoles, such as metronidazole, are effective treatments for gonorrhea, chlamydia, syphilis, *M genitalium,* and trichomoniasis, respectively, but antimicrobial resistance limits oral treatment options for gonorrhea and *M genitalium*. No cure is available for genital herpes. Effective STI prevention interventions include screening, contact tracing of sexual partners, and promoting effective barrier contraception.

CONCLUSIONS AND RELEVANCE Approximately 1 in 5 adults in the US had an STI in 2018. Rates of gonorrhea, chlamydia, and syphilis in the US have increased, while rates of HSV-1 and HSV-2 have declined. Ceftriaxone, doxycycline, penicillin, moxifloxacin, and the nitroimidazoles are effective treatments for gonorrhea, chlamydia, syphilis, *Mycoplasma genitalium*, and trichomoniasis, respectively, but antimicrobial resistance limits oral therapies for gonorrhea and *Mycoplasma genitalium*, and no cure is available for genital herpes.

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Supplemental content

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In 2019, an estimated 2.55 million new sexually transmitted infections (STIs) were reported in the US,[1] with a projected direct medical cost of approximately $1.1 billion for gonorrhea, chlamydia, and syphilis in 2018.[2] In 2018, there were approximately 67.6 million prevalent infections in the US, suggesting that an estimated 1 in 5 adults had an STI.[3] People with STIs are at greater risk of transmitting HIV to others. Among people without HIV, STIs increase rates of HIV acquistion.[4,5] STIs also increase rates of infertility, chronic pelvic pain, ectopic pregnancy, miscarriage, fetal death, and congenital and neonatal infections.[6-9] This review summarizes current evidence regarding the epidemiology, diagnosis, treatment, and prevention of gonorrhea, chlamydia, syphilis, *Mycoplasma genitalium*, trichomoniasis, and genital herpes. For the purposes of clarity, in this article, the terms male and female refer to those assigned male or female at birth, respectively (see eTable 1 in the Supplement for additional clinician resources).

Methods

We searched PubMed and Cochrane databases using Medical Subject Headings for English-language studies of the epidemiology, diagnosis, and treatment of gonorrhea, chlamydia (including lymphogranuloma venereum), syphilis, *Mycoplasma genitalium*, trichomoniasis, and herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) between October 1, 2010, and October 31, 2021. We manually searched the references of selected articles for additional relevant studies (including older studies). Randomized clinical trials, meta-analyses, systematic reviews, and national and international clinical practice guidelines were prioritized for inclusion. Of 1896 reports identified, 81 were included, consisting of 8 randomized trials, 7 meta-analyses, 27 systematic reviews, 5 clinical practice guidelines, 28 observational studies, 3 modeling studies, and 3 retrospective case series.

Gonorrhea

Epidemiology

In 2019, 616 392 new infections with gonorrhea were reported in the US (188.4 cases per 100 000 per year).[1] From 2015 to 2019, the rate increased among men by 60.6% (139.7 to 224.4 cases per 100 000 per year) and the rate increased among women by 43.6% (106.3 to 152.6 cases per 100 000 per year). Rates were highest among people who are Black (581.0 cases per 100 000 per year) and people aged 20 through 24 years (542.4 cases per 100 000 per year for men and 551.9 cases per 100 000 pers year for women). Rates have increased in all US regions and are highest in the southern US (205.4 cases per 100 000 per year).

Clinical Presentations

Gonorrhea may infect the oropharynx, rectum, eye, and urogenital tract in both sexes. Dissemination beyond genital and extragenital sites may occur. Between 86.4% to 92.6% of urogenital infections among women with gonorrhea may be asymptomatic.[10] The proportion of asymptomatic urogenital infections in men is unclear, but in a population-based multicenter study involving 11 408 participants, 55.7% to 86.8% of urogenital infections were asymptomatic.[10] Among both men and women, 53% to 100% of extragenital infections are asymptomatic.[10] After an incubation period of 2 to 8 days, men with gonococcal urethritis may complain of a urethral discharge and dysuria.[11] Rare complications (<1% occurrence) include penile lymphangitis, periurethral abscesses, and urethral strictures. Symptomatic women may report vaginal discharge, vaginal pruritus, intermenstrual bleeding, or menorrhagia. Abdominal pain and dyspareunia suggest pelvic inflammatory disease. Gonococcal conjunctivitis occurs in infants born to infected mothers. In adults, gonococcal conjunctivitis is frequently due to autoinoculation, and outbreaks secondary to nonsexual transmission have occurred. When symptomatic, gonococcal pharyngitis may cause sore throat, pharyngeal exudates, or cervical lymphadenitis; gonococcal proctitis may cause anorectal pain, bleeding, tenesmus, or mucopurulent discharge. Disseminated gonococcal infection may cause purulent arthritis (81%) or the triad of tenosynovitis, dermatitis, and polyarthralgias (19%).[12]

Testing and Screening for Gonorrhea

Nucleic acid amplification tests (NAATs), which differ in their amplification methods and their target nucleic acid sequences, have sensitivities of more than 90% and specificities of 98% or more for detecting gonorrhea at genital and extragenital sites, respectively.[13,14] In women, the preferred specimen is a vaginal swab (including self-collected swabs) given its high sensitivity and ease of collection, but endocervical swabs and first-catch urine (ie, 20-30 mL of the initial urinary stream collected after abstinence from urination for at least 1 hour) are acceptable (**Table 1**).[15] In men, the preferred specimen is a first-catch urine, but urethral swabs are acceptable.[15] NAATs are US Food and Drug Administration (FDA)–cleared for pharyngeal and rectal testing, and they are the preferred diagnostic tests for these sites.[14,15] Among men who have sex with men (MSM), 14% to 85% of gonococcal infections are only detected at extragenital sites,[16] hence the recommendation to test for gonorrhea in MSM at all sites of exposure.[15] Among women, 6% to 50% of gonococcal infections are only detected at extragenital sites[16]; the decision to test extragenital sites in women should be individualized.[15] Infection at extragenital sites is associated with antimicrobial resistance.

The sensitivity of cultures for detecting gonorrhea infection is 50% to 85%, with lower sensitivity at extragenital sites and among people who report no symptoms.[17] Cultures are necessary for antimicrobial susceptibility testing when antimicrobial resistance is suspected. Endocervical and urethral samples are the only appropriate urogenital specimens for cultures (Table 1). Gonorrhea has specific nutritional and environmental requirements for growth in culture: Collected swabs must be transported using specific transport systems, streaked on a selective medium, and incubated in a 5% CO_2 environment.[17] In symptomatic men, the Gram stain is inexpensive and has a specificity of 99% and sensitivity of more than 95% for diagnosing urethral infections. However, Gram stain is inappropriate for use in asymptomatic men and women due to lower sensitivity and specificity.[17] Novel molecular-based diagnostics that detect antimicrobial resistance genetic determinants are under development.[18] At least annual screening for gonorrhea is recommended for sexually active women younger than 25 years and for other groups based on selected characteristics or risk factors (**Table 2**).[13,15]

Treatment and Prevention

In 2019, based on 5480 gonococcal isolates from the Gonococcal Isolate Surveillance Program of the Centers for Disease Control and Prevention (CDC), 35.4% were resistant to ciprofloxacin, 5.1% to azithromycin, and less than 0.5% to cephalosporins or gentamicin.[1] In some regions, such as Western Europe, cephalosporin resistance and multidrug resistant organisms have emerged.[20] Currently, recommended treatment in the US consists of 500 mg of intramuscular ceftriaxone (**Table 3**).[15] Resistance to the macrolides has increased, and azithromycin is no longer an appropriate therapy for gonorrhea. For patients unable to tolerate cephalosporins, a single dose of 5 mg/kg of parenteral gentamicin combined with 2 g of oral azithromycin should be prescribed (Table 3).[21] Most patients with IgE-mediated and T-cell–mediated hypersensitivity to penicillins can tolerate ceftriaxone, which has distinct side-chain determinants, compared with penicillins.[22,23] Ceftriaxone is the only drug that is recommended for treating pharyngeal infections. Patients treated for pharyngeal gonorrheal infections should be tested for cure with either a culture or NAATs in 1 to 2 weeks after treatment is completed.[15] Recommendations for treating disseminated gonococcal infection and gonococcal conjunctivitis are in Table 3. Currently recommended outpatient treatments for pelvic inflammatory disease are cephalosporin-based. For patients with penicillin and cephalosporin allergies, alternative treatment with parenteral clindamycin and gentamicin should be prescribed.[24] A group B outer membrane vesicle meningococcal vaccine provided cross-protection against gonorrhea with an estimated effectiveness of 31% (95% CI, 21%-39%),[25] and a gonococcal vaccine is under development. All sex partners within 60 days prior to an index patient's diagnosis with gonorrhea should be treated presumptively.[15]

Chlamydia

Epidemiology

Chlamydia is caused by the D through K serovars of *Chlamydia trachomatis* and is the most common notifiable STI in the US.

Table 1. Diagnostic Testing for Sexually Transmitted Infections in Women, Men, and Transgender and Gender-Diverse People

Population	Syphilis	Herpes	Gonorrhea and chlamydia	*Mycoplasma genitalium*	Trichomoniasis
Women	In the presence of primary-stage lesions, PCR from swab of lesion exudate or biopsy specimen,[a] Darkfield microscopy on lesion exudate (not for oral lesions),[b] Direct fluorescent antibody testing on lesion exudate, Silver stain on tissue biopsy In the absence of primary-stage lesions, serological testing using a combination of treponemal and nontreponemal (antiphospholipid) antibody tests For neurosyphilis, CSF examination assessing for pleocytosis, protein concentration, and VDRL and/or treponemal antibodies[c]	In the presence of lesions, PCR; Culture In the absence of lesions, glycoprotein-G–based IgG1 and IgG2 serological testing	For urogenital *Chlamydia trachomatis* or *Neisseria gonorrhoeae*, NAATs from the self-collected or clinician-collected vaginal swab (preferred), from a clinician-collected endocervical swab, from a first-catch urine specimen, or from a liquid Papanicolaou smear specimen For extragenital *C trachomatis* or *N gonorrhoeae*, NAATs from self-collected or clinician-collected rectal or pharyngeal specimens For urogenital and extragenital *N gonorrhoeae*, culture from a clinician-collected endocervical swab or from a clinician-collected pharyngeal or rectal swab[d]	For urogenital *M genitalium*, NAATs from self-collected or clinician-collected vaginal swab (preferred), from a clinician-collected endocervical swab, or from a first-catch urine specimen	For urogenital trichomonas, NAATs from self-collected or clinician-collected vaginal swab, from a first-catch urine specimen, or from a liquid Papanicolaou smear specimen; Culture from a clinician-collected vaginal swab; Rapid antigen testing from a self-collected or clinician-collected vaginal swab
Men	As above	As above	For urogenital *N gonorrhoeae* and *C trachomatis*, NAATs from a first-catch urine (preferred), from a clinician-collected urethral swab; For extragenital *N gonorrhoeae* and *C trachomatis*, same as above; For urogenital and extragenital *N gonorrhoeae*, culture from a clinician-collected urethral swab or from a clinician-collected pharyngeal or rectal swab[d]	For urogenital *M genitalium*, NAATs from a first-catch urine (preferred) or from a clinician-collected penile meatal or urethral swab	NAATs from a first-catch urine or from a clinician-collected urethral swab[e]
Transgender and gender-diverse people	As above	As above	For extragenital *N gonorrhoeae* and *C* trachomatis, same as above; For urogenital *N gonorrhoeae* and *C trachomatis* for transgender women, first-catch urine (preferred); For transgender men, self-collected or clinician-collected vaginal swab or first-catch urine depending on anatomy; For gender-diverse people, self-collected or clinician-collected vaginal swab or first-catch urine depending on anatomy	For urogenital *M genitalium* for transgender women, first-catch urine (preferred); For transgender men, self-collected or clinician-collected vaginal swab or first-catch urine depending on anatomy; For gender-diverse people, self-collected or clinician-collected vaginal swab or first-catch urine depending on anatomy	For transgender women, first-catch urine (preferred); For transgender men, self-collected or clinician-collected vaginal swab or first-catch urine depending on anatomy; For gender-diverse people, self-collected or clinician-collected vaginal swab or first-catch urine depending on anatomy

Abbreviations: CSF, cerebrospinal fluid; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction.

[a] Not cleared by the US Food and Drug Administration (FDA).

[b] Oral and anal specimens contain nonsyphilis treponemes that affect the specificity of darkfield microscopy.

[c] CSF treponemal antibodies have a high sensitivity but low specificity; clinicians must interpret the results of these tests cautiously.

[d] Gonorrhea culture has a lower sensitivity than NAATs irrespective of anatomical site; cultures are mainly used to determine antimicrobial susceptibility of the gonococcal strain.

[e] Not cleared by the FDA for testing of men.

In 2019, 1 808 703 incident infections were reported (552.8 per 100 000 per year).[1] From 2015 to 2019, the rate among men increased by 32.1% from 305.2 to 399.9 per 100 000 per year, and the rate among women aged 15 through 24 years (the population targeted for screening) increased by 10.0% from 2994.4 to 3333.8 per 100 000 per year among those aged 15 through 19 years and from 3730.3 to 4109.5 per 100 000 per year among those aged 20 through 24 years. Rates for women are approximately twice that of men, in part because screening recommendations focus on women (see Table 2).[13,15] Rates are highest among young women aged 20 through 24 years (4109.5 cases per 100 000 per year) and are 5.6 times higher in people who are Black (1233.2 cases per 100 000 per year) compared with people who are White (209.7 cases per 100 000 per year). Incidence is highest in the southern US

Table 2. Sexually Transmitted Infection Screening Recommendations for Various Populations That Are Sexually Active

Population	Syphilis	Genital *Chlamydia trachomatis* and *Neisseria gonorrhoeae*	Genital *Trichomonas vaginalis*	Additional notes
Women	Consider screening if they exchanged sex for drugs or money in the past year; have a new sex partner, >1 sex partner, a sex partner with concurrent partners, or a sex partner who has an STI; or are receiving care in high-prevalence settings	<25 y Screen at least annually; ≥25 y, Consider screening if they exchanged sex for drugs or money in the past year; have a new sex partner, >1 sex partner, a sex partner with concurrent partners, or a sex partner who has an STI; or are receiving care in high-prevalence settings	Consider screening at least annually women receiving care in high-prevalence settings and who are at high risk of infection (eg, multiple sex partners, transactional sex, drug misuse, or a history of STI or incarceration)	
MSW	Screen those at increased risk (based on history of incarceration or transactional sex work, geography, race and ethnicity, and <29 y) and consider testing at least annually those at high risk (eg, exchanging sex for money, using methamphetamines, injection drugs, heroin, or having sex with a person who injects drugs or for those receiving care in high-prevalence settings, such as STI clinics)	Consider screening young men in high-prevalence areas or settings	None	
MSM	At least annually	At least annually (rectal *N gonorrhoeae or C trachomatis* and pharyngeal *N gonorrhoeae* depending on sites of contact)	None	For *C trachomatis*, *N gonorrhoeae*, syphilis, and HIV, more frequent screening (every 3-6 mo) if risk factors (multiple partners; sex in conjunction with illicit drug use, including methamphetamines; and sex partners who engage in these activities)
Transgender and gender-diverse people	At least annually	Annual screening for *C trachomatis or N gonorrhoeae* in all those with a cervix <25 y, or in those >25 y with risk factors, screening at rectal and pharyngeal site depending on exposures	None	For *C trachomatis*, *N gonorrhoeae*, syphilis, and HIV, more frequent screening if risk factors
People with HIV	At least annually	At least annually (rectal *C trachomatis* or *N gonorrhoeae* and pharyngeal *N gonorrhoeae* in MSM depending on sites of contact)	Screen at least annually in women	For *C trachomatis*, *N gonorrhoeae*, and syphilis, more frequent screening (every 3-6 mo) for MSM if risk factors (multiple partners; sex in conjunction with illicit drug use, including methamphetamines; and sex partners who engage in these activities)
Pregnant women	First prenatal visit; At 28 wk and at delivery if high risk or based on local laws	All pregnant women if <25 y or at increased risk; Retest for chlamydia during the third trimester for women <25 y or at risk; Pregnant women with chlamydial infection should have a test of cure 3-4 wk after treatment	First prenatal visit if positive for HIV	
Patients taking HIV PrEP[a]				
Women	Every 6 mo	Every 6 mo for *N gonorrhoeae* and every 12 mo for *C trachomatis*; Rectal *C trachomatis* and *N gonorrhoeae* in women who have engaged in anal sex	Consider screening at least annually for women receiving care in high-prevalence areas or settings and for women at high risk of infection (eg, multiple sex partners, transactional sex, drug misuse, or a history of STI or incarceration)	
MSW	Every 6 mo	Every 6 mo for *N gonorrhoeae* and every 12 mo for *C trachomatis*	None	
MSM and transgender women who have sex with men	At least every 6 mo; every 3 mo (or 4 mo if receiving cabotegravir PrEP) among those at high risk (multiple sex partners or had syphilis, *C trachomatis*, or *N gonorrhoeae* at prior visits)	At least every 6 mo (including rectal and pharyngeal); every 3 mo (or 4 mo if receiving cabotegravir PrEP) among those at high risk (multiple sex partners or had syphilis, *C trachomatis*, or *N gonorrhoeae* at prior visits)	None	

Abbreviations: MSM, men who have sex with men; MSW, men who have sex with women; PrEP, preexposure prophylaxis.

[a] Adapted from the Centers for Disease Control and Prevention's Preexposure Prophylaxis for the Prevention of HIV Infection in the US 2021 Update Clinical Practice Guidelines[19] and the 2021 STI Treatment Guidelines.[1]

Table 3. Sexually Transmitted Infection Treatment Recommendations for Adults[a]

Infection	First-line	Alternative	Notes
Gonorrhea			
Urogenital, rectal, pharyngeal	For persons weighing <150 kg, 500 mg of ceftriaxone intramuscularly in a single dose; For persons weighing >150 kg, 1 g of ceftriaxone intramuscularly in a single dose	No alternate agents exist for pharyngeal infections; 240 mg of gentamicin intramuscularly in a single dose plus 2 g of azithromycin orally in a single dose for urogenital and rectal infections for patients with a cephalosporin allergy; 800 mg of cefixime orally in a single dose if ceftriaxone is unavailable	Repeat testing to confirm a cure should be performed 7-14 d after treatment of all pharyngeal infections; Symptoms that persist after treatment should be evaluated with a gonococcal culture in consideration of antimicrobial resistance (if reinfection is deemed unlikely)
Disseminated gonococcal infection	For arthritis or arthritis-dermatitis,1 g of ceftriaxone intramuscularly or intravenously every 24 h; For gonococcal meningitis and endocarditis, 1-2 g of ceftriaxone intravenously every 12-24 h	For arthritis or arthritis-dermatitis, 1 g of cefotaxime intravenously every 8 h	Hospitalization and consultation with an infectious diseases specialist are recommended for initial therapy; For arthritis-dermatitis, treatment may be switched to an oral agent guided by antimicrobial susceptibility testing 24-48 h after substantial clinical improvement for a 7-d total course; For meningitis, parenteral therapy for 10-14 d; For endocarditis, parenteral therapy for at least 4 wk
Gonococcal conjunctivitis	1 g of ceftriaxone intramuscularly in a single dose		A 1-time lavage of the infected eye with saline is recommended; careful clinical follow-up to determine if longer duration of antibiotics is necessary
Chlamydia			
Urogenital, rectal, pharyngeal	100 mg of doxycycline orally 2/d for 7 d	1 g of azithromycin orally in a single dose; 500 mg of levofloxacin orally 1/d for 7 d For pregnant persons, 500 g of amoxicillin orally 3/d for 7 d	Doxycycline is contraindicated in pregnancy; Azithromycin should be used and a test to determine cure should be conducted 3 to 4 wk after completion of therapy in pregnant person
Lympho-granuloma venereum (LGV)	100 mg of doxycycline orally 2/d for 21 d	1 g orally of azithromycin 1g orally weekly for 2 consecutive wk; 500 mg of erythromycin base orally 4/d for 21 d	Shorter courses of doxycycline (ie, 7 d) may be effective for patients who are asymptomatic or have mild symptoms; Doxycycline is contraindicated in pregnancy
Trichomonas			
	For women, 500 mg of metronidazole orally 2/d for 7 d; For men, 2 g metronidazole orally in a single dose	Tinidazole 2g orally in a single dose for both men and women	Higher doses and longer courses of therapy are recommended for nitroimidazole-resistant strains
Genital herpes			
Symptomatic treatment of first episode	1 g of valacyclovir orally 2/d for 7-10 d; 400 mg acyclovir orally 3/d for 7-10 d; 250 mg of famciclovir orally 3/d for 7-10 d	200 mg of acyclovir orally 5/d for 7-10 d	Treatment is not curative but can help reduce symptoms; extending treatment duration by 1 wk may be appropriate for some patients whose lesions have not completely healed
Episodic therapy for recurrent genital herpes	1 g valacyclovir orally daily for 5 d or 500 mg orally 2/d for 3 d 800 mg of acyclovir orally 2/d for 5 d or 800 mg orally 3/d for 3 d 125 mg of famciclovir orally 2/d for 5 d, 1000 mg orally 2/d for 1 d, or 500 mg orally once followed by 250 mg 2/d for 2 d For persons infected with HIV, 1 g of valacyclovir orally 2/d for 5-10 d, 400 mg of acyclovir orally 3/d for 5-10 d, or 500 mg of famciclovir orally 2/d for 5-10 d	400 mg of acyclovir orally 3/d for 5 d For persons infected with HIV, none	The antivirals listed herein have approximately equal efficacy, while the number of required daily and the cost vary
Daily suppressive regimens	500 mg of valacyclovir orally daily or 1 g orally daily, 400 mg of acyclovir orally 2/d, 250 mg of famciclovir orally 2/d; For person infected with HIV, 500 mg of valacyclovir orally 2/d, 400-800 mg of acyclovir 2/d or 3/d, or 500 mg of famciclovir orally 2/d		For valacyclovir, 500 mg 1/d may be less effective among persons with ≥10 recurrences per y
Syphilis			
Primary, secondary, and early latent syphilis	2.4 million units of benzathine penicillin G intramuscularly in a single dose	100 mg of doxycycline orally 2/d for 14 d	For ceftriaxone, 1-2 g/d intramuscularly or intravenously for 10-14 d may also be an alternative For pregnant persons, only benzathine penicillin G is acceptable

(continued)

Table 3. Sexually Transmitted Infection Treatment Recommendations for Adults[a] (continued)

Infection	First-line	Alternative	Notes
Late latent syphilis	7.2 million units total of benzathine penicillin G administered as 3 doses of 2.4 million units intramuscularly each at 1-wk intervals	100 mg of doxycycline orally 2/d for 28 d	For pregnant persons, only benzathine penicillin G is acceptable; For nonpregnant adults, up to a 10-d interval between intramuscular doses may be acceptable
Late syphilis (gummas and cardiovascular but not neurosyphilis)	Benzathine penicillin G: 7.2 million units total, administered as 3 doses of 2.4 million units intramuscularly each at 1-wk intervals		For pregnant persons, only benzathine penicillin G; CSF examination is recommended for tertiary disease and treatment based on results
Neurosyphilis, otic syphilis, and ocular syphilis	18-24 million units/d of aqueous crystalline penicillin G as 3-4 million units intravenously every 4 h or by continuous infusion for 10-14 d	2.4 million units of procaine penicillin G intramuscularly 1/d plus 500 mg of probenecid orally 4/d, both for 10-14 d	Intravenous ceftriaxone may be used as alternative therapy but only if penicillin therapy is not feasible; The concomitant use of steroids has not been systematically assessed, so their utility is not defined
Mycoplasma genitalium	When macrolide resistance is detected or is not known, 100 mg of doxycycline orally 2/d for 7 d followed by 400 mg of moxifloxacin orally 1/d for 7 d; If the organism is determined to be susceptible to macrolides, 100 mg of doxycycline orally 2/d for 7 d followed by 1 g of azithromycin orally on day 1 and 500 mg orally on days 2 through 4		Molecular tests to determine macrolide resistance are not currently cleared by the US Food and Drug Administration but may be available in some clinical settings Suspected resistance to the fluoroquinolones should be managed in conjunction with an expert in infectious diseases

[a] Adapted from the Centers for Disease Control and Prevention 2021 Sexually Transmitted Infections Guidelines.[15]

(573.9 cases per 100 000 per year).[1] In men or transgender women who have sex with men, the prevalence of rectal chlamydia ranged from 2.1% to 23% (median, 8.9%), of which 57% to 70% of infections required extragenital testing for detection.[16]

Clinical Presentations

Chlamydia may infect the oropharynx, rectum, eye, and the urogenital tract of both men and women.[15] Pulmonary infections may occur in infants. More than 70% of urogenital infections in women, more than 80% of urogenital infections in men, and more than 90% of rectal and pharyngeal infections are asymptomatic.[16] Clinical manifestations, when present, include urethritis (characterized by dysuria and urethral discharge), cervicitis (characterized by mucopurulent discharge), pelvic inflammatory disease, epididymitis (fever, testicular pain), or proctitis (rectal pain, discharge, and bleeding). Rare complications include perihepatitis (Fitz-Hugh-Curtis syndrome) and reactive arthritis. Infants may acquire chlamydia during vaginal delivery, resulting in conjunctivitis or pneumonia.[9] Lymphogranuloma venereum (LGV) is an STI caused by the L1 through L3 serovars (ie, antigenic type) of *Chlamydia trachomatis* that has emerged predominantly in populations of men or transgender women who have sex with men, with outbreaks of rectal disease reported in the US and other high-income countries.[26] LGV is characterized by 3 stages. First, a small, painless, transient ulcer appears at the site of inoculation.[27] Second, 2 to 6 weeks later, large and tender inguinal lymph nodes appear. Approximately 30% of these lymph nodes spontaneously perforate. In patients with rectal exposure, the secondary stage primarily consists of proctitis or proctocolitis, with histological findings that may be indistinguishable from inflammatory bowel disease. LGV may also be asymptomatic. The third stage occurs if the infection is untreated and consists of scarring from chronic lymphadenitis, which may lead to lymphedema and genital elephantiasis.

Testing and Screening

NAATs are the tests of choice at all potentially infected sites, and the approach to testing is similar to the one described for gonorrhea (Table 1).[13,15] Chlamydia NAAT tests results are typically positive for LGV but cannot distinguish the L1 through L3 from the D through K serovars.[26] Molecular tests to confirm LGV infection exist but none are FDA cleared or widely available in the US. Consequently, most diagnosis and treatment is presumptive.[15] Sexually active women younger than 25 years should undergo genital screening at least annually and sexually active men and transgender women who have sex with men should undergo genital and rectal screening (if exposed) at least annually (Table 2).[13,15]

Treatment and Prevention

Recommended treatment for chlamydia is 100 mg of doxycycline orally twice daily for 7 days.[15] Alternative regimens include 1 g of azithromycin or 500 mg of levofloxacin once daily for 7 days (Table 3). A clinical trial involving 567 participants with urogenital chlamydia randomized to receive either a 1-g dose of azithromycin or 100-mg dose of doxycycline twice daily for 1 week found that doxycycline cured 100% of participants and the single dose of azithromycin cured 97%.[28] In 2 clinical trials comparing 100 mg of doxycycline twice daily for 7 days with a single 1-g dose of azithromycin for rectal chlamydia, doxycycline was associated with a higher microbiological cure rate. In the first trial,[29] involving 177 MSM participants, 91% in the doxycycline group vs 71% in the azithromycin group achieved cure and in the second trial[30] involving 625 MSM participants, 96.9% in doxycycline group vs 76.4% in the azithromycin group achieved cure.

All sex partners within the last 60 days of an individual's chlamydia diagnosis should be treated presumptively.[15]

First-line treatment for LGV is doxycycline (Table 3).[15] People whose NAAT result was positive for rectal chlamydia and have acute

proctitis with bloody rectal discharge, tenesmus, or perianal or mucosal ulcers should receive 21 days of doxycycline (to cover both D-K and L1-L3 serovars). Those with a positive rectal chlamydia NAAT result and mild or no symptoms may be treated with doxycycline for 7 days.[31] Asymptomatic sex partners who have had contact with a patient with LGV within the 60 days before symptom onset should be treated empirically with 100 mg of doxycycline orally twice a day for 7 days.[15]

Syphilis

Epidemiology

Since 2000, when the incidence was 11.2 cases per 100 000 per year, syphilis rates in the US have increased. In 2019, the incidence of all stages of syphilis was 39.7 per 100 000 per year.[1] In 2019, 38 992 patients were diagnosed with primary or secondary syphilis, an increase of 11.2% from 2018. Men and transgender women who have sex with men make up 56.7% of diagnosed cases of primary or secondary syphilis. Additionally, incidence rates are higher among people who are Black (31 per 100 000 person-year), and residents of western states (16.9 cases per 100 000 person-year). Prevalence is higher among people with HIV (7.1% prevalence among MSM with HIV and 3.4% prevalence among MSM without HIV). Incidence rates of syphilis among women and the incidence of congenital syphilis are increasing. In 2019, 1870 cases of congenital syphilis were reported, representing a 279% increase compared with 2015.[1]

Clinical Presentations

Syphilis is caused by the spirochete *Treponema pallidum* and is predominantly transmitted through sex, from mother-to-child during pregnancy, and rarely via blood transfusions or organ transplants.[32] Primary syphilis, the first stage of infection, typically presents with a single, painless ulcer at the site of inoculation, with regional lymphadenopathy that develops approximately 9 to 90 days after exposure. Ulcers may be multiple, shallow, and painful.[33] Secondary syphilis, defined by bacterial dissemination, occurs 4 to 10 weeks after the primary lesion. The most consistent feature of secondary syphilis is a macular rash. The classic maculopapular rash involving the palms and soles occurs in 48% to 70% of patients. Secondary syphilis may cause alopecia, abdominal pain, and joint swelling.[32]

Without treatment, host immunity controls bacterial replication to induce *latency*, defined by infection without signs or symptoms of syphilis. Early latent is defined as a latent syphilis infection acquired within the previous 12 months, and late latent is one acquired more than 12 months previously. Up to 25% of those with untreated latent syphilis may develop symptoms of secondary syphilis, typically within the first year.[32] Untreated, approximately 70% will maintain lifelong latency and the remainder will develop tertiary disease, consisting of cardiac syphilis affecting 10% of untreated patients 20 to 30 years after infection and gummatous syphilis affecting 15% of untreated patients 1 to 46 years after infection.[32] Neurosyphilis can occur at any stage of infection.[34] Within approximately 6 weeks after infection, between 25% and 60% of patients have evidence of central nervous system dissemination, although only 5% develop symptoms.[32,34] Early neurosyphilis usually presents as meningitis. Late neurosyphilis can result in general paresis or tabes dorsalis. General paresis occurs in 2% to 5% of patients who remain untreated after 2 to 30 years, and tabes dorsalis develops in 2% to 9% of patients who are untreated after 3 to 50 years.[32,34] Ocular and otic syphilis can occur at any stage of infection.[35,36]

Testing and Screening

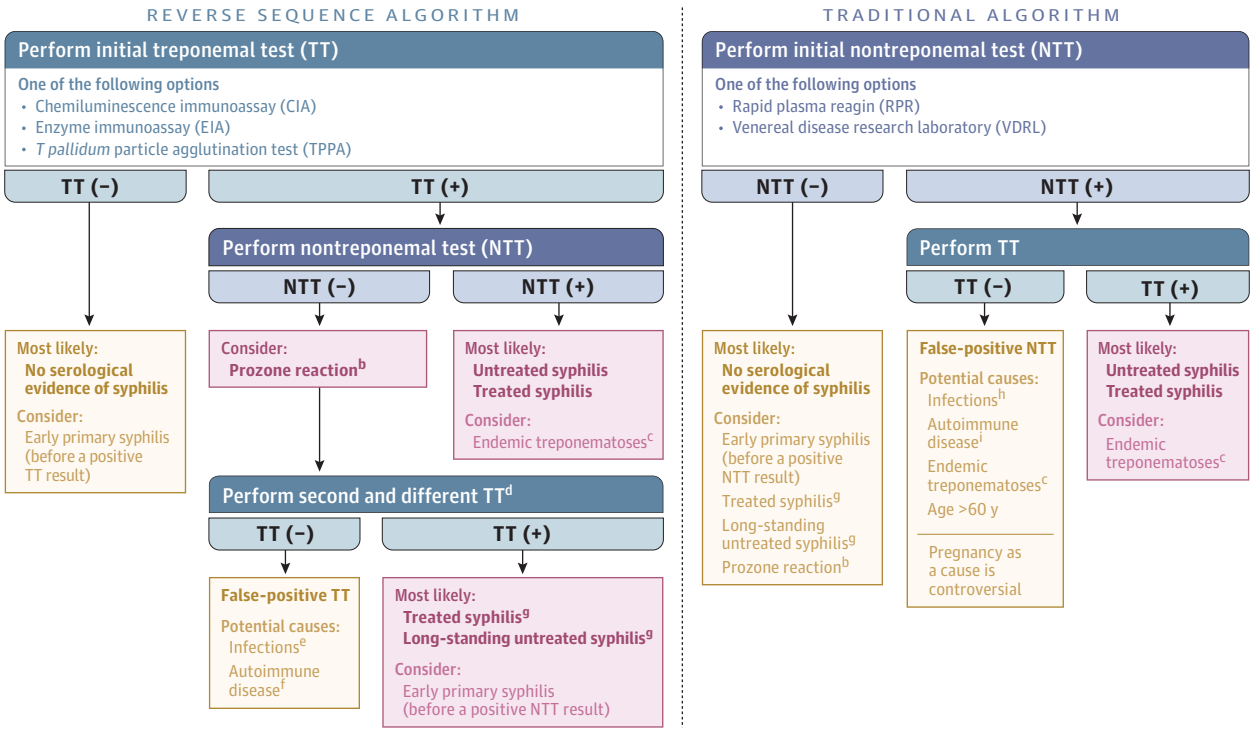
Direct detection is based on demonstration of *T pallidum* on darkfield microscopic examination of primary, moist secondary, or neonatal lesions using polymerase chain reaction (PCR) or histology.[37,38] Typically, diagnosis of syphilis is established with a treponemal test (TT), a test for antibodies produced specifically against *T pallidum*, such as the *T pallidum* particle agglutination assay (TPPA). TTs help establish the diagnosis of syphilis but are not useful for monitoring response to therapy, relapse, or infection. Nontreponemal antiphospholipid antibody tests (NTTs) such as the rapid plasma reagin (RPR) or VDRL tests, cross react with antigens produced in response to *T pallidum* but are not specific for *T pallidum*.[39,40] In contrast to the TTs, the nontreponemal tests yield a quantitative result, or titer, that can be used to monitor disease activity. A titer decline of at least 4-fold is required after antibiotic therapy to indicate successful treatment at 12 months for early syphilis and at 24 months for late syphilis.[15] Serological testing for syphilis may be performed with either an initial nontreponemal antiphospholipid antibody test (referred to as the *traditional algorithm*) or a TT (the reverse sequence algorithm; **Figure**).[44] Both tests may be nonreactive in 30% of persons with primary syphilis. Although TTs generally remain reactive lifelong following infection irrespective of treatment history, the nontreponemal antiphospholipid antibody test may become nonreactive with or without treatment.[32]

No single test confirms neurosyphilis, which relies on the interpretation of the cerebrospinal fluid (CSF)–VDRL test, white blood cell count, and protein.[34] (Table 1). Among 40% of patients with optic syphilis and 90% of patients with otic syphilis, CSF examination result may be normal.[35,36] The CSF-VDRL test is more than 95% specific but only approximately 50% sensitive; conversely the CSF-TTs are highly sensitive but lack specificity.[19] MSM and those with HIV should be screened annually for syphilis.[15] Pregnant persons should be screened at the first prenatal visit, at 28 weeks' gestation, and at the time of delivery[45]; patients using HIV preexposure prophylaxis should be screened every 2 to 6 months (Table 2).[15,46]

Treatment and Prevention

Parenteral penicillin is first-line therapy for all stages of syphilis (Table 3).[47] Administering 2.4 million units of long-acting benzathine penicillin G as a single intramuscular dose is optimal for early stage syphilis (primary and secondary syphilis and early latent syphilis), whereas 2.4 million units administered intramuscularly weekly for 3 consecutive weeks is recommended for late latent syphilis.[15] An alternate therapy is 100 mg of oral doxycycline twice daily for 14 to 28 days. In pregnancy, penicillin is the only recommended therapy. Patients who are allergic to penicillin may require penicillin desensitization. However, based on the specific history of allergy, up to 90% of people with a history of penicillin allergy can safely receive penicillin. After treatment, the Jarisch-Herxheimer reaction, mainly consisting of fevers and chills, can occur as a result of inflammatory cytokine release[48] and should not be confused with a penicillin allergy. Sexual contacts of people with early syphilis require treatment with 2.4 million units of benzathine penicillin G intramuscularly.[15] Neurosyphilis, ocular syphilis, and otic syphilis

Figure. Syphilis Serological Diagnostic Testing[a]



[a] This diagnostic algorithm has not been validated in clinical practice.

[b] False-negative NTTs are due to excess antibody production to syphilis, more common with VDRL than RPR.

[c] Endemic treponematoses are nonsyphilis treponemal infections and are caused by *Treponema pallidum* subspecies pertenue, *T pallidum* subspecies endemicum, and *Treponema carateum*.

[d] The confirmatory second TT should be different from the initial TT, TPPA is preferred if not for the initial test performed (eg, CIA or EIA followed by TPPA).

[e] The most common infections that can cause a false-positive TT result are infections caused by *Borrelia burgdorferi*, which causes Lyme disease;[41] infections caused by the endemic treponematoses; and aoral spirochetes that cause chronic periodontitis and necrotizing ulcerative gingivitis.[42]

[f] The most common autoimmune disease that gives a false-positive TT result is systemic lupus erythematosus.[43]

[g] Reversion is defined as a previously reactive NTT that becomes nonreactive. NTT tests can become nonreactive following treatment, but they can also become nonreactive over time even in the absence of treatment.

[h] Examples of infections that cause false-positive NTT results are HIV, the endemic treponematoses, and leprosy.[40]

[i] Examples of autoimmune diseases that cause false-positive NTT results are systemic lupus erythematosus and antiphospholipid syndrome.

are treated with 18 to 24 million units of intravenous aqueous crystalline penicillin G daily for 10 to 14 days. Limited data support the use of 1 to 2 g of ceftriaxone daily to treat neurosyphilis.[49] Corticosteroids are not established therapies for ocular and otic syphilis. Infants born to those with inadequately treated syphilis require careful physical examination, serology, and usually radiological and CSF examination.[15]

In a pilot clinical trial, 30 MSM with HIV were randomized to receive 100 mg of doxycycline daily for 48 weeks vs placebo. Doxycycline reduced the combined odds of syphilis, chlamydia, and gonorrhea by 73% compared with placebo (6 STIs per 4536 person-days vs 15 STIs per 4284 person-days).[50] In an open label study of 116 MSM, postexposure prophylaxis of 200 mg of doxycycline administered within 24 hours of a sexual encounter was associated with a lower incidence of syphilis compared with controls (12.9 vs 3.7 events per 100 person-years).[51] However, these data are preliminary and doxycycline is not currently recommended to prevent syphilis.[15]

Mycoplasma genitalium

Epidemiology

Mycoplasma genitalium is a recently described STI. It is not a notifiable infection, and few data exist on its prevalence. The FDA-cleared tests for *M genitalium* are now available, and national guidelines include recommendations for testing and treatment.[15] A 2019 US study involving 3300 participants—including both symptomatic and asymptomatic individuals, of whom 1737 were female (median age, 33 years) and 1563 were male (median age 29 years), 61% were Black individuals, and 43.2% were from the southeastern region of the US—reported that prevalence of *M genitalium* at the urogenital site was 10.3%.[52]

Clinical Presentation

M genitalium infects the urogenital tract in men and women. Among 3300 participants identified from 21 US sites, 7.9% of women and 8.8% of asymptomatic men had *M genitalium* detected urogenitally.[53] Between 30% and 40% of men with persistent and recurrent

urethritis are infected with *M genitalium*.[54] Symptoms include dysuria, penile irritation, and urethral discomfort. *M genitalium* has been linked to cervicitis, pelvic inflammatory disease, and infertility in women.[55,56] The symptom profile in women may include symptoms of cervicitis, postcoital bleeding, painful intermenstrual bleeding, and lower abdominal pain.[55] Whether *M genitalium* leads to symptomatic proctitis is unclear.[57] *M genitalium* is detectable in the pharynx, but its clinical significance is unknown.[58]

Testing and Screening

NAATs are FDA cleared for testing urine and for swabs of the urethra, penile meatus, endocervix, and vagina (Table 1).[15] Extragenital testing for *M genitalium* and testing in people without symptoms are not recommended. Guidelines recommend testing men with persistent nongonococcal urethritis, and women with persistent cervicitis for *M genitalium*.[15]

Treatment and Prevention

CDC guidelines recommend sequential treatment with 100 mg of doxycycline orally twice daily for 7 days followed by 400 mg of moxifloxacin orally once daily for 7 days.[15] Azithromycin may be used instead of moxifloxacin if macrolide susceptibility can be ascertained using molecular resistance tests, which are not currently cleared by the FDA (Table 3). Antimicrobial resistance is a major concern. Prevalence of molecular markers for macrolide resistance ranges from 42% to 94% in the US.[59] Treatment failures to moxifloxacin have been reported.[60,61] Doxycycline alone cures approximately 30% of *M genitalium* cases. However, initial treatment with doxycycline may enhance efficacy of the subsequent antibiotic therapy.[62] Partners in the preceding 60 days should be treated using the same regimen used for the index patient.[15]

Genital Herpes

Epidemiology

HSV-1 and HSV-2 cause genital herpes.[63] HSV-2 is predominantly an anogenital pathogen whereas HSV-1 also causes orolabial disease. Herpes is not a reportable STI in the US. The 2015-2016 age-adjusted population seroprevalence estimates for HSV-1 was 48.1% and for HSV-2, 12.1%.[64] Seroprevalence of both viruses has been declining. The seroprevalence of HSV-2 was highest among non-Hispanic Black people (34.6%) followed by Mexican American people (9.4%), non-Hispanic White people (8.1%), and lowest among non-Hispanic Asian people (3.8%).[64] People aged 40 through 49 years had 21.2% seroprevalence vs 0.8% among those aged 14 through 19 years, and women had a seroprevalence of 15.9% vs 8.2% in men.[64]

Twenty-five percent of incident HSV-1 infections in the 15- through 49-year age group are estimated to be genital and approximately 85% are presumed due to oral-genital transmission.[65] Among 3438 women, men, and transgender women who have sex with men, HSV-1 was a more common cause of genital herpes than HSV-2 (2.5 vs 1.1 per 100 person-years).[66] Preexisting HSV-2 infections may provide some protection against acquiring new HSV-1 infections, whereas preexisting HSV-1 infections may decrease the probability of new symptomatic HSV-2 infections. For example, in 174 adolescent girls, the prevalence of HSV-2 symptomatic infection was 8.3% among HSV-1 seropositive girls compared with 33% among HSV-1 seronegative girls.[67]

Clinical Presentations

Seventy percent of infected people are asymptomatic and unaware of their diagnosis.[68] After a 4- to 7-day incubation, patients with a symptomatic initial infection with either HSV-1 or HSV-2 present with multiple, painful (95%-99%), bilateral (77%-82%), erythematous lesions that may progress through papular, vesicular, and ulcerative stages.[68] Lesions have a mean duration of 16.5 to 19.7 days but may persist for weeks.[68] Headache, fever, and lymphadenopathy occur in 39% to 68% of patients during the initial infection. Meningitis may occur in severe infection (16% of patients with incident HSV-1 and 26% with incident HSV-2) and urinary retention may develop. Symptomatic recurrences may be preceded in 43% to 53% of patients by a localized prodrome (eg, itching or burning) and are more frequent with HSV-2.[68] During the year after an initial infection, the median number of symptomatic recurrences for HSV-1 and HSV-2 are 1.3 and 4.0, respectively.[68] Symptoms of recurrent infections are less severe and often resolve within 5 to 10 days, compared with symptoms during the primary infection. Up to 25% of patients who present with symptoms for the first time may not have a recently acquired infection.[69] Encephalitis (more common with HSV-1 infection) and meningitis (more common with HSV-2 infection) may occur during primary infection or anytime thereafter.

Testing and Screening for HSV

NAATs (eg, PCR) performed on swabs from lesions have a sensitivity of 96.7% to 100% (Table 1).[70,71] Culture sensitivity ranges from 30% to 70% and is used when NAATs are unavailable or for antiviral susceptibility testing.[70] When lesions are absent, serological testing can be used to detect IgG antibodies to the glycoprotein-G type–specific antigen. IgG antibodies are usually detectable 2 weeks to 3 months following initial infection. Limitations in the performance characteristics of these assays have been reported: In one study, the specificity of the enzyme immunoassay to detect a HSV-2 infection was 39.8% when the enzyme immunoassay index value was less than 3.0.[72] Consequently, a confirmatory test using the HSV-2 Biokit or Western blot should always be performed after an initial enzyme immunoassay index value of less than 3.0.[15] IgM antibodies may be present in the setting of reactivation disease and testing for IgM antibodies is not recommended.[15] Screening for HSV-1 and HSV- 2 is not routinely recommended because of limitations in the sensitivity and specificity of serological tests, the lack of curative therapy, and the lack of high-quality data demonstrating a reduction in transmission of infection to partners of individuals who are aware of their serostatus.[15]

Treatment and Prevention

Oral and parenteral antivirals are available (acyclovir, valacyclovir, or famciclovir), but none cure the HSV infection (Table 3).[73] Although their efficacy in treating symptoms is equivalent, the frequency of dosing and pricing vary. Antivirals may be used to treat symptoms and reduce rates of recurrences (Table 3).[15] In patients with primary infection, the initial 10-day course of antiviral therapy can be extended by 1 week if lesions persist.[15] Shorter courses are needed for recurrences. Topical antiviral medications lack efficacy and may increase antiviral resistance. There are no licensed preventive or therapeutic vaccines.

Greater viral shedding is associated with higher rates of transmission.[74] Greater shedding occurs after a recent infection,

when lesions are present, with HSV-2 infection, and in immunocompromised persons. In a study with an overall HSV-2 incidence of 7.4 per 100 person-years, male condoms decreased male-to-female transmission by 30% over time, but condoms are less effective at preventing female-to-male-transmission.[75,76] A clinical trial involving 1484 participants randomized to receive 500 mg of valacyclovir once daily or placebo found that valacyclovir combined with condom use reduced new HSV-2 infections by 48%, from 3.6% to 1.9%, compared with placebo.[77] In pregnant women who have a history of symptomatic recurrences, antiviral suppressive therapy with acyclovir, beginning at 36 weeks 'gestation, may be considered.[78]

Trichomonas

Epidemiology

Trichomonas, caused by the protozoan *Trichomonas vaginalis*, is the most prevalent nonviral STI in the US, with an estimated prevalence of 1.2% in men and women aged 18 to 59 years who participated in the 2013-2014 National Health and Nutrition Examination Survey in 2014.[79] The prevalence is higher among women who are Black (8.9%) and among women living with HIV (17.4%).[79,80] In contrast to most other STIs, prevalence may be similar or higher in women older than 40 years, and infection is rare among men and transgender women who have sex with men.

Clinical Presentations

Trichomonas is asymptomatic in approximately 85% of women and 77% of men.[81] Trichomonas causes urethritis, epididymitis, or prostatitis in men, and symptoms may include dysuria and urethral discharge. Trichomonas can infect the vagina, urethra, endocervix, and Skene and Bartholin glands in women. Common symptoms include dysuria, vaginal discharge, and vaginal or vulvar irritation. Among women living with HIV, trichomonas has been associated with pelvic inflammatory disease. Coplitis macularis or "strawberry cervix," in which the cervix has a punctate erythematous appearance, may be observed in approximately 5% of infected women.[81]

Testing and Screening

NAATs are the preferred and most sensitive diagnostic tests are FDA cleared for testing on vaginal, endocervical, or urine samples in women (Table 1).[15] Despite the lack of FDA clearance for testing in men, NAATS may be performed on urine, urethral swabs, or penile meatal swabs if the laboratory has completed Clinical Laboratory Improvement Amendments (CLIA) validation.[15] Trichomonas is commonly diagnosed in women via microscopy (ie, "wet mount"), but the sensitivity is only 51% to 65% for vaginal specimens.[82] The Papanicolaou smear has a 61% sensitivity for diagnosing trichomonas compared with culture.[83] Culture is not widely available, but is necessary to determine antimicrobial susceptibility. A rapid antigen test using a vaginal swab that is FDA cleared and CLIA-waived for testing women has a sensitivity of approximately 82% to 90%.[82] Annual screening is recommended in women with HIV infection and may be considered for other women receiving care in high-prevalence settings or with multiple sex partners, transactional sex, drug misuse, or a history of STI or incarceration (Table 2).[15]

Treatment and Prevention

First-line treatment includes a 2-g single dose of oral metronidazole in men and 500 mg of oral metronidazole twice daily for 7 days for women (Table 3).[15,84] For people with persistent infections, defined as an infection that is not cleared following the use of an approved antibiotic regimen in the absence of reinfection, longer and higher doses of metronidazole or tinidazole may be considered. Appropriate higher doses for persistent infections are 2 g daily of metronidazole or tinidazole for 7 days. Tinidazole is a nitroimidazole with a longer half-life than metronidazole that achieves higher tissue concentrations. If a treatment repeatedly fails with the higher doses of metronidazole or tinidazole, a sample should be sent to the CDC for nitroimidazole-resistance testing.[15] Concurrent treatment of all sex partners is recommended.

Limitations

This review has several limitations. First, only studies published in English were included. Second, relevant publications may have been missed. Third, not all aspects of each STI were covered. Fourth, important conditions such as human papillomavirus and bacterial vaginosis were not included.

Conclusions

Approximately 1 in 5 adults in the US had an STI in 2018. Rates of gonorrhea, chlamydia, and syphilis in the US have increased, while rates of HSV-1 and HSV-2 have declined. Ceftriaxone, doxycycline, penicillin, moxifloxacin, and the nitroimidazoles are effective treatments for gonorrhea, chlamydia, syphilis, *M genitalium*, and trichomoniasis, respectively, but antimicrobial resistance limits oral therapies for gonorrhea and *M genitalium*, and no cure is available for genital herpes.

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