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Sexually Transmitted Infections Treatment Guidelines, 2021

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Sexually Transmitted Infections Treatment Guidelines, 2021

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Summary

These guidelines for the treatment of persons who have or are at risk for sexually transmitted infections (STIs) were updated by CDC after consultation with professionals knowledgeable in the field of STIs who met in Atlanta, Georgia, June 11–14, 2019. The information in this report updates the 2015 guidelines. These guidelines discuss 1) updated recommendations for treatment of Neisseria gonorrhoeae, Chlamydia trachomatis*, and* Trichomonas vaginalis*; 2) addition of metronidazole to the recommended treatment regimen for pelvic inflammatory disease; 3) alternative treatment options for bacterial vaginosis; 4) management of* Mycoplasma genitalium*; 5) human papillomavirus vaccine recommendations and counseling messages; 6) expanded risk factors for syphilis testing among pregnant women; 7) one-time testing for hepatitis C infection; 8) evaluation of men who have sex with men after sexual assault; and 9) two-step testing for serologic diagnosis of genital herpes simplex virus. Physicians and other health care providers can use these guidelines to assist in prevention and treatment of STIs.*

Introduction

The term "sexually transmitted infection" (STI) refers to a pathogen that causes infection through sexual contact, whereas the term "sexually transmitted disease" (STD) refers to a recognizable disease state that has developed from an infection. Physicians and other health care providers have a crucial role in preventing and treating STIs. These guidelines are intended to assist with that effort. Although the guidelines emphasize treatment, prevention strategies and diagnostic recommendations also are discussed.

This report updates *Sexually Transmitted Diseases Treatment Guidelines, 2015* (*1*) and should be regarded as a source of clinical guidance rather than prescriptive standards. Health care providers should always consider the clinical circumstances of each person in the context of local disease prevalence. These guidelines are applicable to any patient care setting that serves persons at risk for STIs, including family planning clinics, HIV care clinics, correctional health care settings, private physicians' offices, Federally Qualified Health Centers, clinics for adolescent care, and other primary care facilities. These guidelines are focused on treatment and counseling and do not address other community services and interventions that are essential to STI and HIV prevention efforts.

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These STI treatment guidelines complement *Recommendations for Providing Quality Sexually Transmitted Diseases Clinical Services, 2020* (*2*) regarding quality clinical services for STIs in primary care and STD specialty care settings. This guidance specifies operational determinants of quality services in various clinical settings, describes on-site treatment and partner services, and indicates when STI-related conditions should be managed through consultation with or referral to a specialist.

Methods

These guidelines were developed by CDC staff who worked with subject matter experts with expertise in STI clinical management from other federal agencies, nongovernmental academic and research institutions, and professional medical organizations. CDC staff identified governmental and nongovernmental subject matter experts on the basis of their expertise and assisted them in developing questions to guide individual literature reviews. CDC staff informed the subject matter experts that they were being consulted to exchange information and observations and to obtain their individual input. All subject matter experts disclosed potential conflicts of interest. STI Treatment Guidelines, 2021, Work Group members are listed at the end of this report.

In 2018, CDC staff identified key questions about treatment and clinical management to guide an update of the 2015 STD treatment guidelines (*1*). To answer these questions and synthesize new information available since publication of the 2015 guidelines, subject matter experts and CDC staff

collaborated to conduct systematic literature reviews by using an extensive MEDLINE database evidence-based approach for each section of the 2015 guidelines (e.g., using English-language published abstracts and peer reviewed journal articles). These systematic reviews were focused on four principal outcomes of STI therapy for each disease or infection: 1) treatment of infection on the basis of microbiologic eradication; 2) alleviation of signs and symptoms; 3) prevention of sequelae; and 4) prevention of transmission, including advantages (e.g., cost-effectiveness, single-dose formulations, and directly observed therapy) and disadvantages (e.g., adverse effects) of specific regimens. The outcome of the literature reviews guided development of background materials, including tables of evidence from peer-reviewed publications summarizing the type of study (e.g., randomized controlled trial or case series), study population and setting, treatments or other interventions, outcome measures assessed, reported findings, and weaknesses and biases in study design and analysis.

In June 2019, the subject matter experts presented their assessments of the literature reviews at an in-person meeting of governmental and nongovernmental participants. Each key question was discussed and pertinent publications were reviewed in terms of strengths, weaknesses, and relevance. Participants evaluated the quality of evidence, provided their input, and discussed findings in the context of the modified rating system used by the U.S. Preventive Services Task Force (USPSTF). The discussions were informal and not structured to reach consensus. CDC staff also reviewed the publications from other professional organizations, including the American College of Obstetricians and Gynecologists (ACOG), USPSTF, the American Cancer Society (ACS), the American Society for Colposcopy and Cervical Pathology (ASCCP), and the Advisory Committee on Immunization Practices (ACIP). The discussion culminated in a list of participants' opinions on all the key STI topic areas for consideration by CDC. (More detailed descriptions of the key questions, search terms, systematic search, evidence tables, and review process are available at https://www.cdc.gov/std/treatment-guidelines/default.htm).

CDC staff then independently reviewed the tables of evidence prepared by the subject matter experts, individual comments from the participants and professional organizations, and existing guidelines from other organizations to determine whether revisions to the 2015 STD treatment guidelines were warranted. CDC staff ranked evidence as high, medium, and low on the basis of each study's strengths and weaknesses according to the USPSTF ratings (https://www.uspreventiveservicestaskforce.org/uspstf/us-preventive-services-task-force-ratings). CDC staff then developed draft recommendations that were peer reviewed by public health and clinical experts as defined by the Office of Management and Budget for influential scientific information. A public webinar was held to provide an overview of the draft recommendations and invite questions and comments on the draft recommendations. The peer review comments, webinar, questions, and responses were considered by CDC staff in developing the final recommendations for the updated STI treatment guidelines. Recommendations for HIV, hepatitis C, cervical cancer screening, STI screening in pregnancy, human papillomavirus (HPV) testing, and hepatitis A virus (HAV) and hepatitis B virus (HBV) vaccination were developed after CDC staff reviewed existing published recommendations. The English-language literature was searched periodically by CDC staff to identify subsequently published articles warranting consideration.

Throughout this report, the evidence used as the basis for specific recommendations is discussed briefly. Publication of comprehensive, annotated discussions of such evidence is planned in a supplemental issue of the journal *Clinical Infectious Diseases* after publication of the treatment guidelines. When more than one therapeutic regimen is recommended and the listed regimens have similar efficacy and similar rates of intolerance or toxicity, the recommendations are listed alphabetically. If differences are specified, regimens are prioritized on the basis of these differences. Recommended regimens should be used primarily; alternative regimens can be considered in instances of notable drug allergy or other medical contraindications to the recommended regimens. Alternative regimens are considered inferior to recommended regimens on the basis of available evidence regarding the principal outcomes and disadvantages of the regimens.

Clinical Prevention Guidance

Prevention and control of STIs are based on the following five major strategies (*3*):

1. Accurate risk assessment and education and counseling of persons at risk regarding ways to avoid STIs through changes in sexual behaviors and use of recommended prevention services
2. Pre-exposure vaccination for vaccine-preventable STIs
3. Identification of persons with an asymptomatic infection and persons with symptoms associated with an STI
4. Effective diagnosis, treatment, counseling, and follow-up of persons who are infected with an STI
5. Evaluation, treatment, and counseling of sex partners of persons who are infected with an STI

STI and HIV Infection Risk Assessment

Primary prevention of STIs includes assessment of behavioral risk (i.e., assessing the sexual behaviors that can place persons at risk for infection) and biologic risk (i.e., testing for risk markers for STI and HIV acquisition or transmission). As part of the clinical encounter, health care providers should routinely obtain sexual histories from their patients and address risk reduction as indicated in this report. Guidance for obtaining a sexual history is available at the Division of STD Prevention resource page (https://www.cdc.gov/std/treatment/resources.htm) and in the curriculum provided by the National Network of STD Clinical Prevention Training Centers (https://www.nnptc.org). Effective interviewing and counseling skills, characterized by respect, compassion, and a nonjudgmental attitude toward all patients, are essential to obtaining a thorough sexual history and delivering effective prevention messages. Effective techniques for facilitating rapport with patients include using open-ended questions (e.g., "Tell me about any new sex partners you've had since your last visit" and "What has your experience with using condoms been like?"); understandable, nonjudgmental language (e.g., "What gender are your sex partners?"and "Have you ever had a sore or scab on your penis?"); and normalizing language (e.g., "Some of my patients have difficulty using a condom with every sex act. How is it for you?"). The "Five P's" approach to obtaining a sexual history is one strategy for eliciting information about the key areas of interest (Box 1). In addition, health care professionals can consider assessing sexual history by asking patients such questions as, "Do you have any questions or concerns about your sexual health?" Additional information about gaining cultural competency when working with certain populations (e.g., gay, bisexual, or other men who have sex with men [MSM]; women who have sex with women [WSW] or with women and men [WSWM]; or transgender men and women or adolescents) is available in sections of these guidelines related to these populations.

In addition to obtaining a behavioral risk assessment, a comprehensive STI and HIV risk assessment should include STI screening as recommended in these guidelines because STIs are biologic markers of risk, particularly for HIV acquisition and transmission among certain MSM. In most clinical settings, STI screening is an essential and underused component of an STI and HIV risk assessment. Persons seeking treatment or evaluation for a particular STI should be screened for HIV and other STIs as indicated by community prevalence and individual risk factors (see Chlamydial Infections; Gonococcal Infections; Syphilis). Persons should be informed about all the tests for STIs they are receiving and notified about tests for common STIs (e.g., genital herpes,

BOX 1. The Five P's approach for health care providers obtaining sexual histories: partners, practices, protection from sexually transmitted infections, past history of sexually transmitted infections, and pregnancy intention

1. Partners
- "Are you currently having sex of any kind?"
- "What is the gender(s) of your partner(s)?"

2. Practices
- "To understand any risks for sexually transmitted infections (STIs), I need to ask more specific questions about the kind of sex you have had recently."
- "What kind of sexual contact do you have or have you had?"
  - "Do you have vaginal sex, meaning 'penis in vagina' sex?"
  - "Do you have anal sex, meaning 'penis in rectum/anus' sex?"
  - "Do you have oral sex, meaning 'mouth on penis/vagina'?"

3. Protection from STIs
- "Do you and your partner(s) discuss prevention of STIs and human immunodeficiency virus (HIV)?"
- "Do you and your partner(s) discuss getting tested?"
- For condoms:
  - "What protection methods do you use? In what situations do you use condoms?"

4. Past history of STIs
- "Have you ever been tested for STIs and HIV?"
- "Have you ever been diagnosed with an STI in the past?"
- "Have any of your partners had an STI?"

Additional questions for identifying HIV and viral hepatitis risk:
- "Have you or any of your partner(s) ever injected drugs?"
- "Is there anything about your sexual health that you have questions about?"

5. Pregnancy intention
- "Do you think you would like to have (more) children in the future?"
- "How important is it to you to prevent pregnancy (until then)?"
- "Are you or your partner using contraception or practicing any form of birth control?"
- "Would you like to talk about ways to prevent pregnancy?"

trichomoniasis, *Mycoplasma genitalium*, and HPV) that are available but not being performed and reasons why they are not always indicated. Persons should be informed of their test results and recommendations for future testing. Efforts should be made to ensure that all persons receive STI care regardless of personal circumstances (e.g., ability to pay, citizenship or immigration status, gender identity, language spoken, or specific sex practices).

STI and HIV Infection Prevention Counseling

After obtaining a sexual history from their patients, all providers should encourage risk reduction by offering prevention counseling. Prevention counseling is most effective if provided in a nonjudgmental and empathetic manner appropriate to the patient's culture, language, sex and gender identity, sexual orientation, age, and developmental level. Prevention counseling for STIs and HIV should be offered to all sexually active adolescents and to all adults who have received an STI diagnosis, have had an STI during the previous year, or have had multiple sex partners. USPSTF recommends intensive behavioral counseling for all sexually active adolescents and for adults at increased risk for STIs and HIV (*4*). Such interactive counseling, which can be resource intensive, is directed at a person's risk, the situations in which risk occurs, and the use of personalized goal-setting strategies. One such approach, known as client-centered STI and HIV prevention counseling, involves tailoring a discussion of risk reduction to the person's situation. Although one large study in STI clinics (Project RESPECT) demonstrated that this approach was associated with lower acquisition of curable STIs (e.g., trichomoniasis, chlamydia, gonorrhea, and syphilis) (*5*), another study conducted 10 years later in the same settings but different contexts (Project AWARE) did not replicate this result (*6*).

With the challenges that intensive behavioral counseling poses, health care professionals might find brief prevention messages and those delivered through video or in a group session to be more accessible for the client. A review of 11 studies evaluated brief prevention messages delivered by providers and health counselors and reported them to be feasible and to decrease subsequent STIs in STD clinic settings (*7*) and HIV care settings (*8*). Other approaches use motivational interviewing to move clients toward achievable risk-reduction goals. Client-centered counseling and motivational interviewing can be used effectively by clinicians and staff trained in these approaches. CDC provides additional information on these and other effective behavioral interventions at https://www.cdc.gov/std/program/interventions.htm. Training in client-centered counseling and motivational interviewing is available through the STD National Network of Prevention Training Centers (https://www.nnptc.org).

In addition to one-on-one STI and HIV prevention counseling, videos and large group presentations can provide explicit information concerning STIs and reducing disease transmission (e.g., how to use condoms consistently and correctly and the importance of routine screening). Group-based strategies have been effective in reducing the occurrence of STIs among persons at risk, including those attending STD clinics (*9*). Brief, online, electronic-learning modules for young MSM have been reported to be effective in reducing incident STIs and offer a convenient client platform for effective interventions (*10*). Because the incidence of certain STIs, most notably syphilis, is higher among persons with HIV infection, use of client-centered STI counseling for persons with HIV continues to be encouraged by public health agencies and other health organizations (https://www.cdc.gov/std/statistics/2019/default.htm). A 2014 guideline from CDC, the Health Resources and Services Administration, and the National Institutes of Health recommends that clinical and nonclinical providers assess a person's behavioral and biologic risks for acquiring or transmitting STIs and HIV, including having sex without condoms, having recent STIs, and having partners recently treated for STIs (https://stacks.cdc.gov/view/cdc/44064). That federal guideline is for clinical and nonclinical providers to offer or make referral for regular screening for multiple STIs, on-site STI treatment when indicated, and risk-reduction interventions tailored to the person's risks. Brief risk-reduction counseling delivered by medical providers during HIV primary care visits, coupled with routine STI screening, has been reported to reduce STI incidence among persons with HIV infection (*8*). Other specific methods have been designed for the HIV care setting (https://www.cdc.gov/hiv/effective-interventions/index.html).

Primary Prevention Methods

Pre-Exposure Vaccination

Pre-exposure vaccination is one of the most effective methods for preventing transmission of HPV, HAV, and HBV, all of which can be sexually transmitted. HPV vaccination is recommended routinely for males and females aged 11 or 12 years and can be administered beginning at age 9 years. HPV vaccination is recommended through age 26 years for those not previously vaccinated (*11*). Sharing clinical decision-making about HPV vaccination is recommended for certain adults aged 27–45 years who are not adequately vaccinated in accordance with existing guidance (https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html).

Hepatitis B vaccination is recommended for all unvaccinated, uninfected persons who are sexually active with more than one partner or are being evaluated or treated for an STI (*12*). In addition, hepatitis A and B vaccines are recommended for MSM, persons who inject drugs, persons with chronic liver disease, and persons with HIV or hepatitis C infections who have not had hepatitis A or hepatitis B (*12*). HAV vaccine is also recommended for persons who are homeless (*13*). Details regarding HAV and HBV vaccination, including routine childhood vaccination, are available at https://www.cdc.gov/hepatitis and at the ACIP website (https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/index.html).

Condoms

External Condoms

When used consistently and correctly, external latex condoms, also known as male condoms, are effective in preventing the sexual transmission of HIV infection (http://www.ashasexualhealth.org/pdfs/Male_and_Female_Condoms.pdf). In heterosexual HIV mixed-status relationships (i.e., those involving one infected and one uninfected partner) in which condoms were used consistently, HIV-negative partners were 71%–80% less likely to become infected with HIV, compared with persons in similar relationships in which condoms were not used (*14*,*15*). Two analyses of MSM mixed-status couple studies estimated the protective effect of condom use to be 70% and 91%, respectively (*16*,*17*). Moreover, studies demonstrate that consistent condom use reduces the risk for other STIs, including chlamydia, gonorrhea, hepatitis B, and trichomoniasis (*18*–*21*). By limiting lower genital tract infections, condoms also might reduce the risk for pelvic inflammatory disease (PID) among women (*22*). In addition, consistent and correct use of latex condoms reduces the risk for HPV infection and HPV-associated diseases, genital herpes, syphilis, and chancroid when the infected area or site of potential exposure is covered (*23*–*27*). Additional information is available at https://www.cdc.gov/condomeffectiveness/index.html and www.factsaboutcondoms.com/professional.php. Condoms are regulated as medical devices and are subject to random sampling and testing by the Food and Drug Administration (FDA). Each latex condom manufactured in the United States is tested electronically for holes before packaging. The rate of condom breakage during sexual intercourse and withdrawal in the United States is approximately two broken condoms per 100 condoms. Rates of breakage and slippage might be slightly higher during anal intercourse (*28*,*29*). The failure of condoms to protect against STIs or unintended pregnancy usually results from inconsistent or incorrect use rather than condom breakage (*30*). Users should check the expiration or manufacture date on the box or individual package. Latex condoms should not be used beyond their expiration date or >5 years after the manufacturing date. Condoms made of materials other than latex are available in the United States and can be classified into two general categories: 1) polyurethane, polyisoprene, or other synthetic condoms and 2) natural membrane condoms.

Polyurethane external condoms provide protection against STIs and HIV and pregnancy comparable to that of latex condoms (*20*,*31*). These can be substituted for latex condoms by persons with latex sensitivity, are typically more resistant to deterioration, and are compatible with use of both oil-based and water-based lubricants. The effectiveness of other synthetic external condoms to prevent STIs has not been extensively studied, and FDA labeling restricts their recommended use to persons who are sensitive to or allergic to latex. Natural membrane condoms (frequently called natural skin condoms or [incorrectly] lambskin condoms) are made from lamb cecum and can have pores up to 1,500 nm in diameter. Although these pores do not allow the passage of sperm, they are more than 10 times the diameter of HIV and more than 25 times that of HBV. Moreover, laboratory studies demonstrate that sexual transmission of viruses, including HBV, herpes simplex virus (HSV), and HIV, can occur with natural membrane condoms (*31*). Therefore, natural membrane condoms are not recommended for prevention of STIs and HIV.

Providers should advise that condoms must be used consistently and correctly to be effective in preventing STIs and HIV while noting that any condom use is better than no condom use. Providing instructions about the correct use of condoms can be useful. Communicating the following recommendations can help ensure that patients use external condoms correctly:

- Use a new condom with each sex act (i.e., oral, vaginal, and anal).
- Carefully handle the condom to avoid damaging it with fingernails, teeth, or other sharp objects.
- Put the condom on after the penis is erect and before any genital, oral, or anal contact with the partner.
- Use only water-based or silicone-based lubricants (e.g., K-Y Jelly, Astroglide, AquaLube, or glycerin) with latex condoms. Oil-based lubricants (e.g., petroleum jelly, shortening, mineral oil, massage oils, body lotions, or cooking oil) can weaken latex and should not be used; however, oil-based lubricants typically can be used with polyurethane or other synthetic condoms.
- Ensure adequate lubrication during vaginal and anal sex, which might require using exogenous water-based lubricants.
- Hold the condom firmly against the base of the penis during withdrawal, and withdraw while the penis is still erect to prevent the condom from slipping off.

Additional information about external condoms is available at https://www.cdc.gov/condomeffectiveness.

Internal Condoms

Condoms for internal vaginal use, also known as female condoms, are available worldwide (e.g., the FC2 Female Condom, Reddy condom, Cupid female condom, and Woman's condom) (*31*,*32*). Use of internal condoms can provide protection from acquisition and transmission of STIs, although data are limited. Internal condoms are more costly compared with external condoms; however, they offer the advantage of being controlled by the receptive partner as an STI and HIV prevention method, and the newer versions might be acceptable to all persons. Although the internal condom also has been used during receptive anal intercourse, efficacy associated with this practice remains unknown (*33*). Additional information about the internal condom is available at http://www.ashasexualhealth.org/pdfs/Male_and_Female_Condoms.pdf.

Cervical Diaphragms

In observational studies, diaphragm use has been demonstrated to protect against cervical gonorrhea, chlamydia, and trichomoniasis (*34*). However, a trial examining the effect of a diaphragm plus lubricant on HIV acquisition among women in Africa reported no additional protective effect when compared with the use of male condoms alone. Likewise, no difference by study arm in the rate of acquisition of chlamydia, gonorrhea, or herpes occurred (*35*,*36*). Diaphragms should not be relied on as the sole source of protection against HIV and other STIs.

Multipurpose Prevention Technologies

Methods that combine STI and HIV prevention with pregnancy prevention are known as multipurpose prevention technologies (MPTs) (*37*) (https://www.who.int/reproductivehealth/topics/linkages/mpts/en). Internal and external condoms are both examples of MPTs because they are effective prevention measures when used correctly for STI and HIV transmission or pregnancy prevention. The multicenter Evidence for Contraception Options and HIV Outcomes (ECHO) trial observed no statistically significant differences in HIV incidence rates among women randomly assigned to one of three contraceptive methods (depot medroxyprogesterone acetate [DMPA], levonorgestrel implant, and copper-containing intrauterine device [IUD]); however, rates of HIV infection were high in all groups, indicating a need for MPTs (*38*). Development of MPTs is complex and ongoing; products under study include microbicides with contraceptive devices (e.g., tenofovir with a vaginal ring contraceptive delivery package) and other innovative methods (*39*).

Topical Microbicides and Spermicides

Nonspecific topical microbicides are ineffective for preventing HIV infection (*40*–*45*). Tenofovir gel has been studied for prevention of herpes simplex virus 2 (HSV-2) and HIV infections (*46*,*47*). Adherence can be low (*48*), and prevention of HIV infection, especially among women, has not been demonstrated (*47*,*49*).Vaginal rings containing dapivirine have provided some reduction in HIV infection (*50*,*51*). For men and transgender women who have anal intercourse, tenofovir gel appears safe when applied before and after anal sex (*52*). Spermicides containing nonoxynol-9 (N-9) might disrupt genital or rectal epithelium and have been associated with an increased risk for HIV infection. Condoms with N-9 are no more effective than condoms without N-9; therefore, N-9 alone or in a condom is not recommended for STI and HIV prevention (*40*). N-9 use also has been associated with an increased risk for bacterial urinary tract infections among women (*53*,*54*).

Nonbarrier Contraception, Female Surgical Sterilization, and Hysterectomy

Contraceptive methods that are not mechanical barriers offer no protection against HIV or other STIs. The ECHO study observed no differences in HIV incidence rates among women randomly assigned to DMPA, levonorgestrel implant, or copper-containing IUD contraceptive methods (*38*). A systematic review of epidemiologic evidence reported that the majority of studies demonstrated no association between use of oral contraceptives and HIV acquisition among women (*55*). Whether hormonal contraception alters a woman's risk for other STIs is uncertain (*56*,*57*).

Sexually active women who use contraceptive methods other than condoms should be counseled about STI and HIV infection prevention measures. These include pre-exposure prophylaxis (PrEP) and postexposure prophylaxis (PEP), limiting the number of sex partners, and correct and consistent use of condoms.

Emergency Contraception

Unprotected intercourse exposes women to risks for STIs and unplanned pregnancy. Providers should offer counseling about the option of emergency contraception if pregnancy is not desired. Options for emergency contraception in the United States include copper-containing IUDs and emergency contraceptive pills (ECPs) (*58*,*59*). More information is available at https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2015/09/emergency-contraception?utm_source=redirect&utm_medium=web&utm_campaign=otn. ECPs are available in the following formulations: ulipristal

acetate in a single dose (30 mg) available by prescription, levonorgestrel in a single dose (1.5 mg) available over the counter or by prescription, or a combined estrogen and progestin pill regimen. Insertion of a copper-containing IUD ≤5 days after unprotected sex can reduce pregnancy risk from a sex act by approximately 99% (*60*). ECPs are most efficacious when initiated as soon as possible after unprotected sex. Ulipristal acetate is effective ≤5 days after unprotected sex, and levonorgestrel is most effective ≤3 days after unprotected sex but has some efficacy at ≤5 days. ECPs are ineffective (but not harmful) if the woman is already pregnant (*61*). A 2019 Cochrane review summarized the efficacy, safety, and convenience of different emergency contraception methods (*61*).

More information about emergency contraception is available in *Contraceptive Technology, 21st Edition* (*31*), in the 2016 U.S. Selected Practice Recommendations (U.S. SPR) for Contraceptive Use (emergency contraception) available at https://www.cdc.gov/reproductivehealth/contraception/mmwr/spr/emergency.html, and in the 2016 U.S. Medical Eligibility Criteria (U.S. MEC) for Contraceptive Use (copper IUDs for emergency contraception) available at https://www.cdc.gov/reproductivehealth/contraception/mmwr/mec/appendixj.html.

Providers should educate males and females about emergency contraception, especially if other methods of contraception were used incorrectly or not at all and pregnancy is not desired (*62*). An advance supply of ECPs can be provided or prescribed so that ECPs will be available when needed (*59*).

Male Circumcision

Male circumcision reduces the risk for HIV infection and certain STIs among heterosexual men. Three randomized, controlled trials performed in regions of sub-Saharan Africa, where generalized HIV epidemics involving predominantly heterosexual transmission were occurring, demonstrated that male circumcision reduces the risk for HIV acquisition among men by 50%–60% (*63*–*65*). In those trials, circumcision also was protective against other STIs, including high-risk genital HPV infection and genital herpes (*66*–*68*). Follow-up studies have demonstrated sustained benefit of circumcision for HIV prevention (*69*) and that the effect is not mediated solely through a reduction in HSV-2 infection or genital ulcer disease (GUD) (*70*).

The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) recommend that male circumcision efforts be scaled up as an effective intervention for preventing heterosexually acquired HIV infection (*71*) in countries with hyperendemic and generalized HIV epidemics within the context of ensuring universal access to comprehensive HIV prevention, treatment, care, and support (https://www.afro.who.int/publications/voluntary-medical-male-circumcision-hiv-prevention). In the United States, the American Academy of Pediatrics (AAP) recommends that newborn male circumcision be available to families that desire it because the benefits of the procedure, including prevention of penile cancers, urinary tract infections, GUD, and HIV infection, outweigh the risks. ACOG has also endorsed AAP's policy statement. In light of these benefits, the American Urological Association states that male circumcision should be considered an option for risk reduction, among other strategies (*72*). Additional information for providers counseling male patients and parents regarding male circumcision for preventing HIV, STIs, and other adverse health outcomes is available at https://www.cdc.gov/hiv/risk/male-circumcision.html.

No definitive data exist to determine whether male circumcision reduces HIV acquisition among MSM, although one meta-analysis of 62 observational studies reported that circumcision was protective against HIV acquisition in low- to middle-income countries but not in high-income countries (*73*). Further studies are needed to confirm any potential benefit of male circumcision for this population.

Pre-Exposure Prophylaxis for HIV

Daily oral antiretroviral PrEP with a fixed-dose combination of emtricitabine (FTC) and either tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) have demonstrated safety (*74*) and a substantial reduction in the rate of HIV acquisition for MSM (*75*). TDF/FTC has demonstrated safety and efficacy for mixed-status heterosexual couples (*76*) and heterosexual men and women recruited individually (*77*); however, no evidence is yet available regarding TAF/FTC among heterosexually active women. In addition, one clinical trial involving persons who inject drugs (*78*) and one involving heterosexual mixed-status couples (*76*) demonstrated substantial efficacy and safety of daily oral PrEP with TDF alone. High adherence to oral PrEP was strongly associated with protection from HIV infection. Studies conducted with MSM have demonstrated that taking PrEP at specific times before and after sexual intercourse was effective in preventing HIV; however, less experience exits with this regimen, it is not FDA cleared, and it has not been studied among other populations (*79*).

Comprehensive clinical practice guidelines are available for providers in prescribing PrEP to reduce the risk for HIV infection (*80*). Among HIV-negative sexually active men and women, bacterial STIs are key indicators of risk for HIV acquisition. Studies have documented the risk for HIV acquisition among MSM within 1 year after infection with rectal gonorrhea or chlamydia (one in 15 men), primary or secondary syphilis (one in 18), and among men with no

rectal STI or syphilis infection (one in 53) (*81*–*83*). Sexually active adults and adolescents should be screened for STIs (e.g., chlamydia, gonorrhea, and syphilis) in accordance with recommendations, and persons with infection should be offered PrEP. The USPSTF recommends that persons at risk for HIV acquisition be offered PrEP (*84*). Persons at risk for HIV acquisition include HIV-negative persons whose sexual partner or partners have HIV infection (especially if viral load is detectable or unknown), persons who have had gonorrhea or syphilis during the previous 6 months, and injecting drug users who share injection equipment (*84*). Clinical practice guidelines recommend STI screening for persons taking PrEP (*80*) because increased rates of STI acquisition have been described (*85*–*87*).

Pre-Exposure Prophylaxis for STIs

Providing HSV treatment to persons with HIV and HSV infection has not demonstrated benefit in reducing HIV acquisition among uninfected partners. A large randomized controlled trial evaluated mixed-status heterosexual couples among the partners with HIV infection who also were seropositive for HSV-2 (*88*). Use of acyclovir had no effect on HIV transmission. These findings are consistent with a previous trial that reported no benefit of acyclovir in preventing HIV acquisition among persons seropositive for HSV-2 (*89*).

Doxycycline prophylaxis has been examined for preventing bacterial STIs. In a pilot study, 30 MSM living with HIV with previous syphilis (two or more episodes since HIV diagnosis) were randomly assigned to doxycycline 100 mg for 48 weeks versus a financial incentive–based behavioral intervention (*90*). That study demonstrated a 73% reduction in any bacterial STI at any site, without substantial differences in sexual behavior. Additional studies examining doxycycline prophylaxis are under way or in development (*91*).

Postexposure Prophylaxis for HIV and STIs

Guidelines for using PEP aimed at preventing HIV and other STIs as a result of sexual exposure are available at https://www.cdc.gov/hiv/pdf/programresources/cdc-hiv-npep-guidelines.pdf. Sexually active persons seeking HIV PEP should be evaluated for PrEP after completing their PEP course and testing negative for HIV. HIV PEP is also discussed elsewhere in this report (see Sexual Assault and Abuse and STIs). Genital hygiene methods (e.g., vaginal washing and douching) after sexual exposure are ineffective in protecting against HIV and STIs and might increase the risk for bacterial vaginosis (BV), certain STIs, and HIV infection (*92*).

STI PEP in the form of doxycycline 200 mg taken after unprotected anal sex has been studied among MSM and transgender women; results demonstrated reduction in incident chlamydia and syphilis by 70% and 73%, respectively, but no effect on gonorrhea (*93*). Other studies are under way or in development regarding doxycycline prophylaxis for bacterial STIs (*91*). No long-term data are available regarding the impact of STI PEP on antimicrobial resistance and the microbiome. Further studies are needed to determine whether STI PEP is an effective and beneficial strategy for STI prevention.

HIV Treatment as Prevention: Antiretroviral Treatment of Persons with HIV to Prevent HIV Among Partners

In 2011, the randomized controlled trial HPTN 052 demonstrated that, among HIV mixed-status heterosexual couples, HIV antiretroviral therapy (ART) for the infected partner decreased the risk for transmission to the uninfected partner by 96% (*94*). Therefore, ART not only is beneficial to the health of persons with HIV infection, it also reduces the risk for transmission. Additional studies of HIV mixed-status couples, heterosexual and MSM couples (PARTNER study), and MSM couples (Opposites Attract and PARTNERS2 studies) reported that patients with HIV taking ART who maintain an undetectable viral load demonstrate no risk for transmitting HIV to their HIV-negative sex partners (*95*–*97*). For those reasons, ART should be offered to all persons with HIV infection to obtain viral suppression. Detailed guidance regarding ART regimens is available in the U.S. Department of Health and Human Services' HIV treatment guidelines (*98*).

HIV Seroadaptive Strategies

Seroadaptive strategies for HIV prevention have largely originated within communities of MSM. They are predicated on knowledge of self and partner HIV status. One specific seroadaptive practice is serosorting, which includes limiting anal sex without a condom to partners with the same HIV status as their own or choosing to selectively use condoms with HIV mixed-status partners. Another practice among mixed-status couples is seropositioning, in which the person with HIV infection is the receptive partner for anal intercourse. Observational studies have consistently reported that serosorting confers greater risk for HIV infection than consistent condom use but has lower risk compared with anal intercourse without a condom and without serosorting (*99*–*101*). Serosorting practices have been associated with increased risk for STIs, including chlamydia and gonorrhea (*102*,*103*).

Serosorting is not recommended for the following reasons: many MSM who have HIV infection do not know they have HIV because they have not been tested recently, men's assumptions about the HIV status of their partners might be wrong, and some men with HIV infection might not disclose or might misrepresent their HIV status. All of these factors increase

the risk that serosorting can lead to HIV infection. Serosorting has not been studied among heterosexually active persons.

Abstinence and Reduction of Number of Sex Partners

Abstinence from oral, vaginal, and anal sex and participating in a long-term, mutually monogamous relationship with a partner known to be uninfected are prevention approaches to avoid transmission of STIs. For persons who are being treated for an STI (or whose partners are undergoing treatment), counseling that encourages abstinence from sexual intercourse until completion of the entire course of medication is vital for preventing reinfection. A trial conducted among women regarding the effectiveness of counseling messages when patients have cervicitis or vaginal discharge demonstrated that women whose sex partners have used condoms might benefit from a hierarchical message that includes condoms but women without such experience might benefit more from an abstinence-only message (*104*). A more comprehensive discussion of abstinence and other sexual practices that can help persons reduce their risk for STIs is available in *Contraceptive Technology, 21st Edition* (*31*).

Partner Services

The term "partner services" refers to a continuum of clinical evaluation, counseling, diagnostic testing, and treatment designed to increase the number of infected persons brought to treatment and to reduce transmission among sexual networks. This continuum includes efforts of health departments, medical providers, and patients themselves. The term "public health partner services" refers to efforts by public health departments to identify the sex and needle-sharing partners of infected persons to ensure their medical evaluation and treatment. Health departments are increasingly incorporating referral to additional services, as indicated, into the partner services continuum. Aside from the general benefit to patients and partners, service referrals and linkage can mitigate the circumstances that increase risk for future STI and HIV acquisition.

The types and comprehensiveness of public health partner services and the specific STIs for which they are offered vary by public health agency, their resources, and the geographic prevalence of STIs. In most areas of the United States, health departments routinely attempt to provide partner services to all persons with infectious syphilis (primary or secondary) and persons with a new diagnosis of HIV infection. Health departments should provide partner services for persons who might have cephalosporin-resistant gonorrhea. In contrast, relatively few U.S. health departments routinely provide STI partner services to persons with gonorrhea, chlamydia, trichomoniasis, or other STIs (*105*). Because STI diagnoses often can serve as risk markers for HIV acquisition (*83*), public health services might include follow-up of MSM with an STI to offer HIV PrEP. Public health services can also include HIV and STI prevention interventions including HIV and STI testing, linkage and relinkage of persons with HIV infection to HIV care clinics, and referral of partners of persons with STIs or HIV infection to HIV PrEP, as indicated (*106–109*). Clinicians should familiarize themselves with public health practices in their area; however, in most instances, providers should understand that responsibility for discussing the treatment of partners of persons with STIs rests with the diagnosing provider and the patient. State laws require a good faith effort by the provider to inform partners, and providers should familiarize themselves with public health laws.

Clinicians who do not notify partners of patients directly can still provide partner services by counseling infected persons and providing them with written information and medication to give to their partners (if recommended and allowable by state law), directly evaluating and treating sex partners, and cooperating with state and local health departments. Clinicians' efforts to ensure treatment of patients' sex partners can reduce the risk for reinfection and potentially diminish transmission of STIs (*110*). Therefore, clinicians should encourage all persons with STIs to notify their sex partners and urge them to seek medical evaluation and treatment. Exceptions to this practice include circumstances posing a risk for intimate partner violence (*111*). Available data are limited regarding the rate of intimate partner violence directly attributable to partner notification (*112*,*113*); however, because of the reported prevalence of intimate partner violence in the general population (*114*), providers should consider the potential risk before notifying partners of persons or encouraging partner notification. Time spent counseling patients about the importance of notifying partners is associated with improved notification outcomes (*115*). When possible, clinicians should advise persons to bring their primary sex partner with them when returning for treatment and should concurrently treat both persons. Although this approach can be effective for a main partner (*116*,*117*), it might not be a feasible approach for additional sex partners. Evidence indicates that providing patients with written information to share with sex partners can increase rates of partner treatment (*110*).

Certain health departments now use technology (e.g., email, texting, mobile applications, and social media outlets) to facilitate partner services for locating and notifying the sex partners of persons with STIs, including HIV (*118*,*119*). Patients now have the option to use Internet sites to send anonymous email or text messages advising partners of their exposure to an STI (*120*); anonymous notification via the

Internet is considered better than no notification at all. However, because the extent to which these sites affect partner notification and treatment is uncertain, patients should be encouraged to notify their partners in person or by telephone, email, or text message; alternatively, patients can authorize a medical provider or public health professional to notify their sex partners.

Expedited Partner Therapy

Expedited partner therapy (EPT) is a harm-reduction strategy and the clinical practice of treating the sex partners of persons with diagnosed chlamydia or gonorrhea, who are unable or unlikely to seek timely treatment, by providing medications or prescriptions to the patient as allowable by law. Patients then provide partners with these therapies without the health care provider having examined the partner (https://www.cdc.gov/std/ept). Unless prohibited by law or other regulations, medical providers should routinely offer EPT to patients with chlamydia when the provider cannot ensure that all of a patient's sex partners from the previous 60 days will seek timely treatment. If the patient has not had sex during the 60 days before diagnosis, providers should offer EPT for the patient's most recent sex partner. Because EPT must be an oral regimen and current gonorrhea treatment involves an injection, EPT for gonorrhea should be offered to partners unlikely to access timely evaluation after linkage is explored. EPT is legal in the majority of states but varies by chlamydial or gonococcal infection. Providers should visit https://www.cdc.gov/std/ept to obtain updated information for their state. Providing patients with packaged oral medication is the preferred approach because the efficacy of EPT using prescriptions has not been evaluated, obstacles to EPT can exist at the pharmacy level (*121*,*122*), and many persons (especially adolescents) do not fill the prescriptions provided to them by a sex partner (*123*,*124*). Medication or prescriptions provided for EPT should be accompanied by educational materials for the partner, including treatment instructions, warnings about taking medications (e.g., if the partner is pregnant or has an allergy to the medication), general health counseling, and a statement advising that partners seek medical evaluation as soon as possible for HIV infection and any symptoms of STIs, particularly PID.

Evidence supporting EPT is based on three U.S. clinical trials involving heterosexual men and women with chlamydia or gonorrhea (*125*–*127*). All three trials reported that more partners were treated when patients were offered EPT. Two reported statistically significant decreases in the rate of reinfection, and one observed a lower risk for persistent or recurrent infection that was statistically nonsignificant. A fourth trial in the United Kingdom did not demonstrate a difference in the risk for reinfection or in the numbers of partners treated between persons offered EPT and those advised to notify their sex partners (*128*). U.S. trials and a meta-analysis of EPT revealed that the magnitude of reduction in reinfection of index patients, compared with patient referral, differed according to the STI and the sex of the index patient (*110*,*125*–*127*). However, across trials, reductions in chlamydia prevalence at follow-up were approximately 20%, and reductions in gonorrhea were approximately 50% at follow-up.

Existing data indicate that EPT also might have a role in partner management for trichomoniasis; however, no partner management intervention has been reported to be more effective than any other in reducing trichomoniasis reinfection rates (*129*,*130*). No data support use of EPT in the routine management of patients with syphilis.

Data are limited regarding use of EPT for gonococcal or chlamydial infections among MSM, compared with heterosexuals (*131*,*132*). Published studies, including recent data regarding extragenital testing, indicated that male partners of MSM with diagnosed gonorrhea or chlamydia might have other bacterial STIs (gonorrhea or syphilis) or HIV (*133*–*135*). Studies have reported that 5% of MSM have a new diagnosis of HIV when evaluated as partners of men with gonococcal or chlamydial infections (*133*,*134*); however, more recent data indicate that, in certain settings, the frequency of HIV infection is much lower (*135*). Considering limited data and potential for other bacterial STIs among MSM partners, shared clinical decision-making regarding EPT is recommended. All persons who receive bacterial STI diagnoses and their sex partners, particularly MSM, should be tested for HIV, and those at risk for HIV infection should be offered HIV PrEP (https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf).

Reporting and Confidentiality

Accurate and timely reporting of STIs is integral to public health efforts in assessing morbidity trends, allocating limited resources, and assisting local health authorities with partner notification and treatment. STI and HIV/AIDS cases should be reported in accordance with state and local statutory requirements. Syphilis (including congenital syphilis), gonorrhea, chlamydia, chancroid, and HIV are reportable diseases in every state. Because the requirements for reporting other STIs differ by state, clinicians should be familiar with the reporting requirements applicable within their jurisdictions.

Reporting can be provider based, laboratory based, or both. Clinicians who are unsure of state and local reporting requirements should seek advice from state or local health department STI programs. STI and HIV reports are kept confidential. In most jurisdictions, such reports are protected

by statute or regulation. Before conducting a follow-up of a person with a positive STI test result, public health professionals should consult the patient's health care provider, if possible, to inform them of the purpose of the public health visit, verify the diagnosis, determine the treatments received, and ascertain the best approaches to patient follow-up.

Retesting After Treatment to Detect Repeat Infections

Retesting 3 months after diagnosis of chlamydia, gonorrhea, or trichomoniasis can detect repeat infection and potentially can be used to enhance population-based prevention (*136*,*137*). Any person who has a positive test for chlamydia or gonorrhea, along with women who have a positive test for trichomonas, should be rescreened 3 months after treatment. Any person who receives a syphilis diagnosis should undergo follow-up serologic syphilis testing per current recommendations and follow-up testing for HIV (see Syphilis). Additional information regarding retesting is available elsewhere in this report (see Chlamydial Infections; Gonococcal Infections; Syphilis; Trichomoniasis).

STI Detection Among Special Populations

Pregnant Women

Intrauterine or perinatally transmitted STIs can have debilitating effects on pregnant women, their fetuses, and their partners. All pregnant women and their sex partners should be asked about STIs, counseled about the possibility of perinatal infections, and provided access to recommended screening and treatment, if needed.

Recommendations for screening pregnant women for STIs to detect asymptomatic infections are based on disease severity and sequelae, prevalence among the population, costs, medicolegal considerations (e.g., state laws), and other factors. The following screening recommendations for pregnant women summarize clinical guidelines from federal agencies and medical professional organizations.

Screening Recommendations

HIV Infection

All pregnant women in the United States should be tested for HIV at the first prenatal visit, even if they have been previously tested (*138*). Testing pregnant women for HIV and prompt linkage to care of women with HIV infection are vital for women's health and reducing perinatal transmission of HIV through ART and obstetrical interventions. HIV testing should be offered as part of the routine panel of prenatal tests (i.e., opt-out testing). For women who decline HIV testing, providers should address their concerns and, when appropriate, continue to encourage testing. Partners of pregnant patients should be offered HIV testing if their status is unknown (*139*).

Retesting in the third trimester (preferably before 36 weeks' gestation) is recommended for women at high risk for acquiring HIV infection. Examples of women at high risk include those who inject drugs, have STIs during pregnancy, have multiple sex partners during pregnancy, have a new sex partner during pregnancy, or have partners with HIV infection; those who are receiving care in health care facilities in settings with HIV incidence ≥1 per 1,000 women per year; those who are incarcerated; those who live in areas with high rates of HIV infection; or those who have signs or symptoms of acute HIV infection (e.g., fever, lymphadenopathy, skin rash, myalgia, arthralgia, headache, oral ulcers, leukopenia, thrombocytopenia, or transaminase elevation) (*140*).

Rapid HIV testing should be performed for any woman in labor who has not been tested for HIV during pregnancy or whose HIV status is unknown, unless she declines. If a rapid HIV test result is positive, ART should be administered without waiting for the results of confirmatory testing (https://clinicalinfo.hiv.gov/sites/default/files/inline-files/PerinatalGL.pdf).

Syphilis

During 2012–2019, congenital syphilis rates in the United States increased from 8.4 to 48.5 cases per 100,000 births, a 477.4% increase (*141*). At least 45 states have a prenatal syphilis testing requirement, with high variability among those requirements (*142*). In the United States, all pregnant women should be screened for syphilis at the first prenatal visit, even if they have been tested previously (*143*). Prenatal screening for syphilis has been reported to be suboptimal in the United States (*144*,*145*). Testing in the third trimester and at delivery can prevent congenital syphilis cases (*146*,*147*). Partners of pregnant women with syphilis should be evaluated, tested, and treated.

When access to prenatal care is not optimal, a stat rapid plasma reagin (RPR) card test and treatment, if that test is reactive, should be administered at the time that a pregnancy is confirmed or when the pregnancy test is performed, if follow-up is uncertain. Pregnant women should be retested for syphilis at 28 weeks' gestation and at delivery if the mother lives in a community with high syphilis rates or is at risk for syphilis acquisition during pregnancy (e.g., misuses drugs or has an STI during pregnancy, having multiple sex partners, having a new sex partner, or having a sex partner with an STI). Neonates should not be discharged from the hospital unless

the syphilis serologic status of the mother has been determined at least once during pregnancy. Any woman who delivers a stillborn infant should be tested for syphilis.

Hepatitis B

All pregnant women should be routinely tested for hepatitis B surface antigen (HBsAg) at the first prenatal visit even if they have been previously vaccinated or tested (*148*). Women who are HBsAg positive should be provided with, or referred for, counseling and medical management. Women who are HBsAg negative but at risk for HBV infection should be vaccinated. Women who were not screened prenatally, those who engage in behaviors that put them at high risk for infection (e.g., having had more than one sex partner during the previous 6 months, having been evaluated or treated for an STI, having had recent or current injection drug use, or having an HBsAg-positive sex partner), and those with clinical hepatitis should be tested at the time of admission to the hospital for delivery. To avoid misinterpreting a transient positive HBsAg result during the 21 days after vaccination, HBsAg testing should be performed before vaccine administration. All laboratories that conduct HBsAg tests should test initially reactive specimens with a licensed neutralizing confirmatory test. When pregnant women are tested for HBsAg at the time of admission for delivery, shortened testing protocols can be used, and initially reactive results should prompt expedited administration of immunoprophylaxis to neonates (*148*). Pregnant women who are HBsAg positive should be reported to the local or state health department to ensure that they are entered into a case-management system and that timely and age-appropriate prophylaxis is provided to their infants. Information concerning the pregnant woman's HBsAg status should be provided to the hospital where delivery is planned and to the health care provider who will care for the newborn. In addition, household and sexual contacts of women who are HBsAg positive should be vaccinated.

Chlamydia

All pregnant women aged <25 years as well as older women at increased risk for chlamydia (e.g., those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI) should be routinely screened for *Chlamydia trachomatis* at the first prenatal visit (*149*). Pregnant women who remain at increased risk for chlamydial infection also should be retested during the third trimester to prevent maternal postnatal complications and chlamydial infection in the neonate. Pregnant women identified as having chlamydia should be treated immediately and have a test of cure to document chlamydial eradication by a nucleic acid amplification test (NAAT) 4 weeks after treatment. All persons diagnosed with a chlamydial infection should be rescreened 3 months after treatment.

Gonorrhea

All pregnant women aged <25 years as well as women aged ≥25 years at increased risk for gonorrhea (e.g., those with other STIs during pregnancy or those with a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI or is exchanging sex for money or drugs) should be screened for *Neisseria gonorrhoeae* at the first prenatal visit (*149*). Pregnant women who remain at high risk for gonococcal infection also should be retested during the third trimester to prevent maternal postnatal complications and gonococcal infection in the neonate. Clinicians should consider the communities they serve and might choose to consult local public health authorities for guidance on identifying groups that are more vulnerable to gonorrhea acquisition on the basis of local disease prevalence. Gonococcal infection, in particular, is concentrated among specific geographic locations and communities (https://www.cdc.gov/std/statistics/2019/default.htm). Pregnant women identified as having gonorrhea should be treated immediately. All persons diagnosed with gonorrhea should be rescreened 3 months after treatment.

Hepatitis C Virus

The rate of hepatitis C virus (HCV) infection has increased among pregnant women in recent years (*150–153*). HCV screening should be performed for all pregnant women during each pregnancy, except in settings where the HCV infection (HCV positivity) rate is <0.1% (*154–156*). The most important risk factor for HCV infection is past or current injecting drug use (*157*). Additional risk factors include having had a blood transfusion or organ transplantation before July 1992, having received clotting factor concentrates produced before 1987, having received an unregulated tattoo, having been on long-term hemodialysis, having other percutaneous exposures, or having HIV infection. All women with HCV infection should receive counseling, supportive care, and linkage to care (https://www.hcvguidelines.org). No vaccine is available for preventing HCV transmission.

Cervical Cancer

Pregnant women should undergo cervical cancer screening and at the same frequency as nonpregnant women; however, management differs slightly during pregnancy (*158*). Colposcopy is recommended for the same indications during pregnancy as for nonpregnant women. However, biopsies may be deferred, and endocervical sampling should not be performed. Treatment should not be performed during pregnancy unless cancer is detected.

Bacterial Vaginosis, Trichomoniasis, and Genital Herpes

Evidence does not support routine screening for BV among asymptomatic pregnant women at high risk for preterm delivery (*159*). Symptomatic women should be evaluated and treated (see Bacterial Vaginosis). Evidence does not support routine screening for *Trichomonas vaginalis* among asymptomatic pregnant women. Women who report symptoms should be evaluated and treated (see Trichomoniasis). In addition, evidence does not support routine HSV-2 serologic screening among asymptomatic pregnant women. However, type-specific serologic tests might be useful for identifying pregnant women at risk for HSV-2 infection and for guiding counseling regarding the risk for acquiring genital herpes during pregnancy. Routine serial cultures for HSV are not indicated for women in the third trimester who have a history of recurrent genital herpes.

For more detailed discussions of STI screening and treatment among pregnant women, refer to the following references: *Screening for HIV Infection: U.S. Preventive Services Task Force Recommendation Statement* (*138*); *Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States* (https://clinicalinfo.hiv.gov/sites/default/files/inline-files/PerinatalGL.pdf); *Guidelines for Perinatal Care* (*160*); *Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices* (*12*); *Screening for Chlamydia and Gonorrhea: U.S. Preventive Services Task Force Recommendation Statement* (*149*); *Screening for Bacterial Vaginosis in Pregnant Persons to Prevent Preterm Delivery: U.S. Preventive Services Task Force Recommendation Statement* (*159*); *Screening for Syphilis Infection in Pregnant Women: U.S. Preventive Services Task Force Recommendation Statement* (*161*); *Serologic Screening for Genital Herpes Infection: U.S. Preventive Services Task Force Recommendation Statement* (*162*); *Screening for HIV Infection in Pregnant Women: A Systematic Review for the U.S. Preventive Services Task Force* (*163*); *Screening for Hepatitis B in Pregnant Women: Updated Evidence Report and Systematic Review for the U.S. Preventive Services Task Force* (*164*); and *CDC Recommendations for Hepatitis C Screening Among Adults — United States, 2020* (*156*).

Adolescents

In the United States, prevalence rates of certain STIs are highest among adolescents and young adults (*141*). For example, reported rates of chlamydia and gonorrhea are highest among females during their adolescent and young adult years, and many persons acquire HPV infection during that time.

Persons who initiate sex early in adolescence are at higher risk for STIs, as are adolescents living in detention facilities; those receiving services at STD clinics; those who are involved in commercial sex exploitation or survival sex and are exchanging sex for drugs, money, food, or housing; young males who have sex with males (YMSM); transgender youths; and youths with disabilities, substance misuse, or mental health disorders. Factors contributing to increased vulnerability to STIs during adolescence include having multiple sex partners, having sequential sex partnerships of limited duration or concurrent partnerships, failing to use barrier protection consistently and correctly, having lower socioeconomic status, and facing multiple obstacles to accessing health care (*141*,*165*).

All 50 states and the District of Columbia explicitly allow minors to consent for their own STI services. No state requires parental consent for STI care, although the age at which a minor can provide consent for specified health care services (i.e., HPV vaccination and HIV testing and treatment) varies among states. In 2019, a total of 18 states allowed but did not require physicians to notify parents of a minor's receipt of STI services, including states where minors can legally provide their own consent to the service (https://www.cdc.gov/hiv/policies/law/states/minors.html).

Protecting confidentiality for STI care, particularly for adolescents enrolled in private health insurance plans, presents multiple problems. After a claim has been submitted, many states mandate that health plans provide a written statement to the beneficiary indicating the service performed, the charges covered, what the insurer allows, and the amount for which the patient is responsible (i.e., explanation of benefits [EOB]) (*166*–*169*). In addition, federal laws obligate notices to beneficiaries when claims are denied, including alerting beneficiaries who need to pay for care until the allowable deductible is reached. For STI testing and treatment-related care, an EOB or medical bill that is received by a parent might disclose services provided and list STI laboratory tests performed or treatment administered. Some states have instituted mechanisms for protecting adolescents' confidentiality and limiting EOBs. Additional risks to confidentiality breaches can inadvertently occur through electronic health records, although technology continues to evolve to assist with ensuring confidential care. AAP and the Society for Adolescent Health and Medicine (SAHM) have published guidance on strategies to address emerging risks for confidentiality breaches associated with health information technology (*169*).

AAP and the SAHM recommend that providers have time alone with their adolescent patients that includes assessment for sexual behavior. The AAP recommendations are available at https://services.aap.org/en/news-room/campaigns-and-toolkits/adolescent-health-care and the SAHM

recommendations are available at https://www.adolescenthealth.org/My-SAHM/Login-or-Create-an-Account.aspx?returnurl=%2fResources%2fClinical-Care-Resources%2fConfidentiality.aspx. Discussions concerning sexual behavior should be tailored for the patient's developmental level and be aimed at identifying risk behaviors (e.g., multiple partners; oral, anal, or vaginal sex; or drug misuse behaviors). Careful, nonjudgmental, and thorough counseling is particularly vital for adolescents who might not feel comfortable acknowledging their engagement in behaviors that make them more vulnerable to acquiring STIs.

Screening Recommendations

Recommendations for screening adolescents for STIs to detect asymptomatic infections are based on disease severity and sequelae, prevalence among the population, costs, medicolegal considerations (e.g., state laws), and other factors. Routine laboratory screening for common STIs is indicated for all sexually active adolescents. The following screening recommendations summarize published clinical prevention guidelines for sexually active adolescents from federal agencies and medical professional organizations.

Chlamydia

Routine screening for *C. trachomatis* infection on an annual basis is recommended for all sexually active females aged <25 years (*149*). Rectal chlamydial testing can be considered for females on the basis of reported sexual behaviors and exposure, through shared clinical decision-making between the patient and the provider (*170*,*171*). Evidence is insufficient to recommend routine screening for *C. trachomatis* among sexually active young males, on the basis of efficacy and cost-effectiveness. However, screening of sexually active young males should be considered in clinical settings serving populations of young men with a high prevalence of chlamydial infections (e.g., adolescent service clinics, correctional facilities, and STD clinics). Chlamydia screening, including pharyngeal or rectal testing, should be offered to all YMSM at least annually on the basis of sexual behavior and anatomic site of exposure (see Men Who Have Sex with Men).

Gonorrhea

Routine screening for *N. gonorrhoeae* on an annual basis is recommended for all sexually active females aged <25 years (*149*). Extragenital gonorrhea screening (pharyngeal or rectal) can be considered for females on the basis of reported sexual behaviors and exposure, through shared clinical-decision between the patient and the provider (*170*,*171*). Gonococcal infection is more prevalent among certain geographic locations and communities (*141*). Clinicians should consider the communities they serve and consult local public health authorities for guidance regarding identifying groups that are more vulnerable to gonorrhea acquisition on the basis of local disease prevalence. Evidence is insufficient to recommend routine screening, on the basis of efficacy and cost-effectiveness, for *N. gonorrhoeae* among asymptomatic sexually active young males who have sex with females only. Screening for gonorrhea, including pharyngeal or rectal testing, should be offered to YMSM at least annually (see Men Who Have Sex with Men).

Providers might consider opt-out chlamydia and gonorrhea screening (i.e., the patient is notified that testing will be performed unless the patient declines, regardless of reported sexual activity) for adolescent and young adult females during clinical encounters. Cost-effectiveness analyses indicate that opt-out chlamydia screening among adolescent and young adult females might substantially increase screening, be cost-saving (*172*), and identify infections among patients who do not disclose sexual behavior (*173*).

HIV Infection

HIV screening should be discussed and offered to all adolescents. Frequency of repeat screenings should be based on the patient's sexual behaviors and the local disease prevelance (*138*). Persons with HIV infection should receive prevention counseling and linkage to care before leaving the testing site.

Cervical Cancer

Guidelines from USPSTF and ACOG recommend that cervical cancer screening begin at age 21 years (*174*,*175*). This recommendation is based on the low incidence of cervical cancer and limited usefulness of screening for cervical cancer among adolescents (*176*). In contrast, the 2020 ACS guidelines recommend that cervical cancer screening begin at age 25 years with HPV testing. This change is recommended because the incidence of invasive cervical cancer in women aged <25 years is decreasing because of vaccination (*177*). Adolescents with HIV infection who have initiated sexual intercourse should have cervical screening cytology in accordance with HIV/AIDS guidelines (https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/human-papillomavirus-disease?view=full).

Other Sexually Transmitted Infections

YMSM and pregnant females should be routinely screened for syphilis (see Pregnant Women; Men Who Have Sex with Men). Local disease prevalence can help guide decision-making regarding screening for *T. vaginalis*, especially among adolescent females in certain areas. Routine screening of adolescents and young adults who are asymptomatic for certain STIs (e.g., syphilis, trichomoniasis, BV, HSV, HAV, and HBV) is not typically recommended.

Primary Prevention Recommendations

Primary prevention and anticipatory guidance for recognizing symptoms and behaviors associated with STIs are strategies that should be incorporated into all types of health care visits for adolescents and young adults. The following recommendations for primary prevention of STIs (i.e., vaccination and counseling) are based on published clinical guidelines for sexually active adolescents and young adults from federal agencies and medical professional organizations.

- HPV vaccination is recommended through age 26 years for those not vaccinated previously at the routine age of 11 or 12 years (https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html).
- The HBV vaccination series is recommended for all adolescents and young adults who have not previously received the universal HBV vaccine series during childhood (*12*).
- The HAV vaccination series should be offered to adolescents and young adults as well as those who have not previously received the universal HAV vaccine series during childhood (https://www.cdc.gov/vaccines/schedules/hcp/imz/child-indications.html#note-hepa).
- Information regarding HIV transmission, prevention, testing, and implications of infection should be regarded as an essential component of the anticipatory guidance provided to all adolescents and young adults as part of routine health care.
- CDC and USPSTF recommend offering HIV PrEP to adolescents weighing ≥35 kg and adults who are HIV negative and at substantial risk for HIV infection (*80*,*178*). YMSM should be offered PrEP in youth-friendly settings with tailored adherence support (e.g., text messaging and visits per existing guidelines). Indications for PrEP, initial and follow-up prescribing guidance, and laboratory testing recommendations are the same for adolescents and adults (https://www.cdc.gov/hiv/risk/prep).
- Medical providers who care for adolescents and young adults should integrate sexuality education into clinical practice. Health care providers should counsel adolescents about the sexual behaviors that are associated with risk for acquiring STIs and should educate patients regarding evidence-based prevention strategies, which includes a discussion about abstinence and other risk-reduction behaviors (e.g., consistent and correct condom use and reduction in the number of sex partners including concurrent partners). Interactive counseling approaches (e.g., patient-centered counseling and motivational interviewing) are effective STI and HIV prevention strategies and are recommended by USPSTF. Educational materials (e.g., handouts, pamphlets, and videos) can reinforce office-based educational efforts.

Children

Management of children who have STIs requires close cooperation among clinicians, laboratorians, and child-protection authorities. Official investigations, when indicated, should be initiated promptly. Certain diseases (e.g., gonorrhea, syphilis, HIV, chlamydia, and trichomoniasis), if acquired after the neonatal period, strongly indicate sexual contact. For other diseases (e.g., HSV, HPV and anogenital warts, and vaginitis), the association with sexual contact is not as clear (see Sexual Assault and Abuse and STIs).

Men Who Have Sex with Men

MSM comprise a diverse group in terms of behaviors, identities, and health care needs (*179*). The term "MSM" often is used clinically to refer to sexual behavior alone, regardless of sexual orientation (e.g., a person might identify as heterosexual but still be classified as MSM). Sexual orientation is independent of gender identity. Classification of MSM can vary in the inclusion of transgender men and women on the basis of whether men are defined by sex at birth (i.e., transgender women included) or current gender identity (i.e., transgender men included). Therefore, sexual orientation as well as gender identity of individual persons and their sex partners should be obtained during health care visits. MSM might be at increased risk for HIV and other STIs because of their sexual network or behavioral or biologic factors, including number of concurrent partners, condomless sex, anal sex, or substance use (*180*–*182*). These factors, along with sexual network or higher community disease prevalence, can increase the risk for STIs among MSM compared with other groups (*183*,*184*).

Performing a detailed and comprehensive sexual history is the first step in identifying vulnerability and providing tailored counseling and care (*3*). Factors associated with increased vulnerability to STI acquisition among MSM include having multiple partners, anonymous partners, and concurrent partners (*185*,*186*). Repeat syphilis infections are common and might be associated with HIV infection, substance use (e.g., methamphetamines), Black race, and multiple sex partners (*187*). Similarly, gonorrhea incidence has increased among MSM and might be more likely to display antimicrobial resistance compared with other groups (*188*,*189*). Gonococcal infection among MSM has been associated with similar risk factors to syphilis, including having multiple anonymous partners and substance use, especially methamphetamines (*190*). Disparities in gonococcal infection are also more pronounced among certain racial and ethnic groups of MSM (*141*).

HIV Risk Among Men Who Have Sex with Men

MSM are disproportionately at risk for HIV infection. In the United States, the estimated lifetime risk for HIV infection among MSM is one in six, compared with heterosexual men at one in 524 and heterosexual women at one in 253 (*191*). These disparities are further exacerbated by race and ethnicity, with African American/Black and Hispanic/Latino MSM having a one in two and a one in four lifetime risk for HIV infection, respectively. For HIV, transmission occurs much more readily through receptive anal sex, compared with penile-vaginal sex (*192*). Similar to other STIs, multiple partners, anonymous partners, condomless sex, and substance use are all associated with HIV infection (*193–196*). Importantly, other STIs also might significantly increase the risk for HIV infection (*197–199*). An estimated 10% of new HIV infections were attributable to chlamydial or gonococcal infection (*81*). A substantial number of MSM remain unaware of their HIV diagnosis (*200*). Clinical care involving MSM, including those who have HIV infection, should involve asking about STI-related risk factors and routine STI testing. Clinicians should routinely ask MSM about their sexual behaviors and symptoms consistent with common STIs, including urethral discharge, dysuria, ulcers, rash, lymphadenopathy, and anorectal symptoms that might be consistent with proctitis (e.g., discharge, rectal bleeding, pain on defecation, or pain during anal sex). However, certain STIs are asymptomatic, especially at rectal and pharyngeal sites, and routine testing is recommended. In addition, clinicians should provide education and counseling regarding evidence-based safer-sex approaches that have demonstrated effectiveness in reducing STI incidence (see HIV Infection, Detection, Counseling, and Referral).

Pre-Exposure Prophylaxis for HIV Prevention

PrEP is the use of medications for preventing an infection before exposure. Studies have demonstrated that a daily oral medication TDF/FTC is effective in preventing HIV acquisition, and specifically among MSM (*74*,*75*,*201*). PrEP guidelines provide information regarding sexually active persons who are at substantial risk for acquiring HIV infection (having had anal or vaginal sex during the previous 6 months with either a partner with HIV infection, a bacterial STI in the past 6 months, or inconsistent or no condom use with a sex partner) or persons who inject drugs (injecting partner with HIV infection or sharing injection equipment) (*80*). Those guidelines provide information regarding daily PrEP use for either TDF/FTC (men or women) or tenofovir alafenamide and emtricitabine for MSM. Screening for bacterial STIs should occur at least every 6 months for all sexually active patients and every 3 months among MSM or among patients with ongoing risk behaviors. MSM taking PrEP might compensate for decreased HIV acquisition risk by using condoms less frequently or modifying their behavior in other ways (*202*,*203*), although data regarding this behavior are inconsistent. Studies have reported that MSM taking PrEP have high rates of STIs, and frequent screening is warranted (*204–206*).

Importance of Rectal and Pharyngeal Testing

Rectal and pharyngeal testing by NAAT for gonorrhea and chlamydia is recognized as an important sexual health consideration for MSM. Rectal gonorrhea and chlamydia are associated with HIV infection (*82*,*207*), and men with repeat rectal infections can be at substantially higher risk for HIV acquisition (*208*). Pharyngeal infections with gonorrhea or chlamydia might be a principal source of urethral infections (*209–211*). Studies have demonstrated that among MSM, prevalence of rectal gonorrhea and chlamydia ranges from 0.2% to 24% and 2.1% to 23%, respectively, and prevalence of pharyngeal gonorrhea and chlamydia ranges from 0.5% to 16.5% and 0% to 3.6%, respectively (*171*). Approximately 70% of gonococcal and chlamydial infections might be missed if urogenital-only testing is performed among MSM (*212–216*) because most pharyngeal and rectal infections are asymptomatic. Self-collected swabs have been reported to be an acceptable means of collection for pharyngeal and rectal specimens (*217–219*), which can enhance patient comfort and reduce clinical workloads.

A detailed sexual history should be taken for all MSM to identify anatomic locations exposed to infection for screening. Clinics that provide services for MSM at high risk should consider implementing routine extragenital screening for *N. gonorrhoeae* and *C. trachomatis* infections, and screening is likely to be cost-effective (*220*).

Screening Recommendations

STI screening among MSM has been reported to be suboptimal. In a cross-sectional sample of MSM in the United States, approximately one third reported not having had an STI test during the previous 3 years, and MSM with multiple sex partners reported less frequent screening (*221*). MSM living with HIV infection and engaged in care also experience suboptimal rates of STI testing (*222*,*223*). Limited data exist regarding the optimal frequency of screening for gonorrhea, chlamydia, and syphilis among MSM, with the majority of evidence derived from mathematical modeling. Models from Australia have demonstrated that increasing syphilis screening frequency from two times a year to four times a year resulted in a relative decrease of 84% from peak prevalence (*224*). In a compartmental model applied to different populations in Canada, quarterly syphilis screening averted more than twice

the number of syphilis cases, compared with semiannual screening (*225*). Furthermore, MSM screening coverage needed for eliminating syphilis among a population is substantially reduced from 62% with annual screening to 23% with quarterly screening (*226*,*227*). In an MSM transmission model that explored the impact of HIV PrEP use on STI prevalence, quarterly chlamydia and gonorrhea screening was associated with an 83% reduction in incidence (*205*). The only empiric data available that examined the impact of screening frequency come from an observational cohort of MSM using HIV PrEP in which quarterly screening identified more bacterial STIs, and semiannual screening would have resulted in delayed treatment of 35% of total identified STI infections (*206*). In addition, quarterly screening was reported to have prevented STI exposure in a median of three sex partners per STI infection (*206*). On the basis of available evidence, quarterly screening for gonorrhea, chlamydia, and syphilis for certain sexually active MSM can improve case finding, which can reduce the duration of infection at the population level, reduce ongoing transmission and, ultimately, prevalence among this population (*228*).

Preventive screening for common STIs is indicated for all MSM. The following screening recommendations summarize published federal agency and USPSTF clinical prevention guidelines for MSM and should be performed at least annually.

HIV Infection

HIV serologic testing is indicated if HIV status is unknown or if HIV negative and the patient or their sex partner has had more than one sex partner since the most recent HIV test.

Syphilis

Syphilis serologic testing is indicated to establish whether persons with reactive tests have untreated syphilis, have partially treated syphilis, or are manifesting a slow or inadequate serologic response to recommended previous therapy.

Gonorrhea and Chlamydia

The following testing is recommended for MSM:

- A test for urethral infection* with *N. gonorrhoeae* and *C. trachomatis* among men who have had insertive intercourse during the preceding year (urine NAAT is preferred).
- A test for rectal infection* with *N. gonorrhoeae* and *C. trachomatis* among men who have had receptive anal intercourse during the preceding year (rectal NAAT is preferred).
- A test for pharyngeal infection* with *N. gonorrhoeae* among men who have had receptive oral intercourse during the preceding year (pharyngeal NAAT is preferred).
- Testing for *C. trachomatis* pharyngeal infection is not recommended.

Basing screening practices solely on history might be suboptimal because providers might feel uncomfortable taking a detailed sexual history (*229*), men might also feel uncomfortable sharing personal sexual information with their provider, and rectal and pharyngeal infections can be identified even in the absence of reported risk behaviors (*171*). Furthermore, the role of saliva, kissing, and rimming (i.e., oral-rectal contact) in the transmission of *N. gonorrhoeae* and *C. trachomatis* has not been well studied (*230*–*232*).

Rectal and pharyngeal testing (provider-collected or self-collected specimens) should be performed for all MSM who report exposure at these sites. Testing can be offered to MSM who do not report exposure at these sites after a detailed explanation, due to known underreporting of risk behaviors. All MSM with HIV infection entering care should be screened for gonorrhea and chlamydia at appropriate anatomic sites of exposure as well as for syphilis.

More frequent STI screening (i.e., for syphilis, gonorrhea, and chlamydia) at 3- to 6-month intervals is indicated for MSM, including those taking PrEP and those with HIV infection, if risk behaviors persist or if they or their sex partners have multiple partners. In addition, providers can consider the benefits of offering more frequent HIV screening (e.g., every 3–6 months) to MSM at increased risk for acquiring HIV infection.

Hepatitis B Virus

All MSM should be screened with HBsAg, HBV core antibody, and HBV surface antibody testing to detect HBV infection (*233*). Vaccination against both HAV and HBV is recommended for all MSM for whom previous infection or vaccination cannot be documented. Serologic testing can be considered before vaccinating if the patient's vaccination history is unknown; however, vaccination should not be delayed. Vaccinating persons who have had previous infection or vaccination does not increase the risk for vaccine-related adverse events (see Hepatitis A Virus; Hepatitis B Virus).

Hepatitis C Virus

CDC recommends HCV screening at least once for all adults aged ≥18 years, except in settings where the prevalence of HCV infection (HCV RNA positivity) is <0.1% (*156*). The American Association for the Study of Liver Diseases/Infectious Diseases Society of America guidelines recommend all MSM with HIV infection be screened for HCV during the

* Regardless of condom use during exposure.

initial HIV evaluation and at least annually thereafter (https://www.hcvguidelines.org). More frequent screening depends on ongoing risk behaviors, high-risk sexual behavior, and concomitant ulcerative STIs or STI-related proctitis. Sexual transmission of HCV can occur and is most common among MSM with HIV infection (*234*–*237*). Screening for HCV in this setting is cost-effective (*238*,*239*). Screening should be performed by using HCV antibody assays followed by HCV RNA testing for those with a positive antibody test. Suspicion for acute HCV infection (e.g., clinical evidence of hepatitis and risk behaviors) should prompt consideration for HCV RNA testing, despite a negative antibody test.

Human Papillomavirus

HPV infection and associated conditions (e.g., anogenital warts and anal squamous intraepithelial lesions) are highly prevalent among MSM. The HPV vaccination is recommended for all men, including MSM and transgender persons or immunocompromised males, including those with HIV infection, through age 26 years (*11*). More information is available at https://www.cdc.gov/hpv/downloads/9vhpv-guidance.pdf.

A digital anorectal examination (DARE) should be performed to detect early anal cancer among persons with HIV and MSM without HIV but who have a history of receptive anal intercourse. Data are insufficient to recommend routine anal cancer screening with anal cytology in populations at risk for anal cancer (see Anal Cancer). Health centers that initiate a cytology-based screening program should only do so if referrals to high-resolution anoscopy (HRA) and biopsy are available.

Herpes Simplex Virus-2

Evaluation for HSV-2 infection with type-specific serologic tests also can be considered if infection status is unknown among persons with previously undiagnosed genital tract infection (see Genital Herpes).

Postexposure Prophylaxis and Pre-Exposure Prophylaxis for STI Prevention

Studies have reported that a benefit might be derived from STI PEP and PrEP for STI prevention. One study demonstrated that monthly oral administration of a 1-g dose of azithromycin reduced infection with *N. gonorrhoeae* and *C. trachomatis* but did not decrease the incidence of HIV transmission (*240*). Among MSM, doxycycline taken as PEP in a single oral dose ≤24 hours after sex decreased infection with *Treponema pallidum* and *C. trachomatis;* however, no substantial effect was observed for infection with *N. gonorrhoeae* (*93*). Doxycycline taken as STI PrEP as 100 mg orally once daily also demonstrated a substantial reduction in gonorrhea, chlamydia, and syphilis among MSM (*90*). However, these studies had limitations because of small sample size, short duration of therapy, and concerns about antibiotic resistance, specifically regarding *N. gonorrhoeae* (*241*). Further study is needed to determine the effectiveness of using antimicrobials for STI PrEP or PEP.

Counseling and Education Approaches

Different counseling and STI prevention strategies are needed to effectively engage different groups of MSM. Outreach efforts should be guided by local surveillance efforts and community input. Engaging MSM at risk through social media, specifically online hookup sites, is an important outreach effort to consider. Hookup sites are Internet sites and mobile telephone applications that men might use for meeting other men for sex. Internet use might facilitate sexual encounters and STI transmission among MSM, and many men report using hookup sites to meet partners (*242*–*245*). The ease and accessibility of meeting partners online might reduce stigma and barriers of meeting partners through other settings. Moreover, these sites offer an opportunity for effective STI prevention messaging (*246*), although the cost might be limiting (*247*). Different groups of MSM might use different hookup sites, and efforts should be guided by local community input. Studies have demonstrated the acceptability and feasibility of reaching MSM through these hookup sites to promote STI prevention efforts (*248*,*249*).

Enteric Infections Among Men Who Have Sex with Men

The importance of sexual transmission of enteric pathogens among MSM has been recognized since the 1970s, after the first report of MSM-associated shigellosis was reported in San Francisco (*250*,*251*). Global increases in the incidence of shigellosis among adult MSM have been more recently observed (*252*–*256*). Sporadic outbreaks of *Shigella sonnei* and *Shigella flexneri* have been reported among MSM (*257*–*262*). Transmission occurs through oral-anal contact or sexual contact, and transmission efficiency is enhanced by both biologic or host and behavioral factors. HIV without viral suppression can be an independent risk factor that can contribute to transmission by increasing shedding of the enteric pathogen, increasing susceptibility of the host, or both (*255*,*263*). Surveillance data in England during 2004–2015 demonstrated that 21% of nontravel-associated *Shigella* diagnoses among MSM were among persons with HIV infection (*255*).

Other enteric organisms might also cause disease among MSM through sexual activities leading to oral-anal contact, including bacteria such as *Escherichia coli* (*264*) and

Campylobacter jejuni or *Campylobacter coli* (*265*,*266*); viruses such as HAV (*267*); and parasites such as *Giardia lamblia* or *Entamoeba histolytic*a (*268*,*269*). Behavioral characteristics associated with the sexual transmission of enteric infections are broadly similar to those associated with other STIs (e.g., gonorrhea, syphilis, and lymphogranuloma venereum [LGV]). This includes multiple sex partners and online hookup sites that increase opportunities for sexual mixing, which might create dense sexual networks that facilitate STI transmission among MSM (*270*). Specific behaviors associated with sexually transmitted enteric infections among MSM involve attendance at sex parties and recreational drug use including chem sex (i.e., using crystal methamphetamine, gamma-butyrolactone, or mephedrone before or during sex), which might facilitate condomless sex, group sex, fisting, use of sex toys, and scat play (*253*,*271*). The growing number of sexually transmitted enteric infections might be attributable in part to the emergence of antimicrobial resistance. This is well reported regarding *Shigella* species, for which rapid intercontinental dissemination of a *S. flexneri* 3a lineage with high-level resistance to azithromycin through sexual transmission among MSM (*272*) and clusters of multidrug resistant shigella cases among MSM have recently been reported (*273*). Multidrug-resistant *Campylobacter* species have also been documented (*266*,*274*). For MSM patients with diarrhea, clinicians should request laboratory examinations, including stool culture; provide counseling about the risk for infection with enteric pathogens during sexual activity (oral-anal, oral-genital, anal-genital, and digital-anal contact) that could expose them to enteric pathogens; and choose treatment, when needed, according to antimicrobial drug susceptibility.

Women Who Have Sex with Women and Women Who Have Sex with Women and Men

WSW and WSWM comprise diverse groups with variations in sexual identity, practices, and risk behaviors. Studies indicate that certain WSW, particularly adolescents, young women, and WSWM, might be at increased risk for STIs and HIV on the basis of reported risk behaviors (*275*–*280*). Studies have highlighted the diversity of sexual practices and examined use of protective or risk-reduction strategies among WSW populations (*281*–*283*). Use of barrier protection with female partners (e.g., gloves during digital-genital sex, external condoms with sex toys, and latex or plastic barriers [also known as dental dams for oral-genital sex]) was infrequent in all studies. Although health organizations have online materials directed to patients, few comprehensive and reliable resources of sexual health information for WSW are available (*284*).

Recent studies regarding STI rates among WSW and WSWM indicate that WSWM experience higher rates of STIs than WSW, with rates comparable with women who have sex with men (WSM) in all studies reviewed (*279*,*285*,*286*). These studies indicate that WSW might experience STIs at lower rates than WSWM and WSM, although still at significant rates (*287*). One study reported higher sexual-risk behaviors among adolescent WSWM and WSW than among adolescent WSM (*280*). WSW report reduced knowledge of STI risks (*288*), and both WSW and WSWM experience barriers to care, especially Black WSW and WSWM (*289*,*290*). In addition, a continuum of sexual behaviors reported by WSW and WSWM indicates the need for providers to not assume lower risk for WSW, highlighting the importance of an open discussion about sexual health.

Few data are available regarding the risk for STIs conferred by sex between women; however, transmission risk probably varies by the specific STI and sexual practice (e.g., oral-genital sex; vaginal or anal sex using hands, fingers, or penetrative sex items; and oral-anal sex) (*291*,*292*). Practices involving digital-vaginal or digital-anal contact, particularly with shared penetrative sex items, present a possible means for transmission of infected cervicovaginal or anal secretions. This possibility is most directly supported by reports of shared trichomonas infections (*293*,*294*) and by concordant drug-resistance genotype testing and phylogenetic linkage analysis identifying HIV transmitted sexually between women (*295*,*296*). The majority of WSW (53%–97%) have had sex with men in the past and continue to do so, with 5%–28% of WSW reporting male partners during the previous year (*292*,*297*–*300*).

HPV can be transmitted through skin-to-skin contact, and sexual transmission of HPV likely occurs between WSW (*301*–*303*). HPV DNA has been detected through polymerase chain reaction (PCR)–based methods from the cervix, vagina, and vulva among 13%–30% of WSW (*301*,*302*) and can persist on fomites, including sex toys (*304*). Among WSW who report no lifetime history of sex with men, 26% had antibodies to HPV-16, and 42% had antibodies to HPV-6 (*301*). High-grade squamous intraepithelial lesions (HSIL) and low-grade squamous intraepithelial lesions (LSIL) have been detected on Papanicolaou smears (Pap tests) among WSW who reported no previous sex with men (*301*,*302*). WSWM are at risk for acquiring HPV from both their female partners and male partners and thus are at risk for cervical cancer. Therefore, routine cervical cancer screening should be offered to all women, regardless of sexual orientation or practices, and young adult WSW and WSWM should be offered HPV vaccination in accordance with recommendations (*11*) (https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html).

Genital transmission of HSV-2 between female sex partners is inefficient but can occur. A U.S. population-based survey among women aged 18–59 years demonstrated an HSV-2 seroprevalence of 30% among women reporting same-sex partners during the previous year, 36% among women reporting same-sex partners in their lifetime, and 24% among women reporting no lifetime same-sex behavior (*299*). HSV-2 seroprevalence among women self-identifying as homosexual or lesbian was 8%, similar to a previous clinic-based study of WSW (*299*,*305*) but was 26% among Black WSW in one study (*287*). The relatively frequent practice of orogenital sex among WSW and WSWM might place them at higher risk for genital infection with HSV-1, a hypothesis supported by the recognized association between HSV-1 seropositivity and previous number of female partners. Thus, sexual transmission of HSV-1 and HSV-2 can occur between female sex partners. This information should be communicated to women as part of sexual health counseling.

Trichomonas is a relatively common infection among WSW and WSWM, with prevalence rates higher than for chlamydia or gonorrhea (*306*,*307*), and direct transmission of trichomonas between female partners has been demonstrated (*293*,*294*).

Limited information is available regarding transmission of bacterial STIs between female partners. Transmission of syphilis between female sex partners, probably through oral sex, has been reported. Although the rate of transmission of *C. trachomatis* or *N. gonorrhoeae* between women is unknown, infection also might be acquired from past or current male partners. Data indicate that *C. trachomatis* infection among WSW can occur (*275*,*286*,*308*,*309*). Data are limited regarding gonorrhea rates among WSW and WSWM (*170*). Reports of same-sex behavior among women should not deter providers from offering and providing screening for STIs, including chlamydia, according to guidelines.

BV is common among women, and even more so among women with female partners (*310*–*312*). Epidemiologic data strongly demonstrate that BV is sexually transmitted among women with female partners. Evidence continues to support the association of such sexual behaviors as having a new partner, having a partner with BV, having receptive oral sex, and having digital-vaginal and digital-anal sex with incident BV (*313*,*314*). A study including monogamous couples demonstrated that female sex partners frequently share identical genital *Lactobacillus* strains (*315*). Within a community-based cohort of WSW, extravaginal (i.e., oral and rectal) reservoirs of BV-associated bacteria were a risk factor for incident BV (*316*). Studies have examined the impact of specific sexual practices on the vaginal microflora (*306*,*317*–*319*) and on recurrent (*320*) or incident (*321*,*322*) BV among WSW. A BV pathogenesis study in WSW reported that *Prevotella bivia, Gardnerella vaginalis*, and *Atopobium vaginae* might have substantial roles in development of incident BV (*323*). These studies have continued to support, although have not proven, the hypothesis that sexual behaviors, specific BV-associated bacteria, and possibly exchange of vaginal or extravaginal microbiota (e.g., oral bacterial communities) between partners might be involved in the pathogenesis of BV among WSW.

Although BV is common among WSW, routine screening for asymptomatic BV is not recommended. Results of one randomized trial used a behavioral intervention to reduce persistent BV among WSW through reduced sharing of vaginal fluid on hands or sex toys. Women randomly assigned to the intervention were 50% less likely to report receptive digital-vaginal contact without gloves than control subjects, and they reported sharing sex toys infrequently. However, these women had no reduction in persistent BV at 1 month posttreatment and no reduction in incident episodes of recurrent BV (*324*). Trials have not been reported examining the benefits of treating female partners of women with BV. Recurrent BV among WSW is associated with having a same-sex partner and a lack of condom use (*325*). Increasing awareness of signs and symptoms of BV among women and encouraging healthy sexual practices (e.g., avoiding shared sex toys, cleaning shared sex toys, and using barriers) might benefit women and their partners.

Sexually active women are at risk for acquiring bacterial, viral, and protozoal STIs from current and previous partners, both male and female. WSW should not be presumed to be at low or no risk for STIs on the basis of their sexual orientation. Report of same-sex behavior among women should not deter providers from considering and performing screening for STIs and cervical cancer according to guidelines. Effective screening requires that care providers and their female patients engage in a comprehensive and open discussion of sexual and behavioral risks that extends beyond sexual identity.

Transgender and Gender Diverse Persons

Transgender persons often experience high rates of stigma and socioeconomic and structural barriers to care that negatively affect health care usage and increase susceptibility to HIV and STIs (*326*–*332*). Persons who are transgender have a gender identity that differs from the sex that they were assigned at birth (*333*,*334*). Transgender women (also known as trans women, transfeminine persons, or women of transgender experience) are women who were assigned male sex at birth (born with male anatomy). Transgender men (also known as trans men, transmasculine persons, or men of transgender experience) are men who were assigned female sex at birth (i.e., born with female anatomy). In addition, certain persons might identify outside the gender binary of male or female or move back and

forth between different gender identities and use such terms as "gender nonbinary," "genderqueer," or "gender fluid" to describe themselves. Persons who use terms such as "agender" or "null gender" do not identify with having any gender. The term "cisgender" is used to describe persons who identify with their assigned sex at birth. Prevalence studies of transgender persons among the overall population have been limited and often are based on small convenience samples.

Gender identity is independent of sexual orientation. Sexual orientation identities among transgender persons are diverse. Persons who are transgender or gender diverse might have sex with cisgender men, cisgender women, or other transgender or gender nonbinary persons.

Clinical Environment Assessment

Providers should create welcoming environments that facilitate disclosure of gender identity and sexual orientation. Clinics should document gender identity and sex assigned at birth for all patients to improve sexual health care for transgender and gender nonbinary persons. Assessment of gender identity and sex assigned at birth has been validated among diverse populations, has been reported to be acceptable (*335*,*336*), and might result in increased patients identifying as transgender (*337*).

Lack of medical provider knowledge and other barriers to care (e.g., discrimination in health care settings or denial of services) often result in transgender and gender nonbinary persons avoiding or delaying preventive care services (*338*–*340*) and incurring missed opportunities for HIV and STI prevention services. Gender-inclusive and trauma-guided health care might increase the number of transgender patients who seek sexual health services, including STI testing (*341*), because transgender persons are at high risk for sexual violence (*342*).

Primary care providers should take a comprehensive sexual history, including a discussion of STI screening, HIV PrEP and PEP, behavioral health, and social determinants of sexual health. Clinicians can improve the experience of sexual health screening and counseling for transgender persons by asking for their choice of terminology or modifying language (e.g., asking patients their gender pronouns) to be used during clinic visits and history taking and examination (*343*). Options for fertility preservation, pregnancy potential, and contraception options should also be discussed, if indicated. For transgender persons who retain a uterus and ovaries, ovulation might continue in the presence of testosterone therapy, and pregnancy potential exists (https://transcare.ucsf.edu).

Transgender Women

A systematic review and meta-analysis of HIV infection among transgender women estimated that HIV prevalence in the United States is 14% among transgender women, with the highest prevalence among Black (44%) and Hispanic (26%) transgender women (*344*). Data also demonstrate high rates of HIV infection among transgender women worldwide (*345*). Bacterial STI prevalence varies among transgender women and is based largely on convenience samples. Despite limited data, international and U.S. studies have indicated elevated incidence and prevalence of gonorrhea and chlamydia among transgender women similar to rates among cisgender MSM (*346*–*348*). A recent study using data from the STD Surveillance Network revealed that the proportions of transgender women with extragenital chlamydial or gonococcal infections were similar to those of cisgender MSM (*349*).

Providers caring for transgender women should have knowledge of their patients' current anatomy and patterns of sexual behavior before counseling them about STI and HIV prevention. The majority of transgender women have not undergone genital-affirmation surgery and therefore might retain a functional penis; in these instances, they might engage in insertive oral, vaginal, or anal sex as well as receptive oral or anal sex. In the U.S. Transgender Survey, 12% of transgender women had undergone vaginoplasty surgery, and approximately 50% more were considering surgical intervention (*350*). Providers should have knowledge about the type of tissue used to construct the neovagina, which can affect future STI and HIV preventive care and screening recommendations. The majority of vaginoplasty surgeries conducted in the United States use penile and scrotal tissue to create the neovagina (*351*). Other surgical techniques use intestinal tissue (e.g., sigmoid colon graft) or split-skin grafts (*352*). Although these surgeries involve penectomy and orchiectomy, the prostate remains intact. Transgender women who have had a vaginoplasty might engage in receptive vaginal, oral, or anal sex.

Neovaginal STIs have infrequently been reported in the literature and include HSV and HPV/genital warts in penile-inversion vaginoplasty, *C. trachomatis* in procedures that involved penile skin and grafts with urethra mucosa or abdominal peritoneal lining (*353*), and *N. gonorrhoeae* in both penile-inversion and colovaginoplasty (*354*–*359*). If the vaginoplasty used an intestinal graft, a risk also exists for bowel-related disease (e.g., adenocarcinoma, inflammatory bowel disease, diversion colitis, and polyps) (*360*–*362*).

Transgender Men

The few studies of HIV prevalence among transgender men indicated that they have a lower prevalence of HIV infection than transgender women. A recent estimate of HIV prevalence among transgender men was 2% (*344*). However, transgender men who have sex with cisgender men might be at elevated

risk for HIV infection (*332*,*363*,*364*). Data are limited regarding STI prevalence among transgender men, and the majority of studies have used clinic-based data or convenience sampling. Recent data from the STD Surveillance Network demonstrated higher prevalence of gonorrhea and chlamydia among transgender men, similar to rates reported among cisgender MSM (*365*).

The U.S. Transgender Survey indicated that the proportion of transgender men and gender diverse persons assigned female sex at birth who have undergone gender-affirmation genital surgery is low. Providers should consider the anatomic diversity among transgender men because a person can undergo a metoidioplasty (a procedure to increase the length of the clitoris), with or without urethral lengthening, and might not have a hysterectomy and oophorectomy and therefore be at risk for bacterial STIs, HPV, HSV, HIV, and cervical cancer (*366*). For transgender men using gender-affirming hormone therapy, the decrease in estradiol levels caused by exogenous testosterone can lead to vaginal atrophy (*367*,*368*) and is associated with a high prevalence of unsatisfactory sample acquisition (*369*). The impact of these hormonal changes on mucosal susceptibility to HIV and STIs is unknown.

Transgender men who have not chosen to undergo hysterectomy with removal of the cervix remain at risk for cervical cancer. These persons often avoid cervical cancer screening because of multiple factors, including discomfort with medical examinations and fear of discrimination (*338*,*370*). Providers should be aware that conducting a speculum examination can be technically difficult after metoidioplasty surgery because of narrowing of the introitus. In these situations, high-risk HPV testing using a swab can be considered; self-collected swabs for high-risk HPV testing has been reported to be an acceptable option for transgender men (*371*).

Screening Recommendations

The following are screening recommendations for transgender and gender diverse persons:

- Because of the diversity of transgender persons regarding surgical gender-affirming procedures, hormone use, and their patterns of sexual behavior, providers should remain aware of symptoms consistent with common STIs and screen for asymptomatic infections on the basis of the patient's sexual practices and anatomy.
- Gender-based screening recommendations should be adapted on the basis of anatomy (e.g., routine screening for *C. trachomatis* and *N. gonorrhoeae)* as recommended for all sexually active females aged <25 years on an annual basis and should be extended to transgender men and nonbinary persons with a cervix among this age group.
- HIV screening should be discussed and offered to all transgender persons. Frequency of repeat screenings should be based on level of risk.
- For transgender persons with HIV infection who have sex with cisgender men and transgender women, STI screening should be conducted at least annually, including syphilis serology, HCV testing, and urogenital and extragenital NAAT for gonorrhea and chlamydia.
- Transgender women who have had vaginoplasty surgery should undergo routine STI screening for all exposed sites (e.g., oral, anal, or vaginal). No data are available regarding the optimal screening method (urine or vaginal swab) for bacterial STIs of the neovagina. The usual techniques for creating a neovagina do not result in a cervix; therefore, no rationale exists for cervical cancer screening (*368*).
- If transgender men have undergone metoidioplasty surgery with urethral lengthening and have not had a vaginectomy, assessment of genital bacterial STIs should include a cervical swab because a urine specimen will be inadequate for detecting cervical infections.
- Cervical cancer screening for transgender men and nonbinary persons with a cervix should follow current screening guidelines (see Human Papillomavirus Infections).

Persons in Correctional Facilities

Multiple studies have demonstrated that persons entering correctional facilities have a high prevalence of STIs, HIV, and viral hepatitis, especially those aged ≤35 years (*141*,*372*,*373*). Risk behaviors for acquiring STIs (e.g., having condomless sex, having multiple sex partners, substance misuse, and engaging in commercial, survival, or coerced sex) are common among incarcerated populations. Before their incarceration, many persons have had limited access to medical care. Other social determinants of health (e.g., insufficient social and economic support or living in communities with high local STI prevalence) are common. Addressing STIs in correctional settings is vital for addressing the overall STI impact among affected populations.

Growing evidence demonstrates the usefulness of expanded STI screening and treatment services in correctional settings, including short-term facilities (jails), long-term institutions (prisons), and juvenile detention centers. For example, in jurisdictions with comprehensive, targeted jail screening, more chlamydial infections among females (and males if screened) are detected and subsequently treated in the correctional setting than in any other single reporting source (*141*,*374*) and might represent the majority of reported cases in certain jurisdictions (*375*). Screening in the jail setting has the potential to reach

substantially more persons at risk than screening among the prison population alone.

Both males and females aged ≤35 years in juvenile and adult detention facilities have been reported to have higher rates of chlamydia and gonorrhea than nonincarcerated persons in the community (*141*,*374*,*376*). Syphilis seroprevalence rates, which can indicate previously treated or current infection, are considerably higher among incarcerated adult men and women than among adolescents, which is consistent with the overall national syphilis trends (*141*,*374*). Detection and treatment of early syphilis in correctional facilities might affect rates of transmission among adults and prevention of congenital syphilis (*377*).

In jails, approximately half of entrants are released back into the community within 48 hours. As a result, treatment completion rates for those screened for STIs and who receive STI diagnoses in short-term facilities might not be optimal. However, because of the mobility of incarcerated populations in and out of the community, the impact of screening in correctional facilities on the prevalence of infections among detainees and subsequent transmission in the community after release might be considerable (*378*). Moreover, treatment completion rates of ≥95% in short-term facilities can be achieved by offering screening at or shortly after intake, thus facilitating earlier receipt of test results and, if needed, follow-up of untreated persons can be conducted through public health outreach.

Universal, opt-out screening for chlamydia and gonorrhea among females aged ≤35 years entering juvenile and adult correctional facilities is recommended (*379*). Males aged <30 years entering juvenile and adult correctional facilities should also be screened for chlamydia and gonorrhea (*380*). Opt-out screening has the potential to substantially increase the number tested and the number of chlamydia and gonorrhea infections detected (*381*–*385*). Point-of-care (POC) NAAT might also be considered if the tests have demonstrated sufficient sensitivity and specificity. Studies have demonstrated high prevalence of trichomoniasis among incarcerated females (*386*–*392*).

Screening Recommendations

Chlamydia and Gonorrhea

Females aged ≤35 years and males aged <30 years housed in correctional facilities should be screened for chlamydia and gonorrhea. This screening should be conducted at intake and offered as opt-out screening.

Trichomonas

Females aged ≤35 years housed in correctional facilities should be screened for trichomonas. This screening should be conducted at intake and offered as opt-out screening.

Syphilis

Opt-out screening for incarcerated persons should be conducted on the basis of the local area and institutional prevalence of early (primary, secondary, or early latent) infectious syphilis. Correctional facilities should stay apprised of local syphilis prevalence. In short-term facilities, screening at entry might be indicated.

Viral Hepatitis

All persons housed in juvenile and adult correctional facilities should be screened at entry for viral hepatitis, including HAV, HBV, and HCV, depending on local prevalence and the person's vaccination status. Vaccination for HAV and HBV should be offered if the person is susceptible.

Cervical Cancer

Women and transgender men who are housed in correctional facilities should be screened for cervical cancer as for women who are not incarcerated (*393*,*394*) (see Cervical Cancer).

HIV Infection

All persons being housed in juvenile and adult correctional facilities should be screened at entry for HIV infection; screening should be offered as opt-out screening. For those identified as being at risk for HIV infection (e.g., with diagnosed gonorrhea or syphilis or persons who inject drugs) and being released into the community, starting HIV PrEP (or providing linkage to a community clinic for HIV PrEP) for HIV prevention should be considered (*395*,*396*). Persons are likely to engage in high-risk activities immediately after release from incarceration (*397*). For those identified with HIV infection, treatment should be initiated. Those persons receiving PrEP or HIV treatment should have linkage to care established before release. Correctional settings should consider implementing other STI prevention approaches, both during incarceration and upon release, which might include educational and behavioral counseling interventions (*398*–*401*), vaccination (e.g., for HPV) (*402*,*403*), condom distribution (*404*,*405*), EPT (*125*), and PrEP to prevent HIV infection (see Primary Prevention Methods).

HIV Infection

Detection, Counseling, and Referral

Infection with HIV causes an acute but brief and nonspecific influenza-like retroviral syndrome that can include fever, malaise, lymphadenopathy, pharyngitis, arthritis, or skin rash. Most persons experience at least one symptom; however, some might be asymptomatic or have no recognition of illness (*406–409*). Acute infection transitions to a multiyear, chronic illness that progressively depletes $CD4^+$ T lymphocytes crucial for maintenance of effective immune function. Ultimately, persons with untreated HIV infection experience symptomatic, life-threatening immunodeficiency (i.e., AIDS).

Effective ART that suppresses HIV replication to undetectable levels reduces morbidity, provides a near-normal lifespan, and prevents sexual transmission of HIV to others (*95–97*,*410–412*). Early diagnosis of HIV and rapid linkage to care are essential for achieving these goals. Guidelines from both the U.S. Department of Health and Human Services and the International AIDS Society–USA Panel recommend that all persons with HIV infection be offered effective ART as soon as possible, both to reduce morbidity and mortality and to prevent HIV transmission (*413*).

STD specialty or sexual health clinics are a vital partner in reducing HIV infections in the United States. These clinics provide safety net services to vulnerable populations in need of HIV prevention services who are not served by the health care system and HIV partner service organizations. Diagnosis of an STI is a biomarker for HIV acquisition, especially among persons with primary or secondary syphilis or, among MSM, rectal gonorrhea or chlamydia (*197*). STD clinics perform only approximately 20% of all federally funded HIV tests nationally but identify approximately 30% of all new infections (*414*). Among testing venues, STD clinics are high performing in terms of linkage to HIV care within 90 days of diagnosis; during 2013–2017, the percentage of persons with a new diagnosis in an STD clinic and linked to care within 90 days increased from 55% to >90% (*415*,*415*).

Screening Recommendations

The following recommendations apply to testing for HIV:

- HIV testing is recommended for all persons seeking STI evaluation who are not already known to have HIV infection. Testing should be routine at the time of the STI evaluation, regardless of whether the patient reports any specific behavioral risks for HIV. Testing for HIV should be performed at the time of STI diagnosis and treatment if not performed at the initial STI evaluation and screening (*82*,*195*,*416*).
- CDC and USPSTF recommend HIV screening at least once for all persons aged 15–65 years (*417*).
- Persons at higher risk for HIV acquisition, including sexually active gay, bisexual, and other MSM, should be screened for HIV at least annually. Providers can consider the benefits of offering more frequent screening (e.g., every 3–6 months) among MSM at increased risk for acquiring HIV (*418*,*419*).
- All pregnant women should be tested for HIV during the first prenatal visit. A second test during the third trimester, preferably at <36 weeks' gestation, should be considered and is recommended for women who are at high risk for acquiring HIV infection, women who receive health care in jurisdictions with high rates of HIV, and women examined in clinical settings in which HIV incidence is ≥1 per 1,000 women screened per year (*138*,*140*).
- HIV screening should be voluntary and free from coercion. Patients should not be tested without their knowledge.
- Opt-out HIV screening (notifying the patient that an HIV test will be performed, unless the patient declines) is recommended in all health care settings. CDC also recommends that consent for HIV screening be incorporated into the general informed consent for medical care in the same manner as other screening or diagnostic tests.
- Requirement of specific signed consent for HIV testing is not recommended. General informed consent for medical care is considered sufficient to encompass informed consent for HIV testing.
- Providers should use a laboratory-based antigen/antibody (Ag/Ab) combination assay as the first test for HIV, unless persons are unlikely to follow up with a provider to receive their HIV test results; in those cases screening with a rapid POC test can be useful.
- Preliminary positive screening tests for HIV should be followed by supplemental testing to establish the diagnosis.
- Providing prevention counseling as part of HIV screening programs or in conjunction with HIV diagnostic testing is not required (*6*). However, persons might be more likely to think about HIV and consider their risk-related behavior when undergoing an HIV test. HIV testing gives providers an opportunity to conduct STI and HIV prevention counseling and communicate risk-reduction messages.
- Acute HIV infection can occur among persons who report recent sexual or needle-sharing behavior or who have had an STI diagnosis.
- Providers should test for HIV RNA if initial testing according to the HIV testing algorithm recommended by CDC is negative or indeterminate when concerned about acute HIV infection (https://stacks.cdc.gov/view/cdc/50872).

- Providers should not assume that a laboratory report of a negative HIV Ag/Ab or antibody test indicates that the requisite HIV RNA testing for acute HIV infection has been conducted. They should consider explicitly requesting HIV RNA testing when concerned about early acute HIV infection.
- Providers should assess eligibility of all persons seeking STI services for HIV PrEP and PEP. For persons with substantial risk whose results are HIV negative, providers should offer or provide referral for PrEP services, unless the last potential HIV exposure occurred <72 hours, in which case PEP might be indicated.

Diagnostic Considerations

HIV infection can be diagnosed by HIV 1/2 Ag/Ab combination immunoassays. All FDA-cleared HIV tests are highly sensitive and specific. Available serologic tests can detect all known subtypes of HIV-1. The majority also detect HIV-2 and uncommon variants of HIV-1 (e.g., group O and group N).

According to an algorithm for HIV diagnosis, CDC recommends that HIV testing begin with a laboratory-based HIV-1/HIV-2 Ag/Ab combination assay, which, if repeatedly reactive, is followed by a laboratory-based assay with a supplemental HIV-1/HIV-2 antibody differentiation assay (https://stacks.cdc.gov/view/cdc/50872). This algorithm confers an additional advantage because it can detect HIV-2 antibodies after the initial immunoassay. Although HIV-2 is uncommon in the United States, accurate identification is vital because monitoring and therapy for HIV-2 differs from that for HIV-1 (*420*). RNA testing should be performed on all specimens with reactive immunoassay but negative supplemental antibody test results to determine whether the discordance represents acute HIV infection.

Rapid POC HIV tests can enable clinicians to make a preliminary diagnosis of HIV infection in <20 minutes. The majority of rapid antibody assays become reactive later in the course of HIV infection than conventional laboratory-based assays and thus can produce negative results among persons recently infected (e.g., acutely infected persons). Furthermore, HIV home-test kits only detect HIV antibodies and therefore will not detect acute HIV infection. If early or acute infection is suspected and a rapid HIV antibody assay is negative, confirmatory testing with combined laboratory-based assays or RNA testing should be performed. CDC recommends that all persons with reactive rapid tests be assessed with a laboratory-based Ag/Ab assay. Additional details about interpretation of results by using the HIV testing algorithm recommended by CDC are available at https://stacks.cdc.gov/view/cdc/48472.

Acute HIV Infection

Providers serving persons at risk for STIs are in a position to diagnose HIV infection during its acute phase. Diagnosing HIV infection during the acute phase is particularly important because persons with acute HIV have highly infectious disease due to the concentration of virus in plasma and genital secretions, which is extremely elevated during that stage of infection (*421*,*422*) (https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/acute-and-recent-early-hiv-infection?view=full). ART during acute HIV infection is recommended because it substantially reduces infection transmission to others, improves laboratory markers of disease, might decrease severity of acute disease, lowers viral setpoint, reduces the size of the viral reservoir, decreases the rate of viral mutation by suppressing replication, and preserves immune function (https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/acute-and-recent-early-hiv-infection?view=full). Persons who receive an acute HIV diagnosis should be referred immediately to an HIV clinical care provider, provided prevention counseling (e.g., advised to reduce the number of partners and to use condoms correctly and consistently), and screened for STIs. Information should be provided regarding availability of PEP for sexual and injecting drug use partners not known to have HIV infection if the most recent contact was <72 hours preceding HIV diagnosis.

When providers test by using the CDC algorithm, specimens collected during acute infection might give indeterminate or negative results because insufficient anti-HIV antibodies and potentially insufficient antigen are present to be reactive on Ag/Ab combination assays and supplemental HIV-1/HIV-2 antibody differentiation assays. Whenever acute HIV infection is suspected (e.g., initial testing according to the CDC algorithm is negative or indeterminate after a possible sexual exposure to HIV within the previous few days to weeks, especially if the person has symptoms or has primary or secondary syphilis, gonorrhea, or chlamydia), additional testing for HIV RNA is recommended. If this additional testing for HIV RNA is also negative, repeat testing in a few weeks is recommended to rule out very early acute infection when HIV RNA might not be detectable. A more detailed discussion of testing in the context of acute HIV infection is available at https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/initiation-antiretroviral-therapy?view=full.

Treatment

ART should be initiated as soon as possible for all persons with HIV infection regardless of $CD4^+$ T-cell count, both for individual health and to prevent HIV transmission (https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf).

Persons with HIV infection who achieve and maintain a viral load suppressed to <200 copies/mL with ART have effectively no risk for sexually transmitting HIV (*95*–*97*,*421*). Early HIV diagnosis and treatment is thus not only vital for individual health but also as a public health intervention to prevent new infections. Knowledge of the prevention benefit of treatment can help reduce stigma and increase the person's commitment to start and remain adherent to ART (*423*). The importance of adherence should be stressed as well as the fact that ART does not protect against other STIs that can be prevented by using condoms. Interventions to assist persons to remain adherent to their prescribed HIV treatment, to otherwise reduce the possibility of transmission to others, and to protect themselves against STIs, have been developed for diverse populations at risk (*424*) (https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf).

Comprehensive HIV treatment and care services might not be available in facilities focused primarily on STI treatment. Providers in such settings should be knowledgeable about HIV treatment and care options available in their communities and promptly link persons who have newly diagnosed HIV infection and any persons with HIV infection who are not engaged in ongoing effective care to a health care provider or facility experienced in caring for persons living with HIV (https://clinicalinfo.hiv.gov/sites/default/files/inline-files/AdultandAdolescentGL.pdf).

Other HIV Management Considerations

Behavioral and psychosocial services are integral to caring for persons with HIV infection. Providers should expect persons to be distressed when first informed that they have HIV. They face multiple adaptive challenges, including coping with the reactions of others to a stigmatizing illness, developing and adopting strategies to maintain physical and emotional health, initiating changes in behavior to prevent HIV transmission to others, and reducing the risk for acquiring additional STIs. Many persons will require assistance gaining access to health care and other support services and coping with changes in personal relationships.

Persons with HIV infection might have additional needs (e.g., referral for substance use or mental health disorders). Others require assistance to secure and maintain employment and housing. Persons capable of reproduction might require family planning counseling, information about reproductive health choices, and referral for reproductive health care.

The following recommendations apply to managing persons with diagnosed HIV infection:

- Link persons with HIV infection to care and start them on ART as soon as possible.
- Report cases (in accordance with local requirements) to public health and initiate partner services.
- Provide prevention counseling to persons with diagnosed HIV infection.
- Ensure all persons with HIV infection are informed that if they achieve and maintain a suppressed viral load, they have effectively no risk for transmitting HIV. Stress that a suppressed viral load is not a substitute for condoms and behavioral modifications because ART does not protect persons with HIV against other STIs.
- Provide additional counseling, either on-site or through referral, about the psychosocial and medical implications of having HIV infection.
- Assess the need for immediate medical care and psychosocial support.
- Link persons with diagnosed HIV infection to services provided by health care personnel experienced in managing HIV infection. Additional services that might be needed include substance misuse counseling and treatment, treatment for mental health disorders or emotional distress, reproductive counseling, risk-reduction counseling, and case management. Providers should follow up to ensure that patients have received services for any identified needs.
- Persons with HIV infection should be educated about the importance of ongoing medical care and what to expect from these services.

STI Screening of Persons with HIV Infection in HIV Care Settings

At the initial HIV care visit, providers should screen all sexually active persons for syphilis, gonorrhea, and chlamydia, and perform screening for these infections at least annually during the course of HIV care (*425*). Specific testing includes syphilis serology and NAAT for *N. gonorrhoeae* and *C. trachomatis* at the anatomic site of exposure. Women should also be screened for trichomoniasis at the initial visit and annually thereafter. Women should be screened for cervical cancer precursor lesions per existing guidelines (*98*).

More frequent screening for syphilis, gonorrhea, and chlamydia (e.g., every 3 or 6 months) should be tailored to individual risk and the local prevalence of specific STIs. Certain STIs can be asymptomatic; their diagnosis might prompt referral for partner services, might identify sexual and needle-sharing partners who can benefit from early diagnosis and treatment of HIV, and might prompt reengagement in care or HIV prevention services (e.g., PEP or PrEP) (*8*). More detailed information on screening, testing, and treatment is provided in pathogen-specific sections of this report.

Partner Services and Reporting

Partner notification is a key component in the evaluation of persons with HIV infection. Early diagnosis and treatment of HIV among all potentially exposed sexual and injecting drug sharing partners can improve their health and reduce new infections. For those partners without HIV infection, partner services also provide an opportunity for offering HIV prevention services, including PrEP or PEP (if exposure was <72 hours previous) and STI testing and treatment.

Health care providers should inform persons with diagnosed HIV infection about any legal obligations of providers to report cases of HIV to public health; the local confidential processes for managing partner services, including that a public health department still might be in contact to follow up in their care and partner services; and the benefits and risks of partner notification and services. Health care providers should also encourage persons with a new HIV diagnosis to notify their partners and provide them with referral information for their partners about HIV testing. Partner notification for exposure to HIV should be confidential. Health care providers can assist in the partner notification process, either directly or by referral to health department partner notification programs. Health department staff are trained to use public health investigation strategies for confidentially locating persons who can benefit from HIV treatment, care, or prevention services. Guidance regarding spousal notification varies by jurisdiction. Detailed recommendations for notification, evaluation, and treatment of exposed partners are available in *Recommendations for Partner Services Programs for HIV Infection, Syphilis, Gonorrhea, and Chlamydial Infections* (*111*).

Special Considerations

Pregnancy

All pregnant women should be tested for HIV during the first prenatal visit. A second test during the third trimester, preferably at <36 weeks' gestation, should be considered and is recommended for women who are at high risk for acquiring HIV, women who receive health care in jurisdictions with high rates of HIV infection, and women served in clinical settings in which prenatal screening identifies ≥1 pregnant woman with HIV per 1,000 women screened (*138*). Diagnostic algorithms for HIV for pregnant women do not differ from those for nonpregnant women (see STI Detection Among Special Populations). Pregnant women should be informed that HIV testing will be performed as part of the routine panel of prenatal tests (*138*); for women who decline HIV testing, providers should address concerns that pose obstacles, discuss the benefits of testing (e.g., early HIV detection, treatment, and care for improving health of the mother and reducing perinatal transmission of HIV), and encourage testing at subsequent prenatal visits. Women who decline testing because they have had a previous negative HIV test result should be informed about the importance of retesting during each pregnancy. Women with no prenatal care should be tested for HIV at the time of delivery.

Testing pregnant women is crucial because knowledge of infection status can help maintain the woman's health, and it enables receipt of interventions (i.e., ART or specialized obstetrical care) that can substantially reduce the risk for perinatal transmission of HIV. Pregnant women with diagnosed HIV infection should be educated about the benefits of ART for their own health and for reducing the risk for HIV transmission to their infant. In the absence of ART, a mother's risk for transmitting HIV to her neonate is approximately 30%; however, risk can be reduced to <2% through ART, obstetrical interventions (i.e., elective cesarean delivery at 38 weeks' pregnancy), and breastfeeding avoidance (https://clinicalinfo.hiv.gov/sites/default/files/inline-files/PerinatalGL.pdf). Pregnant women with HIV infection should be linked to an HIV care provider experienced in managing HIV in pregnancy and provided antenatal and postpartum treatment and advice. Detailed and regularly updated recommendations for managing pregnant patients with HIV infection are available at https://clinicalinfo.hiv.gov/sites/default/files/inline-files/PerinatalGL.pdf.

HIV Infection Among Neonates, Infants, and Children

Diagnosis of HIV infection in a pregnant woman indicates the need for evaluating and managing the HIV-exposed neonate and considering whether the woman's other children, if any, might be infected. Detailed recommendations regarding diagnosis and management of HIV infection among neonates and children of mothers with HIV are beyond the scope of these guidelines but are available at https://clinicalinfo.hiv.gov/en/guidelines. Exposed neonates and children with HIV infection should be referred to physicians with expertise in neonatal and pediatric HIV management.

Diseases Characterized by Genital, Anal, or Perianal Ulcers

In the United States, the majority of young, sexually active patients who have genital, anal, or perianal ulcers have either genital herpes or syphilis. The frequency of each condition differs by geographic area and population; however, genital herpes is the most prevalent of these diseases. More than one etiologic agent (e.g., herpes and syphilis) can be present in any genital, anal, or perianal ulcer. Less common infectious

causes of genital, anal, or perianal ulcers include chancroid, LGV, and granuloma inguinale (donovanosis). GUDs (e.g., syphilis, herpes, and LGV) might also present as oral ulcers. Genital herpes, syphilis, chlamydia, gonorrhea, and chancroid have been associated with an increased risk for HIV acquisition and transmission. Genital, anal, or perianal lesions can also be associated with infectious and noninfectious conditions that are not sexually transmitted (e.g., yeast, trauma, carcinoma, aphthae or Behcet's disease, fixed drug eruption, or psoriasis).

A diagnosis based only on medical history and physical examination frequently can be inaccurate. Therefore, all persons who have genital, anal, or perianal ulcers should be evaluated. Specific evaluation of genital, anal, or perianal ulcers includes syphilis serology tests and darkfield examination from lesion exudate or tissue, or NAAT if available; NAAT or culture for genital herpes type 1 or 2; and serologic testing for type-specific HSV antibody. In settings where chancroid is prevalent, a NAAT or culture for *Haemophilus ducreyi* should be performed.

No FDA-cleared NAAT for diagnosing syphilis is available in the United States; however, multiple FDA-cleared NAATs are available for diagnosing HSV-1 and HSV-2 in genital specimens. Certain clinical laboratories have developed their own syphilis and HSV NAATs and have conducted Clinical Laboratory Improvement Amendment (CLIA) verification studies with genital specimens. Type-specific serology for HSV-2 might aid in identifying persons with genital herpes (see Genital Herpes). In addition, biopsy of ulcers with immunohistochemistry can help identify the cause of ulcers that are unusual or that do not respond to initial therapy. HIV testing should be performed on all persons not known to have HIV infection who present with genital, anal, or perianal ulcers (see Diagnostic Considerations in disease-specific sections). NAAT testing at extragenital sites should be considered for cases in which GUDs are suspected (e.g., oral manifestations of syphilis, herpes, or LGV). Commercially available NAATs have not been cleared by FDA for these indications; however, they can be used by laboratories that have met regulatory requirements for an off-label procedure.

Because early syphilis treatment decreases transmission possibility, public health standards require health care providers to presumptively treat any patient with a suspected case of infectious syphilis at the initial visit, even before test results are available. Presumptive treatment of a patient with a suspected first episode of genital herpes also is recommended because HSV treatment benefits depend on prompt therapy initiation. The clinician should choose the presumptive treatment on the basis of the clinical presentation (i.e., HSV lesions begin as vesicles and primary syphilis as a papule) and epidemiologic circumstances (e.g., high incidence of disease among populations and communities and travel history). For example, syphilis is so common among MSM that any male who has sex with men presenting with a genital ulcer should be presumptively treated for syphilis at the initial visit after syphilis and HSV tests are performed. After a complete diagnostic evaluation, >25% of patients who have genital ulcers might not have a laboratory-confirmed diagnosis (*426*).

Chancroid

Chancroid prevalence has declined in the United States (*141*). When infection does occur, it is usually associated with sporadic outbreaks. Worldwide, chancroid appears to have decreased as well, although infection might still occur in certain Africa regions and the Caribbean. Chancroid is a risk factor in HIV transmission and acquisition (*197*).

Diagnostic Considerations

A definitive diagnosis of chancroid requires identifying *H. ducreyi* on special culture media that is not widely available from commercial sources; even when these media are used, sensitivity is <80% (*427*). No FDA-cleared NAAT for *H. ducreyi* is available in the United States; however, such testing can be performed by clinical laboratories that have developed their own NAAT and have conducted CLIA verification studies on genital specimens.

The combination of one or more deep and painful genital ulcers and tender suppurative inguinal adenopathy indicates the chancroid diagnosis; inguinal lymphadenitis typically occurs in <50% of cases (*428*). For both clinical and surveillance purposes, a probable diagnosis of chancroid can be made if all of the following four criteria are met: 1) the patient has one or more painful genital ulcers; 2) the clinical presentation, appearance of genital ulcers and, if present, regional lymphadenopathy are typical for chancroid; 3) the patient has no evidence of *T. pallidum* infection by darkfield examination or NAAT (i.e., ulcer exudate or serous fluid) or by serologic tests for syphilis performed at least 7–14 days after onset of ulcers; and 4) HSV-1 or HSV-2 NAAT or HSV culture performed on the ulcer exudate or fluid are negative.

Treatment

Successful antimicrobial treatment for chancroid cures the infection, resolves the clinical symptoms, and prevents transmission to others. In advanced cases, genital scarring and rectal or urogenital fistulas from suppurative buboes can result despite successful therapy.

Recommended Regimens for Chancroid
Azithromycin 1 g orally in a single dose
or
Ceftriaxone 250 mg IM in a single dose
or
Ciprofloxacin 500 mg orally 2 times/day for 3 days
or
Erythromycin base 500 mg orally 3 times/day for 7 days

Azithromycin and ceftriaxone offer the advantage of single-dose therapy (*429*). Worldwide, several isolates with intermediate resistance to either ciprofloxacin or erythromycin have been reported. However, because cultures are not routinely performed, and chancroid is uncommon, data are limited regarding prevalence of *H. ducreyi* antimicrobial resistance.

Other Management Considerations

Men who are uncircumcised and persons with HIV infection do not respond as well to treatment as persons who are circumcised or are HIV negative (*430*). Patients should be tested for HIV at the time chancroid is diagnosed. If the initial HIV test results were negative, the provider can consider the benefits of offering more frequent testing and HIV PrEP to persons at increased risk for HIV infection.

Follow-Up

Patients should be reexamined 3–7 days after therapy initiation. If treatment is successful, ulcers usually improve symptomatically within 3 days and objectively within 7 days after therapy. If no clinical improvement is evident, the clinician should consider whether the diagnosis is correct, another STI is present, the patient has HIV infection, the treatment was not used as instructed, or the *H. ducreyi* strain causing the infection is resistant to the prescribed antimicrobial. The time required for complete healing depends on the size of the ulcer; large ulcers might require >2 weeks. In addition, healing can be slower for uncircumcised men who have ulcers under the foreskin. Clinical resolution of fluctuant lymphadenopathy is slower than that of ulcers and might require needle aspiration or incision and drainage, despite otherwise successful therapy. Although needle aspiration of buboes is a simpler procedure, incision and drainage might be preferred because of reduced need for subsequent drainage procedures.

Management of Sex Partners

Regardless of whether disease symptoms are present, sex partners of patients with chancroid should be examined and treated if they had sexual contact with the patient during the 10 days preceding the patient's symptom onset.

Special Considerations

Pregnancy

Data indicate ciprofloxacin presents a low risk to the fetus during pregnancy but has potential for toxicity during breastfeeding (*431*). Alternative drugs should be used if the patient is pregnant or lactating. No adverse effects of chancroid on pregnancy outcome have been reported.

HIV Infection

Persons with HIV infection who have chancroid infection should be monitored closely because they are more likely to experience chancroid treatment failure and to have ulcers that heal slowly (*430*,*432*). Persons with HIV might require repeated or longer courses of therapy, and treatment failures can occur with any regimen. Data are limited concerning the therapeutic efficacy of the recommended single-dose azithromycin and ceftriaxone regimens among persons with HIV infection.

Children

Because sexual contact is the major primary transmission route among U.S. patients, diagnosis of chancroid ulcers among infants and children, especially in the genital or perineal region, is highly suspicious of sexual abuse. However, *H. ducreyi* is recognized as a major cause of nonsexually transmitted cutaneous ulcers among children in tropical regions and, specifically, countries where yaws is endemic (*433–435*). Acquisition of a lower-extremity ulcer attributable to *H. ducreyi* in a child without genital ulcers and reported travel to a region where yaws is endemic should not be considered evidence of sexual abuse.

Genital Herpes

Genital herpes is a chronic, lifelong viral infection. Two types of HSV can cause genital herpes: HSV-1 and HSV-2. Most cases of recurrent genital herpes are caused by HSV-2, and 11.9% of persons aged 14–49 years are estimated to be infected in the United States (*436*). However, an increasing proportion of anogenital herpetic infections have been attributed to HSV-1, which is especially prominent among young women and MSM (*186*,*437*,*438*).

The majority of persons infected with HSV-2 have not had the condition diagnosed, many of whom have mild or unrecognized infections but shed virus intermittently in the anogenital area. Consequently, most genital herpes infections are transmitted by persons unaware that they have the infection or who are asymptomatic when transmission occurs. Management of genital HSV should address the chronic nature of the infection rather than focusing solely on treating acute episodes of genital lesions.

Diagnostic Considerations

Clinical diagnosis of genital herpes can be difficult because the self-limited, recurrent, painful, and vesicular or ulcerative lesions classically associated with HSV are absent in many infected persons at the time of clinical evaluation. If genital lesions are present, clinical diagnosis of genital herpes should be confirmed by type-specific virologic testing from the lesion by NAAT or culture (*186*). Recurrences and subclinical shedding are much more frequent for HSV-2 genital herpes infection than for HSV-1 genital herpes (*439*,*440*). Therefore, prognosis and counseling depend on which HSV type is present. Type-specific serologic tests can be used to aid in the diagnosis of HSV infection in the absence of genital lesions. Both type-specific virologic and type-specific serologic tests for HSV should be available in clinical settings that provide care to persons with or at risk for STIs. HSV-2 genital herpes infection increases the risk for acquiring HIV twofold to threefold; therefore, all persons with genital herpes should be tested for HIV (*441*).

Virologic Tests

HSV NAAT assays are the most sensitive tests because they detect HSV from genital ulcers or other mucocutaneous lesions; these tests are increasingly available (*442*–*444*). Although multiple FDA-cleared assays exist for HSV detection, these tests vary in sensitivity from 90.9% to 100%; however, they are considered highly specific (*445*–*447*). PCR is also the test of choice for diagnosing HSV infections affecting the central nervous system (CNS) and systemic infections (e.g., meningitis, encephalitis, and neonatal herpes). HSV PCR of the blood should not be performed to diagnose genital herpes infection, except in cases in which concern exists for disseminated infection (e.g., hepatitis). In certain settings, viral culture is the only available virologic test. The sensitivity of viral culture is low, especially for recurrent lesions, and decreases rapidly as lesions begin to heal (*443*,*448*). Viral culture isolates and PCR amplicons should be typed to determine whether HSV-1 or HSV-2 is causing the infection. Failure to detect HSV by NAAT or culture, especially in the presence of older lesions or the absence of active lesions, does not indicate an absence of HSV infection because viral shedding is intermittent. Similarly, random or blind genital swabs in the absence of lesions should not be used to diagnose genital HSV infection because sensitivity is low, and a negative result does not exclude the presence of HSV infection.

Cytologic detection of cellular changes associated with HSV infection is an insensitive and nonspecific method of diagnosing genital lesions (i.e., Tzanck preparation) and therefore should not be relied on. Although a direct immunofluorescence assay using fluorescein-labeled monoclonal antibodies is also available for detecting HSV antigen from genital specimens, this assay lacks sensitivity and is not recommended (*449*).

Type-Specific Serologic Tests

Both type-specific and type-common antibodies to HSV develop during the first weeks after infection and persist indefinitely. The majority of available, accurate type-specific HSV serologic assays are based on the HSV-specific glycoprotein G2 (gG2) (HSV-2) and glycoprotein G1 (gG1) (HSV-1). Type-common antibody tests do not distinguish between HSV-1 and HSV-2 infection; therefore, type-specific serologic assays should be requested (*450*–*452*).

Both laboratory-based assays and POC tests that provide results for HSV-2 antibodies from capillary blood or serum during a clinic visit are available. The sensitivity of glycoprotein G type-specific tests for detecting HSV-2 antibody varies from 80% to 98%; false-negative results might be more frequent at early stages of infection (*451*,*453*,*454*). Therefore, in cases of recent suspected HSV-2 acquisition, repeat type-specific antibody testing 12 weeks after the presumed time of acquisition is indicated. The most commonly used test, HerpeSelect HSV-2 enzyme immunoassay (EIA), often is falsely positive at low index values (1.1–3.0) (*457*–*457*). One study reported an overall specificity of 57.4%, with a specificity of 39.8% for index values of 1.1–2.9 (*458*). Because of the poor specificity of commercially available type-specific EIAs, particularly with low index values (<3.0), a confirmatory test (Biokit or Western blot) with a second method should be performed before test interpretation. Use of confirmatory testing with the Biokit or the Western blot assays have been reported to improve accuracy of HSV-2 serologic testing (*459*). The HerpeSelect HSV-2 immunoblot should not be used for confirmation because it uses the same antigen as the HSV-2 EIA. If confirmatory tests are unavailable, patients should be counseled about the limitations of available testing before obtaining serologic tests, and health care providers should be aware that false-positive results occur. Immunoglobulin M (IgM) testing for HSV-1 or HSV-2 is not useful because IgM tests are not type specific and might be positive during recurrent genital or oral episodes of herpes (*460*). Therefore, HSV IgM testing is not recommended.

Because approximately all HSV-2 infections are sexually acquired, presence of type-specific HSV-2 antibody implies anogenital infection. In this instance, education and counseling for persons with genital HSV infections should be provided. The presence of HSV-1 antibody alone is more difficult to interpret. HSV-1 serologic testing does not distinguish between oral and genital infection and typically should not be performed for diagnosing genital HSV-1 infection. Persons with HSV-1 antibodies often have oral HSV infection acquired during childhood, which might be asymptomatic. Lack of symptoms in a person who is HSV-1 seropositive does not

distinguish anogenital from orolabial or cutaneous infection, and, regardless of site of infection, these persons remain at risk for acquiring HSV-2. In addition, HSV-1 serologic testing has low sensitivity for detection of HSV-1 antibody (*458*). However, acquisition of HSV-1 genital herpes is increasing, and HSV-1 genital herpes also can be asymptomatic (*437–439*,*461*,*462*). Diagnosis of HSV-1 infection is confirmed by virologic tests from genital lesions.

Type-specific HSV-2 serologic assays for diagnosing HSV-2 are useful in the following scenarios: recurrent or atypical genital symptoms or lesions with a negative HSV PCR or culture result, clinical diagnosis of genital herpes without laboratory confirmation, and a patient's partner has genital herpes. HSV-2 serologic screening among the general population is not recommended. Patients who are at higher risk for infection (e.g., those presenting for an STI evaluation, especially for persons with ≥10 lifetime sex partners, and persons with HIV infection) might need to be assessed for a history of genital herpes symptoms, followed by type-specific HSV serologic assays to diagnose genital herpes for those with genital symptoms.

Genital Herpes Management

Antiviral medication offers clinical benefits to symptomatic patients and is the mainstay of management. The goals for use of antiviral medications to treat genital herpes infection are to treat or prevent symptomatic genital herpes recurrences and improve quality of life and suppress the virus to prevent transmission to sexual partners. Counseling regarding the natural history of genital herpes, risks for sexual and perinatal transmission, and methods for reducing transmission is also integral to clinical management.

Systemic antiviral drugs can partially control the signs and symptoms of genital herpes when used to treat first clinical and recurrent episodes or when used as daily suppressive therapy. However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued. Randomized trials have indicated that three FDA-approved antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir (*463–471*). Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration, allowing for less frequent dosing than acyclovir. Famciclovir also has high oral bioavailability. Topical therapy with antiviral drugs offers minimal clinical benefit and is discouraged.

First Clinical Episode of Genital Herpes

Newly acquired genital herpes can cause a prolonged clinical illness with severe genital ulcerations and neurologic involvement. Even persons with first-episode herpes who have mild clinical manifestations initially can experience severe or prolonged symptoms during recurrent infection. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy.

Recommended Regimens for First Clinical Episode of Genital Herpes*

Acyclovir† 400 mg orally 3 times/day for 7–10 days
or
Famciclovir 250 mg orally 3 times/day for 7–10 days
or
Valacyclovir 1 g orally 2 times/day for 7–10 days

* Treatment can be extended if healing is incomplete after 10 days of therapy.
† Acyclovir 200 mg orally 5 times/day is also effective but is not recommended because of the frequency of dosing.

Recurrent HSV-2 Genital Herpes

Almost all persons with symptomatic first-episode HSV-2 genital herpes subsequently experience recurrent episodes of genital lesions. Intermittent asymptomatic shedding occurs among persons with HSV-2 genital herpes infection, even those with longstanding clinically silent infection. Antiviral therapy for recurrent genital herpes can be administered either as suppressive therapy to reduce the frequency of recurrences or episodically to ameliorate or shorten the duration of lesions. Certain persons, including those with mild or infrequent recurrent outbreaks, benefit from antiviral therapy; therefore, options for treatment should be discussed. Many persons prefer suppressive therapy, which has the additional advantage of decreasing the risk for transmitting HSV-2 genital herpes to susceptible partners (*472*,*473*).

Suppressive Therapy for Recurrent HSV-2 Genital Herpes

Suppressive therapy reduces frequency of genital herpes recurrences by 70%–80% among patients who have frequent recurrences (*469–472*). Persons receiving such therapy often report having experienced no symptomatic outbreaks. Suppressive therapy also is effective for patients with less frequent recurrences. Long-term safety and efficacy have been documented among patients receiving daily acyclovir, valacyclovir, and famciclovir (*474*). Quality of life is improved for many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment (*475*). Providers should discuss with patients on an annual basis whether they want to continue suppressive therapy because frequency of genital HSV-2 recurrence diminishes over time for many persons. However, neither treatment discontinuation nor laboratory monitoring is necessary because adverse events and development of HSV antiviral resistance related to long-term antiviral use are uncommon.

Treatment with valacyclovir 500 mg daily decreases the rate of HSV-2 transmission for discordant heterosexual couples in which a partner has a history of genital HSV-2 infection (*473*). Such couples should be encouraged to consider suppressive antiviral therapy as part of a strategy for preventing transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy for persons with a history of symptomatic genital herpes also is likely to reduce transmission when used by those who have multiple partners. HSV-2 seropositive persons without a history of symptomatic genital herpes have a 50% decreased risk for genital shedding, compared with those with symptomatic genital herpes (*476*). No data are available regarding efficacy of suppressive therapy for preventing HSV-2 transmission among discordant couples in which a partner has a history of asymptomatic HSV-2 infection identified by a positive HSV-2 serologic test. Among HSV-2 seropositive persons without HIV infection, oral TDF/FTC and intravaginal tenofovir are ineffective at reducing the risk for HSV-2 shedding or recurrences (*477*).

Recommended Regimens for Suppression of Recurrent HSV-2 Genital Herpes

Acyclovir 400 mg orally 2 times/day
or
Valacyclovir 500 mg orally once a day*
or
Valacyclovir 1 g orally once a day
or
Famciclovir 250 mg orally 2 times/day

* Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens for persons who have frequent recurrences (i.e., ≥10 episodes/year).

Famciclovir appears somewhat less effective for suppression of viral shedding (*478*). Ease of administration and cost also are key considerations for prolonged treatment.

Recurrent HSV-1 Genital Herpes

Recurrences are less frequent after the first episode of HSV-1 genital herpes, compared with genital HSV-2 genital herpes, and genital shedding rapidly decreases during the first year of infection (*479*). No data are available regarding the efficacy of suppressive therapy for preventing transmission among persons with HSV-1 genital herpes infection. Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences through shared clinical decision-making between the patient and the provider.

Episodic Therapy for Recurrent HSV-2 Genital Herpes

Episodic treatment of recurrent herpes is most effective if therapy is initiated within 1 day of lesion onset or during the prodrome that precedes some outbreaks. The patient should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin. Acyclovir, famciclovir, and valacyclovir appear equally effective for episodic treatment of genital herpes (*466–470*).

Recommended Regimens for Episodic Therapy for Recurrent HSV-2 Genital Herpes*

Acyclovir 800 mg orally 2 times/day for 5 days
or
Acyclovir 800 mg orally 3 times/day for 2 days
or
Famciclovir 1 g orally 2 times/day for 1 day
or
Famciclovir 500 mg orally once, followed by 250 mg 2 times/day for 2 days
or
Famciclovir 125 mg orally 2 times/day for 5 days
or
Valacyclovir 500 mg orally 2 times/day for 3 days
or
Valacyclovir 1 g orally once daily for 5 days

* Acyclovir 400 mg orally 3 times/day for 5 days is also effective but is not recommended because of frequency of dosing.

Severe Disease

Intravenous (IV) acyclovir therapy (5–10 mg/kg body weight IV every 8 hours) should be provided for patients who have severe HSV disease or complications that necessitate hospitalization (e.g., disseminated infection, pneumonitis, or hepatitis) or CNS complications (e.g., meningitis or encephalitis). HSV-2 meningitis is a rare complication of HSV-2 genital herpes infection that affects women more than men (*480*). IV therapy should be considered until clinical improvement followed by oral antiviral therapy to complete >10 days of total therapy. Longer duration is recommended for CNS complications. HSV-2 meningitis is characterized clinically by signs of headache, photophobia, fever, meningismus, and cerebrospinal fluid (CSF) lymphocytic pleocytosis, accompanied by mildly elevated protein and normal glucose (*481*). Optimal therapies for HSV-2 meningitis have not been well studied (*482*); however, acyclovir 5–10 mg/kg body weight IV every 8 hours until clinical improvement is observed, followed by high-dose oral antiviral therapy (valacyclovir 1 g 3 times/day) to complete a 10- to 14-day course of total therapy, is recommended. For patients with previous episodes of documented HSV-2 meningitis, oral valacyclovir may be used for the entire course during episodes of recurrent HSV-2 meningitis. A randomized clinical trial indicated that suppressive therapy (valacyclovir 500 mg 2 times/day) did not prevent recurrent HSV-2 meningitis episodes; however, the dose might not have been sufficient for CNS penetration (*483*). Valacyclovir

500 mg 2 times/day is not recommended for suppression of HSV-2 meningitis; higher doses have not been studied in clinical trials. HSV meningitis should be distinguished from encephalitis, which requires a longer course (14–21 days) of IV therapy. Impaired renal function warrants an adjustment in acyclovir dosage.

Hepatitis

Hepatitis is a rare manifestation of disseminated HSV infection, often reported among pregnant women who acquire HSV during pregnancy (*484*). Pregnant women in any trimester can present with fever and hepatitis (markedly elevated transaminases) but might not have any genital or skin lesions. HSV hepatitis is associated with fulminant liver failure and high mortality (25%). Therefore, a high index of suspicion for HSV is necessary, with a confirmatory diagnosis by HSV PCR from blood (*485*). Among pregnant women with fever and unexplained severe hepatitis, disseminated HSV infection should be considered, and empiric IV acyclovir should be initiated pending confirmation (*484*).

Prevention

Consistent and correct condom use has been reported in multiple studies to decrease, but not eliminate, the risk for HSV-2 transmission from men to women (*486*–*488*). Condoms are less effective for preventing transmission from women to men (*489*). Two randomized clinical trials of medical male circumcision (MMC) demonstrated a decreased risk for HSV-2 acquisition among men in Uganda and South Africa (*66*,*68*). Results from a third trial conducted in Kenya did not demonstrate a substantial difference in HSV-2 acquisition among men who received MMC (*490*). A systematic review indicated high consistency for decreased risk for HSV-2 acquisition among women with a male partner who underwent MMC (*491*). These data indicate that MMC can be associated with decreased risk for HSV-2 acquisition among adult heterosexual men and with decreased risk for HSV-2 transmission from male to female partners.

Randomized clinical trials have demonstrated that PrEP with daily oral TDF/FTC decreases the risk for HSV-2 acquisition by 30% in heterosexual partnerships (*492*). Pericoital intravaginal tenofovir 1% gel also decreases the risk for HSV-2 acquisition among heterosexual women (*493*). Among MSM and transgender women, daily oral TDF/FTC decreases the risk for severe ulcers with symptomatic genital HSV-2 infection but not for HSV-2 acquisition (*494*). Insufficient evidence exists that TDF/FTC use among those who are not at risk for HIV acquisition will prevent HSV-2 infection, and it should not be used for that sole purpose. Oral TDF does not prevent HSV-2 acquisition among persons with HIV infection who are taking TDF as part of their ART regimen (*495*). No data indicate that antivirals (acyclovir, valacyclovir, or famciclovir) can be taken as PrEP by persons without HSV-2 to prevent its acquisition.

Counseling

Counseling of persons with genital herpes and their sex partners is crucial for management. The goals of counseling include helping patients cope with the infection and preventing sexual and perinatal transmission. Although initial counseling can be provided at the first visit, patients often benefit from learning about the chronic aspects of the disease after the acute illness subsides. Multiple resources, including Internet sites and printed materials, are available to assist patients, their partners, and clinicians who provide counseling (*496*,*497*) (https://www.ashasexualhealth.org and https://www.cdc.gov/std/herpes).

Although the psychological effect of a serologic diagnosis of HSV-2 infection in a person with asymptomatic or unrecognized genital herpes appears minimal and transient (*498*,*499*), certain persons with HSV infection might express anxiety concerning genital herpes that does not reflect the actual clinical severity of their disease; the psychological effect of HSV infection can be substantial. Common concerns about genital herpes include the severity of initial clinical manifestations, recurrent episodes, sexual relationships and transmission to sex partners, and ability to bear healthy children.

Symptomatic HSV-2 Genital Herpes

When counseling persons with symptomatic HSV-2 genital herpes infection, the provider should discuss the following:

- The natural history of the disease, with emphasis on the potential for recurrent episodes, asymptomatic viral shedding, and the attendant risks for sexual transmission of HSV to occur during asymptomatic periods (asymptomatic viral shedding is most frequent during the first 12 months after acquiring HSV-2).
- The effectiveness of daily suppressive antiviral therapy for preventing symptomatic recurrent episodes of genital herpes for persons experiencing a first episode or recurrent genital herpes.
- The effectiveness of daily use of valacyclovir in reducing risk for transmission of HSV-2 among persons without HIV (*473*) and use of episodic therapy to shorten the duration of recurrent episodes.
- The importance of informing current sex partners about genital herpes and informing future partners before initiating a sexual relationship.
- The importance of abstaining from sexual activity with uninfected partners when lesions or prodromal symptoms are present.

- The effectiveness of male latex condoms, which when used consistently and correctly can reduce, but not eliminate, the risk for genital herpes transmission (*486*–*488*).
- The type-specific serologic testing of partners of persons with symptomatic HSV-2 genital herpes to determine whether such partners are already HSV seropositive or whether risk for acquiring HSV exists.
- The low risk for neonatal HSV except when genital herpes is acquired late in pregnancy or if prodrome or lesions are present at delivery.
- The increased risk for HIV acquisition among HSV-2 seropositive persons who are exposed to HIV (*76*,*471*).
- The lack of effectiveness of episodic or suppressive therapy among persons with HIV infection to reduce risk for transmission to partners who might be at risk for HSV-2 acquisition.

Asymptomatic HSV-2 Genital Herpes

When counseling persons with asymptomatic HSV-2 genital herpes infection, the provider should consider the following:

- Asymptomatic persons who receive a diagnosis of HSV-2 by type-specific serologic testing (with confirmatory testing, if needed) should receive education about the symptoms of genital herpes infection (see Diagnostic Considerations).
- Episodic and suppressive antiviral therapies are used predominantly to treat recurrences, prevent recurrences, and prevent transmission to sex partners of persons with symptomatic HSV-2 infection.
- For patients with serological evidence of HSV-2 (with combination testing if needed) without symptomatic recurrences, neither episodic nor suppressive therapy is indicated for prevention of recurrences (see Diagnostic Considerations).
- Among persons with asymptomatic infection, the efficacy of suppressive therapy to prevent HSV-2 transmission to sex partners has not been studied.
- Because of the decreased risk for shedding among those with asymptomatic HSV-2 genital herpes, the benefit of suppressive therapy for preventing transmission is unknown among this population.

HSV-1 Genital Herpes

When counseling persons with HSV-1 genital herpes infection, the provider should consider the following:

- Persons with virologic laboratory-documented symptomatic HSV-1 genital herpes infection should be educated that the risk for recurrent genital herpes and genital shedding is lower with HSV-1 infection, compared with HSV-2 infection.
- Because of the decreased risk for recurrences and shedding, suppressive therapy for HSV-1 genital herpes should be reserved for those with frequent recurrences.
- For patients with frequently recurring HSV-1 genital herpes, suppressive therapy might be considered. Suppressive therapy to prevent HSV-1 transmission to sex partners has not been studied.

For persons with symptomatic HSV-1 genital herpes or asymptomatic HSV-2 genital herpes, suppressive therapy can be considered for those who have substantial psychosocial distress caused by the diagnosis of genital herpes. For women who have genital herpes, the providers who care for them during pregnancy and those who will care for their newborn infant should be informed of their infection (see Genital Herpes During Pregnancy).

Management of Sex Partners

The sex partners of persons who have symptomatic genital herpes can benefit from evaluation and counseling. Symptomatic sex partners should be evaluated and treated in the same manner as patients who have symptomatic genital herpes. Asymptomatic sex partners of patients who have symptomatic genital herpes should be asked about a history of genital symptoms and offered type-specific serologic testing for HSV-2. For partners without genital herpes, no data are available on which to base a recommendation for PEP or PrEP with antiviral medications or that they would prevent acquisition, and this should not be offered to patients as a prevention strategy.

Special Considerations

Drug Allergy, Intolerance, or Adverse Reactions

Allergic and other adverse reactions to oral acyclovir, valacyclovir, and famciclovir are rare. Desensitization to acyclovir has been described (*500*).

HIV Infection

Immunocompromised patients can have prolonged or severe episodes of genital, perianal, or oral herpes. Lesions caused by HSV are common among persons with HIV infection and might be severe, painful, and atypical (*501*). HSV shedding is increased among persons with HIV infection (*502*). Whereas ART reduces the severity and frequency of symptomatic genital herpes, frequent subclinical shedding still occurs (*503*,*504*). Clinical manifestations of genital herpes might worsen during immune reconstitution early after initiation of ART. HSV-2 type-specific serologic testing can be considered for persons with HIV infection during their initial evaluation, particularly among those with a history of genital symptoms indicative of HSV infection.

Recommended therapy for first-episode genital herpes is the same as for persons without HIV infection, although treatment courses might need to be extended for lesion resolution. Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV infection among persons with HIV (*503*,*504*). The risk for GUD increases during the first 6 months after starting ART, especially among persons who have a $CD4^+$ T-cell count <200 cell/mm^3. Suppressive antiviral therapy reduces the risk for GUD among this population and can be continued for 6 months after ART initiation (*504*) when the risk for GUD returns to baseline levels. Suppressive antiviral therapy among persons with HIV and HSV infection does not reduce the risk for either HIV transmission or HSV-2 transmission to susceptible sex partners (*88*,*505*). Suppressive antiviral therapy does not delay HIV disease progression and is not associated with decreased risk for HIV-related inflammation among persons taking ART (*506*). For severe HSV disease, initiating therapy with acyclovir 5–10 mg/kg IV every 8 hours might be necessary.

Recommended Regimens for Daily Suppression of Genital Herpes Among Persons with HIV Infection

Acyclovir 400–800 mg orally 2–3 times/day
or
Famciclovir 500 mg orally 2 times/day
or
Valacyclovir 500 mg orally 2 times/day

Recommended Regimens for Episodic Genital Herpes Infection Among Persons with HIV Infection

Acyclovir 400 mg orally 3 times/day for 5–10 days
or
Famciclovir 500 mg orally 2 times/day for 5–10 days
or
Valacyclovir 1 g orally 2 times/day for 5–10 days

Antiviral-Resistant HSV Infection

If lesions persist or recur in a patient receiving antiviral treatment, acyclovir resistance should be suspected and a viral culture obtained for phenotypic sensitivity testing (*507*). Molecular testing for acyclovir resistance is not available. Such persons should be managed in consultation with an infectious disease specialist, and alternative therapy should be administered. All acyclovir-resistant strains are also resistant to valacyclovir, and the majority are resistant to famciclovir. Foscarnet (40–80 mg/kg body weight IV every 8 hours until clinical resolution is attained) is the treatment of choice for acyclovir-resistant genital herpes (*508*,*509*). Intravenous cidofovir 5 mg/kg body weight once weekly might also be effective. Foscarnet and cidofovir are nephrotoxic medications that require intensive laboratory monitoring and infectious disease specialist consultation. Imiquimod 5% applied to the lesion for 8 hours 3 times/week until clinical resolution is an alternative that has been reported to be effective (*510*,*511*). Topical cidofovir gel 1% can be applied to lesions 2–4 times daily; however, cidofovir must be compounded at a pharmacy (*512*).

Prevention of antiviral resistance remains challenging among persons with HIV infection. Experience with another group of immunocompromised persons (e.g., hematopoietic stem-cell recipients) demonstrated that persons receiving daily suppressive antiviral therapy were less likely to experience acyclovir-resistant HSV infection compared with those who received episodic therapy for outbreaks (*513*).

Genital Herpes During Pregnancy

Prevention of neonatal herpes depends both on preventing acquisition of genital herpes during late pregnancy and avoiding exposure of the neonate to herpetic lesions and viral shedding during delivery. Mothers of newborns who acquire neonatal herpes often lack histories of clinically evident genital herpes (*514*,*515*). The risk for transmission to the neonate from an infected mother is high (30%–50%) among women who acquire genital herpes near the time of delivery and low (<1%) among women with prenatal histories of recurrent herpes or who acquire genital herpes during the first half of pregnancy (*516*,*517*). Women who acquire HSV in the second half of pregnancy should be managed in consultation with maternal-fetal medicine and infectious disease specialists.

All pregnant women should be asked whether they have a history of genital herpes or genital symptoms concerning for HSV infection. At the onset of labor, all women should be questioned thoroughly about symptoms of genital herpes, including prodromal symptoms (e.g., pain or burning at site before appearance of lesion), and all women should be examined thoroughly for herpetic lesions. Women without symptoms or signs of genital herpes or its prodrome can deliver vaginally. Although cesarean delivery does not eliminate the risk for HSV transmission to the neonate (*517*), women with recurrent genital herpetic lesions at the onset of labor should have a cesarean delivery to reduce the risk for neonatal HSV infection.

Routine HSV-2 serologic screening of pregnant women is not recommended. Women without known genital herpes should be counseled to abstain from vaginal intercourse during the third trimester with partners known to have or suspected of having genital herpes. In addition, to prevent HSV-1 genital herpes, pregnant women without known orolabial herpes should be advised to abstain from receptive oral sex during the third trimester with partners known to have or suspected to have orolabial herpes. Type-specific serologic tests can be useful for identifying pregnant women at risk for HSV infection and for guiding counseling regarding the risk for acquiring genital

herpes during pregnancy. For example, such testing might be offered to a woman with no history of genital herpes whose sex partner has HSV infection. Many fetuses are exposed to acyclovir each year, and the medication is believed to be safe for use during all trimesters of pregnancy. A case-control study reported an increased risk for the rare neonatal outcome of gastroschisis among women who used antiviral medications between the month before conception and the third month of pregnancy (*518*). Acyclovir is also believed to be safe during breastfeeding (*431*,*519*). Although data regarding prenatal exposure to valacyclovir and famciclovir are limited, data from animal trials indicate that these drugs also pose a low risk among pregnant women (*520*). Acyclovir can be administered orally to pregnant women with first-episode genital herpes or recurrent herpes and should be administered IV to pregnant women with severe HSV (see Genital Herpes, Hepatitis). Suppressive acyclovir treatment starting at 36 weeks' gestation reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term (*521*–*523*). However, such treatment might not protect against transmission to neonates in all cases (*524*). No data support use of antiviral therapy among asymptomatic HSV-seropositive women without a history of genital herpes. In addition, the effectiveness of antiviral therapy among sex partners with a history of genital herpes to decrease the risk for HSV transmission to a pregnant woman has not been studied. Additional information on the clinical management of genital herpes in pregnancy is available through existing guidelines (*525*).

Recommended Regimen for Suppression of Recurrent Genital Herpes Among Pregnant Women*
Acyclovir 400 mg orally 3 times/day *or* **Valacyclovir** 500 mg orally 2 times/day

* Treatment recommended starting at 36 weeks' gestation.

Neonatal Herpes

Newborn infants exposed to HSV during birth, as documented by virologic testing of maternal lesions at delivery or presumed by observation of maternal lesions, should be followed clinically in consultation with a pediatric infectious disease specialist. Detailed guidance is available regarding management of neonates who are delivered vaginally in the presence of maternal genital herpes lesions and is beyond the scope of these guidelines; more information is available from the AAP (https://redbook.solutions.aap.org). Surveillance cultures or PCR of mucosal surfaces of the neonate to detect HSV infection might be considered before the development of clinical signs of neonatal herpes to guide treatment initiation. In addition, administration of acyclovir might be considered for neonates born to women who acquired HSV near term because the risk for neonatal herpes is high for these newborn infants. All newborn infants who have neonatal herpes should be promptly evaluated and treated with systemic acyclovir. The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 14 days if disease is limited to the skin and mucous membranes, or for 21 days for disseminated disease and disease involving the CNS.

Granuloma Inguinale (Donovanosis)

Granuloma inguinale (donovanosis) is a genital ulcerative disease caused by the intracellular gram-negative bacterium *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*). The disease occurs rarely in the United States; however, sporadic cases have been described in India, South Africa, and South America (*526*–*535*). Although granuloma inguinale was previously endemic in Australia, it is now extremely rare (*536*,*537*). Clinically, the disease is characterized as painless, slowly progressive ulcerative lesions on the genitals or perineum without regional lymphadenopathy; subcutaneous granulomas (pseudobuboes) also might occur. The lesions are highly vascular (i.e., beefy red appearance) and can bleed. Extragenital infection can occur with infection extension to the pelvis, or it can disseminate to intra-abdominal organs, bones, or the mouth. The lesions also can develop secondary bacterial infection and can coexist with other sexually transmitted pathogens.

Diagnostic Considerations

The causative organism of granuloma inguinale is difficult to culture, and diagnosis requires visualization of dark-staining Donovan bodies on tissue crush preparation or biopsy. Although no FDA-cleared molecular tests for the detection of *K. granulomatis* DNA exist, molecular assays might be useful for identifying the causative agent.

Treatment

Multiple antimicrobial regimens have been effective; however, only a limited number of controlled trials have been published (*538*). Treatment has been reported to halt progression of lesions, and healing typically proceeds inward from the ulcer margins. Prolonged therapy is usually required to permit granulation and reepithelialization of the ulcers. Relapse can occur 6–18 months after apparently effective therapy.

Recommended Regimen for Granuloma Inguinale (Donovanosis)
Azithromycin 1 g orally once/week or 500 mg daily for >3 weeks and until all lesions have completely healed

Alternative Regimens
Doxycycline 100 mg orally 2 times/day for at least 3 weeks and until all lesions have completely healed *or* **Erythromycin base** 500 mg orally 4 times/day for >3 weeks and until all lesions have completely healed *or* **Trimethoprim-sulfamethoxazole** one double-strength (160 mg/800 mg) tablet orally 2 time/day for >3 weeks and until all lesions have completely healed

The addition of another antibiotic to these regimens can be considered if improvement is not evident within the first few days of therapy.

Other Management Considerations

Patients should be followed clinically until signs and symptoms have resolved. All persons who receive a diagnosis of granuloma inguinale should be tested for HIV.

Follow-Up

Patients should be followed clinically until signs and symptoms resolve.

Management of Sex Partners

Persons who have had sexual contact with a patient who has granuloma inguinale within the 60 days before onset of the patient's symptoms should be examined and offered therapy. However, the value of empiric therapy in the absence of clinical signs and symptoms has not been established.

Special Considerations

Pregnancy

Use of doxycycline in pregnancy might be associated with discoloration of teeth; however, the risk is not well defined. Doxycycline is compatible with breastfeeding (*431*). Sulfonamides can be associated with neonatal kernicterus among those with glucose-6-phospate dehydrogenase deficiency and should be avoided during the third trimester and while breastfeeding (*431*). For these reasons, pregnant and lactating women with granuloma inguinale should be treated with a macrolide regimen (erythromycin or azithromycin).

HIV Infection

Persons with granuloma inguinale and HIV infection should receive the same regimens as those who do not have HIV.

Lymphogranuloma Venereum

LGV is caused by *C. trachomatis* serovars L1, L2, or L3 (*539*,*540*). LGV can cause severe inflammation and invasive infection, in contrast with *C. trachomatis* serovars A–K that cause mild or asymptomatic infection. Clinical manifestations of LGV can include GUD, lymphadenopathy, or proctocolitis. Rectal exposure among MSM or women can result in proctocolitis, which is the most common presentation of LGV infection (*541*), and can mimic inflammatory bowel disease with clinical findings of mucoid or hemorrhagic rectal discharge, anal pain, constipation, fever, or tenesmus (*542*,*543*). Outbreaks of LGV proctocolitis have been reported among MSM with high rates of HIV infection (*544*–*547*). LGV proctocolitis can be an invasive, systemic infection and, if it is not treated early, can lead to chronic colorectal fistulas and strictures; reactive arthropathy has also been reported. However, reports indicate that rectal LGV can also be asymptomatic (*548*). A common clinical manifestation of LGV among heterosexuals is tender inguinal or femoral lymphadenopathy that is typically unilateral. A self-limited genital ulcer or papule sometimes occurs at the site of inoculation. However, by the time persons seek care, the lesions have often disappeared. LGV-associated lymphadenopathy can be severe, with bubo formation from fluctuant or suppurative inguinal or femoral lymphadenopathy. Oral ulceration can occur and might be associated with cervical adenopathy (*549*–*551*). Persons with genital or colorectal LGV lesions can also experience secondary bacterial infection or can be infected with other sexually and nonsexually transmitted pathogens.

Diagnostic Considerations

A definitive LGV diagnosis can be made only with LGV-specific molecular testing (e.g., PCR-based genotyping). These tests can differentiate LGV from non–LGV *C. trachomatis* in rectal specimens. However, these tests are not widely available, and results are not typically available in a time frame that would influence clinical management. Therefore, diagnosis is based on clinical suspicion, epidemiologic information, and a *C. trachomatis* NAAT at the symptomatic anatomic site, along with exclusion of other etiologies for proctocolitis, inguinal lymphadenopathy, or genital, oral, or rectal ulcers (*551*,*552*). Genital or oral lesions, rectal specimens, and lymph node specimens (i.e., lesion swab or bubo aspirate) can be tested for *C. trachomatis* by NAAT or culture. NAAT is the preferred approach for testing because it can detect both LGV strains and non–LGV *C. trachomatis* strains (*553*). Therefore, all persons presenting with proctocolitis should be tested for chlamydia with a NAAT performed on rectal specimens. Severe symptoms of proctocolitis (e.g., bloody discharge, tenesmus, and rectal

ulcers) indicate LGV. A rectal Gram stain with >10 white blood cells (WBCs) has also been associated with rectal LGV (*545*,*554*,*555*).

Chlamydia serology (complement fixation or microimmunofluorescence) should not be used routinely as a diagnostic tool for LGV because the utility of these serologic methods has not been established, interpretation has not been standardized, and validation for clinical proctitis presentation has not been done. It might support an LGV diagnosis in cases of isolated inguinal or femoral lymphadenopathy for which diagnostic material for *C. trachomatis* NAAT cannot be obtained.

Treatment

At the time of the initial visit (before diagnostic NAATs for chlamydia are available), persons with a clinical syndrome consistent with LGV should be presumptively treated. Presumptive treatment for LGV is indicated among patients with symptoms or signs of proctocolitis (e.g., bloody discharge, tenesmus, or ulceration); in cases of severe inguinal lymphadenopathy with bubo formation, particularly if the patient has a recent history of a genital ulcer; or in the presence of a genital ulcer if other etiologies have been ruled out. The goal of treatment is to cure infection and prevent ongoing tissue damage, although tissue reaction to the infection can result in scarring. Buboes might require aspiration through intact skin or incision and drainage to prevent formation of inguinal or femoral ulcerations.

Recommended Regimen for Lymphogranuloma Venereum
Doxycycline 100 mg orally 2 times/day for 21 days

Alternative Regimens
Azithromycin 1 g orally once weekly for 3 weeks*
or
Erythromycin base 500 mg orally 4 times/day for 21 days

* Because this regimen has not been validated, a test of cure with *C. trachomatis* NAAT 4 weeks after completion of treatment can be considered.

The optimal treatment duration for symptomatic LGV has not been studied in clinical trials. The recommended 21-day course of doxycycline is based on long-standing clinical practice and is highly effective, with an estimated cure rate of >98.5% (*555*,*556*). Shorter courses of doxycycline might be effective on the basis of a small retrospective study of MSM with rectal LGV, 50% of whom were symptomatic, who received a 7- to 14-day course of doxycycline and had a 97% cure rate (*558*). Randomized prospective studies of shorter-course doxycycline for treating LGV are needed. Longer courses of therapy might be required in the setting of fistulas, buboes, and other forms of severe disease (*559*).

A small nonrandomized study from Spain involving patients with rectal LGV demonstrated cure rates of 97% with a regimen of azithromycin 1 g once weekly for 3 weeks (*560*). Pharmacokinetic data support this dosing strategy (*561*); however, this regimen has not been validated. Fluoroquinolone-based treatments also might be effective; however, the optimal duration of treatment has not been evaluated. The clinical significance of asymptomatic LGV is unknown, and it is effectively treated with a 7-day course of doxycycline (*562*).

Other Management Considerations

Patients should be followed clinically until signs and symptoms have resolved. Persons who receive an LGV diagnosis should be tested for other STIs, especially HIV, gonorrhea, and syphilis. Those whose HIV test results are negative should be offered HIV PrEP.

Follow-Up

All persons who have been treated for LGV should be retested for chlamydia approximately 3 months after treatment. If retesting at 3 months is not possible, providers should retest at the patient's next visit for medical care within the 12-month period after initial treatment.

Management of Sex Partners

Persons who have had sexual contact with a patient who has LGV within the 60 days before onset of the patient's symptoms should be evaluated, examined, and tested for chlamydial infection, depending on anatomic site of exposure. Asymptomatic partners should be presumptively treated with a chlamydia regimen (doxycycline 100 mg orally 2 times/day for 7 days).

Special Considerations

Pregnancy

Use of doxycycline in pregnancy might be associated with discoloration of teeth; however, the risk is not well defined (*563*). Doxycycline is compatible with breastfeeding (*431*). Azithromycin might prove useful for LGV treatment during pregnancy, at a presumptive dose of 1 g weekly for 3 weeks; no published data are available regarding an effective dose and duration of treatment. Pregnant and lactating women with LGV can be treated with erythromycin, although this regimen is associated with frequent gastrointestinal side effects. Pregnant women treated for LGV should have a test of cure performed 4 weeks after the initial *C. trachomatis* NAAT-positive test.

HIV Infection

Persons with LGV and HIV infection should receive the same regimens as those who do not have HIV. Prolonged therapy might be required because a delay in resolution of symptoms might occur.

Syphilis

Syphilis is a systemic disease caused by *T. pallidum*. The disease has been divided into stages on the basis of clinical findings, which guide treatment and follow-up. Persons who have syphilis might seek treatment for signs or symptoms. Primary syphilis classically presents as a single painless ulcer or chancre at the site of infection but can also present with multiple, atypical, or painful lesions (*564*). Secondary syphilis manifestations can include skin rash, mucocutaneous lesions, and lymphadenopathy. Tertiary syphilis can present with cardiac involvement, gummatous lesions, tabes dorsalis, and general paresis.

Latent infections (i.e., those lacking clinical manifestations) are detected by serologic testing. Latent syphilis acquired within the preceding year is referred to as early latent syphilis; all other cases of latent syphilis are classified as late latent syphilis or latent syphilis of unknown duration.

T. pallidum can infect the CNS, which can occur at any stage of syphilis and result in neurosyphilis. Early neurologic clinical manifestations or syphilitic meningitis (e.g., cranial nerve dysfunction, meningitis, meningovascular syphilis, stroke, and acute altered mental status) are usually present within the first few months or years of infection. Late neurologic manifestations (e.g., tabes dorsalis and general paresis) occur 10 to >30 years after infection.

Infection of the visual system (ocular syphilis) or auditory system (otosyphilis) can occur at any stage of syphilis but is commonly identified during the early stages and can present with or without additional CNS involvement. Ocular syphilis often presents as panuveitis but can involve structures in both the anterior and posterior segment of the eye, including conjunctivitis, anterior uveitis, posterior interstitial keratitis, optic neuropathy, and retinal vasculitis. Ocular syphilis can result in permanent vision loss. Otosyphilis typically presents with cochleo-vestibular symptoms, including tinnitus, vertigo, and sensorineural hearing loss. Hearing loss can be unilateral or bilateral, have a sudden onset, and progress rapidly. Otosyphilis can result in permanent hearing loss.

Diagnostic Considerations

Darkfield examinations and molecular tests for detecting *T. pallidum* directly from lesion exudate or tissue are the definitive methods for diagnosing early syphilis and congenital syphilis (*565*). Although no *T. pallidum* direct-detection molecular NAATs are commercially available, certain laboratories provide locally developed and validated PCR tests for detecting *T. pallidum* DNA. A presumptive diagnosis of syphilis requires use of two laboratory serologic tests: a nontreponemal test (i.e., Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR] test) and a treponemal test (i.e., the *T. pallidum* passive particle agglutination [TP-PA] assay, various EIAs, chemiluminescence immunoassays [CIAs] and immunoblots, or rapid treponemal assays) (*566*–*568*). At least 18 treponemal-specific tests are cleared for use in the United States. Use of only one type of serologic test (nontreponemal or treponemal) is insufficient for diagnosis and can result in false-negative results among persons tested during primary syphilis and false-positive results among persons without syphilis or previously treated syphilis.

Nontreponemal Tests and Traditional Algorithm

False-positive nontreponemal test results can be associated with multiple medical conditions and factors unrelated to syphilis, including other infections (e.g., HIV), autoimmune conditions, vaccinations, injecting drug use, pregnancy, and older age (*566*,*569*). Therefore, persons with a reactive nontreponemal test should always receive a treponemal test to confirm the syphilis diagnosis (i.e., traditional algorithm). Nontreponemal test antibody titers might correlate with disease activity and are used for monitoring treatment response. Serum should be diluted to identify the highest titer, and results should be reported quantitatively. A fourfold change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32), is considered necessary for demonstrating a clinically significant difference between two nontreponemal test results obtained by using the same serologic test, preferably from the same manufacturer to avoid variation in results. Sequential serologic tests for a patient should be performed using the same testing method (VDRL or RPR), preferably by the same laboratory. VDRL and RPR are equally valid assays; however, quantitative results from the two tests cannot be compared directly with each other because the methods are different, and RPR titers frequently are slightly higher than VDRL titers.

Nontreponemal test titers usually decrease after treatment and might become nonreactive with time. However, for certain persons, nontreponemal antibodies might decrease less than fourfold after treatment (i.e., inadequate serologic response) or might decline appropriately but fail to serorevert and

persist for a long period. Atypical nontreponemal serologic test results (e.g., unusually high, unusually low, or fluctuating titers) might occur regardless of HIV status. When serologic tests do not correspond with clinical findings indicative of primary, secondary, or latent syphilis, presumptive treatment is recommended for persons with risk factors for syphilis, and use of other tests (e.g., biopsy for histology and immunostaining and PCR of lesion) should be considered. For the majority of persons with HIV infection, serologic tests are accurate and reliable for diagnosing syphilis and evaluating response to treatment.

Treponemal Tests and Reverse Sequence Algorithm

The majority of patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of adequate treatment or disease activity. However, 15%–25% of patients treated during the primary stage revert to being serologically nonreactive after 2–3 years (*570*). Treponemal antibody titers do not predict treatment response and therefore should not be used for this purpose.

Clinical laboratories sometimes screen syphilis serologic samples by using automated treponemal immunoassays, typically by EIA or CIA (*571–573*). This reverse sequence algorithm for syphilis testing can identify persons previously treated for syphilis, those with untreated or incompletely treated syphilis, and those with false-positive results that can occur with a low likelihood of infection (*574*). Persons with a positive treponemal screening test should have a standard quantitative nontreponemal test with titer performed reflexively by the laboratory to guide patient management decisions. If the nontreponemal test is negative, the laboratory should perform a treponemal test different from the one used for initial testing, preferably TP-PA or treponemal assay based on different antigens than the original test, to adjudicate the results of the initial test.

If a second treponemal test is positive (e.g., EIA reactive, RPR nonreactive, or TP-PA reactive), persons with a history of previous treatment will require no further management unless sexual history indicates a reexposure. In this instance, a repeat nontreponemal test 2–4 weeks after a confirmed medical history and physical examination is recommended to evaluate for early infection. Those without a history of treatment for syphilis should be offered treatment. Unless a medical history or results of a physical examination indicate a recent infection, previously untreated persons should be treated for syphilis of unknown duration or late latent syphilis.

If the second treponemal test is negative (e.g., EIA reactive, RPR nonreactive, TP-PA nonreactive) and the epidemiologic risk and clinical probability for syphilis are low, further evaluation or treatment is not indicated.

Multiple studies demonstrate that high quantitative index values or high signal-to-cutoff ratio from treponemal EIA or CIA tests correlate with TP-PA positivity, which might eliminate the need for additional confirmatory testing; however, the range of index values varies among different treponemal immunoassays, and the values that correspond to high levels of reactivity with confirmatory testing might differ by immunoassay (*567*,*575–582*).

Cerebrospinal Fluid Evaluation

Further testing with CSF evaluation is warranted for persons with clinical signs of neurosyphilis (e.g., cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, or loss of vibration sense). All patients with ocular symptoms and reactive syphilis serology need a full ocular examination, including cranial nerve evaluation. If cranial nerve dysfunction is present, a CSF evaluation is needed. Among persons with isolated ocular symptoms (i.e., no cranial nerve dysfunction or other neurologic abnormalities), confirmed ocular abnormalities on examination, and reactive syphilis serology, a CSF examination is unnecessary before treatment. CSF analysis can be helpful in evaluating persons with ocular symptoms and reactive syphilis serology who do not have ocular findings or cranial nerve dysfunction on examination. Among patients with isolated auditory abnormalities and reactive syphilis serology, CSF evaluation is likely to be normal and is unnecessary before treatment (*583*,*584*).

Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis in all instances. Diagnosis of neurosyphilis depends on a combination of CSF tests (e.g., CSF cell count, protein, or reactive CSF-VDRL) in the presence of reactive serologic test (nontreponemal and treponemal) results and neurologic signs and symptoms. CSF laboratory abnormalities are common for persons with early syphilis and are of unknown medical significance in the absence of neurologic signs or symptoms (*585*). CSF-VDRL is highly specific but insensitive. For a person with neurologic signs or symptoms, a reactive CSF-VDRL (in the absence of blood contamination) is considered diagnostic of neurosyphilis.

When CSF-VDRL is negative despite clinical signs of neurosyphilis, reactive serologic tests results, lymphocytic pleocytosis, or protein, neurosyphilis should be considered. In that instance, additional evaluation by using fluorescent treponemal-antibody absorption (FTA-ABS) or TP-PA testing on CSF might be warranted. The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive. Fewer data are available regarding CSF TP-PA;

however, the sensitivity and specificity appear similar to the CSF FTA-ABS (*586*). Neurosyphilis is highly unlikely with a negative CSF FTA-ABS or TP-PA test, especially among persons with nonspecific neurologic signs and symptoms (*587*).

Among persons with HIV infection, CSF leukocyte count can be elevated (>5 WBCs/mm^3); the association with CSF leukocyte count and plasma HIV viral suppression has not been well characterized. Using a higher cutoff (>20 WBCs/mm^3) might improve the specificity of neurosyphilis diagnosis among this population (*588*).

Treatment

Penicillin G, administered parenterally, is the preferred drug for treating patients in all stages of syphilis. The preparation used (i.e., benzathine, aqueous procaine, or aqueous crystalline), dosage, and length of treatment depend on the stage and clinical manifestations of the disease. Treatment for late latent syphilis (>1 years' duration) and tertiary syphilis requires a longer duration of therapy because organisms theoretically might be dividing more slowly (the validity of this rationale has not been assessed). Longer treatment duration is required for persons with latent syphilis of unknown duration to ensure that those who did not acquire syphilis within the preceding year are adequately treated.

Selection of the appropriate penicillin preparation is important because *T. pallidum* can reside in sequestered sites (e.g., the CNS and aqueous humor) that are poorly accessed by certain forms of penicillin. Combinations of benzathine penicillin, procaine penicillin, and oral penicillin preparations are not considered appropriate for syphilis treatment. Reports have indicated that practitioners have inadvertently prescribed combination long- and short-acting benzathine-procaine penicillin (Bicillin C-R) instead of the standard benzathine penicillin product (Bicillin L-A) recommended in the United States for treating primary, secondary, and latent syphilis. Practitioners, pharmacists, and purchasing agents should be aware of the similar names of these two products to avoid using the incorrect combination therapy agent for treating syphilis (*589*).

Penicillin's effectiveness for treating syphilis was well established through clinical experience even before the value of randomized controlled clinical trials was recognized. Therefore, approximately all recommendations for treating syphilis are based not only on clinical trials and observational studies, but on many decades of clinical experience.

Special Considerations

Pregnancy

Parenteral penicillin G is the only therapy with documented efficacy for syphilis during pregnancy. Pregnant women with syphilis at any stage who report penicillin allergy should be desensitized and treated with penicillin (see Management of Persons Who Have a History of Penicillin Allergy).

Jarisch-Herxheimer Reaction

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, myalgia, and fever that can occur within the first 24 hours after the initiation of any syphilis therapy; it is a reaction to treatment and not an allergic reaction to penicillin. Patients should be informed about this possible adverse reaction and how to manage it if it occurs. The Jarisch-Herxheimer reaction occurs most frequently among persons who have early syphilis, presumably because bacterial loads are higher during these stages. Antipyretics can be used to manage symptoms; however, they have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction might induce early labor or cause fetal distress in pregnant women; however, this should not prevent or delay therapy (*590*) (see Syphilis During Pregnancy).

Management of Sex Partners

Sexual transmission of *T. pallidum* is thought to occur only when mucocutaneous syphilitic lesions are present. Such manifestations are uncommon after the first year of infection. Persons exposed through sexual contact with a person who has primary, secondary, or early latent syphilis should be evaluated clinically and serologically and treated according to the following recommendations:

- Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis <90 days before the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative.
- Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis >90 days before the diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain. If serologic tests are negative, no treatment is needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and syphilis stage.
- In certain areas or among populations with high syphilis infection rates, health departments recommend notification and presumptive treatment of sex partners of persons with

syphilis of unknown duration who have high nontreponemal serologic test titers (i.e., >1:32) because high titers might be indicative of early syphilis. These partners should be managed as if the index patient had early syphilis.
- Long-term sex partners of persons who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation's findings.
- The following sex partners of persons with syphilis are considered at risk for infection and should be confidentially notified of the exposure and need for evaluation: partners who have had sexual contact within 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis, within 6 months plus duration of symptoms for those with secondary syphilis, and within 1 year for persons with early latent syphilis.

Primary and Secondary Syphilis

Treatment

Parenteral penicillin G has been used effectively for achieving clinical resolution (i.e., the healing of lesions and prevention of sexual transmission) and for preventing late sequelae. However, no comparative trials have been conducted to guide selection of an optimal penicillin regimen. Substantially fewer data are available for nonpenicillin regimens.

Recommended Regimen for Primary and Secondary Syphilis* Among Adults
Benzathine penicillin G 2.4 million units IM in a single dose

* Recommendations for treating syphilis among persons with HIV infection and pregnant women are discussed elsewhere in this report (see Syphilis Among Persons with HIV Infection; Syphilis During Pregnancy).

Available data demonstrate that use of additional doses of benzathine penicillin G, amoxicillin, or other antibiotics do not enhance efficacy of this recommended regimen when used to treat primary and secondary syphilis, regardless of HIV status (*591–593*).

Recommended Regimen for Syphilis Among Infants and Children
Benzathine penicillin G 50,000 units/kg body weight IM, up to the adult dose of 2.4 million units in a single dose

Infants and children aged ≥1 month who receive a syphilis diagnosis should have birth and maternal medical records reviewed to assess whether they have congenital or acquired syphilis (see Congenital Syphilis). Infants and children aged ≥1 month with primary and secondary syphilis should be managed by a pediatric infectious disease specialist and evaluated for sexual abuse (e.g., through consultation with child protective services) (see Sexual Assault or Abuse of Children).

Other Management Considerations

All persons who have primary and secondary syphilis should be tested for HIV at the time of diagnosis and treatment. Those persons whose HIV test results are negative should be offered HIV PrEP. In geographic areas in which HIV prevalence is high, persons who have primary or secondary syphilis should be offered PrEP and retested for HIV in 3 months if the initial HIV test result was negative.

Persons who have syphilis and symptoms or signs indicating neurologic disease (e.g., cranial nerve dysfunction, meningitis, stroke, or altered mental state) should have an evaluation that includes CSF analysis. Persons with syphilis who have symptoms or signs of ocular syphilis (e.g., uveitis, iritis, neuroretinitis, or optic neuritis) should have a thorough cranial nerve examination and ocular slit-lamp and ophthalmologic examinations. CSF evaluation is not always needed for persons with ocular syphilis if no evidence of cranial nerves 2, 3, 4, 5, and 6 dysfunction or other evidence of neurologic disease exists. If symptoms and signs of otic syphilis are present then an otologic examination is needed; CSF evaluation in persons with otic syphilis does not aid in the clinical management and therefore is not recommended (see Cerebrospinal Fluid Evaluation). Treatment should be guided by the results of these evaluations. Invasion of CSF by *T. pallidum* accompanied by CSF laboratory abnormalities is common among adults who have primary or secondary syphilis but has unknown medical significance (*585*). In the absence of clinical neurologic findings, no evidence supports variation from the recommended treatment regimen for primary or secondary syphilis. Symptomatic neurosyphilis after treatment with the penicillin regimens recommended for primary and secondary syphilis is rare. Therefore, unless clinical signs or symptoms of neurologic or ophthalmic involvement are present, routine CSF analysis is not recommended for persons who have primary or secondary syphilis.

Follow-Up

Clinical and serologic evaluation should be performed at 6 and 12 months after treatment; more frequent evaluation might be prudent if opportunity for follow-up is uncertain or if repeat infection is a clinical concern. Serologic response (i.e., titer) should be compared with the titer at the time of treatment. However, assessing serologic response to treatment can be difficult, and definitive criteria for cure or failure by serologic criteria have not been well established. In addition, nontreponemal test titers might decrease more slowly for persons previously treated for syphilis (*594*,*595*).

Persons who have signs or symptoms that persist or recur and those with at least a fourfold increase in nontreponemal

test titer persisting for >2 weeks likely were reinfected or experienced treatment failure. Among persons who have neurologic findings or persons with no neurologic findings without any reported sexual exposure during the previous 3–6 months indicating that treatment failure might be possible, a CSF examination is recommended with treatment guided by CSF findings. These persons should also be reevaluated for HIV infection.

Among persons with no neurologic findings after a thorough neurologic examination and who are sexually active, reinfection is likely and repeat treatment for early syphilis is recommended. These persons should also be reevaluated for HIV infection.

Failure of nontreponemal test titers to decrease fourfold within 12 months after therapy for primary or secondary syphilis (inadequate serologic response) might be indicative of treatment failure. However, clinical trial data have demonstrated that 10%–20% of persons with primary and secondary syphilis treated with the recommended therapy will not achieve the fourfold decrease in nontreponemal titer within 12 months after treatment (*591*,*596*,*597*). Serologic response to treatment appears to be associated with multiple factors, including the person's syphilis stage (earlier stages are more likely to decrease fourfold and become nonreactive), initial nontreponemal antibody titers (titers <1:8 are less likely to decline fourfold than higher titers), and age (titers among older patients might be less likely to decrease fourfold than those of younger patients) (*596*–*598*). Optimal management of persons who have an inadequate serologic response after syphilis treatment is unclear. At a minimum, these persons should receive additional neurologic examinations, clinical and serologic follow-up annually, and reevaluation for HIV infection. If neurologic symptoms or signs are identified, a CSF evaluation is recommended, with findings guiding management. If additional follow-up cannot be ensured, retreatment is recommended. Because treatment failure might be the result of unrecognized CNS infection, CSF examination can be considered in situations in which follow-up is uncertain.

For retreatment, weekly injections of benzathine penicillin G 2.4 million units intramuscularly (IM) for 3 weeks is recommended, unless CSF examination indicates that neurosyphilis is present (see Neurosyphilis, Ocular Syphilis, and Otosyphilis). Serologic titers might not decrease, despite a negative CSF examination and a repeated 3-week therapy course (*599*). In these circumstances, the benefit of additional therapy or repeated CSF examinations is unclear, and it is not typically recommended. Serologic and clinical monitoring at least annually should continue to monitor for any sustained increases in nontreponemal titer.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Data to support use of alternatives to penicillin in treating primary and secondary syphilis are limited. However, multiple therapies might be effective for nonpregnant persons with penicillin allergy who have primary or secondary syphilis. Doxycycline (100 mg orally 2 times/day for 14 days) (*600*,*601*) and tetracycline (500 mg orally 4 times/day for 14 days) have been used for years and can be effective. Compliance is likely to be better with doxycycline than tetracycline because tetracycline can cause more gastrointestinal side effects and requires more frequent dosing. Limited clinical studies, along with biologic and pharmacologic evidence, indicate that ceftriaxone (1 g daily either IM or IV for 10 days) is effective for treating primary and secondary syphilis; however, the optimal dose and duration of ceftriaxone therapy have not been defined (*602*,*603*). Azithromycin as a single 2-g oral dose has been effective for treating primary and secondary syphilis among certain populations (*602*,*604*,*605*). However, because of *T. pallidum* chromosomal mutations associated with azithromycin and other macrolide resistance and documented treatment failures in multiple U.S. geographic areas, azithromycin should not be used as treatment for syphilis (*606*–*608*). Thorough clinical and serologic follow-up of persons receiving any alternative therapy is essential.

Persons with a penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin G. Skin testing for penicillin allergy might be useful in circumstances in which the reagents and expertise are available for performing the test adequately (see Management of Persons Who Have a History of Penicillin Allergy).

Pregnancy

Pregnant women with primary or secondary syphilis who are allergic to penicillin should be desensitized and treated with penicillin G. Skin testing or oral graded penicillin dose challenge might be helpful in identifying women at risk for acute allergic reactions (see Management of Persons Who Have a History of Penicillin Allergy; Syphilis During Pregnancy).

HIV Infection

Persons with HIV infection who have primary or secondary syphilis should be treated similarly to those without HIV (see Syphilis Among Persons with HIV Infection).

Latent Syphilis

Latent syphilis is defined as syphilis characterized by seroreactivity without other evidence of primary, secondary, or tertiary disease. Persons who have latent syphilis and who acquired syphilis during the preceding year are classified as having early latent syphilis (early nonprimary, nonsecondary). Persons can receive a diagnosis of early latent syphilis if, during the year preceding the diagnosis, they had a documented seroconversion or a sustained (>2 weeks) fourfold or greater increase in nontreponemal test titers in a previously treated person; unequivocal symptoms of primary or secondary syphilis; or a sex partner documented to have primary, secondary, or early latent syphilis. In addition, for persons with reactive nontreponemal and treponemal tests whose only possible exposure occurred during the previous 12 months, early latent syphilis can be assumed.

In the absence of these conditions associated with latent syphilis, an asymptomatic person should be considered to have latent syphilis of unknown duration or late latent syphilis (>1 year's duration). Nontreponemal serologic titers usually are higher early in the course of syphilis infection. However, early latent syphilis cannot be reliably diagnosed solely on the basis of nontreponemal titers. All persons with latent syphilis should have careful examination of all accessible mucosal surfaces to evaluate for mucosal lesions (primary or secondary syphilis) before making a latent syphilis diagnosis. Physical examination should include the oral cavity, perianal area, perineum, rectum, and genitals (vagina and cervix for women; scrotum, penis, and underneath the foreskin for uncircumcised men).

Treatment

Because latent syphilis is not transmitted sexually, the objective of treating persons in this disease stage is to prevent medical complications of syphilis. Latent syphilis can also be vertically transmitted to a fetus; therefore, the goal of treating a pregnant woman is to prevent congenital syphilis. Although clinical experience supports the effectiveness of penicillin in achieving this goal, limited evidence is available for guiding choice of specific regimens or duration. Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early latent syphilis do not enhance efficacy, regardless of HIV status (*592*,*593*,*609*).

Recommended Regimens for Latent Syphilis* Among Adults
Early latent syphilis: Benzathine penicillin G 2.4 million units IM in a single dose
Late latent syphilis: Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

* Recommendations for treating syphilis in persons with HIV and pregnant women are discussed elsewhere in this report (see Syphilis Among Persons with HIV Infection; Syphilis During Pregnancy).

Infants and children aged ≥1 month with diagnosed latent syphilis should be managed by a pediatric infectious disease specialist and receive a CSF examination. In addition, birth and maternal medical records should be reviewed to assess whether these infants and children have congenital or acquired syphilis. For those with congenital syphilis, treatment should be undertaken as described (see Congenital Syphilis). Those with acquired syphilis should be evaluated for sexual abuse (e.g., through consultation with child protection services) (see Sexual Assault or Abuse of Children). These regimens are for children who are not allergic to penicillin who have acquired syphilis and who have normal CSF examinations.

Other Management Considerations

All persons who have latent syphilis should be tested for HIV at the time of diagnosis or treatment. Those persons whose HIV test results are negative should be offered HIV PrEP. In geographic areas in which the prevalence of HIV infection is high or among populations vulnerable to HIV acquisition, persons who have early latent or late latent syphilis should be offered PrEP and retested for HIV in 3 months if the first HIV test result was negative.

Persons who receive a diagnosis of latent syphilis and have neurologic or ocular signs and symptoms (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, or symptoms or signs of meningitis or stroke) should be evaluated for neurosyphilis, ocular syphilis, or otosyphilis according to their clinical presentation (see Neurosyphilis, Ocular Syphilis, and Otosyphilis).

If a person receives a delayed dose of penicillin in a course of weekly therapy for late latent syphilis or syphilis of unknown duration, the course of action that should be recommended is unclear. Clinical experience indicates that an interval of 10–14 days between doses of benzathine penicillin for latent syphilis might be acceptable before restarting the sequence of injections (i.e., if dose 1 is administered on day 0, dose 2 is administered on days 10–14). Pharmacologic considerations indicate that an interval of 7–9 days between doses, if feasible, might be preferred (*610*–*612*). Delayed doses are not optimal for pregnant women receiving therapy for latent syphilis (*613*). Pregnant women who have delays in any therapy dose >9 days between doses should repeat the full course of therapy.

Follow-Up

Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months. These serologic titers should be compared with the titer at the time of treatment. Persons with at least a fourfold sustained increase in nontreponemal test titer persisting for >2 weeks or who experienced signs or symptoms attributable to primary or secondary syphilis

were likely reinfected or experienced treatment failure. These persons should be retreated and reevaluated for HIV infection. Among persons who have neurologic findings after a thorough neurologic examination or among persons with no neurologic findings and no sexual exposure during the previous year, a CSF examination is recommended. Treatment should be guided by CSF findings. Among persons with no neurologic findings after neurologic examination and who are sexually active, treatment with weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks is recommended.

Optimal management of persons who have less than a fourfold decrease in titers 24 months after treatment (i.e., an inadequate serologic response) is unclear, especially if the initial titer was <1:8. At a minimum, these persons should receive additional clinical and serologic follow-up and be evaluated for HIV infection. If neurologic symptoms or signs are identified, a CSF evaluation is recommended, with the findings guiding management. If additional follow-up cannot be ensured or if an initially high titer (>1:32) does not decrease at least fourfold 24 months after treatment, retreatment with weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks is recommended. Because treatment failure might be the result of unrecognized CNS infection, CSF examination can be considered in such situations where follow-up is uncertain or initial high titers do not decrease after 24 months.

If the CSF examination is negative, repeat treatment for latent syphilis is recommended. Serologic titers might not decrease despite a negative CSF examination and a repeated course of therapy, especially if the initial nontreponemal titer is low (<1:8); in these circumstances, the need for additional therapy or repeated CSF examinations is unclear but is usually not recommended. Serologic and clinical monitoring at least annually should continue to monitor for any sustained increases in nontreponemal titer.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

The effectiveness of alternatives to penicillin in treating latent syphilis has not been well documented. Nonpregnant patients allergic to penicillin who have clearly defined early latent syphilis should respond to antibiotics recommended as alternatives to penicillin for treating primary and secondary syphilis (see Primary and Secondary Syphilis). The only acceptable alternatives for treating late latent syphilis or syphilis of unknown duration are doxycycline (100 mg orally 2 times/day) or tetracycline (500 mg orally 4 times/day), each for 28 days. The efficacy of these alternative regimens among persons with HIV infection has not been well studied. These therapies should be used only in conjunction with close serologic and clinical follow-up, especially among persons with HIV infection. On the basis of biologic plausibility and pharmacologic properties, ceftriaxone might be effective for treating latent syphilis. However, the optimal dose and duration of ceftriaxone therapy have not been defined; treatment decisions should be discussed in consultation with a specialist. Persons with a penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin G. Skin testing for penicillin allergy might be useful in circumstances in which the reagents and expertise are available for performing the test adequately (see Management of Persons Who Have a History of Penicillin Allergy).

Pregnancy

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin G. Skin testing for penicillin allergy might be useful in circumstances in which the reagents and expertise are available for performing the test adequately (see Management of Persons Who Have a History of Penicillin Allergy; Syphilis During Pregnancy).

HIV Infection

Persons with HIV infection who have latent syphilis should be treated similarly to persons who do not have HIV (see Syphilis Among Persons with HIV Infection).

Tertiary Syphilis

Tertiary syphilis refers to gummas, cardiovascular syphilis, psychiatric manifestations (e.g., memory loss or personality changes), or late neurosyphilis. Guidelines for all forms of neurosyphilis (e.g., early or late neurosyphilis) are discussed elsewhere in these recommendations (see Neurosyphilis, Ocular Syphilis, and Otosyphilis). Persons with gummas and cardiovascular syphilis who are not allergic to penicillin and have no evidence of neurosyphilis by clinical and CSF examination should be treated with the following regimen.

Recommended Regimen for Tertiary Syphilis Among Adults
Tertiary syphilis with normal CSF examination: Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

Other Management Considerations

All persons who have tertiary syphilis should receive a CSF examination before therapy is initiated and have an HIV test.

Those persons whose HIV test results are negative should be offered HIV PrEP. Persons with CSF abnormalities should be treated with a neurosyphilis regimen. Certain providers treat all persons who have cardiovascular syphilis with a neurosyphilis regimen. These persons should be managed in consultation with an infectious disease specialist. Limited information is available concerning clinical response and follow-up of persons who have tertiary syphilis.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Any person allergic to penicillin should be treated in consultation with an infectious disease specialist.

Pregnancy

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin G. Skin testing or oral graded penicillin dose challenge might be helpful in identifying women at risk for acute allergic reactions (see Management of Persons Who Have a History of Penicillin Allergy; Syphilis During Pregnancy).

HIV Infection

Persons with HIV infection who have tertiary syphilis should be treated as described for persons without HIV (see Syphilis Among Persons with HIV Infection).

Neurosyphilis, Ocular Syphilis, and Otosyphilis

Treatment

CNS involvement can occur during any stage of syphilis, and CSF laboratory abnormalities are common among persons with early syphilis, even in the absence of clinical neurologic findings. No evidence exists to support variation from recommended diagnosis and treatment for syphilis at any stage for persons without clinical neurologic findings, except tertiary syphilis. If clinical evidence of neurologic involvement is observed (e.g., cognitive dysfunction, motor or sensory deficits, cranial nerve palsies, or symptoms or signs of meningitis or stroke), a CSF examination should be performed before treatment.

Syphilitic uveitis or other ocular syphilis manifestations (e.g., neuroretinitis and optic neuritis) can occur at any stage of syphilis and can be isolated abnormalities or associated with neurosyphilis. All persons with ocular symptoms and reactive syphilis serology need a full ocular examination, including cranial nerve evaluation. If cranial nerve dysfunction is present, a CSF evaluation is needed. Among persons with isolated ocular symptoms (no cranial nerve dysfunction or other neurologic abnormalities), reactive syphilis serology, and confirmed ocular abnormalities on examination, CSF examination is unnecessary before treatment. CSF analysis might be helpful in evaluating persons with ocular symptoms and reactive syphilis serology who do not have ocular findings on examination. If ocular syphilis is suspected, immediate referral to and management in collaboration with an ophthalmologist is crucial. Ocular syphilis should be treated similarly to neurosyphilis, even if a CSF examination is normal.

Hearing loss and other otologic symptoms can occur at any stage of syphilis and can be isolated abnormalities or associated with neurosyphilis, especially of cranial nerve 8. However, among persons with isolated auditory symptoms, normal neurologic examination, and reactive syphilis serology, CSF examination is likely to be normal and is not recommended before treatment. Otosyphilis should be managed in collaboration with an otolaryngologist and treated by using the same regimen as for neurosyphilis.

Recommended Regimen for Neurosyphilis, Ocular Syphilis, or Otosyphilis Among Adults
Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion for 10–14 days

If compliance with therapy can be ensured, the following alternative regimen might be considered.

Alternative Regimen
Procaine penicillin G 2.4 million units IM once daily *plus* **Probenecid** 500 mg orally 4 times/day, both for 10–14 days

The durations of the recommended and alternative regimens for neurosyphilis are shorter than the duration of the regimen used for latent syphilis. Therefore, benzathine penicillin, 2.4 million units IM once per week for 1–3 weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

Other Management Considerations

The following are other considerations in the management of persons who have neurosyphilis:

- All persons who have neurosyphilis, ocular syphilis, or otosyphilis should be tested for HIV at the time of diagnosis. Those whose HIV test results are negative should be offered HIV PrEP.

- Although systemic steroids are used frequently as adjunctive therapy for otosyphilis and for ocular syphilis, such drugs have not been proven to be beneficial.

Follow-Up

Data from two studies indicate that, among immunocompetent persons and persons with HIV infection who are on effective ART, normalization of the serum RPR titer predicts normalization of abnormal CSF parameters after neurosyphilis treatment (*614*,*615*). Therefore, repeated CSF examinations are unnecessary for persons without HIV infection or persons with HIV infection who are on ART and who exhibit serologic and clinical responses after treatment.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Limited data indicate that ceftriaxone 1–2 g daily either IM or IV for 10–14 days can be used as an alternative treatment for persons with neurosyphilis (*603*,*616*,*617*). Cross-sensitivity between ceftriaxone and penicillin can occur; however, the risk for penicillin cross-reactivity between third-generation cephalosporins is negligible (*618*–*621*) (see Management of Persons Who Have a History of Penicillin Allergy). If concern exists regarding ceftriaxone safety for a patient with neurosyphilis, skin testing should be performed to confirm penicillin allergy and, if necessary, penicillin desensitization in consultation with a specialist is recommended. Other regimens have not been adequately evaluated for treatment of neurosyphilis.

Pregnancy

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin G. Skin testing or oral graded penicillin dose challenge might be helpful in identifying women at risk for acute allergic reactions (see Management of Persons Who Have a History of Penicillin Allergy).

HIV Infection

Persons with HIV infection who have neurosyphilis should be treated as described for persons without HIV (see Syphilis Among Persons with HIV Infection).

Syphilis Among Persons with HIV Infection

Diagnostic Considerations

Interpretation of treponemal and nontreponemal serologic tests for persons with HIV infection is the same as for persons without HIV. Although rare, unusual serologic responses have been observed among persons with HIV infection who have syphilis. The majority of reports have involved posttreatment serologic titers that were higher than expected (i.e., high serofast) or fluctuated, and false-negative serologic test results and delayed appearance of seroreactivity have also been reported (*622*).

When clinical findings are indicative of syphilis, but serologic tests are nonreactive or their interpretation is unclear, alternative tests (e.g., biopsy of a lesion, darkfield examination, or PCR of lesion material) might be useful for diagnosis. Neurosyphilis, ocular syphilis, and otosyphilis should be considered in the differential diagnosis of neurologic, ocular, and other signs and symptoms among persons with HIV infection.

Treatment

Persons with HIV infection who have early syphilis might be at increased risk for neurologic complications (*623*) and might have higher rates of inadequate serologic response with recommended regimens. The magnitude of these risks is not defined precisely but is likely small. Although long-term (>1 year) comparative data are lacking, no treatment regimens for syphilis have been demonstrated to be more effective in preventing neurosyphilis among persons with HIV infection than the syphilis regimens recommended for persons without HIV (*609*). Careful follow-up after therapy is essential. Using ART per current HIV guidelines might improve clinical outcomes among persons coinfected with HIV and syphilis; concerns regarding adequate treatment of syphilis among persons with HIV infection might not apply to those with HIV virologic suppression (*624*,*625*).

Primary and Secondary Syphilis Among Persons with HIV Infection

Recommended Regimen for Primary and Secondary Syphilis Among Persons with HIV Infection
Benzathine penicillin G 2.4 million units IM in a single dose

Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in primary and secondary syphilis among persons with HIV infection do not result in enhanced efficacy (*592*,*593*,*609*).

Other Management Considerations

The majority of persons with HIV infection respond appropriately to the recommended benzathine penicillin G treatment regimen for primary and secondary syphilis (*626*). CSF abnormalities (e.g., mononuclear pleocytosis and elevated protein levels) can be common among persons with HIV, even those without syphilis. The clinical and prognostic significance of such CSF laboratory abnormalities among persons with primary and secondary syphilis who lack neurologic symptoms

is unknown. Certain studies have demonstrated that among persons with HIV infection and syphilis, CSF abnormalities are associated with a $CD4^+$ T-cell count of ≤350 cells/mL or an RPR titer of ≥1:32 (*614*,*627*). However, CSF examination followed by treatment for neurosyphilis on the basis of laboratory abnormalities has not been associated with improved clinical outcomes in the absence of neurologic signs and symptoms. All persons with HIV infection and primary and secondary syphilis should have a thorough neurologic, ocular, and otic examination (*614*,*622*,*625*). CSF examination should be reserved for those with an abnormal neurologic examination.

Follow-Up

Persons with HIV infection and primary or secondary syphilis should be evaluated clinically and serologically for possible treatment failure at 3, 6, 9, 12, and 24 months after therapy; those who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or a sustained [>2 weeks] fourfold or greater increase in titer) should be managed in the same manner as persons without HIV infection (i.e., depending on history of sexual activity and on findings of neurologic examination, either repeat treatment with weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks or CSF examination and repeat treatment guided by CSF findings) (see Primary and Secondary Syphilis).

In addition, CSF examination and retreatment can be considered for persons whose nontreponemal test titers do not decrease fourfold within 24 months of therapy. If CSF examination is normal, treatment with benzathine penicillin G administered as 2.4 million units IM at weekly intervals for 3 weeks is recommended. Serologic titers might not decrease despite a negative CSF examination and a repeated 3-week course of therapy (*599*). Especially if the initial nontreponemal titer is low (<1:8) in these circumstances, the benefit of additional therapy or repeated CSF examinations is unclear but is not usually recommended. Serologic and clinical monitoring at least annually should continue to monitor for any sustained increases in nontreponemal titer.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Persons with HIV infection who are allergic to penicillin and have primary or secondary syphilis should be managed according to the recommendations for persons without HIV who are allergic to penicillin (see Primary and Secondary Syphilis). Persons with penicillin allergy whose compliance with alternative therapy or follow-up cannot be ensured should be desensitized and treated with penicillin G (see Management of Persons Who Have a History of Penicillin Allergy). Using penicillin alternatives has not been well studied among persons with HIV infection; azithromycin is not recommended for persons with HIV and primary or secondary syphilis infection. Alternative therapies should be used only in conjunction with close serologic and clinical follow-up. Persons with HIV and latent syphilis should be treated similarly to persons who do not have HIV (see Latent Syphilis).

Latent Syphilis Among Persons with HIV Infection

Recommended Regimen for Early Latent Syphilis Among Persons with HIV Infection
Benzathine penicillin G 2.4 million units IM in a single dose

Recommended Regimen for Late Latent Syphilis or Latent Syphilis of Unknown Duration Among Persons with HIV Infection
Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM at 1-week intervals

Other Management Considerations

All persons with HIV and latent syphilis infection should undergo a thorough neurologic, ocular, and otic examination; those with neurologic symptoms or signs should undergo immediate CSF examination. In the absence of neurologic symptoms or signs, CSF examination has not been associated with improved clinical outcomes and therefore is not recommended. Those with ocular or otic symptoms or signs should be evaluated for ocular syphilis and otosyphilis according to those clinical presentations (see Neurosyphilis, Ocular Syphilis, and Otosyphilis).

Follow-Up

Patients with HIV and latent syphilis infection should be evaluated clinically and serologically at 6, 12, 18, and 24 months after therapy. Those persons who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or a sustained [>2 weeks] fourfold or greater increase in titer) should be managed in the same manner as persons without HIV (i.e., depending on history of sexual activity and on findings of neurologic examination, either repeat treatment with weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks or CSF examination and repeat treatment guided by CSF findings) (see Latent Syphilis).

In addition, CSF examination and retreatment can be considered for persons whose nontreponemal test titers do not decrease fourfold within 24 months of therapy. If CSF examination is normal, treatment with benzathine penicillin G administered as 2.4 million units IM at weekly intervals for

3 weeks is recommended. Serologic titers might not decrease despite a negative CSF examination and a repeated 3-week course of therapy (*599*). Especially if the initial nontreponemal titer is low (<1:8) in these circumstances, the benefit of additional therapy or repeated CSF examinations is unclear but is not usually recommended. Serologic and clinical monitoring at least annually should continue to ensure nontreponemal titers remain stable without any sustained titer increases.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

The efficacy of alternative nonpenicillin regimens for latent syphilis for persons living with HIV infection has not been well studied, and these therapies should be used only in conjunction with close serologic and clinical follow-up. Patients with penicillin allergy whose compliance with alternative therapy or follow-up cannot be ensured should be desensitized and treated with penicillin G (see Management of Persons Who Have a History of Penicillin Allergy).

Neurosyphilis, Ocular Syphilis, and Otic Syphilis Among Persons with HIV Infection

All persons with HIV and syphilis infection should receive a careful neurologic ocular and otic examination. Persons with HIV infection and neurosyphilis should be treated according to the recommendations for persons with neurosyphilis and without HIV infection (see Neurosyphilis, Ocular Syphilis, and Otosyphilis).

Follow-Up

Persons with HIV and neurosyphilis infection should be managed according to the recommendations for persons without HIV infection. Serum RPR can be followed for necessary treatment success rather than following CSF parameters (see Neurosyphilis, Ocular Syphilis, and Otosyphilis). Limited data indicate that changes in CSF parameters might occur more slowly among persons with HIV infection, especially those with more advanced immunosuppression (*588*,*624*).

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Persons with HIV who are allergic to penicillin and have neurosyphilis infection should be managed according to the recommendations for persons without HIV infection with neurosyphilis who are allergic to penicillin (see Neurosyphilis, Ocular Syphilis, and Otosyphilis). Small observational studies conducted among persons with HIV and neurosyphilis report that ceftriaxone 1–2 g IV daily for 10–14 days might be effective as an alternative agent (*628–630*). The possibility of cross-sensitivity between ceftriaxone and penicillin exists; however, the risk for penicillin cross-reactivity between third-generation cephalosporins is negligible (*619–621*,*631*) (see Management of Persons Who Have a History of Penicillin Allergy). If concern exists regarding the safety of ceftriaxone for a person with HIV and neurosyphilis, skin testing should be performed to confirm penicillin allergy and, if necessary, penicillin desensitization in consultation with a specialist is recommended. Other regimens have not been adequately evaluated for treatment of neurosyphilis.

Syphilis During Pregnancy

All women should be screened serologically for syphilis at the first prenatal care visit (*174*), which is mandated by the majority of states (*142*). Among populations for whom receipt of prenatal care is not optimal, serologic screening and treatment (if serologic test is reactive) should be performed at the time of pregnancy testing (*632*). Antepartum screening can be performed by manual nontreponemal antibody testing (e.g., RPR) by using the traditional syphilis screening algorithm or by treponemal antibody testing (e.g., immunoassays) using the reverse sequence algorithm.

Pregnant women with positive treponemal screening tests (e.g., EIA, CIA, or immunoblot) should have additional quantitative nontreponemal testing because titers are essential for monitoring treatment response. Serologic testing should also be performed twice during the third trimester: at 28 weeks' gestation and at delivery for pregnant women who live in communities with high rates of syphilis and for women who have been at risk for syphilis acquisition during pregnancy.

Maternal risk factors for syphilis during pregnancy include sex with multiple partners, sex in conjunction with drug use or transactional sex, late entry to prenatal care (i.e., first visit during the second trimester or later) or no prenatal care, methamphetamine or heroine use, incarceration of the woman or her partner, and unstable housing or homelessness (*174*,*633–636*). Moreover, as part of the management of pregnant women who have syphilis, providers should obtain information concerning ongoing risk behaviors and treatment of sex partners to assess the risk for reinfection.

Any woman who has a fetal death after 20 weeks' gestation should be tested for syphilis. No mother or neonate should leave the hospital without maternal serologic status having been

documented at least once during pregnancy. Any woman who at the time of delivery has no prenatal care history or has been at risk for syphilis acquisition during pregnancy (e.g., misuses drugs; has had another STI during pregnancy; or has had multiple sex partners, a new partner, or a partner with an STI) should have the results of a syphilis serologic test documented before discharge.

Diagnostic Considerations

Pregnant women seropositive for syphilis should be considered infected unless an adequate treatment history is clearly documented in the medical records and sequential serologic antibody titers have decreased as recommended for the syphilis stage. The risk for antepartum fetal infection or congenital syphilis at delivery is related to the syphilis stage during pregnancy, with the highest risk occurring during the primary and secondary stages. Quantitative maternal nontreponemal titer, especially if >1:8, might be a marker of early infection and bacteremia. However, risk for fetal infection is still substantial among pregnant women with late latent syphilis and low titers. Pregnant women with stable, serofast low nontreponemal titers who have previously been treated for syphilis might not require additional treatment; however, increasing or high antibody titers in a pregnant woman previously treated might indicate reinfection or treatment failure, and treatment should be offered.

If an automated treponemal test (e.g., EIA or CIA) is used for antepartum syphilis screening, all positive tests should be reflexed to a quantitative nontreponemal test (e.g., RPR or VDRL). If the nontreponemal test is negative, the results are considered discrepant and a second treponemal test (TP-PA is preferred) should be performed, preferably on the same specimen.

If the second treponemal test is positive (e.g., EIA positive, RPR negative, or TP-PA positive), current or previous syphilis infection can be confirmed. For women with a history of adequately treated syphilis who do not have ongoing risk, no further treatment is necessary. Women without a history of treatment should have the syphilis stage determined and should be treated accordingly with a recommended penicillin regimen.

If the second treponemal test is negative (e.g., EIA positive, RPR negative, or TP-PA negative), the positive EIA or CIA is more likely to represent a false-positive test result for women who are living in communities with low rates of syphilis, have a partner who is uninfected, and have no history of treated syphilis (*637*,*638*). If the woman is at low risk for syphilis, lacks signs or symptoms of primary syphilis, has a partner with no clinical or serologic evidence of syphilis, and is likely to follow up with clinical care, repeat serologic testing within 4 weeks can be considered to determine whether the EIA or CIA remains positive or if the RPR, VDRL, or TP-PA result becomes positive. If both the RPR and TP-PA remain negative, no further treatment is necessary. If follow-up is not likely, women with an isolated reactive treponemal test and without a history of treated syphilis should be treated according to the syphilis stage.

Treatment

Penicillin G is the only known effective antimicrobial for treating fetal infection and preventing congenital syphilis (*639*). Evidence is insufficient to determine the optimal penicillin regimen during pregnancy (*640*).

Recommended Regimen for Syphilis During Pregnancy
Pregnant women should be treated with the recommended penicillin regimen for their stage of infection

Other Management Considerations

The following recommendations should be considered for pregnant women with syphilis infection:

- Certain evidence indicates that additional therapy is beneficial for pregnant women to prevent congenital syphilis. For women who have primary, secondary, or early latent syphilis, a second dose of benzathine penicillin G 2.4 million units IM can be administered 1 week after the initial dose (*641*–*643*).
- When syphilis is diagnosed during the second half of pregnancy, management should include a sonographic fetal evaluation for congenital syphilis. However, this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis (e.g., hepatomegaly, ascites, hydrops, fetal anemia, or a thickened placenta) indicate a greater risk for fetal treatment failure (*644*); cases accompanied by these signs should be managed in consultation with obstetric specialists. A second dose of benzathine penicillin G 2.4 million units IM after the initial dose might be beneficial for fetal treatment in these situations.
- Women treated for syphilis during the second half of pregnancy are at risk for premature labor or fetal distress if the treatment precipitates the Jarisch-Herxheimer reaction (*590*). These women should be advised to seek obstetric attention after treatment if they notice any fever, contractions, or decrease in fetal movements. Stillbirth is a rare complication of treatment; however, concern for this complication should not delay necessary treatment. No data are available to support that corticosteroid treatment alters the risk for treatment-related complications during pregnancy.
- Missed doses >9 days between doses are not acceptable for pregnant women receiving therapy for late latent syphilis (*613*). An optimal interval between doses is 7 days for pregnant women. If a pregnant woman does not return for the next dose on day 7, every effort should be made

to contact her and link her to immediate treatment within 2 days to avoid retreatment. Pregnant women who miss a dose of therapy should repeat the full course of therapy.
- All women who have syphilis should be offered testing for HIV at the time of diagnosis.

Follow-Up

Coordinated prenatal care and treatment are vital because providers should document that women are adequately treated for the syphilis stage and ensure that the clinical and antibody responses are appropriate for the patient's disease stage. If syphilis is diagnosed and treated at or before 24 weeks' gestation, serologic titers should not be repeated before 8 weeks after treatment (e.g., at 32 weeks' gestation) but should be repeated again at delivery. Titers should be repeated sooner if reinfection or treatment failure is suspected. For syphilis diagnosed and treated after 24 weeks' gestation, serologic titers should be repeated at delivery.

A majority of women will not achieve a fourfold decrease in titers before delivery, although this does not indicate treatment failure (*645*). However, a fourfold increase in titer after treatment (e.g., from 1:8 to 1:32) that is sustained for >2 weeks is concerning for reinfection or treatment failure. Nontreponemal titers can increase immediately after treatment, presumably related to the treatment response. Therefore, unless symptoms and signs exist of primary or secondary syphilis, follow-up titer should not be repeated until approximately 8 weeks after treatment. Inadequate maternal treatment is likely if delivery occurs within 30 days of therapy, clinical signs of infection are present at delivery, or the maternal antibody titer at delivery is fourfold higher than the pretreatment titer.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

No proven alternatives to penicillin are available for treatment of syphilis during pregnancy. Pregnant women who have a history of penicillin allergy should be desensitized and treated with penicillin G. Skin testing or oral graded penicillin dose challenge might be helpful in identifying women at risk for acute allergic reactions (see Management of Persons Who Have a History of Penicillin Allergy).

Tetracycline and doxycycline are to be avoided in the second and third trimesters of pregnancy (*431*). Erythromycin and azithromycin should not be used because neither reliably cures maternal infection nor treats an infected fetus (*640*). Data are insufficient to recommend ceftriaxone or other cephalosporins for treatment of maternal infection and prevention of congenital syphilis (*646*,*647*).

HIV Infection

Placental inflammation from congenital syphilis infection might increase the risk for perinatal transmission of HIV. All women with HIV infection should be evaluated for syphilis and receive a penicillin regimen appropriate for the syphilis stage. Data are insufficient to recommend any alternative regimens for pregnant women with syphilis and HIV infection (see Syphilis Among Persons with HIV).

Congenital Syphilis

The rate of reported congenital syphilis in the United States has increased dramatically since 2012. During 2019, a total of 1,870 cases of congenital syphilis were reported, including 94 stillbirths and 34 infant deaths (*141*). The 2019 national rate of 48.5 cases per 100,000 live births represents a 41% increase relative to 2018 (34.3 cases per 100,000 live births) and a 477% increase relative to 2012 (8.4 cases per 100,000 live births). During 2015–2019, the rate of congenital syphilis increased 291.1% (12.4 to 48.5 per 100,000 live births), which mirrors increases in the rate of primary and secondary syphilis among females aged 15–44 years (a 171.9% increase, from 3.2 to 8.7 per 100,000 females).

Effective prevention and detection of congenital syphilis depend on identifying syphilis among pregnant women and, therefore, on the routine serologic screening of pregnant women during the first prenatal visit and at 28 weeks' gestation and at delivery for women who live in communities with high rates of syphilis, women with HIV infection, or those who are at increased risk for syphilis acquisition. Certain states have recommended screening three times during pregnancy for all women; clinicians should screen according to their state's guidelines.

Maternal risk factors for syphilis during pregnancy include sex with multiple partners, sex in conjunction with drug use or transactional sex, late entry to prenatal care (i.e., first visit during the second trimester or later) or no prenatal care, methamphetamine or heroine use, incarceration of the woman or her partner, and unstable housing or homelessness (*174*,*633*–*636*). Moreover, as part of the management of pregnant women who have syphilis, providers should obtain information concerning ongoing risk behaviors and treatment of sex partners to assess the risk for reinfection.

Routine screening of neonatal sera or umbilical cord blood is not recommended because diagnosis at that time does not prevent congenital syphilis in certain newborns. No mother or newborn infant should leave the hospital without maternal

serologic status having been documented at least once during pregnancy. Any woman who had no prenatal care before delivery or is considered at increased risk for syphilis acquisition during pregnancy should have the results of a syphilis serologic test documented before she or her neonate is discharged. A quantitative RPR is needed at the time of delivery to compare with the neonate's nontreponemal test result. If a stat RPR is unavailable and a rapid treponemal test is performed at delivery, the results should be confirmed by using standard syphilis serologic laboratory tests (e.g., RPR and treponemal test) and algorithms.

Evaluation and Treatment of Neonates

Diagnosis of congenital syphilis can be difficult because maternal nontreponemal and treponemal immunoglobulin G (IgG) antibodies can be transferred through the placenta to the fetus, complicating the interpretation of reactive serologic tests for syphilis among neonates (infants aged <30 days). Therefore, treatment decisions frequently must be made on the basis of identification of syphilis in the mother; adequacy of maternal treatment; presence of clinical, laboratory, or radiographic evidence of syphilis in the neonate; and comparison of maternal (at delivery) and neonatal nontreponemal serologic titers (e.g., RPR or VDRL) by using the same test, preferably conducted by the same laboratory. Any neonate at risk for congenital syphilis should receive a full evaluation and testing for HIV.

All neonates born to mothers who have reactive nontreponemal and treponemal test results should be evaluated with a quantitative nontreponemal serologic test (RPR or VDRL) performed on the neonate's serum because umbilical cord blood can become contaminated with maternal blood and yield a false-positive result, and Wharton's jelly within the umbilical cord can yield a false-negative result. The nontreponemal test performed on the neonate should be the same type of nontreponemal test performed on the mother.

Conducting a treponemal test (e.g., TP-PA, immunoassay-EIA, CIA, or microbead immunoassay) on neonatal serum is not recommended because it is difficult to interpret, as passively transferred maternal antibodies can persist for >15 months. Commercially available IgM tests are not recommended.

All neonates born to women who have reactive nontreponemal serologic tests for syphilis at delivery should be examined thoroughly for evidence of congenital syphilis (e.g., nonimmune hydrops, conjugated or direct hyperbilirubinemia[†] or cholestatic jaundice or cholestasis, hepatosplenomegaly, rhinitis, skin rash, or pseudoparalysis of an extremity). Pathologic examination of the placenta or umbilical cord using specific staining (e.g., silver) or a *T. pallidum* PCR test using a CLIA-validated test should be considered; direct fluorescence antibody (DFA-TP) reagents are unavailable (*565*). Darkfield microscopic examination or PCR testing of suspicious lesions or body fluids (e.g., bullous rash or nasal discharge) also should be performed. In addition to these tests, for stillborn infants, skeletal survey demonstrating typical osseous lesions might aid in the diagnosis of congenital syphilis because these abnormalities are not detected on fetal ultrasound.

The following scenarios describe the recommended congenital syphilis evaluation and treatment of neonates born to women who had reactive nontreponemal and treponemal serologic tests for syphilis during pregnancy (e.g., RPR reactive, TP-PA reactive or EIA reactive, RPR reactive) and have a reactive nontreponemal test at delivery (e.g., RPR reactive). Maternal history of infection with *T. pallidum* and treatment for syphilis should be considered when evaluating and treating the neonate for congenital syphilis in most scenarios, except when congenital syphilis is proven or highly probable.

Scenario 1: Confirmed Proven or Highly Probable Congenital Syphilis

Any neonate with

- an abnormal physical examination that is consistent with congenital syphilis;
- a serum quantitative nontreponemal serologic titer that is fourfold[§] (or greater) higher than the mother's titer at delivery (e.g., maternal titer = 1:2, neonatal titer ≥1:8 or maternal titer = 1:8, neonatal titer ≥1:32)[¶]; or
- a positive darkfield test or PCR of placenta, cord, lesions, or body fluids or a positive silver stain of the placenta or cord.

Recommended Evaluation

- CSF analysis for VDRL, cell count, and protein[**]

[†] Direct hyperbilirubinemia is direct bilirubin level >2 mg/dL (34 umol/L) or 20% of the total bilirubin level.

[§] One dilution is within the test performance of nontreponemal tests and is not a significant change.

[¶] The absence of a fourfold or greater titer for a neonate does not exclude congenital syphilis.

[**] Interpretation of CSF test results requires a nontraumatic lumbar puncture (i.e., a CSF sample that is not contaminated with blood). CSF test results obtained during the neonatal period can be difficult to interpret; normal values differ by gestational age and are higher among preterm infants. Studies indicate that 95% of healthy neonates have values of ≤16–19 WBCs/mm^3 or protein levels of ≤115–118 mg/dL on CSF examination. During the second month of life, 95% of healthy infants have ≤9–11 WBCs/mm^3 or protein levels of ≤89–91 mg/dL. Lower values (i.e., 5 WBCs/mm^3 and protein level of 40 mg/dL) might be considered the upper limits of normal for older infants. Other causes of elevated values should be considered when an infant is being evaluated for congenital syphilis (**Sources:** Kestenbaum LA, Ebberson J, Zorc JJ, Hodinka RL, Shah SS. Defining cerebrospinal fluid white blood cell count reference values in neonates and young infants. Pediatrics 2010;125:257–64; Shah SS, Ebberson J, Kestenbaum LA, Hodinka RL, Zorc JJ. Age-specific reference values for cerebrospinal fluid protein concentration in neonates and young infants. J Hosp Med 2011;6:22–7; Thomson J, Sucharew H, Cruz AT, et al.; Pediatric Emergency Medicine Collaborative Research Committee [PEM CRC] HSV Study Group. Cerebrospinal fluid reference values for young infants undergoing lumbar puncture. Pediatrics 2018;141:e20173405.)

- Complete blood count (CBC) and differential and platelet count
- Long-bone radiographs
- Other tests as clinically indicated (e.g., chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, and auditory brain stem response)

Recommended Regimens, Confirmed or Highly Probable Congenital Syphilis

Aqueous crystalline penicillin G 100,000–150,000 units/kg/body weight/day, administered as 50,000 units/kg body weight/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days
or
Procaine penicillin G 50,000 units/kg body weight/dose IM in a single daily dose for 10 days

If >1 day of therapy is missed, the entire course should be restarted. Data are insufficient regarding use of other antimicrobial agents (e.g., ampicillin). When possible, a full 10-day course of penicillin is preferred, even if ampicillin was initially provided for possible sepsis (*648–650*). Using agents other than penicillin requires close serologic follow-up for assessing therapy adequacy.

Scenario 2: Possible Congenital Syphilis

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal to or less than fourfold of the maternal titer at delivery (e.g., maternal titer = 1:8, neonatal titer ≤1:16) and one of the following:

- The mother was not treated, was inadequately treated, or has no documentation of having received treatment.
- The mother was treated with erythromycin or a regimen other than those recommended in these guidelines (i.e., a nonpenicillin G regimen).††
- The mother received the recommended regimen but treatment was initiated <30 days before delivery.

Recommended Evaluation

- CSF analysis for VDRL, cell count, and protein**
- CBC, differential, and platelet count
- Long-bone radiographs

This evaluation is not necessary if a 10-day course of parenteral therapy is administered, although such evaluations might be useful. For instance, a lumbar puncture might document CSF abnormalities that would prompt close follow-up. Other tests (e.g., CBC, platelet count, and long-bone radiographs) can be performed to further support a diagnosis of congenital syphilis.

†† A women treated with a regimen other than recommended in these guidelines should be considered untreated.

Recommended Regimens, Possible Congenital Syphilis

Aqueous crystalline penicillin G 100,000–150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days
or
Procaine penicillin G 50,000 units/kg body weight/dose IM in a single daily dose for 10 days
or
Benzathine penicillin G 50,000 units/kg body weight/dose IM in a single dose

Before using the single-dose benzathine penicillin G regimen, the recommended evaluation (i.e., CSF examination, long-bone radiographs, and CBC with platelets) should be normal, and follow-up should be certain. If any part of the neonate's evaluation is abnormal or not performed, if the CSF analysis is uninterpretable because of contamination with blood, or if follow-up is uncertain, a 10-day course of penicillin G is required.

If the neonate's nontreponemal test is nonreactive and the provider determines that the mother's risk for untreated syphilis is low, treatment of the neonate with a single IM dose of benzathine penicillin G 50,000 units/kg body weight for possible incubating syphilis can be considered without an evaluation. Neonates born to mothers with untreated early syphilis at the time of delivery are at increased risk for congenital syphilis, and the 10-day course of penicillin G should be considered even if the neonate's nontreponemal test is nonreactive, the complete evaluation is normal, and follow-up is certain.

Scenario 3: Congenital Syphilis Less Likely

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal or less than fourfold of the maternal titer at delivery (e.g., maternal titer = 1:8, neonatal titer ≤1:16) and both of the following are true:

- The mother was treated during pregnancy, treatment was appropriate for the infection stage, and the treatment regimen was initiated ≥30 days before delivery.
- The mother has no evidence of reinfection or relapse.

Recommended Evaluation

No evaluation is recommended.

Recommended Regimen, Congenital Syphilis Less Likely

Benzathine penicillin G 50,000 units/kg body weight/dose IM in a single dose*

* Another approach involves not treating the newborn if follow-up is certain but providing close serologic follow-up every 2–3 months for 6 months for infants whose mothers' nontreponemal titers decreased at least fourfold after therapy for early syphilis or remained stable for low-titer, latent syphilis (e.g., VDRL <1:2 or RPR <1:4).

Scenario 4: Congenital Syphilis Unlikely

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer equal to or less than fourfold of the maternal titer at delivery[§] and both of the following are true:

- The mother's treatment was adequate before pregnancy.
- The mother's nontreponemal serologic titer remained low and stable (i.e., serofast) before and during pregnancy and at delivery (e.g., VDRL ≤1:2 or RPR ≤1:4).

Recommended Evaluation

No evaluation is recommended.

Recommended Regimen, Congenital Syphilis Unlikely

No treatment is required. However, any neonate with reactive nontreponemal tests should be followed serologically to ensure the nontreponemal test returns to negative (see Follow-Up). Benzathine penicillin G 50,000 units/kg body weight as a single IM injection might be considered, particularly if follow-up is uncertain and the neonate has a reactive nontreponemal test.

The following situations describe management of neonates born to women screened during pregnancy by using the reverse sequence algorithm with reactive treponemal serologic tests and a nonreactive nontreponemal serologic test.

Reactive maternal treponemal serologies with a nonreactive nontreponemal serology (e.g., EIA reactive, RPR nonreactive, or TP-PA reactive) during pregnancy. Syphilis is highly unlikely for neonates born to mothers with a nonreactive nontreponemal test after adequate treatment for syphilis during pregnancy or documentation of adequate treatment before pregnancy (with no evidence of reinfection of relapse). If testing is performed again at delivery and 1) the maternal nontreponemal test remains nonreactive and 2) the neonate has a normal physical examination and nonreactive nontreponemal test (e.g., RPR nonreactive), the provider should consider managing similarly to Scenario 4 without a laboratory evaluation and with no treatment required. Benzathine penicillin G 50,000 units/kg body weight as a single IM injection might be considered if syphilis exposure is possible within 1 month of delivery and follow-up of the mother and infant is uncertain.

Isolated reactive maternal treponemal serology (e.g., EIA reactive, RPR nonreactive, or TP-PA nonreactive) during pregnancy. Syphilis is unlikely for neonates born to mothers screened with the reverse sequence algorithm with isolated reactive maternal treponemal serology. Among low-prevalence populations, these are likely false-positive results and might become nonreactive with repeat testing (*638*). If these neonates have a normal physical examination and the risk for syphilis is low in the mother, no evaluation and treatment are recommended for the neonate. If syphilis exposure is possible or unknown in the mother or the mother desires further evaluation to definitively rule out syphilis, repeat serology within 4 weeks is recommended to evaluate for early infection (see Syphilis During Pregnancy).

Isolated reactive maternal treponemal serology (e.g., rapid treponemal test) at delivery. For mothers with late or no prenatal care with a reactive rapid treponemal test at delivery, confirmatory laboratory-based testing should be performed; however, results should not delay evaluation and treatment of the neonate. These neonates should be evaluated and treated with a 10-day course of penicillin as recommended in Scenario 1, and consultation with a specialist is recommended.

Follow-Up

All neonates with reactive nontreponemal tests should receive thorough follow-up examinations and serologic testing (i.e., RPR or VDRL) every 2–3 months until the test becomes nonreactive.

For a neonate who was not treated because congenital syphilis was considered less likely or unlikely, nontreponemal antibody titers should decrease by age 3 months and be nonreactive by age 6 months, indicating that the reactive test result was caused by passive transfer of maternal IgG antibody. At age 6 months, if the nontreponemal test is nonreactive, no further evaluation or treatment is needed; if the nontreponemal test is still reactive, the infant is likely infected and should be treated.

Treated neonates who exhibit persistent nontreponemal test titers by age 6–12 months should be reevaluated through CSF examination and managed in consultation with an expert. Retreatment with a 10-day course of a penicillin G regimen might be indicated.

Neonates with a negative nontreponemal test at birth and whose mothers were seroreactive at delivery should be retested at age 3 months to rule out serologically negative incubating congenital syphilis at the time of birth. Treponemal tests should not be used to evaluate treatment response because the results are qualitative, and passive transfer of maternal IgG treponemal antibody might persist for >15 months.

Neonates whose initial CSF evaluations are abnormal do not need repeat lumbar puncture unless they exhibit persistent nontreponemal serologic test titers at age 6–12 months. Persistent nontreponemal titers and CSF abnormalities should be managed in consultation with an expert.

Special Considerations

Penicillin Allergy

Neonates who require treatment for congenital syphilis but who have a history of penicillin allergy or develop an allergic reaction presumed secondary to penicillin should

be desensitized and then treated with penicillin G (see Management of Persons Who Have a History of Penicillin Allergy). Skin testing remains unavailable for neonates because the procedure has not been standardized for this age group. Data are insufficient regarding use of other antimicrobial agents (e.g., ceftriaxone) for congenital syphilis among neonates. If a nonpenicillin G agent is used, close clinical and serologic follow-up is required in consultation with an expert. Repeat CSF examination should be performed if the initial CSF examination was abnormal.

Penicillin Shortage

During periods when the availability of aqueous crystalline penicillin G is compromised, the following is recommended (https://www.cdc.gov/std/treatment/drug-notices.htm):

- For neonates with clinical evidence of congenital syphilis (see Scenario 1), check local sources for aqueous crystalline penicillin G (potassium or sodium) and notify CDC and FDA of limited supply. If IV penicillin G is limited, substitute some or all daily doses with procaine penicillin G (50,000 units/kg body weight/dose IM/day in a single daily dose for 10 days).
- If aqueous or procaine penicillin G is unavailable, ceftriaxone (50–75 mg/kg body weight/day IV every 24 hours) can be considered with thorough clinical and serologic follow-up and in consultation with an expert because evidence is insufficient to support using ceftriaxone for treating congenital syphilis. Ceftriaxone should be used with caution in neonates with jaundice.
- For neonates without any clinical evidence of congenital syphilis (see Scenario 2 and Scenario 3), use
  - procaine penicillin G 50,000 units/kg body weight/dose/day IM in a single dose for 10 days, or
  - benzathine penicillin G 50,000 units/kg body weight IM as a single dose.
- If any part of the evaluation for congenital syphilis is abnormal or was not performed, CSF examination is not interpretable, or follow-up is uncertain, procaine penicillin G is recommended. A single dose of ceftriaxone is inadequate therapy.
- For premature neonates who have no clinical evidence of congenital syphilis (see Scenario 2 and Scenario 3) and might not tolerate IM injections because of decreased muscle mass, IV ceftriaxone can be considered with thorough clinical and serologic follow-up and in consultation with an expert. Ceftriaxone dosing should be adjusted according to birthweight.

HIV Infection

Evidence is insufficient to determine whether neonates who have congenital syphilis and HIV infection or whose mothers have HIV require different therapy or clinical management than is recommended for all neonates. All neonates with congenital syphilis should be managed similarly, regardless of HIV status.

Evaluation and Treatment of Infants and Children with Congenital Syphilis

Infants and children aged ≥1 month who are identified as having reactive serologic tests for syphilis (e.g., RPR reactive, TP-PA reactive or EIA reactive, RPR reactive) should be examined thoroughly and have maternal serology and records reviewed to assess whether they have congenital or acquired syphilis (see Primary and Secondary Syphilis; Latent Syphilis; Sexual Assault or Abuse of Children). In the case of extremely early or incubating syphilis at the time of delivery, all maternal serologic tests might have been negative; thus, infection might be undetected until a diagnosis is made later in the infant or child. Any infant or child at risk for congenital syphilis should receive a full evaluation and testing for HIV infection.

International adoptee, immigrant, or refugee children from countries where treponemal infections (e.g., yaws or pinta) are endemic might have reactive nontreponemal and treponemal serologic tests, which cannot distinguish between syphilis and other subspecies of *T. pallidum* (*651*). These children might also have syphilis (*T. pallidum* subspecies *pallidum*) and should be evaluated for congenital syphilis.

Recommended Evaluation

The following evaluations should be performed:

- CSF analysis for VDRL, cell count, and protein
- CBC, differential, and platelet count
- Other tests as clinically indicated (e.g., long-bone radiographs, chest radiograph, liver function tests, abdominal ultrasound, ophthalmologic examination, neuroimaging, and auditory brain-stem response)

Recommended Regimen for Congenital Syphilis Among Infants and Children
Aqueous crystalline penicillin G 200,000–300,000 units/kg body weight/day IV, administered as 50,000 units/kg body weight every 4–6 hours for 10 days

If the infant or child has no clinical manifestations of congenital syphilis and the evaluation (including the CSF examination) is normal, treatment with <3 weekly doses of benzathine penicillin G 50,000 units/kg body weight IM can be considered. A single dose of benzathine penicillin G 50,000 units/kg body weight IM up to the adult dose of

2.4 million units in a single dose can be considered after the 10-day course of IV aqueous penicillin G to provide more comparable duration for treatment in those who have no clinical manifestations and normal CSF. All of these treatment regimens should also be adequate for children who might have other treponemal infections.

Follow-Up

Thorough follow-up examinations and serologic testing (i.e., RPR or VDRL) of infants and children treated for congenital syphilis after the neonatal period (aged >30 days) should be performed every 3 months until the test becomes nonreactive or the titer has decreased fourfold. The serologic response after therapy might be slower for infants and children than neonates. If these titers increase at any point >2 weeks or do not decrease fourfold after 12–18 months, the infant or child should be evaluated (e.g., CSF examination), treated with a 10-day course of parenteral penicillin G, and managed in consultation with an expert. Treponemal tests (e.g., EIA, CIA, or TP-PA) should not be used to evaluate treatment response because the results are qualitative and persist after treatment, and passive transfer of maternal IgG treponemal antibody might persist for >15 months after delivery. Infants or children whose initial CSF evaluations are abnormal do not need repeat lumbar puncture unless their serologic titers do not decrease fourfold after 12–18 months. After 18 months of follow-up, abnormal CSF indices that persist and cannot be attributed to other ongoing illness indicate that retreatment is needed for possible neurosyphilis and should be managed in consultation with an expert.

Special Considerations

Penicillin Allergy

Infants and children who require treatment for congenital syphilis but who have a history of penicillin allergy or develop an allergic reaction presumed secondary to penicillin should be desensitized and treated with penicillin G (see Management of Persons Who Have a History of Penicillin Allergy). Skin testing remains unavailable for infants and children because the procedure has not been standardized for this age group. Data are insufficient regarding use of other antimicrobial agents (e.g., ceftriaxone) for congenital syphilis among infants and children. If a nonpenicillin G agent is used, close clinical, serologic, and CSF follow-up is required in consultation with an expert.

Penicillin Shortage

During periods when availability of penicillin G is compromised, management options are similar to options for the neonate (see Evaluation and Treatment of Neonates).

- For infants and children with clinical evidence of congenital syphilis, if IV penicillin is limited after checking local sources and notifying CDC and FDA about limited supplies, procaine penicillin G (50,000 units/kg body weight/dose IM up to the adult dose of 2.4 million units a day in a single daily dose for 10 days) is recommended.
- If procaine penicillin G is not available, ceftriaxone (in doses for age and weight) can be considered with thorough clinical and serologic follow-up. Infants and children receiving ceftriaxone should be managed in consultation with an expert because evidence is insufficient to support use of ceftriaxone for treatment of congenital syphilis among infants or children. For infants aged ≥30 days, use ceftriaxone 75 mg/kg body weight/day IV or IM in a single daily dose for 10–14 days (dose adjustment might be necessary on the basis of current weight). For children, ceftriaxone 100 mg/kg body weight/day in a single daily dose is recommended.
- For infants and children without any clinical evidence of infection (see Scenario 2 and Scenario 3), use
  - procaine penicillin G 50,000 units/kg body weight/dose IM up to the adult dose of 2.4 million units a day in a single dose for 10 days, or
  - benzathine penicillin G 50,000 units/kg body weight IM up to the adult dose of 2.4 million units as a single dose.
- If any part of the evaluation for congenital syphilis is abnormal or not performed, CSF examination is not interpretable, or follow-up is uncertain, procaine penicillin G is recommended. In these scenarios, a single dose of ceftriaxone is inadequate therapy.

HIV Infection

Evidence is insufficient to determine whether infants and children who have congenital syphilis and HIV infection or whose mothers have HIV require different therapy or clinical management than what is recommended for all infants and children. All infants and children with congenital syphilis should be managed similarly, regardless of HIV status.

Management of Persons Who Have a History of Penicillin Allergy

Penicillin and other ß-lactam antibiotics have a crucial role in treating STIs. Penicillin is recommended for all clinical stages of syphilis, and no proven alternatives exist for treating neurosyphilis, congenital syphilis, or syphilis during pregnancy. Ceftriaxone, a third-generation cephalosporin, is recommended for gonorrhea treatment. For extragenital site infections, especially pharyngeal, failure rates of nonceftriaxone

regimens can be substantial. In most clinical settings, patients who report a penicillin allergy are not treated with ß-lactam antimicrobials. For patients with a diagnosis of gonorrhea and a concomitant reported allergy to penicillin, ceftriaxone is often avoided, even though the cross-reactivity between penicillin allergy and third-generation cephalosporins is low (*652*–*654*).

Prevalence of reported allergy to penicillin is approximately 10% among the U.S. population and higher among hospital inpatients and residents in health care–related facilities (*655*–*658*). One large study in an STI clinic revealed that 8.3% of patients reported penicillin or another ß-lactam antibiotic allergy (*659*). Penicillin allergy is often overreported, with the majority of patients who report penicillin allergy able to tolerate the medication (*660*). The prevalence of reported penicillin allergy in low-income countries is unknown; however, limited data indicate that penicillin is one of the most frequently reported antibiotic allergies (*661*).

Patients often are incorrectly labeled as allergic to penicillin and are therefore denied the benefit of a ß-lactam therapy. The presence of a penicillin allergy label considerably reduces prescribing options for affected patients. Moreover, penicillin allergy labels lead to the use of more expensive and less effective drugs and can result in adverse consequences, including longer length of hospital stay and increased risk for infection. Multiple studies have described that persons with reported penicillin or another ß-lactam antibiotic allergy have higher rates of surgical-site infections, methicillin-resistant *Staphylococcus aureus* infections, and higher medical care usage (*653*,*662*–*664*).

The overreported prevalence of penicillin allergy is secondary to imprecise use of the term "allergy" by families and clinicians and lack of clarity to differentiate between immunoglobulin E (IgE)-mediated hypersensitivity reactions, drug intolerances, and other idiosyncratic reactions that can occur days after exposure. Approximately 80% of patients with a true IgE-mediated allergic reaction to penicillin have lost the sensitivity after 10 years (*658*). Thus, patients with recent reactions are more likely to be allergic than patients with remote reactions, and patients who had allergic reactions in the distant past might no longer be reactive.

In a Baltimore, Maryland, STI clinic study, only 7.1% of the patients who reported allergy to penicillin or to another ß-lactam antibiotic had an objective positive test for penicillin allergy (*659*). Moreover, in studies that have incorporated penicillin skin testing and graded oral challenge among persons with reported penicillin allergy, the true rates of allergy are low, ranging from 1.5% to 6.1% (*665*–*667*). Studies in preoperative surgical patients with reported penicillin allergy, evaluated for cardiovascular surgery (*668*) or orthopedics (*669*), have rates of skin test positivity <8.5%. However, when patients with high-risk penicillin allergy histories are excluded, 99% of patients could receive ß-lactams. In hospitalized patients and other populations with comorbidities, the typical rates of validated penicillin allergy among patients who report a history of penicillin allergy are 2.5%–9.0% (*670*–*673*).

Cross-Reactivity with Cephalosporins

Penicillin and cephalosporins both contain a ß-lactam ring. This structural similarity has led to considerable confusion regarding cross-reactivity of these drugs and the risks for allergic reactions from cephalosporins among penicillin-allergic patients. In most clinical settings, patients with reported penicillin allergy are precluded from treatment with such cephalosporin antibiotics as ceftriaxone. Third-generation cephalosporins (e.g., ceftriaxone and cefixime) have lower cross-reactivity with IgE-mediated penicillin-allergic patients (<1%) compared with first- and second-generation cephalosporins (range: 1%–8%). Moreover, anaphylaxis secondary to cephalosporins is extremely rare among persons who report a penicillin allergy and is estimated to occur at a rate of one per 52,000 persons (*652*). Data from the Kaiser health care system reported that among 3,313 patients with self-reported cephalosporin allergy who received a cephalosporin (mostly first generation), no cases of anaphylaxis were reported (*652*). Use of third- and fourth-generation cephalosporins and carbapenems is safe for patients without a history of any IgE-mediated symptoms (e.g., anaphylaxis or urticaria) from penicillin during the preceding 10 years.

Validating Penicillin or Another ß-Lactam Antibiotic Allergy

Evaluating a patient who reports a penicillin or another ß-lactam antibiotic allergy involves three steps: 1) obtaining a thorough medical history, including previous exposures to penicillin or other ß-lactam antibiotics (*658*); 2) performing a skin test evaluation by using the penicillin major and minor determinants; and 3) among those who have a negative penicillin skin test, performing an observed oral challenge with 250 mg amoxicillin before proceeding directly to treatment with the indicated ß-lactam therapy (*667*,*675*).

For persons who have a positive skin test reactive to penicillin (either to the major or minor determinants), treatment with a ß-lactam antibiotic is not usually advised, and other effective antimicrobials should be used (*656*,*658*). For persons among whom the only therapy option is a penicillin antibiotic (e.g., a patient with neurosyphilis or a pregnant woman with syphilis) and among whom a penicillin skin test is positive, induction of penicillin tolerance (also referred to as desensitization) is required (*675*). Desensitization protocols to penicillin should

be performed by allergists, and they require a monitored inpatient environment.

Penicillin Skin Testing

Penicillin skin testing with a major determinant analog (penicilloyl-polylysine) and minor determinants (benzylpenicilloate, benzylpenilloate, or benzylpenicillin isomers of penicillin) are used for skin test evaluation for IgE-dependent penicillin allergy and can reliably identify persons at high risk for IgE-mediated reactions to penicillin (*658*,*660*,*676*). Until recently, penicillin skin testing in the United States only included the major determinant benzyl penicillin poly-L-lysine (Pre-Pen) in addition to penicillin G. This test identifies approximately 90%–99% of the IgE-mediated penicillin-allergic patients. Because the remaining 1%–10% of penicillin-allergic patients who are not captured by this penicillin skin test are due to minor determinants IgE antibodies, the standard practice is to follow skin testing with an observed oral challenge of amoxicillin 250 mg with 1 hour of observation. If the skin test and oral challenge are both negative, the risk for IgE-mediated anaphylaxis approaches zero and is equivalent to that of a person who has never reported an allergy to penicillin.

A revised version of the penicillin skin test kit, which includes the major determinant reagent Pre-Pen, minor determinants, and amoxicillin, is being evaluated by FDA. This penicillin skin test kit has been evaluated among 455 patients (*677*) with previous allergy history and has a negative predictive value of 98%. If approved, this kit might eliminate the need for oral challenge.

Penicillin skin testing has become a clinically significant element in antibiotic stewardship programs, and the procedure has been increasingly used by hospital-based pharmacists, hospitalists, and infectious disease physicians (*670*,*672*,*673*,*678*,*679*) as part of overall antibiotic stewardship interventions. When integrated into stewardship, the rates of ß-lactam antibiotic use increased substantially (*670*).

Recommendations

Persons with a history of severe adverse cutaneous reaction (e.g., Stevens-Johnson syndrome or toxic epidermal necrolysis) and other severe non–IgE-mediated reactions (e.g., interstitial nephritis or hemolytic anemia) are not candidates for penicillin skin testing or challenge. Penicillin and any other ß-lactam antibiotics should be avoided indefinitely among these patients, who should be referred to an allergy center for further evaluation. Similarly, patients who deny penicillin allergy, but who report previous IgE-type reactions to cephalosporins, should be referred to an allergist for specific cephalosporin testing.

In a time of increasing antimicrobial resistance, following recommended use of antibiotic treatments is crucial. STI programs and clinicians should promote increased access to penicillin allergy testing. Allergy testing is being provided by clinicians in primary care and hospital settings. If appropriate, STI programs and ambulatory settings should consider developing expanded access to penicillin or ß-lactam allergy assessment.

Persons with high-risk symptom histories (e.g., anaphylaxis within the previous 10 years) should not be administered penicillin or a ß-lactam antibiotic in an ambulatory setting. Furthermore, these persons with high-risk symptoms should not receive penicillin skin testing or amoxicillin oral challenge in an ambulatory STI setting and should be referred to an allergist for further evaluation.

High-risk symptom histories include development of the following after penicillin or ß-lactam administration: anaphylaxis within 6 hours or severe adverse cutaneous reaction (e.g., eosinophilia and systemic symptoms, Stevens-Johnson syndrome, toxic epidermal necrolysis, or acute generalized exanthematous pustulosis) and other severe non–IgE-mediated reactions (e.g., kidney or hepatic injury, hemolytic anemia, or thrombocytopenia).

Direct Treatment Approach for Ceftriaxone

Among persons with confirmed IgE-mediated penicillin allergy, the level of cross-reactivity with third-generation cephalosporins is low (*652*,*680*,*681*). If a patient has a low-risk history for an IgE-mediated penicillin allergy, ambulatory settings often treat with third-generation cephalosporins without further testing. Low-risk history includes one nonspecific symptom (e.g., gastrointestinal intolerance, headache, fatigue, or nonurticarial rash) (Box 2). In addition, a family history of penicillin or ß-lactam allergy alone is not a contraindication for treatment with ß-lactam antibiotics. This practice is increasingly being used in ambulatory settings and for preoperative prophylaxis (*658*,*663*,*680*,*682*–*684*).

BOX 2. Low-risk history in patients who report penicillin allergy

Gastrointestinal symptoms

Headache

Pruritis without rash

Localized rash

Delayed onset rash (>24 hours)

Symptoms unknown

Family history of penicillin or another drug allergy

Patient denies allergy but it is on the medical record

Patients at Low Risk for Oral Challenge

If the patient gives only a low-risk history of IgE-mediated penicillin allergy that includes symptoms such gastrointestinal intolerance, headache, fatigue, or nonspecific pruritus, or gives a family history only, an oral challenge can be administered to document the absence of allergy (Box 2). If the reaction occurred in the distant past (>10 years), the likelihood is reduced even further (*653*,*658*,*663*,*682*,*683*,*685*,*686*). The risk for severe amoxicillin-mediated anaphylaxis has decreased over time and is rare. In the United Kingdom during 1972–2007, one fatal case of amoxicillin-medicated anaphylaxis was reported (*684*).

Skin Testing for Penicillin Allergy

Skin testing for penicillin allergy should be performed if any indication exists that the symptoms were secondary to an IgE-mediated hypersensitivity. Testing is also indicated as a potential diagnostic procedure to definitively rule out penicillin allergy and document a negative allergy status in the medical record (i.e., delabeling). Because penicillin allergy testing does not test for multiple minor determinants, a person with a negative skin test should follow up with an oral challenge to confirm the negative status.

Persons with negative results of a penicillin skin test, followed by an amoxicillin oral challenge, can receive conventional penicillin therapy safely if needed. Persons with positive skin test results and for whom no other clinical options exist (e.g., neurosyphilis and syphilis in a pregnant woman) should be referred to an allergist and desensitized before initiating treatment.

Testing Procedures

Penicillin skin testing includes use of skin test reagents for identifying persons at risk for adverse reactions (Box 3), followed by initial pinprick screening with penicillin major determinants (Pre-Pen) and penicillin G, followed by intradermal testing if pinprick results are negative. Penicillin testing procedures are performed in accordance with the Pre-Pen test kit instructions (https://penallergytest.com/wp-content/uploads/PRE-PEN-Package-Insert.pdf). Saline negative controls and histamine positive controls are an integral part of the procedure. Penicillin skin testing should not be performed for patients who have taken antihistamines within the past 7 days.

Skin testing can be safely performed by trained nonallergists and has been implemented as an antimicrobial stewardship intervention by internal medicine physicians, pharmacists, hospitalists, and infectious disease physicians (*670*,*673*,*678*,*679*). Patients tested should also receive documentation of status, and the results should be entered in the medical record.

Penicillin skin testing during pregnancy is considered safe. For pregnant persons who report a penicillin or ß-lactam allergy, penicillin allergy is an important consideration in treating syphilis during pregnancy and the potential for group B streptococcal infection and preoperative prophylaxis if a cesarean delivery is required. However, oral challenges should not be performed unless in a setting where additional support services are available.

Managing Persons Being Tested

Patients who have a positive skin test should not receive ß-lactam drugs in the ambulatory setting and should be referred to an allergist or penicillin allergy expert for further evaluation. The allergy testing results should be documented in the medical record. Patients who test negative should be informed that their risk for anaphylaxis is extremely low and is equivalent to a person who does not report an allergy history. If treatment with penicillin or ceftriaxone is indicated, it can be administered safely. Documentation of testing results should be provided to the patient.

Desensitization

Desensitization is required for persons who have a documented penicillin allergy and for whom no therapeutic alternatives exist (e.g., syphilis during pregnancy and persons with neurosyphilis). Modified protocols might be considered

BOX 3. Skin test reagents for identifying persons at risk for adverse reactions to penicillin

Major determinant

- Benzylpenicilloyl polylysine injection (Pre-Pen) (AllerQuest) (6×10^{-5}M)

Minor determinant precursors

- Benzylpenicillin G (10^{-2}M, 3.3 mg/mL, 10,000 units/mL)
- Benzylpenicilloate (10^{-2}M, 3.3 mg/mL)
- Benzylpenicilloate (or penicilloyl propylamine) (10^{-2}M, 3.3 mg/mL)

Aged penicillin is not an adequate source of minor determinants. Penicillin G should either be freshly prepared or come from a fresh-frozen source.

Positive control

- Commercial histamine for scratch testing (1.0 mg/mL)

Negative control

- Diluent (usually saline) or allergen diluent

Source: Adapted from Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. Ann Intern Med 1987;107:204–15.

on the basis of the clinical syndrome, drug of choice, and route of administration (*687–690*). Patients might require referral to a specialty center where desensitization can be performed.

Allergy Referral Resources

With increased access to skin testing kits and the need to better target therapy for gonorrhea and syphilis, programs should identify local allergy consultant resources.

Diseases Characterized by Urethritis and Cervicitis

Urethritis

Urethritis, as characterized by urethral inflammation, can result from either infectious or noninfectious conditions. Symptoms, if present, include dysuria, urethral pruritis, and mucoid, mucopurulent, or purulent discharge. Signs of urethral discharge on examination can also be present among persons without symptoms. Although *N. gonorrhoeae* and *C. trachomatis* are well established as clinically important infectious causes of urethritis, *M. genitalium* has been strongly associated with urethritis and, less commonly, prostatitis (*691–697*). If POC diagnostic tools (e.g., Gram, methylene blue [MB], or gentian violet [GV] stain microscopy) are unavailable, drug regimens effective against both gonorrhea and chlamydia should be administered. Further testing to determine the specific etiology is recommended for preventing complications, reinfection, and transmission because a specific diagnosis might improve treatment compliance, delivery of risk-reduction interventions, and partner services. Both chlamydia and gonorrhea are reportable to health departments. NAATs are preferred for detecting *C. trachomatis* and *N. gonorrhoeae*, and urine is the preferred specimen for males (*553*). NAAT-based tests for diagnosing *T. vaginalis* among men with urethritis have not been cleared by FDA; however, laboratories have performed the CLIA-compliant validation studies (*698*) needed to provide such testing.

Etiology

Multiple organisms can cause infectious urethritis. The presence of gram-negative intracellular diplococci (GNID) or purple intracellular diplococci (MB or GV) on urethral smear is indicative of presumed gonococcal infection, which is frequently accompanied by chlamydial infection. Nongonococcal urethritis (NGU), which is diagnosed when microscopy of urethral secretions indicate inflammation without GNID or MB or GV purple intracellular diplococci, is caused by *C. trachomatis* in 15%–40% of cases; however, prevalence varies by age group, with a lower proportion of disease occurring among older men (*699*). Documentation of chlamydial infection as NGU etiology is essential because of the need for partner referral for evaluation and treatment to prevent complications of chlamydia, especially for female partners. Complications of *C. trachomatis*–associated NGU among males include epididymitis, prostatitis, and reactive arthritis.

M. genitalium is associated with symptoms of urethritis and urethral inflammation and accounts for 15%–25% of NGU cases in the United States (*691–693*,*696*,*697*,*700*). Among men with symptoms of urethritis, *M. genitalium* was detected in 11% of those with urethritis in Australia (*701*), 12%–15% in the United Kingdom (*702–704*), 15% in South Africa (*696*), 19% in China (*705*), 21% in Korea, 22% in Japan (*706*), and 28.7% in the United States (range: 20.4%–38.8%) (*697*). Data are inconsistent regarding other *Mycoplasma* and *Ureaplasma* species as etiologic agents of urethritis (*707*). The majority of men with *Ureaplasma* infections do not have overt disease unless a high organism load is present.

T. vaginalis can cause urethritis among heterosexual men; however, the prevalence varies substantially by U.S. geographic region, age, and sexual behavior and within specific populations. Studies among men with and without overt urethritis in developed countries document relatively low rates of *T. vaginalis* in the Netherlands (0.5%) (*708*), Japan (1.3%) (*706*,*709*), the United States (2.4%) (*710*), and the United Kingdom (3.6%) (*703*). Studies in other countries have documented higher rates, such as in Croatia (8.2%) (*711*) and Zimbabwe (8.4%) (*712*), particularly among symptomatic patients.

Neisseria meningitidis can colonize mucosal surfaces and cause urethritis (*713*). Urogenital *N. meningitidis* rates and duration of carriage, prevalence of asymptomatic and symptomatic infection, and modes of transmission have not been systematically described; however, studies indicate that *N. meningitidis* can be transmitted through oral-penile contact (i.e., fellatio) (*714–716*). *N. meningitidis* has similar colony morphology appearance on culture and cannot be distinguished from *N. gonorrhoeae* on Gram stain. Identification of *N. meningitidis* as the etiologic agent with presumed gonococcal urethritis on the basis of Gram stain but negative NAAT for gonorrhea requires a confirmation by culture. Meningococcal urethritis is treated with the same antimicrobial regimens as gonococcal urethritis. Although evidence is limited regarding the risk for sexual transmission or recurrent infections with meningococcal urethritis, treatment of sex partners of patients with meningococcal urethritis with the same antimicrobial regimens as for exposure to gonococcal infection can be considered. No indication exists for treating

persons with *N. meningitidis* identified in their oropharynx when not also associated with symptomatic urethritis.

In other instances, NGU can be caused by HSV, Epstein-Barr virus, and adenovirus (*699*) acquired by fellatio (i.e., oral-penile contact). In a retrospective review of 80 cases of HSV urethritis in Australia (*717*), the majority of infections were associated with HSV-1 with clinical findings of meatitis (62%), genital ulceration (37%), and dysuria (20%). Adenovirus can present with dysuria, meatal inflammation, and conjunctivitis (*718*). Enteric bacteria have been identified as an uncommon cause of NGU and might be associated with insertive anal intercourse (*699*).

Other bacterial pathogens have been implicated as potential causes of clinical urethritis, either in clustered case series or as sporadic cases such as *Haemophilus influenzae* and *Haemophilus parainfluenzae* (*719–723*). *Haemophilus* was identified in 12.6% of cases among 413 men (mostly MSM reporting insertive oral sex) (*724*), and high rates of azithromycin resistance (39.5%) were identified among *Haemophilus* urethritis patients (*725*). Individual case reports have linked NGU to multiple bacterial species, including *Corynebacterium propinquum* (*726*), *Kurthia gibsonii* (*727*), *Corynebacterium glucuronolyticum* (*728*,*729*), *Corynebacterium striatrium* (*730*), *Aerococcus urinae* (*731*), and *Neisseria elongata* (*732*). Diagnostic testing and treatment for less-common organisms are reserved for situations in which these infections are suspected (e.g., sexual partner with trichomoniasis, urethral lesions, or severe dysuria and meatitis) or when NGU is not responsive to recommended therapy.

Even in settings that provide comprehensive diagnostic testing, etiology can remain obscure in half of cases. Idiopathic NGU was reported in 772 (59%) of 1,295 first presentations of NGU among men seeking sexual health services in Australia (*701*). In a case-control study of 211 men with NGU symptoms in Denmark, no identifiable pathogen was identified in 24% of acute cases and 33% of chronic cases (*733*). NGU's importance if not caused by a defined pathogen is uncertain; neither complications (e.g., urethral stricture or epididymitis) nor adverse outcomes among sex partners have been identified in these cases.

Associations between NGU and insertive anal and oral exposure have been reported (*734*), as have higher rates of BV-associated *Leptotrichia* or *Sneathia* species among heterosexual men with urethritis (*735*). These studies increase concern for possible undetected infectious rectal or vaginal pathogens, or alternatively, a transient reactive dysbiosis after exposure to a new microbiome or even a noninfectious reactive etiology (*736*).

Diagnostic Considerations

Clinicians should attempt to obtain objective evidence of urethral inflammation. If POC diagnostic tests (e.g., Gram stain or MB or GV microscopy) are unavailable, urethritis can be documented on the basis of any of the following signs or laboratory tests:

- Mucoid, mucopurulent, or purulent discharge on examination.
- Gram stain is a POC diagnostic test for evaluating urethritis that is highly sensitive and specific for documenting both urethritis and the presence or absence of gonococcal infection; MB or GV stain of urethral secretions is an alternative POC diagnostic test with performance characteristics similar to Gram stain; thus, the cutoff number for WBCs per oil immersion field should be the same (*737*).
  - Presumed gonococcal infection is established by documenting the presence of WBCs containing GNID in Gram stain or intracellular purple diplococci in MB or GV smears; men should be tested for *C. trachomatis* and *N. gonorrhoeae* by NAATs and presumptively treated and managed accordingly for gonococcal infection (see Gonococcal Infections).
  - If no intracellular gram-negative or purple diplococci are present, men should receive NAATs for *C. trachomatis* and *N. gonorrhoeae* and can be managed for NGU as recommended (see Nongonococcal Urethritis).
  - Gram stain of urethral secretions exist that demonstrate ≥2 WBCs per oil immersion field (*738*). The microscopy diagnostic cutoff might vary, depending on background prevalence (≥2 WBCs/high power field [HPF] in high-prevalence settings [STI clinics] or ≥5 WBCs/HPF in lower-prevalence settings).[§§]

[§§] For urethral microscopy, the cutoff for diagnosing urethritis is ≥2 WBCs/HPF (**Sources:** Rietmeijer CA, Mettenbrink CJ. Recalibrating the Gram stain diagnosis of male urethritis in the era of nucleic acid amplification testing. Sex Transm Dis 2012;39:18–20; Rietmeijer CA, Mettenbrink CJ. The diagnosis of nongonococcal urethritis in men: can there be a universal standard? Sex Transm Dis 2017;44:195–6). An additional evaluation supported this cutoff by demonstrating NGU sensitivity of 92.6% for cutoff of ≥2 versus 55.6% sensitivity for cutoff of ≥5 (**Source:** Sarier M, Sepin N, Duman I, et al. Microscopy of Gram-stained urethral smear in the diagnosis of urethritis: which threshold value should be selected? Andrologia 2018;50:e13143). Diagnostic cutoffs for 369 symptomatic and asymptomatic heterosexual men seeking STI care in Seattle revealed a maximal sensitivity and specificity achieved with a cutoff of ≥5 WBCs/HPF. Using a lower cutoff of ≥2 WBCs/HPF would miss 13% of *C. trachomatis* and *M. genitalium* and overtreat 45% of persons who have negative tests (**Source:** Leipertz G, Chambers L, Lowens S, et al. P796 Reassessing the Gram stain smear [GSS] polymorphonuclear leukocyte [PMN] cutoff for diagnosing non-gonococcal urethritis [NGU]. Sex Transm Infect 2019;95[Suppl 1]:A339). Another study discussed that the WBC/HPF cutoff value should discriminate on the basis of the prevalence of chlamydia, mycoplasma, and gonorrhea among a clinic population (**Source:** Moi H, Hartgill U, Skullerud KH, Reponen EJ, Syvertsen L, Moghaddam A. Microscopy of stained urethral smear in male urethritis: which cutoff should be used? Sex Transm Dis 2017;44:189–94).

- Positive leukocyte esterase test on first-void urine or microscopic examination of sediment from a spun first-void urine demonstrating ≥10 WBCs/HPF.

Men evaluated in settings in which Gram stain or MB or GV smear is unavailable who meet at least one criterion for urethritis (i.e., urethral discharge, positive leukocyte esterase test on first void urine, or microscopic examination of first-void urine sediment with ≥10 WBCs/HPF) should be tested for *C. trachomatis* and *N. gonorrhoeae* by NAATs and treated with regimens effective against gonorrhea and chlamydia.

If symptoms are present but no evidence of urethral inflammation is present, NAATs for *C. trachomatis* and *N. gonorrhoeae* might identify infections (*739*). Persons with chlamydia or gonorrhea should receive recommended treatment, and sex partners should be referred for evaluation and treatment. If none of these clinical criteria are present, empiric treatment of men with symptoms of urethritis is recommended only for those at high risk for infection who are unlikely to return for a follow-up evaluation or test results. Such men should be treated with drug regimens effective against gonorrhea and chlamydia.

Nongonococcal Urethritis

NGU is a nonspecific diagnosis that can have various infectious etiologies. *C. trachomatis* has been well established as an NGU etiology; however, prevalence varies across populations and accounts for <50% of overall cases (*712*,*740*–*742*). *M. genitalium* is estimated to account for 10%–25% of cases (*696*,*697*,*701*,*703*,*704*,*706*,*733*,*743*), and *T. vaginalis* for 1%–8% of cases depending on population and location (*703*,*706*,*708*,*710*,*712*). Other etiologies include different bacteria, such as *Haemophilus* species (*724*,*725*), *N. meningitidis* (*713*,*716*), HSV (*706*,*717*), and adenovirus (*744*). However, even when extensive testing is performed, no pathogens are identified in approximately half of cases (*701*,*733*).

Diagnostic Considerations

Clinical presentation can include urethral discharge, irritation, dysuria, or meatal pruritus (*697*,*743*,*745*). NGU is confirmed for symptomatic men when diagnostic evaluation of urethral secretions indicates inflammation, without evidence of diplococci by Gram, MB, or GV smear on microscopy (*712*,*746*,*747*). Visible discharge or secretions can be collected by a swab without inserting it into the urethra; if no visible secretions, the swab can be inserted into the urethral meatus and rotated, making contact with the urethral wall before removal. If microscopy is unavailable, urine testing for leukocyte esterase can be performed on first-void urine, and microscopic examination of sediment from a spun first-void urine demonstrating ≥10 WBCs/HPF has a high negative predictive value.

All men who have suspected or confirmed NGU should be tested for chlamydia and gonorrhea by using NAATs. A specific diagnosis can potentially reduce complications, reinfection, and transmission. *M. genitalium* testing should be performed for men who have persistent or recurrent symptoms after initial empiric treatment. Testing for *T. vaginalis* should be considered in areas or among populations with high prevalence, in cases where a partner is known to be infected, or for men who have persistent or recurrent symptoms after initial empiric treatment.

Treatment

Ideally, treatment should be pathogen based; however, diagnostic information might not be immediately available. Presumptive treatment should be initiated at NGU diagnosis. Doxycycline is highly effective for chlamydial urethral infections and is also effective for chlamydial infections of the rectum; it also has some activity against *M. genitalium*. In contrast, reports have increased of azithromycin treatment failures for chlamydial infection (*748*,*749*), and the incidence of macrolide resistance in *M. genitalium* also has been rapidly rising (*697*,*702*,*705*,*750*,*751*). Pharmacokinetic data indicate that changing azithromycin dosing from a single-dose strategy to a multiday strategy might protect against inducing resistance in *M. genitalium* infections (*745*,*752*) (see *Mycoplasma genitalium*).

Recommended Regimen for Nongonococcal Urethritis
Doxycycline 100 mg orally 2 times/day for 7 days

Alternative Regimens
Azithromycin 1 g orally in a single dose *or* **Azithromycin** 500 mg orally in a single dose; then 250 mg orally daily for 4 days

To maximize compliance with recommended therapies, medications should be dispensed on-site at the clinic, and, regardless of the number of doses involved in the regimen, the first dose should be directly observed. Erythromycin is no longer recommended for NGU because of its gastrointestinal side effects and dosing frequency. Levofloxacin is no longer recommended for NGU because of its inferior efficacy, especially for *M. genitalium.*

Management Considerations

To minimize transmission and reinfections, men treated for NGU should be instructed to abstain from sexual intercourse until they and their partners have been treated (i.e., until

completion of a 7-day regimen and symptoms have resolved or for 7 days after single-dose therapy). Men with NGU should be tested for HIV and syphilis.

Follow-Up

Men should be provided their testing results obtained as part of the NGU evaluation. Those with a specific diagnosis of chlamydia, gonorrhea, or trichomoniasis should be offered partner services and instructed to return 3 months after treatment for repeat testing because of high rates of reinfection, regardless of whether their sex partners were treated (*136*,*137*,*753*,*754*) (see Chlamydial Infections; Gonococcal Infections; Trichomoniasis).

If symptoms persist or recur after therapy completion, men should be instructed to return for reevaluation and should be tested for *M. genitalium* and *T. vaginalis*. Symptoms alone, without documentation of signs or laboratory evidence of urethral inflammation, are insufficient basis for retreatment. Providers should be alert to the possible diagnosis of chronic prostatitis or chronic pelvic pain syndrome in men experiencing persistent perineal, penile, or pelvic pain or discomfort; voiding symptoms; pain during or after ejaculation; or new-onset premature ejaculation lasting for >3 months. Men with persistent pain should be referred to a urologist with expertise in pelvic pain disorders.

Management of Sex Partners

All sex partners of men with NGU within the preceding 60 days should be referred for evaluation and testing and presumptive treatment with a drug regimen effective against chlamydia. All partners should be evaluated and treated according to the management section for their respective pathogen; EPT could be an alternate approach if a partner is unable to access timely care. To avoid reinfection, sex partners should abstain from sexual intercourse until they and their partners are treated.

Persistent or Recurrent Nongonococcal Urethritis

The objective diagnosis of persistent or recurrent NGU should be made before considering additional antimicrobial therapy. Symptomatic recurrent or persistent urethritis might be caused by treatment failure or reinfection after successful treatment. Among men who have persistent symptoms after treatment without objective signs of urethral inflammation, the value of extending the duration of antimicrobials has not been demonstrated. Treatment failure for chlamydial urethritis has been estimated at 6%–12% (*755*). The most common cause of persistent or recurrent NGU is *M. genitalium*, especially after doxycycline therapy (*756*,*757*). Treatment failure for *M. genitalium* is harder to determine because certain men achieve clinical cure (i.e., resolution of symptoms) but can still have detectable *M. genitalium* in urethral specimens (*758*).

The initial step in recurrent urethritis is assessing compliance with treatment or potential reexposure to an untreated sex partner (*697*,*743*). If the patient did not comply with the treatment regimen or was reexposed to an untreated partner, retreatment with the initial regimen can be considered. If therapy was appropriately completed and no reexposure occurred, therapy is dependent on the initial treatment regimen. Ideally, diagnostic testing among men with recurrent or persistent symptoms, including those with gonorrhea, chlamydia, *M. genitalium*, and trichomoniasis, can be used to guide further management decisions.

T. vaginalis is also known to cause urethritis among men who have sex with women. In areas where *T. vaginalis* is prevalent, men who have sex with women with persistent or recurrent urethritis should be tested for *T. vaginalis* and presumptively treated with metronidazole 2 g orally in a single dose or tinidazole 2 g orally in a single dose; their partners should be referred for evaluation and treatment, if needed.

If *T. vaginalis* is unlikely (MSM with NGU or negative *T. vaginalis* NAAT), men with recurrent NGU should be tested for *M. genitalium* by using an FDA-cleared NAAT. Treatment for *M. genitalium* includes a two-stage approach, ideally using resistance-guided therapy. If *M. genitalium* resistance testing is available it should be performed, and the results should be used to guide therapy (see *Mycoplasma genitalium*). If *M. genitalium* resistance testing is not available, doxycycline 100 mg orally 2 times/day for 7 days followed by moxifloxacin 400 mg orally once daily for 7 days should be used. The rationale for this approach is that although not curative, doxycycline decreases the *M. genitalium* bacterial load, thereby increasing likelihood of moxifloxacin success (*759*). Higher doses of azithromycin have not been effective for *M. genitalium* after azithromycin treatment failures. Men with persistent or recurrent NGU after treatment for *M. genitalium* or *T. vaginalis* should be referred to an infectious disease or urology specialist.

Special Considerations

HIV Infection

NGU might facilitate HIV transmission (*760*). Persons with NGU and HIV infection should receive the same treatment regimen as those who do not have HIV.

Cervicitis

Two major diagnostic signs characterize cervicitis: 1) a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen (commonly referred to as mucopurulent cervicitis), and

2) sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os. Either or both signs might be present. Cervicitis frequently is asymptomatic; however, certain women might report an abnormal vaginal discharge and intermenstrual vaginal bleeding (e.g., especially after sexual intercourse). The criterion of using an increased number of WBCs on endocervical Gram stain in the diagnosis of cervicitis has not been standardized; it is not sensitive, has a low positive predictive value for *C. trachomatis* and *N. gonorrhoeae* infections, and is not available in most clinical settings (*297*,*761*). Leukorrhea, defined as >10 WBCs/HPF on microscopic examination of vaginal fluid, might be a sensitive indicator of cervical inflammation with a high negative predictive value (i.e., cervicitis is unlikely in the absence of leukorrhea) (*762*,*763*). Finally, although the presence of gram-negative intracellular diplococci on Gram stain of endocervical exudate might be specific for diagnosing gonococcal cervical infection when evaluated by an experienced laboratorian, it is not a sensitive indicator of infection (*764*).

Etiology

C. trachomatis or *N. gonorrhoeae* is the most common etiology of cervicitis defined by diagnostic testing. Trichomoniasis, genital herpes (especially primary HSV-2 infection), or *M. genitalium* (*761*,*765*–*768*) also have been associated with cervicitis. However, in many cases of cervicitis, no organism is isolated, especially among women at relatively low risk for recent acquisition of these STIs (e.g., women aged >30 years) (*769*). Limited data indicate that BV and frequent douching might cause cervicitis (*770*–*772*). The majority of persistent cases of cervicitis are not caused by reinfection with *C. trachomatis* or *N. gonorrhoeae;* other factors might be involved (e.g., persistent abnormality of vaginal flora, *M. genitalium,* douching or exposure to other types of chemical irritants, dysplasia, or idiopathic inflammation in the zone of ectopy). Available data do not indicate an association between group B streptococcus colonization and cervicitis (*773*,*774*). No specific evidence exists for a role for *Ureaplasma parvum* or *Ureaplasma urealyticum* in cervicitis (*707*,*761*,*765*,*775*,*776*).

Diagnostic Considerations

Because cervicitis might be a sign of upper genital tract infection (e.g., endometritis), women should be assessed for signs of PID and tested for *C. trachomatis* and *N. gonorrhoeae* with NAAT on vaginal, cervical, or urine samples (*553*) (see Chlamydial Infections; Gonococcal Infections). Women with cervicitis also should be evaluated for concomitant BV and trichomoniasis. Because sensitivity of microscopy for detecting *T. vaginalis* is relatively low (approximately 50%), symptomatic women with cervicitis and negative wet-mount microscopy for trichomonads should receive further testing (i.e., NAAT, culture, or other FDA-cleared diagnostic test) (see Trichomoniasis). Testing for *M. genitalium* with the FDA-cleared NAAT can be considered. Although HSV-2 infection has been associated with cervicitis, the utility of specific testing (i.e., PCR or culture) for HSV-2 is unknown. Testing for *U. parvum, U. urealyticum, Mycoplasma hominis*, or genital culture for group B streptococcus is not recommended.

Treatment

Multiple factors should affect the decision to provide presumptive therapy for cervicitis. Presumptive treatment with antimicrobials for *C. trachomatis* and *N. gonorrhoeae* should be provided for women at increased risk (e.g., those aged <25 years and women with a new sex partner, a sex partner with concurrent partners, or a sex partner who has an STI), if follow-up cannot be ensured, or if testing with NAAT is not possible. Trichomoniasis and BV should be treated if detected (see Bacterial Vaginosis; Trichomoniasis). For women at lower risk for STIs, deferring treatment until results of diagnostic tests are available is an option. If treatment is deferred and *C. trachomatis* and *N. gonorrhoeae* NAATs are negative, a follow-up visit to determine whether the cervicitis has resolved can be considered.

Recommended Regimen for Cervicitis*
Doxycycline 100 mg orally 2 times/day for 7 days

* Consider concurrent treatment for gonococcal infection if the patient is at risk for gonorrhea or lives in a community where the prevalence of gonorrhea is high (see Gonococcal Infections).

Alternative Regimen
Azithromycin 1 g orally in a single dose

Other Management Considerations

To minimize transmission and reinfection, women treated for cervicitis should be instructed to abstain from sexual intercourse until they and their partners have been treated (i.e., until completion of a 7-day regimen or for 7 days after single-dose therapy) and symptoms have resolved. Women who receive a cervicitis diagnosis should be tested for syphilis and HIV in addition to other recommended diagnostic tests.

Follow-Up

Women receiving treatment should return to their provider for a follow-up visit to determine whether cervicitis has resolved. For women who are untreated, a follow-up visit gives providers an opportunity to communicate test results obtained as part of the cervicitis evaluation. Providers should treat on the basis of any positive test results and determine whether

cervicitis has resolved. Women with a specific diagnosis of chlamydia, gonorrhea, or trichomoniasis should be offered partner services and instructed to return in 3 months after treatment for repeat testing because of high rates of reinfection, regardless of whether their sex partners were treated (*753*). If symptoms persist or recur, women should be instructed to return for reevaluation.

Management of Sex Partners

Management of sex partners of women treated for cervicitis should be tailored for the specific infection identified or suspected. All sex partners during the previous 60 days should be referred for evaluation, testing, and presumptive treatment if chlamydia, gonorrhea, or trichomoniasis was identified. EPT and other effective partner referral strategies are alternative approaches for treating male partners of women who have chlamydial or gonococcal infection (*125–127*) (see Partner Services). To avoid reinfection, sex partners should abstain from sexual intercourse until they and their partners are treated.

Persistent or Recurrent Cervicitis

Women with persistent or recurrent cervicitis despite antimicrobial therapy should be reevaluated for possible reexposure or treatment failure. If relapse or reinfection with a specific infection has been excluded, BV is not present, and sex partners have been evaluated and treated, management options for persistent cervicitis are undefined. In addition, the usefulness of repeated or prolonged administration of antimicrobial therapy for persistent symptomatic cervicitis remains unknown. The etiology of persistent cervicitis, including the potential role of *M. genitalium* (*777*), is unclear. *M. genitalium* might be considered for cases of cervicitis that persist after azithromycin or doxycycline therapy in which reexposure to an infected partner or medical nonadherence is unlikely. Among women with persistent cervicitis who were previously treated with doxycycline or azithromycin, testing for *M. genitalium* can be considered and treatment initiated on the basis of results of diagnostic testing (*318*) (see *Mycoplasma genitalium*). For women with persistent symptoms that are clearly attributable to cervicitis, referral to a gynecologic specialist can be considered for evaluation of noninfectious causes (e.g., cervical dysplasia or polyps) (*778*).

Special Considerations

HIV Infection

Women with cervicitis and HIV infection should receive the same treatment regimen as those who do not have HIV. Cervicitis can increase cervical HIV shedding, and treatment reduces HIV shedding from the cervix and thereby might reduce HIV transmission to susceptible sex partners (*779–783*).

Pregnancy

Diagnosis and treatment of cervicitis for pregnant women does not differ from that for women who are not pregnant (see Diagnostic Considerations; Treatment).

Contraceptive Management

According to *U.S. Medical Eligibility Criteria for Contraceptive Use, 2016*, leaving an IUD in place during treatment for cervicitis is advisable (*58*). However, current recommendations specify that an IUD should not be placed if active cervicitis is diagnosed (*59*).

Chlamydial Infections

Chlamydial Infection Among Adolescents and Adults

Chlamydial infection is the most frequently reported bacterial infectious disease in the United States, and prevalence is highest among persons aged ≤24 years (*141*,*784*). Multiple sequelae can result from *C. trachomatis* infection among women, the most serious of which include PID, ectopic pregnancy, and infertility. Certain women who receive a diagnosis of uncomplicated cervical infection already have subclinical upper genital tract infection.

Asymptomatic infection is common among both men and women. To detect chlamydial infection, health care providers frequently rely on screening tests. Annual screening of all sexually active women aged <25 years is recommended, as is screening of older women at increased risk for infection (e.g., women aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI) (*149*). In a community-based cohort of female college students, incident chlamydial infection was also associated with BV and high-risk HPV infection (*785*). Although chlamydia incidence might be higher among certain women aged ≥25 years in certain communities, overall, the largest proportion of infection is among women aged <25 years (*141*).

Chlamydia screening programs have been demonstrated to reduce PID rates among women (*786*,*787*). Although evidence is insufficient to recommend routine screening for *C. trachomatis* among sexually active young men because of certain factors (i.e., feasibility, efficacy, and cost-effectiveness), screening of sexually active young men should be considered in clinical settings with a high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, or STD specialty

clinics) or for populations with a high burden of infection (e.g., MSM) (*149*,*788*). Among women, the primary focus of chlamydia screening should be to detect and treat chlamydia, prevent complications, and test and treat their partners, whereas targeted chlamydia screening for men should be considered only when resources permit, prevalence is high, and such screening does not hinder chlamydia screening efforts for women (*789*–*791*). More frequent screening than annual for certain women (e.g., adolescents) or certain men (e.g., MSM) might be indicated on the basis of risk behaviors.

Diagnostic Considerations

For women, *C. trachomatis* urogenital infection can be diagnosed by vaginal or cervical swabs or first-void urine. For men, *C. trachomatis* urethral infection can be diagnosed by testing first-void urine or a urethral swab. NAATs are the most sensitive tests for these specimens and are the recommended test for detecting *C. trachomatis* infection (*553*). NAATs that are FDA cleared for use with vaginal swab specimens can be collected by a clinician or patient in a clinical setting. Patient-collected vaginal swab specimens are equivalent in sensitivity and specificity to those collected by a clinician using NAATs (*792*,*793*), and this screening strategy is highly acceptable among women (*794*,*795*). Optimal urogenital specimen types for chlamydia screening by using NAAT include first-catch urine (for men) and vaginal swabs (for women) (*553*). Recent studies have demonstrated that among men, NAAT performance on self-collected meatal swabs is comparable to patient-collected urine or provider-collected urethral swabs (*796*–*798*). Patient collection of a meatal swab for *C. trachomatis* testing might be a reasonable approach for men who are either unable to provide urine or prefer to collect their own meatal swab over providing urine. Previous evidence indicates that the liquid-based cytology specimens collected for Pap smears might be acceptable specimens for NAAT, although test sensitivity using these specimens might be lower than that associated with use of cervical or vaginal swab specimens (*799*); regardless, certain NAATs have been cleared by FDA for use on liquid-based cytology specimens.

Rectal and oropharyngeal *C. trachomatis* infection among persons engaging in receptive anal or oral intercourse can be diagnosed by testing at the anatomic exposure site. NAATs have been demonstrated to have improved sensitivity and specificity, compared with culture, for detecting *C. trachomatis* at rectal and oropharyngeal sites (*553*,*800*–*804*), and certain NAAT platforms have been cleared by FDA for these anatomic sites (*805*). Data indicate that NAAT performance on self-collected rectal swabs is comparable to clinician-collected rectal swabs, and this specimen collection strategy for rectal *C. trachomatis* screening is highly acceptable among men (*217*,*806*). Self-collected rectal swabs are a reasonable alternative to clinician-collected rectal swabs for *C. trachomatis* screening by NAAT, especially when clinicians are not available or when self-collection is preferred over clinician collection. Annual screening for rectal *C. trachomatis* infection should be performed among men who report sexual activity at the rectal site. Extragenital chlamydial testing at the rectal site can be considered for females on the basis of reported sexual behaviors and exposure through shared clinical decision-making bythe patient and the provider. The majority of persons with *C. trachomatis* detected at oropharyngeal sites do not have oropharyngeal symptoms. The clinical significance of oropharyngeal *C. trachomatis* infection is unclear, and prevalence is low, even among populations at high risk. However, when gonorrhea testing is performed at the oropharyngeal site, chlamydia test results might be reported because certain NAATs detect both bacteria from a single specimen.

POC tests for *C. trachomatis* among asymptomatic persons can expedite treatment of infected persons and their sex partners. Among symptomatic patients, POC tests for *C. trachomatis* can optimize treatment by limiting unnecessary presumptive treatment at the time of clinical decision-making and improve antimicrobial stewardship. Thus, using a POC test will likely be a cost-effective diagnostic strategy for *C. trachomatis* infection (*807*). Newer NAAT-based POC tests have promising performance and are becoming commercially available (*807*–*809*).

Treatment

Treating persons with *C. trachomatis* prevents adverse reproductive health complications and continued sexual transmission. Furthermore, treating their sex partners can prevent reinfection and infection of other partners. Treating pregnant women usually prevents transmission of *C. trachomatis* to neonates during birth. Treatment should be provided promptly for all persons with chlamydial infection; treatment delays have been associated with complications (e.g., PID) in a limited proportion of women (*810*).

Recommended Regimen for Chlamydial Infection Among Adolescents and Adults
Doxycycline 100 mg orally 2 times/day for 7 days

Alternative Regimens
Azithromycin 1 g orally in a single dose *or* **Levofloxacin** 500 mg orally once daily for 7 days

A meta-analysis and a Cochrane systematic review evaluated data from randomized clinical trials of azithromycin versus doxycycline for treating urogenital chlamydial infection

determined that microbiologic treatment failure among men was higher for azithromycin than for doxycycline (*748*,*749*). Observational studies have also demonstrated that doxycycline is more efficacious for rectal *C. trachomatis* infection for men and women than azithromycin (*748*,*811*). A randomized trial for the treatment of rectal chlamydia infection among MSM reported microbiologic cure was 100% with doxycycline and 74% with azithromycin (*812*). A published review reported that *C. trachomatis* was detected at the anorectal site among 33%–83% of women who had urogenital *C. trachomatis* infection, and its detection was not associated with report of receptive anorectal sexual activity (*813*).

Although the clinical significance of oropharyngeal *C. trachomatis* infection is unclear and routine oropharyngeal screening is not recommended, oropharyngeal *C. trachomatis* can be sexually transmitted to genital sites (*211*,*814*); therefore, if *C. trachomatis* is identified from an oropharyngeal specimen while screening for pharyngeal gonorrhea, it should be treated. Evidence is limited regarding the efficacy of antimicrobial regimens for oropharyngeal chlamydia; however, a recently published observational study indicates doxycycline might be more efficacious than azithromycin for oropharyngeal chlamydia (*815*).

Available evidence supports that doxycycline is efficacious for *C. trachomatis* infections of urogenital, rectal, and oropharyngeal sites. Although azithromycin maintains high efficacy for urogenital *C. trachomatis* infection among women, concern exists regarding effectiveness of azithromycin for concomitant rectal *C. trachomatis* infection, which can occur commonly among women and cannot be predicted by reported sexual activity. Inadequately treated rectal *C. trachomatis* infection among women who have urogenital chlamydia can increase the risk for transmission and place women at risk for repeat urogenital *C. trachomatis* infection through autoinoculation from the anorectal site (*816*). Doxycycline is also available in a delayed-release 200-mg tablet formulation, which requires once-daily dosing for 7 days and is as effective as doxycycline 100 mg twice daily for 7 days for treating urogenital *C. trachomatis* infection in men and women. It is more costly but also has lower frequency of gastrointestinal side effects (*817*). Levofloxacin is an effective treatment alternative but is more expensive. Erythromycin is no longer recommended because of the frequency of gastrointestinal side effects, which can result in nonadherence. When nonadherence to doxycycline regimen is a substantial concern, azithromycin 1 g regimen is an alternative treatment option but might require posttreatment evaluation and testing because it has demonstrated lower treatment efficacy among persons with rectal infection.

Among persons receiving multidose regimens, medication should be dispensed with all doses involved, on-site and in the clinic, and the first dose should be directly observed. To maximize adherence with recommended therapies, on-site, directly observed single-dose therapy with azithromycin should always be available for persons for whom adherence with multiday dosing is a considerable concern.

Other Management Considerations

To minimize disease transmission to sex partners, persons treated for chlamydia should be instructed to abstain from sexual intercourse for 7 days after single-dose therapy or until completion of a 7-day regimen and resolution of symptoms if present. To minimize risk for reinfection, patients also should be instructed to abstain from sexual intercourse until all of their sex partners have been treated. Persons who receive a diagnosis of chlamydia should be tested for HIV, gonorrhea, and syphilis. MSM who are HIV negative with a rectal chlamydia diagnosis should be offered HIV PrEP.

Follow-Up

Test of cure to detect therapeutic failure (i.e., repeat testing 4 weeks after completing therapy) is not advised for nonpregnant persons treated with the recommended or alternative regimens, unless therapeutic adherence is in question, symptoms persist, or reinfection is suspected. Moreover, using chlamydial NAATs at <4 weeks after completion of therapy is not recommended because the continued presence of nonviable organisms (*553*,*818*,*819*) can lead to false-positive results.

A high prevalence of *C. trachomatis* infection has been observed among women and men who were treated for chlamydial infection during the preceding months (*753*,*755*,*820*–*822*). The majority of posttreatment infections do not result from treatment failure but rather from reinfection caused by failure of sex partners to receive treatment or initiation of sexual activity with a new infected partner (*823*), indicating a need for improved education and treatment of sex partners. Repeat infections confer an elevated risk for PID and other complications among women. Men and women who have been treated for chlamydia should be retested approximately 3 months after treatment, regardless of whether they believe their sex partners were treated; scheduling the follow-up visit at the time of treatment is encouraged (*753*). If retesting at 3 months is not possible, clinicians should retest whenever persons next seek medical care <12 months after initial treatment.

Management of Sex Partners

Sex partners should be referred for evaluation, testing, and presumptive treatment if they had sexual contact with the

partner during the 60 days preceding the patient's onset of symptoms or chlamydia diagnosis. Although the exposure intervals defining identification of sex partners at risk are based on limited data, the most recent sex partner should be evaluated and treated, even if the time of the last sexual contact was >60 days before symptom onset or diagnosis.

If health department partner management strategies (e.g., disease intervention specialists) are impractical or unavailable for persons with chlamydia, and if a provider is concerned that sex partners are unable to promptly access evaluation and treatment services, EPT should be considered as permitted by law (see Partner Services). Compared with standard patient referral of partners, this approach to therapy, which involves delivering the medication itself or a prescription by the patient or collaborating pharmacy, has been associated with decreased rates of persistent or recurrent chlamydia among women (*125*–*127*). Providers should provide patients with written educational materials to give to their partners about chlamydia, which should include notification that partners have been exposed and information about the importance of treatment. These materials also should inform partners about potential therapy-related allergies and adverse effects, along with symptoms indicative of complications (e.g., testicular pain among men and pelvic or abdominal pain among women). Educational materials for female partners should include information about the importance of seeking medical evaluation, especially if PID symptoms are present; undertreatment of PID among female partners and missed opportunities for diagnosing other STIs among women are concerning. MSM with chlamydia have a high risk for coexisting infections, especially undiagnosed HIV, among their partners and might have partners without HIV who could benefit from HIV PrEP. Data are also limited regarding effectiveness of EPT in reducing persistent or recurrent chlamydia among MSM (*123*,*133*,*134*); thus, shared clinical decision-making regarding EPT for MSM is recommended. Having partners accompany patients when they return for treatment is another strategy that has been used successfully for ensuring partner treatment (see Partner Services). To avoid reinfection, sex partners should be instructed to abstain from condomless sexual intercourse until they and their sex partners have been treated (i.e., after completion of a 7-day regimen) and any symptoms have resolved.

Special Considerations

Pregnancy

Clinical experience and published studies indicate that azithromycin is safe and effective during pregnancy (*824*–*826*). Doxycycline is contraindicated during the second and third trimesters of pregnancy because of risk for tooth discoloration. Human data reveal that levofloxacin presents a low risk to the fetus during pregnancy but has potential for toxicity during breastfeeding; however, data from animal studies increase concerns regarding cartilage damage to neonates (*431*).

Test of cure (i.e., repeat testing after completion of therapy) to document chlamydial eradication, preferably by NAAT, at approximately 4 weeks after therapy completion during pregnancy is recommended because severe sequelae can occur among mothers and neonates if the infection persists. In addition, all pregnant women who have chlamydial infection diagnosed should be retested 3 months after treatment. Detection of *C. trachomatis* infection during the third semester is not uncommon among adolescent and young adult women, including those without *C. trachomatis* detected at the time of initial prenatal screening (*827*). Women aged <25 years and those at increased risk for chlamydia (i.e., those who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI) should be screened at the first prenatal visit and rescreened during the third trimester to prevent maternal postnatal complications and chlamydial infection in the infant (*149*).

Recommended Regimen for Chlamydial Infection During Pregnancy
Azithromycin 1 g orally in a single dose

Alternative Regimen
Amoxicillin 500 mg orally 3 times/day for 7 days

Because of concerns regarding chlamydia persistence after exposure to penicillin-class antibiotics that has been demonstrated in animal and in vitro studies, amoxicillin is listed as an alternative therapy for *C. trachomatis* for pregnant women (*828*,*829*). Erythromycin is no longer recommended because of the frequency of gastrointestinal side effects that can result in therapy nonadherence. In addition, systematic reviews and meta-analyses have noted an association with macrolide antimicrobials, especially erythromycin, during pregnancy and adverse child outcomes, indicating cautious use in pregnancy (*830*–*831*).

HIV Infection

Persons who have chlamydia and HIV infection should receive the same treatment regimen as those who do not have HIV.

Chlamydial Infection Among Neonates

Prenatal screening and treatment of pregnant women is the best method for preventing chlamydial infection among

neonates. *C. trachomatis* infection of neonates results from perinatal exposure to the mother's infected cervix. Initial *C. trachomatis* neonatal infection involves the mucous membranes of the eye, oropharynx, urogenital tract, and rectum, although infection might be asymptomatic in these locations. Instead, *C. trachomatis* infection among neonates is most frequently recognized by conjunctivitis that develops 5–12 days after birth. *C. trachomatis* also can cause a subacute, afebrile pneumonia with onset at ages 1–3 months. Although *C. trachomatis* has been the most frequent identifiable infectious cause of ophthalmia neonatorum, neonatal chlamydial infections, including ophthalmia and pneumonia, have occurred less frequently since institution of widespread prenatal screening and treatment of pregnant women. Neonates born to mothers at high risk for chlamydial infection, with untreated chlamydia, or with no or unconfirmed prenatal care, are at high risk for infection. However, presumptive treatment of the neonate is not indicated because the efficacy of such treatment is unknown. Infants should be monitored to ensure prompt and age-appropriate treatment if symptoms develop. Processes should be in place to ensure communication between physicians and others caring for the mother and the newborn to ensure thorough monitoring of the newborn after birth.

Ophthalmia Neonatorum Caused by *C. trachomatis*

A chlamydial etiology should be considered for all infants aged ≤30 days who experience conjunctivitis, especially if the mother has a history of chlamydial infection. These infants should receive evaluation and age-appropriate care and treatment.

Preventing Ophthalmia Neonatorum Caused by *C. trachomatis*

Neonatal ocular prophylaxis with erythromycin, the only agent available in the United States for this purpose, is ineffective against chlamydial ophthalmia neonatorum (or pneumonia) (*833*). As an alternative, prevention efforts should focus on prenatal screening for *C. trachomatis,* including

- screening pregnant women at risk for *C. trachomatis* infection at the first prenatal visit (e.g., women aged <25 years and those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI);
- treating all pregnant women with *C. trachomatis* during pregnancy and performing a test of cure 4 weeks after treatment to verify chlamydial eradication; these women should also be retested 3 months after treatment and again in the third trimester or at time of delivery, and their partners should also be tested and treated;
- retesting pregnant women during the third trimester who initially tested negative but remained at increased risk for acquiring infection (e.g., women aged <25 years and those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI); and
- screening at delivery those pregnant women who were not screened for *C. trachomatis* during pregnancy if at risk or who had no prenatal care; physicians and others caring for the mother and the newborn should communicate to ensure follow-up on the results of laboratory tests performed at delivery, and if positive, prompt and age-appropriate treatment for the newborn and the mother.

Neonates born to mothers for whom prenatal chlamydia screening has been confirmed and the results are negative are not at high risk for infection.

Diagnostic Considerations

Sensitive and specific methods for diagnosing chlamydial ophthalmia in the neonate include both tissue culture and nonculture tests (e.g., DFA tests and NAATs). DFA is the only nonculture FDA-cleared test for detecting chlamydia from conjunctival swabs. NAATs are not cleared by FDA for detecting chlamydia from conjunctival swabs, and clinical laboratories should verify the procedure according to CLIA regulations. Specimens for culture isolation and nonculture tests should be obtained from the everted eyelid by using a Dacron (DuPont)-tipped swab or the swab specified by the manufacturer's test kit; for culture and DFA, specimens must contain conjunctival cells, not exudate alone. Ocular specimens from neonates being evaluated for chlamydial conjunctivitis also should be tested for *N. gonorrhoeae* (see Ophthalmia Neonatorum Caused by *N. gonorrhoeae*).

Treatment

Recommended Regimen for Chlamydial Infection Among Neonates
Erythromycin base or ethyl succinate 50 mg/kg body weight/day orally, divided into 4 doses daily for 14 days*

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

Although data regarding use of azithromycin for treating neonatal chlamydial infection are limited, available data demonstrate that a short therapy course might be effective (*834*). Topical antibiotic therapy alone is inadequate for treating ophthalmia neonatorum caused by chlamydia and is unnecessary when systemic treatment is administered.

Follow-Up

Because the efficacy of erythromycin treatment for ophthalmia neonatorum is approximately 80%, a second course of therapy might be required (*834*,*835*). Data regarding the efficacy of azithromycin for ophthalmia neonatorum are limited. Therefore, follow-up of infants is recommended to determine whether the initial treatment was effective. The possibility of concomitant chlamydial pneumonia should be considered (see Infant Pneumonia Caused by *C. trachomatis*).

Management of Mothers and Their Sex Partners

Mothers of infants who have ophthalmia caused by chlamydia and the sex partners of these women should be evaluated and presumptively treated for chlamydia (see Chlamydial Infection Among Adolescents and Adults).

Infant Pneumonia Caused by *C. trachomatis*

Chlamydial pneumonia among infants typically occurs at age 1–3 months and is a subacute pneumonia. Characteristic signs of chlamydial pneumonia among infants include a repetitive staccato cough with tachypnea and hyperinflation and bilateral diffuse infiltrates on a chest radiograph. In addition, peripheral eosinophilia (≥400 cells/mm^3) occurs frequently. Because clinical presentations differ, all infants aged 1–3 months suspected of having pneumonia, especially those whose mothers have a history of, are at risk for (e.g., aged <25 years and those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI), or suspected of having a chlamydial infection should be tested for *C. trachomatis* and treated if infected.

Diagnostic Considerations

Specimens for chlamydial testing should be collected from the nasopharynx. Tissue culture is the definitive standard diagnostic test for chlamydial pneumonia. Nonculture tests (e.g., DFA and NAAT) can be used. DFA is the only nonculture FDA-cleared test for detecting *C. trachomatis* from nasopharyngeal specimens; however, DFA of nasopharyngeal specimens has a lower sensitivity and specificity than culture. NAATs are not cleared by FDA for detecting chlamydia from nasopharyngeal specimens, and clinical laboratories should verify the procedure according to CLIA regulations (*553*). Tracheal aspirates and lung biopsy specimens, if collected, should be tested for *C. trachomatis*.

Treatment

Because test results for chlamydia often are unavailable at the time initial treatment decisions are being made, treatment for *C. trachomatis* pneumonia frequently is based on clinical and radiologic findings, age of the infant (i.e., 1–3 months), and risk for chlamydia in the mother (i.e., aged <25 years, history of chlamydial infection, multiple sex partners, a sex partner with a concurrent partner, or a sex partner with a history of an STI). In the absence of laboratory results in a situation with a high degree of suspicion of chlamydial infection and the mother is unlikely to return with the infant for follow-up, exposed infants can be presumptively treated with the shorter-course regimen of azithromycin 20 mg/kg body weight/day orally, 1 dose daily for 3 days.

Recommended Regimen for Chlamydial Pneumonia Among Infants
Erythromycin base or ethyl succinate 50 mg/kg body weight/day orally divided into 4 doses daily for 14 days

Alternative Regimen
Azithromycin suspension 20 mg/kg/day orally, 1 dose daily for 3 days

Follow-Up

Because erythromycin effectiveness in treating pneumonia caused by *C. trachomatis* is approximately 80%, a second course of therapy might be required (*836*). Data regarding effectiveness of azithromycin in treating chlamydial pneumonia are limited. Follow-up of infants is recommended to determine whether the pneumonia has resolved, although certain infants with chlamydial pneumonia continue to have abnormal pulmonary function tests later during childhood.

Management of Mothers and Their Sex Partners

Mothers of infants who have chlamydial pneumonia and the sex partners of these women should be evaluated, tested, and presumptively treated for chlamydia (see Chlamydial Infection Among Adolescents and Adults).

Chlamydial Infection Among Infants and Children

Sexual abuse should be considered a cause of chlamydial infection among infants and children. However, perinatally transmitted *C. trachomatis* infection of the nasopharynx, urogenital tract, and rectum can persist for 2–3 years (see Sexual Assault or Abuse of Children).

Diagnostic Considerations

NAATs can be used to test vaginal and urine specimens from girls and urine in boys (see Sexual Assault or Abuse of Children). Data are lacking regarding use of NAATs for specimens from extragenital sites (rectum and pharynx) among boys and girls (*553*); other nonculture tests (e.g., DFA) are

not recommended because of specificity concerns. Although data regarding NAATs for specimens from extragenital sites for children are more limited and performance is test dependent (*553*), no evidence supports that NAAT performance for detecting *C. trachomatis* for extragenital sites among children would differ from that among adults. Because of the implications of a diagnosis of *C. trachomatis* infection in a child, only CLIA-validated, FDA-cleared NAAT should be used for extragenital site specimens (*837*).

Recommended Regimens for Chlamydial Infection Among Infants and Children

For infants and children weighing <45 kg: Erythromycin base or ethyl succinate 50 mg/kg body weight/day orally divided into 4 doses daily for 14 days

Data are limited regarding the effectiveness and optimal dose of azithromycin for treating chlamydial infection among infants and children weighing <45 kg.

For children weighing ≥45 kg but aged <8 years: Azithromycin 1 g orally in a single dose

For children aged ≥8 years: Azithromycin 1 g orally in a single dose
or
Doxycycline 100 mg orally 2 times/day for 7 days

Other Management Considerations

See Sexual Assault or Abuse of Children.

Follow-Up

A test of cure to detect therapeutic failure ensures treatment effectiveness and should be obtained at a follow-up visit approximately 4 weeks after treatment is completed.

Gonococcal Infections

Gonococcal Infection Among Adolescents and Adults

In the United States, an estimated 1,568,000 new *N. gonorrhoeae* infections occur each year (*141*,*838*), and gonorrhea is the second most commonly reported bacterial communicable disease. Urethral infections caused by *N. gonorrhoeae* can produce symptoms among men that cause them to seek curative treatment soon enough to prevent sequelae, but often not soon enough to prevent transmission to others. Among women, gonococcal infections are commonly asymptomatic or might not produce recognizable symptoms until complications (e.g., PID) have occurred. PID can result in tubal scarring that can lead to infertility or ectopic pregnancy.

Annual screening for *N. gonorrhoeae* infection is recommended for all sexually active women aged <25 years and for older women at increased risk for infection (e.g., those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, or a sex partner who has an STI) (*149*). Additional risk factors for gonorrhea include inconsistent condom use among persons who are not in mutually monogamous relationships, previous or coexisting STIs, and exchanging sex for money or drugs. Clinicians should consider the communities they serve and consult local public health authorities for guidance regarding identifying groups at increased risk. Gonococcal infection, in particular, is concentrated in specific geographic locations and communities. MSM at high risk for gonococcal infection (e.g., those with multiple anonymous partners or substance abuse) or those at risk for HIV acquisition should be screened at all anatomic sites of exposure every 3–6 months (see Men Who Have Sex with Men). At least annual screening is recommended for all MSM. Screening for gonorrhea among heterosexual men and women aged >25 years who are at low risk for infection is not recommended (*149*). A recent travel history with sexual contacts outside the United States should be part of any gonorrhea evaluation.

Diagnostic Considerations

Specific microbiologic diagnosis of *N. gonorrhoeae* infection should be performed for all persons at risk for or suspected of having gonorrhea; a specific diagnosis can potentially reduce complications, reinfections, and transmission. Culture, NAAT, and POC NAAT, such as GeneXpert (Cepheid), are available for detecting genitourinary infection with *N. gonorrhoeae* (*149*); culture requires endocervical (women) or urethral (men) swab specimens. Culture is also available for detecting rectal, oropharyngeal, and conjunctival gonococcal infection. NAATs and POC NAATs) allow for the widest variety of FDA-cleared specimen types, including endocervical and vaginal swabs and urine for women, urethral swabs and urine for men, and rectal swabs and pharyngeal swabs for men and women (www.accessdata.fda.gov/cdrh_docs/reviews/K121710.pdf). However, product inserts for each NAAT manufacturer should be consulted carefully because collection methods and specimen types vary. Certain NAATs that have been demonstrated to detect commensal *Neisseria* species might have comparable low specificity when testing oropharyngeal specimens for *N. gonorrhoeae* (*553*). NAAT sensitivity for detecting *N. gonorrhoeae* from urogenital and nongenital anatomic sites is superior to culture but varies by NAAT type (*553*,*800*–*803*). For urogenital infections, optimal specimen types for gonorrhea screening using NAATs include first-void urine for men and vaginal swab specimens for women (*553*). Patient-collected samples can be used in place of provider-collected samples in clinical settings when testing by NAAT

for urine (men and women), vaginal swabs, rectal swabs, and oropharyngeal swabs after patient instructions have been provided (*209*,*806*,*839*–*842*). Patient-collected specimens are reasonable alternatives to provider-collected swabs for gonorrhea screening by NAAT.

In cases of suspected or documented treatment failure, clinicians should perform both culture and antimicrobial susceptibility testing because NAATs cannot provide antimicrobial susceptibility results. Because *N. gonorrhoeae* has demanding nutritional and environmental growth requirements, optimal recovery rates are achieved when specimens are inoculated directly and when the growth medium is promptly incubated in an increased carbon dioxide (CO_2) environment (*553*). Nonnutritive swab transport systems are available that might maintain gonococcal viability for <48 hours in ambient temperatures (*843*–*845*).

Because of its high specificity (>99%) and sensitivity (>95%), a Gram stain of urethral discharge or secretions that demonstrate polymorphonuclear leukocytes with intracellular gram-negative diplococci can be considered diagnostic for infection with *N. gonorrhoeae* among symptomatic men. However, because of lower sensitivity, a negative Gram stain should not be considered sufficient for ruling out infection among asymptomatic men. Infection detection by using Gram stain of endocervical, pharyngeal, and rectal specimens also is insensitive and is not recommended. MB or GV stain of urethral secretions is an alternative POC diagnostic test with performance characteristics similar to Gram stain. Gonococcal infection is diagnosed among symptomatic men by documenting the presence of a WBC-containing intracellular purple diplococci in MB or GV smears.

Antimicrobial-Resistant *N. gonorrhoeae*

Gonorrhea treatment is complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobials (*846*–*848*). In 1986, the Gonococcal Isolate Surveillance Project (GISP), a national sentinel surveillance system, was established to monitor trends in antimicrobial susceptibilities of urethral *N. gonorrhoeae* strains in the United States (*849*). The epidemiology of antimicrobial resistance guides decisions about gonococcal treatment recommendations and has evolved because of shifts in antimicrobial resistance patterns. During 2007, emergence of fluoroquinolone-resistant *N. gonorrhoeae* in the United States prompted CDC to cease recommending fluoroquinolones for gonorrhea treatment, leaving cephalosporins as the only remaining class of antimicrobials available for gonorrhea treatment in the United States (*850*). Reflecting concern about emerging gonococcal resistance, CDC's 2010 STD treatment guidelines recommended dual therapy for gonorrhea with a cephalosporin plus either azithromycin or doxycycline, even if NAAT for *C. trachomatis* was negative at the time of treatment (*851*). However, during 2006–2011, the minimum concentrations of cefixime needed to inhibit in vitro growth of the *N. gonorrhoeae* strains circulating in the United States and other countries increased, demonstrating that cefixime effectiveness might be waning (*851*). In addition, treatment failures with cefixime or other oral cephalosporins were reported in Asia (*852*–*855*), Europe (*856*–*860*), South Africa (*861*), and Canada (*862*,*863*). During that time, case reports of ceftriaxone treatment failures for pharyngeal infections reported in Australia (*864*,*865*), Japan (*866*), and Europe were concerning (*856*,*867*). Consequently, CDC no longer recommends cefixime as a first-line regimen for gonorrhea treatment in the United States (*868*). Since 2013, the proportion of GISP isolates that demonstrate reduced susceptibility (minimal inhibitory concentration [MIC] ≥2.0 μg/mL) to azithromycin has increased almost tenfold, to 5.1% in 2019 (*141*). Unlike the appearance of ciprofloxacin resistance in the early 2000s, and cefixime reduced-susceptibility isolates during 2010–2011, emergence of azithromycin resistance is not concentrated among certain populations (e.g., MSM in the western United States). Azithromycin has unique pharmacokinetic properties that might predispose to resistance due to its prolonged half-life (*869*,*870*). With the exception of a small cluster of gonorrhea strains with azithromycin resistance and reduced susceptibility to cefixime and ceftriaxone among seven patients during 2016, all gonorrhea strains identified by GISP are susceptible to either or both azithromycin and ceftriaxone or cefixime. In addition, since 2013, antimicrobial stewardship has become an urgent public health concern in the United States as described in *Antimicrobial Resistant Threats in the United States* (*871*). Emergence of azithromycin resistance is not isolated to *N. gonorrhoeae*; it has also been demonstrated in *M. genitalium* and such enteric pathogens as *Shigella* and *Campylobacter* (see *Mycoplasma genitalium*; Proctitis, Proctocolitis, and Enteritis). Finally, concern exists regarding azithromycin treatment efficacy for chlamydia (see Chlamydial Infections).

Dual therapy for gonococcal infection with ceftriaxone and azithromycin recommended in previous guidance might have mitigated emergence of reduced susceptibility to ceftriaxone in *N. gonorrhoeae*; however, concerns regarding potential harm to the microbiome and the effect on other pathogens diminishes the benefits of maintaining dual therapy. Consequently, only ceftriaxone is recommended for treating gonorrhea in the United States (*872*). Clinicians remaining vigilant for treatment failures is paramount, and CDC plans to continue to monitor for changing ceftriaxone MICs until additional antimicrobials or a vaccine is available. In cases in which chlamydial infection has not been excluded,

patients should also receive antichlamydial therapy. CDC and state health departments participate in CDC-supported gonorrhea surveillance activities (https://www.cdc.gov/std/gisp) and can provide the most current information regarding gonococcal susceptibility.

Criteria for resistance to cefixime and ceftriaxone have not been defined by the Clinical and Laboratory Standards Institute (CLSI). However, isolates with cefixime or ceftriaxone MICs ≥0.5 μg/mL are considered to have decreased susceptibility (*873*). In the United States, the proportion of isolates in GISP demonstrating decreased susceptibility to ceftriaxone or cefixime has remained low; during 2019, <0.1% of isolates with decreased susceptibility (MIC ≥0.5 μg/mL) to ceftriaxone or cefixime were identified (*141*). Because increasing MICs might predict resistance emergence, GISP established lower cephalosporin MIC threshold values that are lower than the susceptibility breakpoints set by CLSI to provide greater sensitivity in detecting decreasing gonococcal susceptibility for surveillance purposes. The percentage of isolates with cefixime MICs ≥0.25 μg/mL increased from 0.1% during 2006 to 1.4% during 2011 (*851*,*874*) and declined to 0.3% during 2019 (*141*). The percentage of isolates with ceftriaxone MICs ≥0.125 μg/mL increased from <0.1% in 2006 to 0.4% in 2011 and decreased to 0.1% in 2019 (*141*). Isolates with high-level cefixime and ceftriaxone MICs (MICs = 1.5–8.0 μg/mL and MICs = 1.5–4.0 μg/mL, respectively) have been identified in Japan (*866*), France (*867*,*875*), Spain (*876*,*877*), the United Kingdom, and Australia (*878*,*879*). Decreased susceptibility of *N. gonorrhoeae* to cephalosporins and other antimicrobials is expected to continue; state and local surveillance for antimicrobial resistance is crucial for guiding local therapy recommendations (*846*,*847*). Although approximately 3% of all U.S. men who have gonococcal infections are sampled through GISP, surveillance by clinicians also is crucial. Clinicians who diagnose *N. gonorrhoeae* infection in a person with suspected cephalosporin treatment failure should perform culture and AST of relevant clinical specimens, consult an infectious disease specialist or an STD clinical expert (https://www.stdccn.org/render/Public) for guidance in clinical management, and report the case to CDC through state and local public health authorities within 24 hours. Isolates should be saved and sent to CDC through local and state public health laboratory mechanisms. Health departments should prioritize notification and culture evaluation for sexual partners of persons with *N. gonorrhoeae* infection thought to be associated with cephalosporin treatment failure or persons whose isolates demonstrate decreased susceptibility to cephalosporin. Agar dilution is the reference standard and preferred method of antimicrobial susceptibility testing with *N. gonorrhoeae*. Antibiotic gradient strips, such as Etest (bioMérieux), can be used and are considered an acceptable alternative for quantitative antimicrobial susceptibility testing with *N. gonorrhoeae* when manufacturer instructions are followed. Disc diffusion only provides qualitative susceptibility results.

Uncomplicated Gonococcal Infection of the Cervix, Urethra, or Rectum

Recommended Regimen for Uncomplicated Gonococcal Infection of the Cervix, Urethra, or Rectum Among Adults and Adolescents
Ceftriaxone 500 mg* IM in a single dose for persons weighing <150 kg
If chlamydial infection has not been excluded, treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.
* For persons weighing ≥150 kg, 1 g ceftriaxone should be administered.

Although clinical data confirm that a single injection of ceftriaxone 250 mg is >99% (95% confidence interval [CI]: 97.6%–99.7%) effective in curing anogenital gonorrhea of circulating isolates (MIC = 0.03 μg/mL), a higher dose is likely necessary for isolates with elevated MICs (*880*,*881*). Effective treatment of uncomplicated urogenital gonorrhea with ceftriaxone requires concentrations higher than the strain MIC for approximately 24 hours; although individual variability exists in the pharmacokinetics of ceftriaxone, a 500-mg dose of ceftriaxone is expected to achieve in approximately 50 hours MIC >0.03 μg/mL (*880*,*881*). The pharmacokinetics of ceftriaxone might be different in the pharynx with longer times higher than the strain MIC likely needed to prevent selection of mutant strains in the pharynx (*882*).

Single-dose injectable cephalosporin regimens, other than ceftriaxone, that are safe and have been effective against uncomplicated urogenital and anorectal gonococcal infections in the past include ceftizoxime (500 mg IM), cefoxitin (2 g IM with probenecid 1 g orally), and cefotaxime (500 mg IM). None of these injectable cephalosporins offer any advantage over ceftriaxone 250 mg for urogenital infection, and efficacy for pharyngeal infection is less certain (*883*,*884*). Because the ceftriaxone dose has been increased and the pharmacokinetics of other cephalosporins have not been evaluated, these dosing regimens might be at a disadvantage over ceftriaxone 500 mg.

Alternative Regimens if Ceftriaxone Is Not Available
Gentamicin 240 mg IM in a single dose *plus* **Azithromycin** 2 g orally in a single dose *or* **Cefixime*** 800 mg orally in a single dose
* If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.

In one clinical trial, dual treatment with single doses of IM gentamicin 240 mg plus oral azithromycin 2 g cured 100% of cases (lower one-sided 95% CI bound: 98.5%) and can be considered an alternative to ceftriaxone for persons with cephalosporin allergy (*885*). This trial was not powered enough to provide reliable estimates of the efficacy of these regimens for treatment of rectal or pharyngeal infection; however, this regimen cured the few extragenital infections among study participants. Notably, gastrointestinal adverse events, primarily vomiting <1 hour after dosing, occurred among 3%–4% of persons treated with gentamicin plus azithromycin, necessitating retreatment with ceftriaxone and azithromycin. A similar trial that studied gentamicin 240 mg plus azithromycin 1 g determined lower cure rates at extragenital sites; 80% (95% CI: 72%–88%) of pharyngeal and 90% (95% CI: 84%–95%) of rectal infections were cured with this regimen (*886*). Gemifloxacin plus azithromycin has been studied and is no longer recommended as an alternative regimen because of limited availability, cost, and antimicrobial stewardship concerns (*885*).

An 800-mg oral dose of cefixime should be considered only as an alternative cephalosporin regimen because it does not provide as high, nor as sustained, bactericidal blood levels as a 500-mg IM dose of ceftriaxone. Furthermore, it demonstrates limited efficacy for treatment of pharyngeal gonorrhea (92.3% cure; 95% CI: 74.9%–99.1%); in older clinical studies, cefixime cured 97.5% of uncomplicated urogenital and anorectal gonococcal infections (95% CI: 95.4%–99.8%) (*883*,*884*). The increase in the prevalence of isolates obtained through GISP with elevated cefixime MICs might indicate early stages of development of clinically significant gonococcal resistance to cephalosporins. Changes in cefixime MICs can result in decreasing effectiveness of cefixime for treating urogenital gonorrhea. Furthermore, as cefixime becomes less effective, continued used of cefixime might hasten the development of resistance to ceftriaxone, a safe, well-tolerated, injectable cephalosporin and the last antimicrobial known to be highly effective in a single dose for treatment of gonorrhea at all anatomic infection sites. Other oral cephalosporins (e.g., cefpodoxime and cefuroxime) are not recommended because of inferior efficacy and less favorable pharmacodynamics (*883*).

Monotherapy with azithromycin 2 g orally as a single dose has been demonstrated to be 99.2% effective against uncomplicated urogenital gonorrhea (95% CI: 97.3%–99.9%) (*883*). However, monotherapy is not recommended because of concerns about the ease with which *N. gonorrhoeae* can develop resistance to macrolides, the high proportion of isolates with azithromycin decreased susceptibility, and documented azithromycin treatment failures (*859*). Strains of *N. gonorrhoeae* circulating in the United States are not adequately susceptible to penicillin, tetracycline, and older macrolides (e.g., erythromycin), and thus use of these antimicrobials cannot be recommended.

Spectinomycin is effective (98.2% in curing uncomplicated urogenital and anorectal gonococcal infections) but has poor efficacy for pharyngeal infections (*883*,*887*). It is unavailable in the United States, and the gentamicin alternative regimen has replaced the need for spectinomycin, if a cephalosporin allergy exists, in the United States.

Uncomplicated Gonococcal Infection of the Pharynx

The majority of gonococcal infections of the pharynx are asymptomatic and can be relatively common among certain populations (*800*,*801*,*888–890*). Although these infections rarely cause complications, they have been reported to be a major source of community transmission and might be a driver of antimicrobial resistance (*891*,*892*). Gonococcal infections of the pharynx are more difficult to eradicate than infections at urogenital and anorectal sites (*862*). Few antimicrobial regimens reliably cure >90% of gonococcal pharyngeal infections (*883*,*884*). Providers should ask their patients with urogenital or rectal gonorrhea about oral sexual exposure; if reported, pharyngeal testing should be performed.

Recommended Regimen for Uncomplicated Gonococcal Infection of the Pharynx Among Adolescents and Adults
Ceftriaxone 500 mg* IM in a single dose for persons weighing <150 kg
* For persons weighing ≥150 kg, 1 g ceftriaxone should be administered.

If chlamydial infection is identified when pharyngeal gonorrhea testing is performed, treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days. No reliable alternative treatments are available for pharyngeal gonorrhea. For persons with an anaphylactic or other severe reaction (e.g., Stevens Johnson syndrome) to ceftriaxone, consult an infectious disease specialist for an alternative treatment recommendation.

Other Management Considerations

To maximize adherence with recommended therapies and reduce complications and transmission, medication for gonococcal infection should be provided on-site and directly observed. If medications are unavailable when treatment is indicated, linkage to an STI treatment facility should be provided for same-day treatment. To minimize disease transmission, persons treated for gonorrhea should be instructed to abstain from sexual activity for 7 days after treatment and until all sex partners are treated (7 days after receiving treatment and resolution of symptoms, if present).

All persons who receive a diagnosis of gonorrhea should be tested for other STIs, including chlamydia, syphilis, and HIV. Those persons whose HIV test results are negative should be offered HIV PrEP.

Follow-Up

A test of cure (i.e., repeat testing after completion of therapy) is unnecessary for persons who receive a diagnosis of uncomplicated urogenital or rectal gonorrhea who are treated with any of the recommended or alternative regimens. Any person with pharyngeal gonorrhea should return 7–14 days after initial treatment for a test of cure by using either culture or NAAT; however, testing at 7 days might result in an increased likelihood of false-positive tests. If the NAAT is positive, effort should be made to perform a confirmatory culture before retreatment, especially if a culture was not already collected. All positive cultures for test of cure should undergo antimicrobial susceptibility testing. Symptoms that persist after treatment should be evaluated by culture for *N. gonorrhoeae* (with or without simultaneous NAAT) and antimicrobial susceptibility. Persistent urethritis, cervicitis, or proctitis also might be caused by other organisms (see Urethritis; Cervicitis; Proctitis).

A high prevalence of *N. gonorrhoeae* infection has been observed among men and women previously treated for gonorrhea (*137*,*753*,*754*,*893*). The majority of these infections result from reinfection caused by failure of sex partners to receive treatment or the initiation of sexual activity with a new infected partner, indicating a need for improved patient education and treatment of sex partners. Men or women who have been treated for gonorrhea should be retested 3 months after treatment regardless of whether they believe their sex partners were treated; scheduling the follow-up visit at the time of treatment is encouraged. If retesting at 3 months is not possible, clinicians should retest whenever persons next seek medical care <12 months after initial treatment.

Management of Sex Partners

Recent sex partners (i.e., persons having sexual contact with the infected patient <60 days preceding onset of symptoms or gonorrhea diagnosis) should be referred for evaluation, testing, and presumptive treatment. If the patient's last potential sexual exposure was >60 days before onset of symptoms or diagnosis, the most recent sex partner should be treated.

If health department partner-management strategies (e.g., disease intervention specialists) are impractical or unavailable for persons with gonorrhea and partners' access to prompt clinical evaluation and treatment is limited, EPT can be delivered to the partner by the patient or a collaborating pharmacy as permitted by law (see Partner Services). Treatment of the sexual partner with cefixime 800 mg as a single dose is recommended, provided that concurrent chlamydial infection has been excluded. If a chlamydia test result has not been documented, the partner may be treated with a single dose of oral cefixime 800 mg plus oral doxycycline 100 mg 2 times/day for 7 days. If adherence with multiday dosing is a considerable concern, azithromycin 1 g can be considered but has lower treatment efficacy among persons with rectal chlamydia (see Chlamydial Infections). Provision of medication by EPT should be accompanied by written materials (*125*,*127*) for educating partners about gonorrhea, their exposure to gonorrhea, and the importance of therapy. These materials should also educate partners about seeking clinical evaluation for adverse reactions or complications and general follow-up when able. Educational materials for female partners should include information about the importance of seeking medical evaluation for PID, especially if symptomatic; undertreatment of PID among female partners and missed opportunities for diagnosing other STIs among women are of concern. MSM with gonorrhea have a high risk for coexisting infections (especially undiagnosed HIV) among their partners, and they might have partners without HIV who could benefit from PrEP. Data are also limited regarding the effectiveness of EPT in reducing persistent or recurrent gonorrhea among MSM (*133*,*135*); thus, shared clinical decision-making regarding EPT for MSM is recommended (see Partner Services). To avoid reinfection, sex partners should be instructed to abstain from condomless sexual intercourse for 7 days after they and their sex partners have completed treatment and after resolution of symptoms, if present.

Suspected Cephalosporin Treatment Failure

Cephalosporin treatment failure is the persistence of *N. gonorrhoeae* infection despite recommended cephalosporin treatment; such failure is indicative of infection with cephalosporin-resistant gonorrhea among persons whose partners were treated and whose risk for reinfection is low. Suspected treatment failure has been reported among persons receiving oral and injectable cephalosporins (*852*–*855*,*857*,*859*,*861*,*863*,*864*,*867*,*875*,*894*). Treatment failure should be considered for persons whose symptoms do not resolve within 3–5 days after recommended treatment and report no sexual contact during the posttreatment follow-up period and persons with a positive test of cure (i.e., positive culture >72 hours or positive NAAT >7 days after receiving recommended treatment) when no sexual contact is reported during the posttreatment follow-up period (*874*). Treatment failure should also be considered for persons who have a positive culture on test of cure, if obtained, if evidence exists of decreased susceptibility to cephalosporins on antimicrobial

susceptibility testing, regardless of whether sexual contact is reported during the posttreatment follow-up period.

The majority of suspected treatment failures in the United States are likely to be reinfections rather than actual treatment failures (*137*,*753*,*754*,*894*). However, in cases in which reinfection is unlikely and treatment failure is suspected, before retreatment, relevant clinical specimens should be obtained for culture (preferably with simultaneous NAAT) and antimicrobial susceptibility testing if *N. gonorrhoeae* is isolated. Phenotypic antimicrobial susceptibility testing should be performed by using Etest or agar dilution. All isolates of suspected treatment failures should be sent to CDC for antimicrobial susceptibility testing by agar dilution; local laboratories should store isolates for possible further testing if needed. Testing or storage of specimens or isolates should be facilitated by the state or local health department according to local public health protocol. Instructions for shipping isolates to CDC are available at https://www.cdc.gov/std/gonorrhea/arg/specimen_shipping_instructions1-29-08.pdf.

For persons with suspected cephalosporin treatment failure, the treating clinician should consult an infectious disease specialist, the National Network of STD Clinical Prevention Training Center clinical consultation line (https://www.stdccn.org/render/Public), the local or state health department STI program, or CDC (telephone: 800-232-4636) for advice about obtaining cultures, antimicrobial susceptibility testing and treatment. Suspected treatment failure should be reported to CDC through the local or state health department <24 hours after diagnosis.

Patients with suspected treatment failures should first be retreated routinely with the initial regimen used (ceftriaxone 500 mg IM), with the addition of doxycycline if chlamydia infection exists, because reinfections are more likely than actual treatment failures. However, in situations with a higher likelihood of treatment failure than reinfection, relevant clinical specimens should be obtained for culture (preferably with simultaneous NAAT) and antimicrobial susceptibility testing before retreatment. Dual treatment with single doses of IM gentamicin 240 mg plus oral azithromycin 2 g can be considered, particularly when isolates are identified as having elevated cephalosporin MICs (*885*,*886*,*895*). Persons with suspected treatment failure after treatment with the alternative regimen (cefixime or gentamicin) should be treated with ceftriaxone 500 mg as a single IM dose or as a single dose with or without an antichlamydial agent on the basis of chlamydia infection status. A test of cure at relevant clinical sites should be obtained 7–14 days after retreatment; culture is the recommended test, preferably with simultaneous NAAT, and antimicrobial susceptibility testing of *N. gonorrhoeae* if isolated. Clinicians should ensure that the patients' sex partners from the preceding 60 days are evaluated promptly with culture and presumptively treated by using the same regimen used for the patients.

Special Considerations

Drug Allergy, Intolerance, and Adverse Reactions

The risk for penicillin cross-reactivity is highest with first-generation cephalosporins but is rare (<1%) with third-generation cephalosporins (e.g., ceftriaxone and cefixime) (*631*,*680*,*896*). Clinicians should first thoroughly assess a patient's allergy history, including type of reaction, associated medications, and previous prescription records. If IgE-mediated penicillin allergy is strongly suspected, dual treatment with single doses of IM gentamicin 240 mg plus oral azithromycin 2 g can be administered (*885*,*886*). If a patient is asymptomatic and the treating facility is able to perform gyrase A (*gyrA*) testing to identify ciprofloxacin susceptibility (wild type), oral ciprofloxacin 500 mg in a single dose can be administered. Providers treating persons with IgE-mediated cephalosporin or penicillin allergy should refer to the section of these guidelines regarding evaluation (see Management of Persons Who Have a History of Penicillin Allergy).

Pregnancy

Pregnant women infected with *N. gonorrhoeae* should be treated with ceftriaxone 500 mg in a single IM dose plus treatment for chlamydia if infection has not been excluded. When cephalosporin allergy or other considerations preclude treatment with this regimen, consultation with an infectious disease specialist or an STD clinical expert is recommended. Gentamicin use is cautioned during pregnancy because of risk for neonatal birth defects, nephrotoxicity, or ototoxicity (*897*) (https://www.stdccn.org/render/Public).

HIV Infection

Persons who have gonorrhea and HIV infection should receive the same treatment regimen as those who do not have HIV.

Gonococcal Conjunctivitis

In the only published study of the treatment regarding gonococcal conjunctivitis among adults, all 12 study participants responded to a single 1-g IM injection of ceftriaxone (*898*). Because gonococcal conjunctivitis is uncommon and data regarding treatment of gonococcal conjunctivitis among adults are limited, consultation with an infectious disease specialist should be considered.

Recommended Regimen for Gonococcal Conjunctivitis Among Adolescents and Adults

Ceftriaxone 1 g IM in a single dose

Providers should consider one-time lavage of the infected eye with saline solution.

Management of Sex Partners

Patients should be instructed to refer their sex partners for evaluation and treatment (see Gonococcal Infections, Management of Sex Partners).

Disseminated Gonococcal Infection

Infrequently, *N. gonorrhoeae* can cause disseminated infection. Disseminated gonococcal infection (DGI) frequently results in petechial or pustular acral skin lesions, asymmetric polyarthralgia, tenosynovitis, or oligoarticular septic arthritis (*899–901*). Rarely, DGI is complicated by perihepatitis associated with gonococcal PID, endocarditis, or meningitis. Certain strains of *N. gonorrhoeae* that cause DGI can cause minimal genital inflammation, and urogenital or anorectal infections are often asymptomatic among DGI patients. If DGI is suspected, NAATs or culture specimens from all exposed urogenital and extragenital sites should be collected and processed, in addition to disseminated sites of infection (e.g., skin, synovial fluid, blood, or CSF). All *N. gonorrhoeae* isolates should be tested for antimicrobial susceptibility. Risk factors for dissemination have included female sex, menstruation, pregnancy, and terminal complement deficiency (*899*); however, reports are increasing among men (*900*,*901*). Persons receiving eculizumab, a monoclonal antibody that inhibits terminal complement activation, also might be at higher risk for DGI (*902*).

Hospitalization and consultation with an infectious disease specialist are recommended for initial therapy, especially for persons who might not comply with treatment, have an uncertain diagnosis, or have purulent synovial effusions or other complications. Examination for clinical evidence of endocarditis and meningitis should be performed.

Treatment of Arthritis and Arthritis-Dermatitis Syndrome

Recommended Regimen for Gonococcal-Related Arthritis and Arthritis-Dermatitis Syndrome

Ceftriaxone 1 g IM or IV every 24 hours

If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.

Alternative Regimens

Cefotaxime 1 g IV every 8 hours
or
Ceftizoxime 1 g every 8 hours
If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.

When treating for the arthritis-dermatitis syndrome, the provider can switch to an oral agent guided by antimicrobial susceptibility testing 24–48 hours after substantial clinical improvement, for a total treatment course of >7 days.

Treatment of Gonococcal Meningitis and Endocarditis

Recommended Regimen for Gonococcal Meningitis and Endocarditis

Ceftriaxone 1–2 g IV every 24 hours

If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally 2 times/day for 7 days.

No recent studies have been published regarding treatment of DGI involving the CNS or cardiovascular system. The duration of treatment for DGI in these situations has not been systematically studied and should be determined in consultation with an infectious disease specialist. Treatment for DGI should be guided by the results of antimicrobial susceptibility testing. Length of treatment should be determined based on clinical presentation. Therapy for meningitis should be continued with recommended parenteral therapy for 10–14 days. Parenteral antimicrobial therapy for endocarditis should be administered for >4 weeks. Treatment of gonococcal perihepatitis should be managed in accordance with the recommendations for PID in these guidelines.

Management of Sex Partners

Gonococcal infection frequently is asymptomatic among sex partners of persons who have DGI. Providers should instruct patients to refer partners with whom they have had sexual contact during the previous 60 days for evaluation, testing, and presumptive treatment (see Gonococcal Infections, Management of Sex Partners).

Gonococcal Infection Among Neonates

Prenatal screening and treatment of pregnant women for gonorrhea is the best method for preventing *N. gonorrhoeae* infection among neonates. Gonococcal infection among neonates results from perinatal exposure to the mother's infected cervix. It is usually an acute illness that manifests 2–5 days after birth. Prevalence of infection among neonates depends on the prevalence of infection among pregnant women and whether pregnant women are screened and treated for gonorrhea during

pregnancy. The most severe manifestations of *N. gonorrhoeae* infection among neonates are ophthalmia neonatorum and sepsis, which can include arthritis and meningitis. Less severe manifestations include rhinitis, vaginitis, urethritis, and scalp infection at sites of previous fetal monitoring.

Preventing Ophthalmia Neonatorum Caused by *N. gonorrhoeae*

Ocular prophylaxis and preventive gonorrhea screening and treatment of infected pregnant women are especially important because ophthalmia neonatorum can result in perforation of the globe of the eye and blindness (*903*). Ocular prophylaxis for gonococcal ophthalmia neonatorum has a long history of preventing sight-threatening gonococcal ocular infections. Cases in the United States are uncommon, which is likely attributable to gonorrhea screening programs for women, including pregnant women, that have contributed substantially to reduction in ophthalmia neonatorum (*904*). Neonatal ocular prophylaxis with erythromycin, the only agent available in the United States, is required by law in most states and is recommended because of safety, low cost, and ease of administration. It can contribute to preventing gonococcal blindness because not all pregnant women are screened for gonorrhea. The USPSTF recommends ocular prophylaxis with erythromycin ointment for all newborns <24 hours after birth (*903*). In addition to continuing routine ocular prophylaxis, prevention should focus on prenatal screening for *N. gonorrhoeae,* including

- screening pregnant women at risk (e.g., women aged <25 years and those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, a sex partner who has an STI, or live in a community with high rates of gonorrhea) for *N. gonorrhoeae* infection at the first prenatal visit;
- treating all pregnant women with *N. gonorrhoeae* infection during pregnancy and retesting in 3 months, in the third trimester or at time of delivery (sex partners should be tested and treated);
- retesting pregnant women in the third trimester who initially tested negative but remained at increased risk for acquiring infection (e.g., women aged <25 years and those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, a sex partner who has an STI, or live in a community with high rates of gonorrhea); and
- screening for gonorrhea at delivery for women not tested during pregnancy and at risk for infection (e.g., women aged <25 years and those aged ≥25 years who have a new sex partner, more than one sex partner, a sex partner with concurrent partners, a sex partner who has an STI, or live in a community with high rates of gonorrhea) or received no prenatal care; providers caring for the mother and the newborn should communicate to ensure follow-up on the results of laboratory tests performed at delivery, and if positive, prompt appropriate treatment of the newborn and mother.

Erythromycin is the only ophthalmic ointment recommended for use among neonates. Silver nitrate and tetracycline ophthalmic ointments are no longer manufactured in the United States, bacitracin is ineffective, and povidone iodine has not been studied adequately (*905*,*906*). Gentamicin ophthalmic ointment has been associated with severe ocular reactions (*907*,*908*). If erythromycin ointment is unavailable, infants at risk for exposure to *N. gonorrhoeae,* especially those born to a mother at risk for gonococcal infection or with no prenatal care, can be administered ceftriaxone 25–50 mg/kg body weight IV or IM, not to exceed 250 mg in a single dose.

Recommended Regimen to Prevent Ophthalmia Neonatorum Caused by *N. gonorrhoeae*
Erythromycin 0.5% ophthalmic ointment in each eye in a single application at birth

Erythromycin ophthalmic ointment should be instilled into both eyes of neonates as soon as possible after delivery, regardless of whether they are delivered vaginally or by cesarean delivery. Ideally, ointment should be applied by using single-use tubes or ampules rather than multiple-use tubes. If prophylaxis is delayed (i.e., not administered in the delivery room), a monitoring system should be established to ensure that all newborns receive prophylaxis <24 hours after delivery.

Diagnostic Considerations

Newborns at increased risk for gonococcal ophthalmia include those who did not receive ophthalmic prophylaxis and whose mothers had no prenatal care, have a history of STIs during pregnancy, or have a history of substance misuse. Gonococcal ophthalmia is strongly suspected when intracellular gram-negative diplococci are identified on Gram stain of conjunctival exudate, justifying presumptive treatment for gonorrhea after appropriate cultures and antimicrobial susceptibility testing for *N. gonorrhoeae* are performed. Presumptive treatment for *N. gonorrhoeae* might be indicated for newborns at increased risk for gonococcal ophthalmia who have increased WBCs (no GNID) in a Gram-stained smear of conjunctival exudate. Nongonococcal causes of neonatal ophthalmia include *Moraxella catarrhalis* and other *Neisseria* species, which are organisms that are indistinguishable from *N. gonorrhoeae* on Gram-stained smear but can be differentiated in the microbiology laboratory.

Treatment of Gonococcal Ophthalmia Neonatorum

Recommended Regimen for Gonococcal Ophthalmia Neonatorum

Ceftriaxone 25–50 mg/kg body weight IV or IM in a single dose, not to exceed 250 mg

One dose of ceftriaxone is adequate therapy for gonococcal ophthalmia. Ceftriaxone should be administered cautiously to neonates with hyperbilirubinemia, especially those born prematurely. Cefotaxime 100 mg/kg body weight IV or IM as a single dose can be administered for those neonates unable to receive ceftriaxone because of simultaneous administration of IV calcium. Topical antibiotic therapy alone is inadequate and unnecessary if systemic treatment is administered.

Other Management Considerations

Chlamydial testing should be performed simultaneously from the inverted eyelid specimen (see Ophthalmia Neonatorum Caused by *C. trachomatis*). Newborns who have gonococcal ophthalmia should be evaluated for signs of disseminated infection (e.g., sepsis, arthritis, and meningitis). Newborns who have gonococcal ophthalmia should be managed in consultation with an infectious disease specialist.

Management of Mothers and Their Sex Partners

Mothers of newborns with ophthalmia neonatorum caused by *N. gonorrhoeae* should be evaluated, tested, and presumptively treated for gonorrhea, along with their sex partners (see Gonococcal Infection Among Adolescents and Adults).

Disseminated Gonococcal Infection and Gonococcal Scalp Abscesses Among Neonates

DGI might present as sepsis, arthritis, or meningitis and is a rare complication of neonatal gonococcal infection. Localized gonococcal infection of the scalp can result from fetal monitoring through scalp electrodes. Detecting gonococcal infection among neonates who have sepsis, arthritis, meningitis, or scalp abscesses requires cultures of blood, CSF, or joint aspirate. Specimens obtained from the conjunctiva, vagina, oropharynx, and rectum are useful for identifying the primary site or sites of infection. Antimicrobial susceptibility testing of all isolates should be performed. Positive Gram-stained smears of abscess exudate, CSF, or joint aspirate provide a presumptive basis for initiating treatment for *N. gonorrhoeae*.

Treatment

Recommended Regimens for Disseminated Gonococcal Infection Among Neonates

Ceftriaxone 25–50 mg/kg body weight/day IV or IM in a single daily dose for 7 days, with a duration of 10–14 days if meningitis is documented

or

Cefotaxime 25 mg/kg body weight/day IV or IM every 12 hours for 7 days, with a duration of 10–14 days if meningitis is documented

Ceftriaxone should be administered cautiously to neonates with hyperbilirubinemia, especially those born prematurely. Cefotaxime 100 mg/kg body weight IV or IM as a single dose can be administered for those neonates unable to receive ceftriaxone because of simultaneous administration of IV calcium.

Other Management Considerations

Chlamydial testing should be performed simultaneously among neonates with gonococcal infection (see Chlamydial Infection Among Neonates). Neonates who have DGI should be managed in consultation with an infectious disease specialist.

Management of Mothers and Their Sex Partners

Mothers of newborns who have DGI or scalp abscesses caused by *N. gonorrhoeae* should be evaluated, tested, and presumptively treated for gonorrhea, along with their sex partners (see Gonococcal Infection Among Adolescents and Adults).

Neonates Born to Mothers Who Have Gonococcal Infection

Neonates born to mothers who have untreated gonorrhea are at high risk for infection. Neonates should be tested for gonorrhea at exposed sites (e.g., conjunctiva, vagina, rectum, and oropharynx) and treated presumptively for gonorrhea.

Treatment in the Absence of Signs of Gonococcal Infection

Recommended Regimen for Neonates Without Signs of Gonococcal Infection

Ceftriaxone 20–50 mg/kg body weight IV or IM in a single dose, not to exceed 250 mg

Other Management Considerations

Ceftriaxone should be administered cautiously to neonates with hyperbilirubinemia, especially those born prematurely. Cefotaxime 100 mg/kg body weight IV or IM as a single dose can be administered for those neonates unable to receive ceftriaxone because of simultaneous administration of IV calcium. Age-appropriate chlamydial testing should be

performed simultaneously among neonates with gonococcal infection (see Chlamydial Infection Among Neonates). Follow-up examination is not required.

Management of Mothers and Their Sex Partners

Mothers who have gonorrhea and their sex partners should be evaluated, tested, and presumptively treated for gonorrhea (see Gonococcal Infection Among Adolescents and Adults).

Gonococcal Infection Among Infants and Children

Sexual abuse is the most frequent cause of gonococcal infection among infants and children (see Sexual Assault or Abuse of Children). For preadolescent girls, vaginitis is the most common manifestation of this infection; gonococcal-associated PID after vaginal infection can be less common among preadolescents than adults. Among sexually abused children, anorectal and pharyngeal infections with *N. gonorrhoeae* are frequently asymptomatic.

Diagnostic Considerations

Culture can be used to test urogenital and extragenital sites for girls and boys. NAAT can be used to test for *N. gonorrhoeae* from vaginal and urine specimens from girls and urine for boys (see Sexual Assault or Abuse of Children). Although data regarding NAAT from extragenital sites (rectum and pharynx) among children are more limited, and performance is test dependent, no evidence supports that performance of NAAT for detection of *N. gonorrhoeae* among children differs from that among adults (*553*). Because of the implications of a *N. gonorrhoeae* diagnosis in a child, only validated FDA-cleared NAAT assays should be used with extragenital specimens. Consultation with an expert is necessary before using NAAT to minimize the possibility of cross-reaction with nongonococcal *Neisseria* species and other commensals (e.g., *N. meningitidis*, *Neisseria sicca*, *Neisseria lactamica*, *Neisseria cinerea*, or *M. catarrhalis*) and to ensure correct interpretation of results.

Gram stains are inadequate for evaluating prepubertal children for gonorrhea and should not be used to diagnose or exclude gonorrhea. If evidence of DGI exists, gonorrhea culture and antimicrobial susceptibility testing should be obtained from relevant clinical sites (see Disseminated Gonococcal Infection).

Recommended Regimen for Uncomplicated Gonococcal Vulvovaginitis, Cervicitis, Urethritis, Pharyngitis, or Proctitis Among Infants and Children Weighing ≤45 kg

Ceftriaxone 25–50 mg/kg body weight IV or IM in a single dose, not to exceed 250 mg IM

Recommended Regimen for Uncomplicated Gonococcal Vulvovaginitis, Cervicitis, Urethritis, Pharyngitis, or Proctitis Among Children Weighing >45 kg

Treat with the regimen recommended for adults
(see Gonococcal Infections)

Recommended Regimen for Bacteremia or Arthritis Among Children Weighing ≤45 kg

Ceftriaxone 50 mg/kg body weight (maximum dose: 2 g) IM or IV in a single dose daily every 24 hours for 7 days

Recommended Regimen for Bacteremia or Arthritis Among Children Weighing >45 kg

Ceftriaxone 1 g IM or IV in a single dose daily every 24 hours for 7 days

Other Management Considerations

Follow-up cultures are unnecessary. Only parenteral cephalosporins (i.e., ceftriaxone) are recommended for use among children. All children identified as having gonococcal infections should be tested for *C. trachomatis*, syphilis, and HIV (see Sexual Assault or Abuse of Children).

Mycoplasma genitalium

M. genitalium causes symptomatic and asymptomatic urethritis among men and is the etiology of approximately 15%–20% of NGU, 20%–25% of nonchlamydial NGU, and 40% of persistent or recurrent urethritis (*697*,*909*,*910*). Infection with *C. trachomatis* is common in selected geographic areas (*911*–*913*), although *M. genitalium* is often the sole pathogen. Data are insufficient to implicate *M. genitalium* infection with chronic complications among men (e.g., epididymitis, prostatitis, or infertility). The consequences of asymptomatic infection with *M. genitalium* among men are unknown.

Among women, *M. genitalium* has been associated with cervicitis, PID, preterm delivery, spontaneous abortion, and infertility, with an approximately twofold increase in the risk for these outcomes among women infected with *M. genitalium* (*766*). *M. genitalium* infections among women are also frequently asymptomatic, and the consequences associated with asymptomatic *M. genitalium* infection are unknown.

M. genitalium can be detected among 10%–30% of women with clinical cervicitis (*767*,*770*,*772*,*914*–*916*). The existing evidence between *M. genitalium* and cervicitis is mostly supportive of a causal association. Elevated proinflammatory cytokines have been demonstrated among women with *M. genitalium*, with return to baseline levels after clearance of the pathogen (*917*).

M. genitalium is identified in the cervix or endometrium of women with PID more often than in women without PID (*918–924*). Prevalence of *M. genitalium* among women with PID ranges from 4% to 22% (*925*,*926*) and was reported as 60% in one study of women with postabortal PID (*918*). The association with PID is supported by early studies among nonhuman primates that determined that endosalpingitis develops after inoculation with *M. genitalium* (*927*). Recent studies evaluating the lower and upper genital tract using highly sensitive *M. genitalium* NAAT assays or the role of *M. genitalium* in histologically defined endometritis have reported significantly elevated risk for PID (*928*). However, most studies of *M. genitalium* and PID, even those that controlled extensively for other infections and behavioral and biologic risk, are cross-sectional. The few prospective studies that have evaluated the role of *M. genitalium* in establishing subsequent PID demonstrated increased PID risk; however, these were not statistically significant associations, often because of a lack of statistical power. No clinical trial data are available that demonstrate that treating *M. genitalium* cervical infection prevents development of PID or endometritis. Although data regarding the benefits of testing women with PID for *M. genitalium* and the importance of directing treatment against this organism are limited, the associations of *M. genitalium* with cervicitis and PID in cross-sectional studies using NAAT testing are consistent (*928*).

Data from case-control serologic studies (*929–931*) and a meta-analysis of clinical studies (*766*) indicate a potential role in causing infertility. However, seroassays are suboptimal and inconclusive. Similarly, evidence for a role for *M. genitalium* infection during pregnancy as a cause of perinatal complications, including preterm delivery, spontaneous abortion, or low birthweight, are conflicting because evidence is insufficient to attribute cause (*766*,*932–934*). Data are limited regarding ectopic pregnancy and neonatal *M. genitalium* infection (*935*,*936*).

Rectal infection with *M. genitalium* has been reported among 1%–26% of MSM (*937–940*) and among 3% of women (*941*). Rectal infections often are asymptomatic, although higher prevalence of *M. genitalium* has been reported among men with rectal symptoms. Similarly, although asymptomatic *M. genitalium* has been detected in the pharynx, no evidence exists of it causing oropharyngeal symptoms or systemic disease.

Urogenital *M. genitalium* infection is associated with HIV among both men and women (*942–944*); however, the data are from case-control and cross-sectional studies. Risk for HIV infection is increased among women with *M. genitalium*, and evidence indicates that HIV shedding occurs more often among persons with *M. genitalium* and HIV infection who are not taking ART than among persons without *M. genitalium* (*942*,*944*).

Antimicrobial Resistance

Resistance to azithromycin has been rapidly increasing and has been confirmed in multiple studies. Prevalence of molecular markers for macrolide resistance, which highly correlates with treatment failure, ranges from 44% to 90% in the United States, Canada, Western Europe, and Australia (*697*,*702*,*945–953*). Treatment with azithromycin alone has been reported to select for resistance (*705*,*954*,*955*), with treatment of macrolide-susceptible infections with a 1-g dose of azithromycin resulting in selection of resistant-strain populations in 10%–12% of cases. The prevalence of quinolone resistance markers is much lower (*697*,*956–959*). The first clinical treatment failures after moxifloxacin were associated specifically with the S83I mutation in the *parC* gene (*954*,*960*). Prevalence of the S83I mutation in the United States ranges from 0% to 15% (*947*); however, correlation with fluoroquinolone treatment failure is less consistent than that with mutations associated with macrolide resistance (*953*,*961*,*962*). Clinically relevant quinolone resistance often is associated with coexistent macrolide resistance (*954*).

Diagnostic Considerations

M. genitalium is an extremely slow-growing organism. Culture can take up to 6 months, and technical laboratory capacity is limited to research settings. NAAT for *M. genitalium* is FDA cleared for use with urine and urethral, penile meatal, endocervical, and vaginal swab samples (https://www.hologic.com/package-inserts/diagnostic-products/aptima-mycoplasma-genitalium-assay). Molecular tests for macrolide (i.e., azithromycin) or quinolone (i.e., moxifloxacin) resistance markers are not commercially available in the United States. However, molecular assays that incorporate detection of mutations associated with macrolide resistance are under evaluation.

Men with recurrent NGU should be tested for *M. genitalium* using an FDA-cleared NAAT. If resistance testing is available, it should be performed and the results used to guide therapy. Women with recurrent cervicitis should be tested for *M. genitalium*, and testing should be considered among women with PID. Testing should be accompanied with resistance testing, if available. Screening of asymptomatic *M. genitalium* infection among women and men or extragenital testing for *M. genitalium* is not recommended. In clinical practice, if testing is unavailable, *M. genitalium* should be suspected in cases of persistent or recurrent urethritis or cervicitis and considered for PID.

Treatment

M. genitalium lacks a cell wall, and thus antibiotics targeting cell-wall biosynthesis (e.g., ß-lactams including penicillins and cephalosporins) are ineffective against this organism. Because of the high rates of macrolide resistance with treatment failures (*707*) and efficient selection of additional resistance, a 1-g dose of azithromycin should not be used.

Two-stage therapy approaches, ideally using resistance-guided therapy, are recommended for treatment. Resistance-guided therapy has demonstrated cure rates of >90% and should be used whenever possible (*759*,*963*); however, it requires access to macrolide-resistance testing. As part of this approach, doxycycline is provided as initial empiric therapy, which reduces the organism load and facilitates organism clearance, followed by macrolide-sensitive *M. genitalium* infections treated with high-dose azithromycin; macrolide-resistant infections are treated with moxifloxacin (*964*,*965*).

Recommended Regimens if *M. genitalium* Resistance Testing Is Available

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

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

Recommended Regimen if *M. genitalium* Resistance Testing Is Not Available

If *M. genitalium* is detected by an FDA-cleared NAAT: Doxycycline 100 mg orally 2 times/day for 7 days, followed by **moxifloxacin** 400 mg orally once daily for 7 days

Although the majority of *M. genitalium* strains are sensitive to moxifloxacin, resistance has been reported, and adverse side effects and cost should be considered with this regimen. In settings without access to resistance testing and when moxifloxacin cannot be used, an alternative regimen can be considered, based on limited data: doxycycline 100 mg orally 2 times/day for 7 days, followed by azithromycin (1 g orally on day 1 followed by 500 mg once daily for 3 days) and a test of cure 21 days after completion of therapy (*963*). Because of the high prevalence of macrolide resistance and high likelihood of treatment failure, this regimen should be used only when a test of cure is possible, and no other alternatives exist. If symptomatic treatment failure or a positive test of cure occurs after this regimen, expert consultation is recommended. Data are limited regarding use of minocycline in instances of treatment failure (*966*).

Recommended PID treatment regimens are not effective against *M. genitalium*. Initial empiric therapy for PID, which includes doxycycline 100 mg orally 2 times/day for 14 days, should be provided at the time of presentation for care. If *M. genitalium* is detected, a regimen of moxifloxacin 400 mg orally once daily for 14 days has been effective in eradicating the organism. Nevertheless, no data have been published that assess the benefits of testing women with PID for *M. genitalium,* and the importance of directing treatment against this organism is unknown.

Follow-Up

Test of cure is not recommended for asymptomatic persons who received treatment with a recommended regimen. In settings in which *M. genitalium* testing is available, persons with persistent urethritis, cervicitis, or PID accompanied by detection of *M. genitalium* should be treated with moxifloxacin.

Management of Sex Partners

Recent studies report a high concordance of *M. genitalium* among partners of males, females, and MSM; however, no studies have determined whether reinfection is reduced with partner treatment (*940*,*967*,*968*). Sex partners of patients with symptomatic *M. genitalium* infection can be tested, and those with a positive test can be treated to possibly reduce the risk for reinfection. If testing the partner is not possible, the antimicrobial regimen that was provided to the patient can be provided.

Special Considerations

HIV Infection

Persons who have *M. genitalium* and HIV infection should receive the same treatment regimen as those persons without HIV.

Diseases Characterized by Vulvovaginal Itching, Burning, Irritation, Odor, or Discharge

The majority of women will have a vaginal infection, characterized by discharge, itching, burning, or odor, during their lifetime. With the availability of complementary and alternative therapies and over-the-counter medications for candidiasis, symptomatic women often seek these products before or in addition to an evaluation by a medical provider.

Obtaining a medical history alone has been reported to be insufficient for accurate diagnosis of vaginitis and can lead to inappropriate administration of medication (*969*). Therefore, a careful history, examination, and laboratory testing to determine the etiology of any vaginal symptoms are warranted. Information regarding sexual behaviors and

practices, sex of sex partners, menses, vaginal hygiene practices (e.g., douching), and self-treatment with oral and intravaginal medications or other products should be elicited. The infections most frequently associated with vaginal symptoms are BV (i.e., replacement of the vaginal flora by an overgrowth of anaerobic bacteria including *G. vaginalis*, *Prevotella bivia*, *A. vaginae*, *Megasphaera* type 1, and numerous other fastidious or uncultivated anaerobes), trichomoniasis, and vulvovaginal candidiasis (VVC). Cervicitis can also cause an abnormal vaginal discharge. Although VVC is usually not sexually transmitted, it is included in this section because it is frequently diagnosed among women who have vaginal symptoms or are being evaluated for an STI.

Multiple diagnostic methods are available for identifying the etiology of vaginal symptoms. Clinical laboratory testing can identify the vaginitis cause in the majority of women and is discussed in detail in the sections of this report dedicated to each condition. In the clinician's office, the cause of vaginal symptoms can often be determined by pH, a potassium hydroxide (KOH) test, and microscopic examination of a wet mount of fresh samples of vaginal discharge. The pH of the vaginal secretions can be measured by pH paper; an elevated pH (i.e., >4.5) is common with BV or trichomoniasis (although trichomoniasis can also be present with a normal vaginal pH). Because pH testing is not highly specific, vaginal discharge should be further examined microscopically by first diluting one sample in 1 or 2 drops of 0.9% normal saline solution on one slide and a second sample in 10% KOH solution (samples that emit an amine odor immediately upon application of KOH suggest BV or trichomoniasis). Coverslips are then placed on the slides, and they are examined under a microscope at low and high power. The saline-solution specimen might display motile trichomonads or clue cells (i.e., epithelial cells with borders obscured by small anaerobic bacteria), which are characteristic of BV. The KOH specimen typically is used to identify hyphae or blastospores observed with candidiasis. However, absence of trichomonads in saline or fungal elements in KOH samples does not rule out these infections because the sensitivity of microscopy is approximately 50% compared with NAAT (trichomoniasis) or culture (yeast) (*670*). Presence of WBCs without evidence of trichomonads or yeast might also indicate cervicitis (see Cervicitis).

In settings where pH paper, KOH, and microscopy are unavailable, a broad range of clinical laboratory tests, described in the diagnosis section for each disease, can be used. Presence of objective signs of vulvovaginal inflammation in the absence of vaginal pathogens after laboratory testing indicates the possibility of mechanical, chemical, allergic, or other noninfectious causes of vulvovaginal signs or symptoms. For women with persistent symptoms and no clear etiology, referral to a specialist should be considered.

Bacterial Vaginosis

BV is a vaginal dysbiosis resulting from replacement of normal hydrogen peroxide and lactic-acid–producing *Lactobacillus* species in the vagina with high concentrations of anaerobic bacteria, including *G. vaginalis*, *Prevotella* species, *Mobiluncus* species, *A. vaginae*, and other BV-associated bacteria. A notable feature is the appearance of a polymicrobial biofilm on vaginal epithelial cells (*970*). Certain women experience transient vaginal microbial changes, whereas others experience them for longer intervals (*971*). BV is a highly prevalent condition and the most common cause of vaginal discharge worldwide (*972*). However, in a nationally representative survey, the majority of women with BV were asymptomatic (*310*).

BV is associated with having multiple male sex partners, female partners, sexual relationships with more than one person (*973*), a new sex partner, lack of condom use (*974*), douching (*975*,*976*), and HSV-2 seropositivity (*977*). Male circumcision reduces the risk for BV among women (*978*). In addition, BV prevalence increases during menses (*979*,*980*). Women who have never been sexually active are rarely affected (*981*). The cause of the microbial alteration that precipitates BV is not fully understood, and whether BV results from acquisition of a single sexually transmitted pathogen is unknown. BV prevalence has been reported to increase among women with copper-containing IUDs (*972*,*982*). Hormonal contraception does not increase risk for BV (*983*) and might protect against BV development (*983*,*984*). Vitamin D deficiency has not been reported to be a risk factor for BV (*985*).

Women with BV are at increased risk for STI acquisition, such as HIV, *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis* (*977*), *M. genitalium* (*986*), HPV (*987*), and HSV-2 (*988*); complications after gynecologic surgery; complications of pregnancy; and recurrence of BV (*971*,*989–991*). BV also increases HIV infection acquisition (*992*) because specific BV-associated bacteria can increase susceptibility to HIV (*993*,*994*) and the risk for HIV transmission to male sex partners (*187*). Evaluation of short-term valacyclovir suppression among women with HSV-2 did not decrease the risk for BV, despite effective suppression of HSV-2 (*995*).

Although BV-associated bacteria can be identified on male genitalia (*996*,*997*), treatment of male sex partners has not been beneficial in preventing the recurrence of BV (*998*). Among WSW, a high level of BV concordance occurs between sex partners (*292*); however, no studies have evaluated treatment of female sex partners of WSW to prevent BV recurrence.

Diagnostic Considerations

BV can be diagnosed by using clinical criteria (i.e., Amsel's diagnostic criteria) (*999*) or by determining the Nugent score from a vaginal Gram stain (*1000*). Vaginal Gram stain, considered the reference standard laboratory method for diagnosing BV, is used to determine the relative concentration of lactobacilli (i.e., long gram-positive rods), small gram-negative and gram-variable rods (i.e., *G. vaginalis* or *Bacteroides*), and curved gram-negative rods (i.e., *Mobiluncus*) characteristic of BV. A Nugent score of 0–3 is consistent with a *Lactobacillus*-predominant vaginal microbiota, 4–6 with intermediate microbiota (emergence of *G. vaginalis*), and 7–10 with BV. Clinical diagnosis of BV by Amsel criteria requires at least three of the following four symptoms or signs:

- Homogeneous, thin discharge (milklike consistency) that smoothly coats the vaginal walls
- Clue cells (e.g., vaginal epithelial cells studded with adherent bacteria) on microscopic examination
- pH of vaginal fluid >4.5
- A fishy odor of vaginal discharge before or after addition of 10% KOH (i.e., the whiff test)

Detection of at least three Amsel criteria has been correlated with results by Gram stain (*1001*). The sensitivity and specificity of the Amsel criteria are 37%–70% and 94%–99%, respectively, compared with the Nugent score (*1002*).

In addition to the Amsel criteria, multiple POC tests are available for BV diagnosis. The Osom BV Blue test (Sekisui Diagnostics) detects vaginal sialidase activity (*1003*,*1004*). The Affirm VP III (Becton Dickinson) is an oligonucleotide probe test that detects high concentrations of *G. vaginalis* nucleic acids (>5 x 10^5 CFU of *G. vaginalis*/mL of vaginal fluid) for diagnosing BV, *Candida* species, and *T. vaginalis.* This test has been reported to be most useful for symptomatic women in conjunction with vaginal pH measurement and presence of amine odor (sensitivity of 97%); specificity is 81% compared with Nugent. Finally, the FemExam Test Card (Cooper Surgical) measures vaginal pH, presence of trimethylamine (a metabolic by-product of *G. vaginalis*), and proline aminopeptidase (*1005*). Sensitivity is 91% and specificity is 61%, compared with Nugent. This test has primarily been studied in resource-poor settings (*1005*), and although it has been reported to be beneficial compared with syndromic management, it is not a preferred diagnostic method for BV diagnosis.

Multiple BV NAATs are available for BV diagnosis among symptomatic women (*1002*). These tests are based on detection of specific bacterial nucleic acids and have high sensitivity and specificity for BV (i.e., *G. vaginalis*, *A. vaginae*, BVAB2, or *Megasphaera* type 1) (*1006*) and certain lactobacilli (i.e., *Lactobacillus crispatus*, *Lactobacillus jensenii*, and *Lactobacillus gasseri*). They can be performed on either clinician- or self-collected vaginal specimens with results available in <24 hours, depending on the availability of the molecular diagnostic platform (*1002*). Five quantitative multiplex PCR assays are available: Max Vaginal Panel (Becton Dickinson) (*1007*), Aptima BV (Hologic), NuSwab VG (LabCorp) (*1008*), OneSwab BV Panel PCR with Lactobacillus Profiling by qPCR (Medical Diagnostic Laboratories) (*1009*), and SureSwab BV (Quest Diagnostics). Two of these assays are FDA cleared (BD Max Vaginal Panel and Aptima BV), and the other three are laboratory-developed tests.

The Max Vaginal Panel provides results by an algorithmic analysis of molecular DNA detection of *Lactobacillus* species (*L. crispatus* and *L. jensenii*) in addition to *G. vaginalis*, *A. vaginae*, BVAB2, and *Megasphaera* type 1. This test has 90.5% sensitivity and 85.8% specificity for BV diagnosis, compared with Amsel criteria and Nugent score. It also provides results for *Candida* species and *T. vaginalis*. The Aptima BV detects *G. vaginalis*, *A. vaginae*, and certain *Lactobacillus* species including *L. crispatus*, *L. jensenii*, and *L. gasseri,* with sensitivity and specificity ranging from 95.0% to 97.3% and 85.8% to 89.6%, respectively (using either clinician- or patient-collected vaginal swabs). The three laboratory-developed tests (NuSwab VG, OneSwab BV Panel PCR with Lactobacillus Profiling by qPCR, and SureSwab BV) have to be internally validated before use for patient care yet have good sensitivity and specificity, similar to FDA-cleared assays. BV NAATs should be used among symptomatic women only (e.g., women with vaginal discharge, odor, or itch) because their accuracy is not well defined for asymptomatic women. Despite the availability of BV NAATs, traditional methods of BV diagnosis, including the Amsel criteria, Nugent score, and the Affirm VP III assay, remain useful for diagnosing symptomatic BV because of their lower cost and ability to provide a rapid diagnosis. Culture of *G. vaginalis* is not recommended as a diagnostic tool because it is not specific. Cervical Pap tests have no clinical utility for diagnosing BV because of their low sensitivity and specificity.

Treatment

Treatment for BV is recommended for women with symptoms. Established benefits of therapy among nonpregnant women are to relieve vaginal symptoms and signs of infection. Other potential benefits of treatment include reduction in the risk for acquiring *C. trachomatis, N. gonorrhoeae*, *T. vaginalis*, *M. genitalium*, HIV, HPV, and HSV-2 (*971*,*986*–*988*,*990*,*1010*). No data are available that directly compare the efficacy of oral and topical medications for treating BV.

Recommended Regimens for Bacterial Vaginosis

Metronidazole 500 mg orally 2 times/day for 7 days
or
Metronidazole gel 0.75% one full applicator (5 g) intravaginally, once daily for 5 days
or
Clindamycin cream 2% one full applicator (5 g) intravaginally at bedtime for 7 days

A review regarding alcohol consumption during metronidazole treatment reported no in vitro studies, animal models, reports of adverse effects, or clinical studies providing convincing evidence of a disulfiram-like interaction between alcohol and metronidazole (*1011*). The previous warning against simultaneous use of alcohol and metronidazole was based on laboratory experiments and individual case histories in which the reported reactions were equally likely to have been caused by alcohol alone or by adverse effects of metronidazole.

Metronidazole does not inhibit acetaldehyde dehydrogenase, as occurs with disulfiram. Ethanol alone or ethanol-independent side effects of metronidazole might explain the suspicion of disulfiram-like effects. Thus, refraining from alcohol use while taking metronidazole (or tinidazole) is unnecessary. Clindamycin cream is oil based and might weaken latex condoms and diaphragms for 5 days after use (refer to clindamycin product labeling for additional information).

Women should be advised to refrain from sexual activity or to use condoms consistently and correctly during the BV treatment regimen. Douching might increase the risk for relapse, and no data support use of douching for treatment or symptom relief.

Alternative Regimens

Clindamycin 300 mg orally 2 times/day for 7 days
or
Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days*
or
Secnidazole 2 g oral granules in a single dose†
or
Tinidazole 2 g orally once daily for 2 days
or
Tinidazole 1 g orally once daily for 5 days

* Clindamycin ovules use an oleaginous base that might weaken latex or rubber products (e.g., condoms and diaphragms). Use of such products within 72 hours after treatment with clindamycin ovules is not recommended.
† Oral granules should be sprinkled onto unsweetened applesauce, yogurt, or pudding before ingestion. A glass of water can be taken after administration to aid in swallowing.

Alternative regimens include secnidazole oral granules (*1012–1014*), multiple oral tinidazole regimens (*1015*), or clindamycin (oral or intravaginal) (*1016*). In a phase 3 clinical trial of secnidazole 2 g oral granules versus placebo, BV clinical cure rates at days 21–30 were 53% in the secnidazole arm compared with 19% in the placebo arm ($p<0.001$) (*1013*). Secnidazole is listed as an alternative regimen, due to its higher cost and lack of long-term outcomes compared with recommended BV treatments. A patient savings card for secnidazole is available at https://www.solosec.com/savings-card.

Additional BV treatment regimens include metronidazole 1.3% vaginal gel in a single dose (*1017,1018*) and clindamycin phosphate (Clindesse) 2% vaginal cream in a single dose (*1019*). In a phase 3 clinical trial of metronidazole 1.3% vaginal gel versus placebo, BV clinical cure rates at day 21 were 37.2% in the metronidazole 1.3% vaginal gel arm, compared with 26.6% in the placebo arm ($p = 0.01$) (*1018*). A patient savings card for metronidazole 1.3% vaginal gel is available at https://nuvessa.com/nuvessa_files/19_Nuvessa_WEB_Card_032819.pdf. In a multicenter, randomized, single-blind, parallel-group study of Clindesse 2% vaginal cream single dose versus clindamycin 2% vaginal cream at bedtime for 7 days among 540 women with BV, no statistically significant difference existed between groups in clinical cure at days 21–30 (64.3% versus 63.2%; $p = 0.95$) (*1019*); however, this study had methodologic problems. A patient savings card for Clindesse 2% vaginal cream is available at https://www.clindesse.com/pdf/CLINDESSE_SavingsCard.pdf.

BV biofilm disrupting agents (i.e., TOL-463) (*1020*) are being investigated to determine their role in enhancing the likelihood of BV cure relative to approved therapies. Studies have evaluated the clinical and microbiologic efficacy of intravaginal *Lactobacillus* and other probiotic formulations to treat BV and restore normal vaginal microbiota (*1021–1025*); overall, no studies support these products as an adjunctive or replacement therapy for women with BV.

Other Management Considerations

All women with BV should be tested for HIV and other STIs.

Follow-Up

Follow-up visits are unnecessary if symptoms resolve. Because persistent or recurrent BV is common, women should be advised to return for evaluation if symptoms recur. Limited data are available regarding optimal management strategies for women with persistent or recurrent BV. Using a different recommended treatment regimen can be considered for women who have a recurrence; however, retreatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence (*1026*). For women with multiple recurrences after completion of a recommended regimen, either 0.75% metronidazole gel or 750 mg metronidazole vaginal suppository twice weekly for >3 months has been reported to reduce recurrences, although this benefit does not persist when

suppressive therapy is discontinued (*1027*,*1028*). Limited data indicate that for women with multiple recurrences, an oral nitroimidazole (metronidazole or tinidazole 500 mg 2 times/day for 7 days), followed by intravaginal boric acid 600 mg daily for 21 days and suppressive 0.75% metronidazole gel twice weekly for 4–6 months, might be an option for women with recurrent BV (*1029*). Monthly oral metronidazole 2 g administered with fluconazole 150 mg has also been evaluated as suppressive therapy; this regimen reduced the BV incidence and promoted colonization with normal vaginal microbiota (*1030*). A randomized controlled trial of a dendrimer-based microbicide 1% vaginal gel (Astodrimer) also reported favorable results in prolonging the time to BV recurrence, compared with placebo (*1031*). In addition, a clinical trial of *L. crispatus* CTV-05 (Lactin-V), administered vaginally in 4 consecutive daily doses for 4 days in week 1 followed by twice weekly doses for 10 weeks (after initial treatment with 5 days of 0.75% vaginal metronidazole gel), reported a substantially lower incidence of BV recurrence at 12 weeks in the Lactin-V arm, compared with placebo (*1032*); however this medication is not yet FDA cleared or commercially available. High-dose Vitamin D supplementation has not been determined to decrease BV recurrence in randomized controlled trials (*1033*) and is not recommended.

Management of Sex Partners

Data from earlier clinical trials indicate that a woman's response to therapy and the likelihood of relapse or recurrence are not affected by treatment of her sex partner (*998*). Therefore, routine treatment of sex partners is not recommended. However, a pilot study reported that male partner treatment (i.e., metronidazole 400 mg orally 2 times/day in conjunction with 2% clindamycin cream applied topically to the penile skin 2 times/day for 7 days) of women with recurrent BV had an immediate and sustained effect on the composition of the vaginal microbiota, with an overall decrease in bacterial diversity at day 28 (*1034*). Male partner treatment also had an immediate effect on the composition of the penile microbiota; however, this was not as pronounced at day 28, compared with that among women. A phase 3 multicenter randomized double-blinded trial evaluating the efficacy of a 7-day oral metronidazole regimen versus placebo for treatment of male sex partners of women with recurrent BV did not find that male partner treatment reduced BV recurrence in female partners, although women whose male partners adhered to multidose metronidazole were less likely to experience treatment failure (*1035*).

Special Considerations

Drug Allergy, Intolerance, or Adverse Reactions

Intravaginal clindamycin cream is preferred in case of allergy or intolerance to metronidazole or tinidazole. Intravaginal metronidazole gel can be considered for women who are not allergic to metronidazole but do not tolerate oral metronidazole.

Pregnancy

BV treatment is recommended for all symptomatic pregnant women because symptomatic BV has been associated with adverse pregnancy outcomes, including premature rupture of membranes, preterm birth, intra-amniotic infection, and postpartum endometritis (*989*,*991*,*1036*). Studies have been undertaken to determine the efficacy of BV treatment among this population, including two trials demonstrating that oral metronidazole was efficacious during pregnancy by using the 250 mg 3 times/day regimen (*1037*,*1038*); however, oral metronidazole administered as a 500 mg 2 times/day regimen can also be used. One trial involving a limited number of participants revealed treatment with oral metronidazole 500 mg 2 times/day for 7 days to be equally effective as metronidazole gel 0.75% for 5 days, with cure rates of 70% by using Amsel criteria to define cure (*1039*). Another trial demonstrated a cure rate of 85% by using Gram-stain criteria after treatment with oral clindamycin 300 mg 2 times/day for 7 days (*1040*–*1043*).

Although older studies indicated a possible link between using vaginal clindamycin during pregnancy and adverse outcomes for the newborn, newer data demonstrate that this treatment approach is safe for pregnant women (*1044*). Although metronidazole crosses the placenta, no evidence of teratogenicity or mutagenic effects among infants has been reported in multiple cross-sectional, case-control, and cohort studies of pregnant women (*1041*–*1043*). These data indicate that metronidazole therapy poses low risk during pregnancy. Data from human studies are limited regarding the use of tinidazole in pregnancy; however, animal data demonstrate that such therapy poses moderate risk. Thus, tinidazole should be avoided during pregnancy (*431*). Data are insufficient regarding efficacy and adverse effects of secnidazole, Clindesse 2% vaginal cream, metronidazole 1.3% vaginal gel, and 750-mg vaginal metronidazole tablets during pregnancy; thus, their use should be avoided.

Oral therapy has not been reported to be superior to topical therapy for treating symptomatic BV in effecting cure or preventing adverse outcomes of pregnancy. Pregnant women can be treated with any of the recommended regimens for nonpregnant women, in addition to the alternative regimens of oral clindamycin and clindamycin ovules.

Treatment of asymptomatic BV among pregnant women at high risk for preterm delivery (i.e., those with a previous preterm birth or late miscarriage) has been evaluated by multiple studies, which have yielded mixed results. Seven trials have evaluated treatment of pregnant women with asymptomatic BV at high risk for preterm delivery: one revealed harm (*1045*), two reported no benefit (*1046*,*1047*), and four demonstrated benefit (*1037*,*1038*,*1048*,*1049*).

Treatment of asymptomatic BV among pregnant women at low risk for preterm delivery has not been reported to reduce adverse outcomes of pregnancy in a large multicenter randomized controlled trial (*1050*). Therefore, routine screening for BV among asymptomatic pregnant women at high or low risk for preterm delivery for preventing preterm birth is not recommended.

Metronidazole is secreted in breast milk. With maternal oral therapy, breastfed infants receive metronidazole in doses that are less than those used to treat infections among infants, although the active metabolite adds to the total infant exposure. Plasma levels of the drug and metabolite are measurable but remain less than maternal plasma levels (https://www.ncbi.nlm.nih.gov/books/NBK501922/?report=classic). Although multiple reported case series identified no evidence of metronidazole-associated adverse effects for breastfed infants, certain clinicians recommend deferring breastfeeding for 12–24 hours after maternal treatment with a single 2-g dose of metronidazole (*1051*). Lower doses produce a lower concentration in breast milk and are considered compatible with breastfeeding (*1052*,*1053*).

HIV Infection

BV appears to recur with higher frequency among women who have HIV infection (*1054*). Women with HIV infection and BV should receive the same treatment regimen as those who do not have HIV.

Trichomoniasis

Trichomoniasis is estimated to be the most prevalent nonviral STI worldwide, affecting approximately 3.7 million persons in the United States (*838*,*1055*). Because trichomoniasis is not a reportable disease (*1056*), and no recommendations are available for general screening for *T. vaginalis*, the epidemiology of trichomoniasis has largely come from population-based and clinic-based surveillance studies. The U.S. population-based *T. vaginalis* prevalence is 2.1% among females and 0.5% among males, with the highest rates among Black females (9.6%) and Black males (3.6%), compared with non-Hispanic White women (0.8%) and Hispanic women (1.4%) (*1057*,*1058*). Unlike chlamydia and gonorrhea, *T. vaginalis* prevalence rates are as high among women aged >24 years as they are for women aged <24 years (*1057*). Among persons attending nine geographically diverse STD clinics, the trichomonas prevalence was 14.6% among women (*1059*), and a study of STD clinic attendees in Birmingham, Alabama, identified a prevalence of 27% among women and 9.8% among men (*1060*). Symptomatic women have a four times higher rate of infection than asymptomatic women (26% versus 6.5%) (*1061*). Rates are also high among incarcerated persons of both sexes at 9%–32% of incarcerated women (*386*,*387*,*391*,*392*,*1062*) and 3.2%–8% of incarcerated men (*388*). Women with a history of incarceration are two to five times more likely to have *T. vaginalis* (*387*,*388*,*1063*,*1064*). Other risk factors for *T. vaginalis* include having two or more sex partners during the previous year, having less than a high school education, and living below the national poverty level (*1065*). Women with BV are at higher risk for *T. vaginalis* (*1066*). Male partners of women with trichomoniasis are likely to have infection (*1067*), although the prevalence of trichomoniasis among MSM is low (*179*,*1068*).

The majority of persons who have trichomoniasis (70%–85%) either have minimal or no genital symptoms, and untreated infections might last from months to years (*137*,*1069*,*1070*). Men with trichomoniasis sometimes have symptoms of urethritis, epididymitis, or prostatitis, and women with trichomoniasis sometimes have vaginal discharge, which can be diffuse, malodorous, or yellow-green with or without vulvar irritation, and might have a strawberry-appearing cervix, which is observed more often on colposcopy than on physical examination (*1071*). Although many persons might be unaware of their infection, it is readily passed between sex partners during penile-vaginal sex (*1072*) or through transmission of infected vaginal fluids or fomites among women who have sex with women (*275*,*294*).

Among persons who are sexually active, the best way to prevent genital trichomoniasis is through consistent and correct use of condoms (external or internal) (*18*). Partners of men who have been circumcised might have a somewhat reduced risk for *T. vaginalis* infection (*1072*,*1073*). Douching is not recommended because it might increase the risk for vaginal infections, including trichomoniasis (*1074*).

T. vaginalis causes reproductive morbidity and has been reported to be associated with a 1.4-times greater likelihood of preterm birth, premature rupture of membranes, and infants who are small for gestational age (*1075*). *T. vaginalis* was also determined to be associated with a 2.1-fold increased risk for cervical cancer in a meta-analysis (*1076*). Another meta-analysis of six studies reported a slightly elevated but not statistically significant association between *T. vaginalis* and prostate cancer (*1077*).

T. vaginalis infection is associated with a 1.5-fold increased risk for HIV acquisition and is associated with an increase in HIV vaginal shedding, which is reduced with *T. vaginalis* treatment among women without viral suppression (*1078*,*1079*). Among women with HIV infection, *T. vaginalis* infection is associated with increased risk for PID (*1080*–*1082*).

Diagnostic testing for *T. vaginalis* should be performed for women seeking care for vaginal discharge. Annual screening might be considered for persons receiving care in high-prevalence settings (e.g., STD clinics and correctional facilities) and for asymptomatic women at high risk for infection (e.g., multiple sex partners, transactional sex, drug misuse, or a history of STIs or incarceration). However, data are lacking regarding whether screening and treatment for asymptomatic trichomoniasis in high-prevalence settings for women at high risk can reduce any adverse health events and health disparities or reduce community infection burden. Decisions about screening can be guided by local epidemiology of *T. vaginalis* infection. Routine annual screening for *T. vaginalis* among asymptomatic women with HIV infection is recommended because of these adverse events associated with trichomoniasis and HIV infection.

Extragenital *T. vaginalis* is possible but highly uncommon compared with genital infections. A study of 500 men in San Francisco, California, reported a 0.6% rate of rectal *T. vaginalis* (*1083*); however, this might reflect deposition of *T. vaginalis* DNA and not necessarily active infection. Few studies of extragenital *T. vaginalis* among women have been published. The efficacy, benefit, and cost-effectiveness of extragenital screening are unknown, and no tests are FDA cleared for extragenital testing; therefore, rectal and oral testing for *T. vaginalis* is not recommended.

Diagnostic Considerations

Wet-mount microscopy traditionally has been used as the preferred diagnostic test for *T. vaginalis* among women because it is inexpensive and can be performed at the POC; however, it has low sensitivity (44%–68%) compared with culture (*1084*–*1086*). To improve detection, clinicians using wet mounts should attempt to evaluate slides immediately after specimen collection because sensitivity decreases quickly to 20% within 1 hour after collection (*1087*). More highly sensitive and specific molecular diagnostic options are available, which should be used in conjunction with a negative wet mount when possible.

NAATs are highly sensitive, detecting more *T. vaginalis* infections than wet-mount microscopy among women (*1060*). The Aptima *T. vaginalis* assay (Beckton Dickinson) is FDA cleared for detection of *T. vaginalis* from symptomatic or asymptomatic women. Reliable samples include clinician-collected endocervical swabs, clinician-collected vaginal swabs, female urine specimens, and liquid Pap smear specimens collected in PreservCyt Solution (Hologic) (*698*,*1088*). This assay detects RNA by transcription-mediated amplification with a sensitivity of 95.3%–100% and specificity of 95.2%–100%, compared with wet mount and culture (*1088*,*1089*). Among women, vaginal swabs and urine specimens have <100% concordance (*1084*). This assay has not been FDA cleared for use among men and should be internally validated in accordance with CLIA regulations before use with urine or urethral swabs from men. The Probe Tec TV Q^x Amplified DNA Assay (Becton Dickinson) is FDA cleared for detection of *T. vaginalis* from vaginal (patient-collected or clinician-collected) swabs, endocervical swabs, or urine specimens from women and has sensitivity of 98.3% and specificity of 99.6%, compared with wet mount and culture (*1090*). Similar to the Aptima *T. vaginalis* assay, this test is only FDA cleared for use among women and should be internally validated for use with men. The Max CTGCTV2 assay (Becton Dickinson) is also FDA cleared for detection of *T. vaginalis* in patient-collected or clinician-collected vaginal swab specimens and male and female urine specimens, with sensitivity and specificity of 96.2%–100% and 99.1%–100%, respectively, depending on the specimen type, compared with wet mount and culture (*1091*). GeneXpert TV (Cepheid) is a moderately complex rapid test that can be performed in ≤1 hour and can be used at the POC (*1092*). It has been FDA cleared for use with female urine specimens, endocervical swabs, patient-collected or clinician-collected vaginal specimens, and male urine specimens, with sensitivity and specificity of 99.5%–100% and 99.4%–99.9% (*1007*), respectively, compared with wet mount and culture.

Multiple FDA-cleared rapid tests are available for detecting *T. vaginalis* with improved sensitivities and specificities, compared with wet mount. The Osom trichomonas rapid test (Sekisui Diagnostics) is an antigen-detection test that uses immunochromatographic capillary flow dipstick technology that can be performed at the POC by using clinician-obtained vaginal specimens. Results are available in approximately 10–15 minutes, with sensitivities of 82%–95% and specificity of 97%–100%, compared with wet mount, culture, and transcription-mediated amplification (*1089*,*1093*,*1094*). A study of 209 women aged 14–22 years reported that >99% could correctly perform and interpret a vaginal self-test by using the Osom assay, with a high correlation with clinician interpretation (96% agreement; $\kappa = 0.87$) (*1094*). The Osom test should not be used with men because of low sensitivity (38% compared with Aptima) (*1095*). The Solana trichomonas assay (Quidel) is another rapid test for the qualitative detection of *T. vaginalis* DNA and can yield results <40 minutes after

specimen collection. This assay is FDA cleared for diagnosing *T. vaginalis* from female vaginal and urine specimens from asymptomatic and symptomatic women with sensitivity >98%, compared with NAAT for vaginal specimens, and >92% for urine specimens (*1096*). The Amplivue trichomonas assay (Quidel) is another rapid test providing qualitative detection of *T. vaginalis* that has been FDA cleared for vaginal specimens from symptomatic and asymptomatic women, with sensitivity of 90.7% and specificity of 98.9%, compared with NAAT (*1097*). Neither the Osom assay nor the Affirm VP III test is FDA cleared for use with specimens from men.

Culture, such as the InPouch system (BioMed Diagnostics), was considered the most sensitive method for diagnosing *T. vaginalis* infection before molecular detection methods became available. Culture has sensitivity of 44%–75% and specificity of <100% (*698*,*1086*,*1098*). For women, vaginal secretions are the preferred specimen type for culture because urine culture is less sensitive (*698*,*1099*,*1100*). For men, culture specimens require a urethral swab, urine sediment, or semen. To improve diagnostic yield, multiple specimens from men can be used to inoculate a single culture. Cultures require an incubator and are necessary for *T. vaginalis* drug susceptibility testing. The InPouch specimen should be examined daily for 5 days over a 7-day period to reduce the possibility of false negatives (*1101*).

Although *T. vaginalis* might be an incidental finding on a Pap test, neither conventional nor liquid-based Pap smears are considered diagnostic tests for trichomoniasis; however, women with *T. vaginalis* identified on a Pap smear should be retested with sensitive diagnostic tests and treated if infection is confirmed (*1102*,*1103*).

Treatment

Treatment reduces symptoms and signs of *T. vaginalis* infection and might reduce transmission. Treatment recommendations for women are based on a meta-analysis (*1104*) and a multicenter, randomized trial of mostly symptomatic women without HIV infection (*1105*). The study demonstrated that multidose metronidazole (500 mg orally 2 times/day for 7 days) reduced the proportion of women retesting positive at a 1-month test of cure visit by half, compared with women who received the 2-g single dose.No published randomized trials are available that compare these doses among men.

Recommended Regimen for Trichomoniasis Among Women
Metronidazole 500 mg orally 2 times/day for 7 days

Recommended Regimen for Trichomoniasis Among Men
Metronidazole 2 g orally in a single dose

Alternative Regimen for Women and Men
Tinidazole 2 g orally in a single dose

The nitroimidazoles are the only class of medications with clinically demonstrated efficacy against *T. vaginalis* infections. Tinidazole is usually more expensive, reaches higher levels in serum and the genitourinary tract, has a longer half-life than metronidazole (12.5 hours versus 7.3 hours), and has fewer gastrointestinal side effects (*1106*,*1107*). In randomized clinical trials, recommended metronidazole regimens have resulted in cure rates of approximately 84%–98% (*1108*), and the recommended tinidazole regimen has resulted in cure rates of approximately 92%–100% (*1108*–*1112*). Randomized controlled trials comparing single 2-g doses of metronidazole and tinidazole indicated that tinidazole is equivalent or superior to metronidazole in achieving parasitologic cure and symptom resolution (*1110*,*1113*,*1114*).

Metronidazole gel does not reach therapeutic levels in the urethra and perivaginal glands. Because it is less efficacious than oral metronidazole, it is not recommended.

Other Management Considerations

Providers should advise persons with *T. vaginalis* infections to abstain from sex until they and their sex partners are treated (i.e., when therapy has been completed and any symptoms have resolved). Testing for other STIs, including HIV, syphilis, gonorrhea, and chlamydia, should be performed for persons with *T. vaginalis*.

Follow-Up

Because of the high rate of reinfection among women treated for trichomoniasis, retesting for *T. vaginalis* is recommended for all sexually active women <3 months after initial treatment regardless of whether they believe their sex partners were treated (*137*,*1115*). If retesting at 3 months is not possible, clinicians should retest whenever persons next seek medical care <12 months after initial treatment. Data are insufficient to support retesting men after treatment.

Management of Sex Partners

Concurrent treatment of all sex partners is vital for preventing reinfections. Current partners should be referred for presumptive therapy. Partners also should be advised to abstain from intercourse until they and their sex partners have been treated and any symptoms have resolved. EPT might have a role in partner management for trichomoniasis (*129*,*1116*) and can be used in states where permissible by law (https://www.cdc.gov/std/ept/legal/default.htm); however, no partner management intervention has been demonstrated to be superior in reducing reinfection rates (*129*,*130*). Although

no definitive data exist to guide treatment for partners of persons with persistent or recurrent trichomoniasis among whom nonadherence and reinfection are unlikely, partners might benefit from being evaluated and receiving treatment (see Recurrent Trichomoniasis).

Recurrent Trichomoniasis

A recurrent infection can result from treatment failure (antimicrobial-resistant *T. vaginalis* or host-related problems), lack of adherence, or reinfection from an untreated sex partner. In the case of a recurrent infection, the origin of the repeat infection should be assessed because most recurrent infections likely result from reinfection. Retesting can be considered in cases of persistent or recurrent trichomoniasis with culture, the preferred test. If NAAT is used, it should not be conducted before 3 weeks after treatment completion because of possible detection of residual nucleic acid that is not clinically relevant (*1117*).

The nitroimidazoles are the only class of antimicrobials known to be effective against trichomonas infection. Metronidazole resistance occurs in 4%–10% of cases of vaginal trichomoniasis (*1116*,*1118*). Tinidazole resistance is less well studied but was present in 1% of infections in one study (*1116*). Overall, more *T. vaginalis* isolates have reported susceptibility to tinidazole than metronidazole (*1119*). Multidose oral metronidazole is more effective than single-dose treatment, particularly for women who are symptomatic or have a history of *T. vaginalis* (*1120*).

Nitroimidazole-resistant trichomoniasis is concerning because few alternatives to standard therapy exist. If treatment failure occurs in a woman after completing a regimen of metronidazole 500 mg 2 times/day for 7 days and she has been reexposed to an untreated partner, a repeat course of the same regimen is recommended. If no reexposure has occurred, she should be treated with metronidazole or tinidazole 2 g once daily for 7 days. If a man has persistent *T. vaginalis* after a single 2-g dose of metronidazole and has been reexposed to an untreated partner, he should be retreated with a single 2-g dose of metronidazole. If he has not been reexposed, he should be administered a course of metronidazole 500 mg 2 times/day for 7 days.

For persons who are experiencing persistent infection not attributable to reexposure, clinicians should request a kit from CDC to perform drug-resistance testing (https://www.cdc.gov/laboratory/specimen-submission/detail.html?CDCTestCode=CDC-10239). CDC is experienced with susceptibility testing for nitroimidazole-resistant *T. vaginalis* and can provide guidance regarding treatment in cases of drug resistance. On the basis of drug resistance testing, an alternative treatment regimen might be recommended. Treatments for infections demonstrating in vitro resistance can include metronidazole or tinidazole 2 g daily for 7 days. If a patient has treatment failure after the 7-day regimen of high-dose oral metronidazole or tinidazole, two additional treatment options have been determined to have successful results for women. The first is high-dose oral tinidazole 2 g daily plus intravaginal tinidazole 500 mg 2 times/day for 14 days (*1121*). If this regimen fails, high-dose oral tinidazole (1 g 3 times/day) plus intravaginal paromomycin (4 g of 6.25% intravaginal paromomycin cream nightly) for 14 days should be considered (*1122*).

Alternative regimens might be effective but have not been systemically evaluated; therefore, consultation with an infectious disease specialist is recommended. Clinical improvement has been reported with intravaginal boric acid (*1123,1124*) but not with nitazoxanide (*1123–1125*). The following topically applied agents have minimal success (<50%) and are not recommended: intravaginal betadine (povidone-iodine), clotrimazole, acetic acid, furazolidone, GV, nonoxynol-9, and potassium permanganate (*1126*). No other topical microbicide has been reported to be effective against trichomoniasis.

Special Considerations

Drug Allergy, Intolerance, and Adverse Reactions

Metronidazole and tinidazole are both nitroimidazoles. Patients with an IgE-mediated-type hypersensitivity reaction to 5-nitroimidazole antimicrobials should be managed by metronidazole desensitization according to published regimens (*1127*,*1128*) and in consultation with an allergy specialist. The optimal treatment for patients with *T. vaginalis* who are unable to be desensitized has not been systematically investigated and is based on case reports, some of which report using paromomycin or boric acid for treating *T. vaginalis* (*1123*,*1129*).

Pregnancy

T. vaginalis infection among pregnant women is associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm delivery, and delivery of infants who are small for gestational age (*1075*). One randomized trial of pregnant women with asymptomatic trichomoniasis reported no substantial difference in preterm birth after treatment with 2 g of metronidazole 48 hours apart during 16–23 and 24–29 weeks' gestation, compared with placebo (*1130*). However, that trial had multiple limitations, including use of an atypical metronidazole regimen. Another multicenter observational study of asymptomatic pregnant women in sub-Sahara African, the majority with HIV infection, reported neither trichomoniasis nor its treatment appeared to influence the risk for preterm birth or a low-birthweight infant (*1131*).

Although metronidazole crosses the placenta, data indicate that it poses a low risk to the developing fetus (*1040*,*1042*,*1132*). No evidence of teratogenicity or mutagenic effects among infants has been found in multiple cross-sectional and cohort studies among pregnant women examining single-dose (2 g) and multidose metronidazole regimens (*1040*,*1131–1135*).

Symptomatic pregnant women, regardless of pregnancy stage, should be tested and treated. Treatment of *T. vaginalis* infection can relieve symptoms of vaginal discharge for pregnant women and reduce sexual transmission to partners. Although perinatal transmission of trichomoniasis is uncommon, treatment might also prevent respiratory or genital infection in the newborn (*1136*,*1137*). Clinicians should counsel symptomatic pregnant women with trichomoniasis about the potential risks and benefits of treatment and about the importance of partner treatment and condom use in the prevention of sexual transmission. The benefit of routine screening for *T. vaginalis* in asymptomatic pregnant women has not been established.

Metronidazole is secreted in breast milk. With maternal oral therapy, breastfed infants receive metronidazole in doses that are lower than those used to treat infections among infants, although the active metabolite adds to the total infant exposure. Plasma levels of the drug and metabolite are measurable but remain less than maternal plasma levels (https://www.ncbi.nlm.nih.gov/books/NBK501922). Although multiple reported case series studies demonstrated no evidence of adverse effects among infants exposed to metronidazole in breast milk, clinicians sometimes advise deferring breastfeeding for 12–24 hours after maternal treatment with metronidazole (*1051*). In one study, maternal treatment with metronidazole (400 mg 3 times/day for 7 days) produced a lower concentration in breast milk and was considered compatible with breastfeeding over longer periods (*1052*).

Data from studies involving human subjects are limited regarding tinidazole use during pregnancy; however, animal data indicate this drug poses moderate risk. Thus, tinidazole should be avoided for pregnant women, and breastfeeding should be deferred for 72 hours after a single 2-g oral dose of tinidazole (https://www.ncbi.nlm.nih.gov/books/NBK501922).

HIV Infection

Up to 53% of women with HIV have *T. vaginalis* infection (*1115*,*1138*). *T. vaginalis* infection among these women is substantially associated with pelvic inflammatory disease (*1082*). Among women who are not virally suppressed, treatment of trichomoniasis is associated with decreases in genital tract HIV viral load and viral shedding (*1079*,*1139*); however, no difference might occur among women who are virally suppressed (*1140*). Because of the high prevalence of *T. vaginalis* among women with HIV and the potential for adverse reproductive health, poor birth outcomes, and possibly amplified HIV transmission, routine screening and prompt treatment are recommended for all women with HIV infection; screening should occur at entry to care and then at least annually thereafter.

A randomized clinical trial involving women with HIV and *T. vaginalis* infection demonstrated that a single dose of metronidazole 2 g orally was less effective than 500 mg 2 times/day for 7 days (*1105*). Factors that might interfere with standard single-dose treatment for trichomoniasis among women with HIV include high rates of asymptomatic BV infection, ART use, changes in vaginal ecology, and impaired immunity (*1141*). Thus, to improve cure rates, women with HIV who receive a diagnosis of *T. vaginalis* infection should be treated with metronidazole 500 mg orally 2 times/day for 7 days. For pregnant women with HIV, screening at the first prenatal visit and prompt treatment, as needed, are recommended because *T. vaginalis* infection is a risk factor for vertical transmission of HIV (*1142*).

Treatment

Treatment reduces symptoms and signs of *T. vaginalis* infection, cures infection, and might reduce transmission. Likelihood of adverse outcomes among women with HIV infection is also reduced with *T. vaginalis* therapy.

Recommended Regimen for Trichomonas and HIV Infection Among Women
Metronidazole 500 mg orally 2 times/day for 7 days

If a woman with HIV infection experiences treatment failure, the protocol outlined is recommended (see Recurrent Trichomonas). Other management considerations, follow-up, and management of sex partners should be performed as for women without HIV infection. Treatment of men with HIV infection should follow the same guidelines as for men without HIV.

For women with HIV who receive a diagnosis of *T. vaginalis* infection, retesting is recommended 3 months after treatment; NAAT is encouraged because of higher sensitivity of these tests. Data are insufficient to support retesting of men with trichomonas and HIV infection.

Vulvovaginal Candidiasis

VVC usually is caused by *Candida albicans* but can occasionally be caused by other *Candida* species or yeasts. Typical symptoms of VVC include pruritus, vaginal soreness, dyspareunia, external dysuria, and abnormal vaginal discharge. None of these symptoms is specific for VVC. An estimated 75% of women will have at least one episode of VVC, and 40%–45% will have two or more episodes. On the basis of

clinical presentation, microbiology, host factors, and response to therapy, VVC can be classified as either uncomplicated or complicated (Box 4). Approximately 10%–20% of women will have complicated VVC, requiring special diagnostic and therapeutic considerations.

Uncomplicated Vulvovaginal Candidiasis

Diagnostic Considerations

A diagnosis of *Candida* vaginitis is clinically indicated by the presence of external dysuria and vulvar pruritus, pain, swelling, and redness. Signs include vulvar edema, fissures, excoriations, and thick curdy vaginal discharge. Most healthy women with uncomplicated VVC have no identifiable precipitating factors. The diagnosis can be made in a woman who has signs and symptoms of vaginitis when either a wet preparation (saline, 10% KOH) of vaginal discharge demonstrates budding yeasts, hyphae, or pseudohyphae, or a culture or other test yields a positive result for a yeast species. *Candida* vaginitis is associated with normal vaginal pH (<4.5). Use of 10% KOH in wet preparations improves the visualization of yeast and mycelia by disrupting cellular material that might obscure the yeast or pseudohyphae. Examination of a wet mount with KOH preparation should be performed for all women with symptoms or signs of VVC, and women with a positive result should be treated. For those with negative wet mounts but existing signs or symptoms, vaginal cultures for *Candida* should be considered. If *Candida* cultures cannot be performed for these women, empiric treatment can be considered. Identifying *Candida* by culture in the absence of symptoms or signs is not an indication for treatment because approximately 10%–20% of women harbor *Candida* species and other yeasts in the vagina. The majority of PCR tests for yeast are not FDA cleared, and providers who use these tests should be familiar with the performance characteristics of the specific test used. Yeast culture, which can identify a broad group of pathogenic yeasts, remains the reference standard for diagnosis.

BOX 4. Classification of vulvovaginal candidiasis

Uncomplicated vulvovaginal candidiasis (VVC)

- Sporadic or infrequent VVC
  and
- Mild-to-moderate VVC
  and
- Likely to be *Candida albicans*
  and
- Nonimmunocompromised women

Complicated VVC

- Recurrent VVC (three or more episodes of symptomatic VVC in <1 year)
  or
- Severe VVC
  or
- Non–*albicans* candidiasis
  or
- Women with diabetes, immunocompromising conditions (e.g., HIV infection), underlying immunodeficiency, or immunosuppressive therapy (e.g., corticosteroids)

Source: Sobel JD, Faro S, Force RW, et al. Vulvovaginal candidiasis: epidemiologic, diagnostic, and therapeutic considerations. Am J Obstet Gynecol 1998;178:203–11.

Treatment

Short-course topical formulations (i.e., single dose and regimens of 1–3 days) effectively treat uncomplicated VVC. Treatment with azoles results in relief of symptoms and negative cultures in 80%–90% of patients who complete therapy.

Recommended Regimens for Vulvovaginal Candidiasis

Over-the-Counter Intravaginal Agents
Clotrimazole 1% cream 5 g intravaginally daily for 7–14 days
or
Clotrimazole 2% cream 5 g intravaginally daily for 3 days
or
Miconazole 2% cream 5 g intravaginally daily for 7 days
or
Miconazole 4% cream 5 g intravaginally daily for 3 days
or
Miconazole 100 mg vaginal suppository one suppository daily for 7 days
or
Miconazole 200 mg vaginal suppository one suppository for 3 days
or
Miconazole 1,200 mg vaginal suppository one suppository for 1 day
or
Tioconazole 6.5% ointment 5 g intravaginally in a single application

Prescription Intravaginal Agents
Butoconazole 2% cream (single-dose bioadhesive product) 5 g intravaginally in a single application
or
Terconazole 0.4% cream 5 g intravaginally daily for 7 days
or
Terconazole 0.8% cream 5 g intravaginally daily for 3 days
or
Terconazole 80 mg vaginal suppository one suppository daily for 3 days

Oral Agent
Fluconazole 150 mg orally in a single dose

The creams and suppositories in these regimens are oil based and might weaken latex condoms and diaphragms. Patients should refer to condom product labeling for further information. Even women who have previously received a diagnosis of VVC by a clinician are not necessarily more likely to be able to diagnose themselves; therefore, any woman whose symptoms persist after using an over-the-counter preparation or who has a recurrence of symptoms <2 months

after treatment for VVC should be evaluated clinically and tested. Unnecessary or unapproved use of over-the-counter preparations is common and can lead to a delay in treatment of other vulvovaginitis etiologies, which can result in adverse outcomes. No substantial evidence exists to support using probiotics or homeopathic medications for treating VVC.

Follow-Up

Follow-up typically is not required. However, women with persistent or recurrent symptoms after treatment should be instructed to return for follow-up visits.

Management of Sex Partners

Uncomplicated VVC is not usually acquired through sexual intercourse, and data do not support treatment of sex partners. A minority of male sex partners have balanitis, characterized by erythematous areas on the glans of the penis in conjunction with pruritus or irritation. These men benefit from treatment with topical antifungal agents to relieve symptoms.

Special Considerations

Drug Allergy, Intolerance, and Adverse Reactions

Topical agents usually cause no systemic side effects, although local burning or irritation might occur. Oral azoles occasionally cause nausea, abdominal pain, and headache. Therapy with the oral azoles has rarely been associated with abnormal elevations of liver enzymes. Clinically important interactions can occur when oral azoles are administered with other drugs (*1141*).

Complicated Vulvovaginal Candidiasis

Diagnostic Considerations

Vaginal culture or PCR should be obtained from women with complicated VVC to confirm clinical diagnosis and identify non–*albicans Candida*. *Candida glabrata* does not form pseudohyphae or hyphae and is not easily recognized on microscopy. *C. albicans* azole resistance is becoming more common in vaginal isolates (*1144*,*1145*), and non–*albicans Candida* is intrinsically resistant to azoles; therefore, culture and susceptibility testing should be considered for patients who remain symptomatic.

Recurrent Vulvovaginal Candidiasis

Recurrent VVC, usually defined as three or more episodes of symptomatic VVC in <1 year, affects <5% of women but carries a substantial economic burden (*1146*). Recurrent VVC can be either idiopathic or secondary (related to frequent antibiotic use, diabetes, or other underlying host factors). The pathogenesis of recurrent VVC is poorly understood, and the majority of women with recurrent VVC have no apparent predisposing or underlying conditions. *C. glabrata* and other non–*albicans Candida* species are observed in 10%–20% of women with recurrent VVC. Conventional antimycotic therapies are not as effective against these non–*albicans* yeasts as against *C. albicans*.

Treatment

Most episodes of recurrent VVC caused by *C. albicans* respond well to short-duration oral or topical azole therapy. However, to maintain clinical and mycologic control, a longer duration of initial therapy (e.g., 7–14 days of topical therapy or a 100-mg, 150-mg, or 200-mg oral dose of fluconazole every third day for a total of 3 doses [days 1, 4, and 7]) is recommended, to attempt mycologic remission, before initiating a maintenance antifungal regimen.

Oral fluconazole (i.e., a 100-mg, 150-mg, or 200-mg dose) weekly for 6 months is the indicated maintenance regimen. If this regimen is not feasible, topical treatments used intermittently can also be considered. Suppressive maintenance therapies are effective at controlling recurrent VVC but are rarely curative long-term (*1147*). Because *C. albicans* azole resistance is becoming more common, susceptibility tests, if available, should be obtained among symptomatic patients who remain culture positive despite maintenance therapy. These women should be managed in consultation with a specialist.

Severe Vulvovaginal Candidiasis

Severe VVC (i.e., extensive vulvar erythema, edema, excoriation, and fissure formation) is associated with lower clinical response rates among patients treated with short courses of topical or oral therapy. Either 7–14 days of topical azole or 150 mg of fluconazole in two sequential oral doses (second dose 72 hours after initial dose) is recommended.

Non–*albicans* Vulvovaginal Candidiasis

Because approximately 50% of women with a positive culture for non–*albicans Candida* might be minimally symptomatic or have no symptoms, and because successful treatment is often difficult, clinicians should make every effort to exclude other causes of vaginal symptoms for women with non–*albicans* yeast (*1148*). The optimal treatment of non–*albicans* VVC remains unknown; however, a longer duration of therapy (7–14 days) with a nonfluconazole azole regimen (oral or topical) is recommended. If recurrence occurs, 600 mg of boric acid in a gelatin capsule administered vaginally once daily for 3 weeks is indicated. This regimen has clinical and mycologic eradication rates of approximately 70% (*1149*). If symptoms recur, referral to a specialist is advised.

Management of Sex Partners

No data exist to support treating sex partners of patients with complicated VVC. Therefore, no recommendation can be made.

Special Considerations

Compromised Host

Women with underlying immunodeficiency, those with poorly controlled diabetes or other immunocompromising conditions (e.g., HIV), and those receiving immunosuppression therapy (e.g., corticosteroid treatment) might not respond as well to short-term therapies. Efforts to correct modifiable conditions should be made, and more prolonged (i.e., 7–14 days) conventional treatment is necessary.

Pregnancy

VVC occurs frequently during pregnancy. Only topical azole therapies, applied for 7 days, are recommended for use among pregnant women. Epidemiologic studies indicate a single 150-mg dose of fluconazole might be associated with spontaneous abortion (*1150*) and congenital anomalies; therefore, it should not be used (*1151*).

HIV Infection

Vaginal *Candida* colonization rates among women with HIV infection are higher than among women without HIV with similar demographic and risk behavior characteristics, and the colonization rates correlate with increasing severity of immunosuppression (*1152*). Symptomatic VVC is also more frequent among women with HIV infection and similarly correlates with severity of immunodeficiency (*1153*). In addition, among women with HIV, systemic azole exposure is associated with isolation of non–*albicans Candida* species from the vagina.

Treatment for uncomplicated and complicated VVC among women with HIV infection should not differ from that for women who do not have HIV. Although long-term prophylactic therapy with fluconazole 200 mg weekly has been effective in reducing *C. albicans* colonization and symptomatic VVC (*1154*), this regimen is not recommended for women with HIV infection in the absence of complicated VVC (*98*). Although VVC is associated with increased HIV seroconversion among HIV-negative women and increased HIV cervicovaginal levels among women with HIV infection, the effect of treatment for VVC on HIV acquisition and transmission remains unknown.

Pelvic Inflammatory Disease

PID comprises a spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis (*1155–1157*). Sexually transmitted organisms, especially *N. gonorrhoeae* and *C. trachomatis*, often are implicated. Recent studies report that the proportion of PID cases attributable to *N. gonorrhoeae* or *C. trachomatis* is decreasing; of women who received a diagnosis of acute PID, approximately 50% have a positive test for either of those organisms (*1158–1160*). Micro-organisms that comprise the vaginal flora, such as strict and facultative anaerobes (*1160*) and *G. vaginalis*, *H. influenzae*, enteric gram-negative rods, and *Streptococcus agalactiae,* have been associated with PID (*1161*). In addition, cytomegalovirus (CMV), *T. vaginalis*, *M. hominis*, and *U. urealyticum* might be associated with certain PID cases (*1072*). Data also indicate that *M. genitalium* might have a role in PID pathogenesis (*765*,*928*) and might be associated with milder symptoms (*919*,*923*,*928*), although one study failed to demonstrate a substantial increase in PID after detection of *M. genitalium* in the lower genital tract (*925*).

Screening and treating sexually active women for chlamydia and gonorrhea reduces their risk for PID (*1162*,*1163*). Although BV is associated with PID, whether PID incidence can be reduced by identifying and treating women with BV is unclear (*1161*). Whether screening young women for *M. genitalium* is associated with a reduction in PID is unknown.

Diagnostic Considerations

Acute PID is difficult to diagnose because of the considerable variation in symptoms and signs associated with this condition. Women with PID often have subtle or nonspecific symptoms or are asymptomatic. Delay in diagnosis and treatment probably contributes to inflammatory sequelae in the upper genital tract. Laparoscopy can be used to obtain a more accurate diagnosis of salpingitis and a more complete bacteriologic diagnosis. However, this diagnostic tool frequently is not readily available, and its use is not easily justifiable when symptoms are mild or vague. Moreover, laparoscopy will not detect endometritis and might not detect subtle inflammation of the fallopian tubes. Consequently, a PID diagnosis usually is based on imprecise clinical findings (*1164–1166*).

Data indicate that a clinical diagnosis of symptomatic PID has a positive predictive value for salpingitis of 65%–90%, compared with laparoscopy (*1167–1170*). The positive predictive value of a clinical diagnosis of acute PID depends on the epidemiologic characteristics of the population, with higher positive predictive values among sexually active young women (particularly adolescents), women attending STD clinics, and

those who live in communities with high rates of gonorrhea or chlamydia. Regardless of positive predictive value, no single historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of acute PID. Combinations of diagnostic findings that improve either sensitivity (i.e., detect more women who have PID) or specificity (i.e., exclude more women who do not have PID) do so only at the expense of the other. For example, requiring two or more findings excludes more women who do not have PID and reduces the number of women with PID who are identified.

Episodes of PID often go unrecognized. Although certain cases are asymptomatic, others are not diagnosed because the patient or the health care provider do not recognize the implications of mild or nonspecific symptoms or signs (e.g., abnormal bleeding, dyspareunia, and vaginal discharge). Even women with mild or asymptomatic PID might be at risk for infertility (*1157*). Because of the difficulty of diagnosis and the potential for damage to the reproductive health of women, health care providers should maintain a low threshold for the clinical diagnosis of PID (*1158*). The recommendations for diagnosing PID are intended to assist health care providers to recognize when PID should be suspected and when additional information should be obtained to increase diagnostic certainty. Diagnosis and management of other causes of lower abdominal pain (e.g., ectopic pregnancy, acute appendicitis, ovarian cyst, ovarian torsion, or functional pain) are unlikely to be impaired by initiating antimicrobial therapy for PID. Presumptive treatment for PID should be initiated for sexually active young women and other women at risk for STIs if they are experiencing pelvic or lower abdominal pain, if no cause for the illness other than PID can be identified, or if one or more of the following three minimum clinical criteria are present on pelvic examination: cervical motion tenderness, uterine tenderness, or adnexal tenderness.

More specific criteria for diagnosing PID include endometrial biopsy with histopathologic evidence of endometritis; transvaginal sonography or magnetic resonance imaging techniques demonstrating thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies indicating pelvic infection (e.g., tubal hyperemia); and laparoscopic findings consistent with PID. A diagnostic evaluation that includes some of these more extensive procedures might be warranted in certain cases. Endometrial biopsy is warranted for women undergoing laparoscopy who do not have visual evidence of salpingitis because endometritis is the only sign of PID for certain women.

Requiring that all three minimum criteria be present before the initiation of empiric treatment can result in insufficient sensitivity for a PID diagnosis. After deciding whether to initiate empiric treatment, clinicians should also consider the risk profile for STIs. More elaborate diagnostic evaluation frequently is needed because incorrect diagnosis and management of PID might cause unnecessary morbidity. For example, the presence of signs of lower genital tract inflammation (predominance of leukocytes in vaginal secretions, cervical discharge, or cervical friability), in addition to one of the three minimum criteria, increases the specificity of the diagnosis. One or more of the following additional criteria can be used to enhance the specificity of the minimum clinical criteria and support a PID diagnosis:

- Oral temperature >38.3°C (>101°F)
- Abnormal cervical mucopurulent discharge or cervical friability
- Presence of abundant numbers of WBCs on saline microscopy of vaginal fluid
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*

The majority of women with PID have either mucopurulent cervical discharge or evidence of WBCs on a microscopic evaluation of a saline preparation of vaginal fluid (i.e., wet prep). If the cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, a PID diagnosis is unlikely, and alternative causes of pain should be considered. A wet prep of vaginal fluid also can detect the presence of concomitant infections (e.g., BV or trichomoniasis).

Treatment

PID treatment regimens should provide empiric, broad-spectrum coverage of likely pathogens. Multiple parenteral and oral antimicrobial regimens have been effective in achieving clinical and microbiologic cure in randomized clinical trials with short-term follow-up (*1171–1173*). However, only a limited number of studies have assessed and compared these regimens with regard to infection elimination in the endometrium and fallopian tubes or determined the incidence of long-term complications (e.g., tubal infertility and ectopic pregnancy) after antimicrobial regimens (*1159*,*1164*,*1174*). The optimal treatment regimen and long-term outcome of early treatment of women with subclinical PID are unknown. All regimens used to treat PID should also be effective against *N. gonorrhoeae* and *C. trachomatis* because negative endocervical screening for these organisms does not rule out upper genital tract infection. Anaerobic bacteria have been isolated from the upper genital tract of women who have PID, and data from in vitro studies have revealed that some anaerobes (e.g., *Bacteroides fragilis*) can cause tubal and epithelial destruction. BV is often present among women who have PID (*22*,*1160*,*1161*,*1175*).

Addition of metronidazole to IM or oral PID regimens more effectively eradicates anaerobic organisms from the upper genital tract (*1160*). Until treatment regimens that do not cover anaerobic microbes have been demonstrated to prevent long-term sequelae (e.g., infertility and ectopic pregnancy) as successfully as the regimens that are effective against these microbes, using regimens with anaerobic activity should be considered. Treatment should be initiated as soon as the presumptive diagnosis has been made because prevention of long-term sequelae is dependent on early administration of recommended antimicrobials. For women with PID of mild or moderate clinical severity, parenteral and oral regimens appear to have similar efficacy. The decision of whether hospitalization is necessary should be based on provider judgment and whether the woman meets any of the following criteria:

- Surgical emergencies (e.g., appendicitis) cannot be excluded
- Tubo-ovarian abscess
- Pregnancy
- Severe illness, nausea and vomiting, or oral temperature >38.5°C (101°F)
- Unable to follow or tolerate an outpatient oral regimen
- No clinical response to oral antimicrobial therapy

No evidence is available to indicate that adolescents have improved outcomes from hospitalization for treatment of PID, and the clinical response to outpatient treatment is similar among younger and older women. The decision to hospitalize adolescents with acute PID should be based on the same criteria used for older women.

Parenteral Treatment

Randomized trials have demonstrated the efficacy of parenteral regimens (*1160*,*1171*,*1172*,*1176*). Clinical experience should guide decisions regarding transition to oral therapy, which usually can be initiated within 24–48 hours of clinical improvement. For women with tubo-ovarian abscesses, >24 hours of inpatient observation is recommended.

Recommended Parenteral Regimens for Pelvic Inflammatory Disease

Ceftriaxone 1 g by every 24 hours
plus
Doxycycline 100 mg orally or IV every 12 hours
plus
Metronidazole 500 mg orally or IV every 12 hours
or
Cefotetan 2 g IV every 12 hours
plus
Doxycycline 100 mg orally or IV every 12 hours
or
Cefoxitin 2 g IV every 6 hours
plus
Doxycycline 100 mg orally or IV every 12 hours

Because of the pain associated with IV infusion, doxycycline should be administered orally when possible. Oral and IV administration of doxycycline and metronidazole provide similar bioavailability. Oral metronidazole is well absorbed and can be considered instead of IV for women without severe illness or tubo-ovarian abscess when possible. After clinical improvement with parenteral therapy, transition to oral therapy with doxycycline 100 mg 2 times/day and metronidazole 500 mg 2 times/day is recommended to complete 14 days of antimicrobial therapy.

Alternative Parenteral Regimens

Only limited data are available to support using other parenteral second- or third- generation cephalosporins (e.g., ceftizoxime or cefotaxime). Because these cephalosporins are less active than cefotetan or cefoxitin against anaerobic bacteria, the addition of metronidazole should be considered.

Ampicillin-sulbactam plus doxycycline has been investigated in at least one clinical trial and has broad-spectrum coverage (*1177*). Ampicillin-sulbactam plus doxycycline is effective against *C. trachomatis*, *N. gonorrhoeae*, and anaerobes for women with tubo-ovarian abscess. Another trial demonstrated short-term clinical cure rates with azithromycin monotherapy or combined with metronidazole (*1178*).

When using the clindamycin and gentamicin alternative parenteral regimen, women with clinical improvement after 24–28 hours can be transitioned to clindamycin (450 mg orally 4 times/day) or doxycycline (100 mg orally 2 times/day) to complete the 14-day therapy. However, when tubo-ovarian abscess is present, clindamycin (450 mg orally 4 times/day) or metronidazole (500 mg orally 2 times/day) should be used to complete 14 days of therapy with oral doxycycline to provide more effective anaerobic coverage.

Alternative Parenteral Regimens

Ampicillin-sulbactam 3 g IV every 6 hours
plus
Doxycycline 100 mg orally or IV every 12 hours
or
Clindamycin 900 mg IV every 8 hours
plus
Gentamicin loading dose IV or IM (2 mg/kg body weight), followed by a maintenance dose (1.5 mg/kg body weight) every 8 hours; single daily dosing (3–5 mg/kg body weight) can be substituted

Intramuscular or Oral Treatment

IM or oral therapy can be considered for women with mild-to-moderate acute PID because the clinical outcomes among women treated with these regimens are similar to those treated with IV therapy (*1158*). Women who do not respond to IM or

oral therapy within 72 hours should be reevaluated to confirm the diagnosis and be administered therapy IV.

Recommended Intramuscular or Oral Regimens for Pelvic Inflammatory Disease

Ceftriaxone 500 mg* IM in a single dose
plus
Doxycycline 100 mg orally 2 times/day for 14 days with **metronidazole** 500 mg orally 2 times/day for 14 days
or
Cefoxitin 2 g IM in a single dose and **probenecid** 1 g orally administered concurrently in a single dose
plus
Doxycycline 100 mg orally 2 times/day for 14 days with **metronidazole** 500 mg orally 2 times/day for 14 days
or
Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)
plus
Doxycycline 100 mg orally 2 times/day for 14 days with **metronidazole** 500 mg orally 2 times/day for 14 days

* For persons weighing ≥150 kg, 1 g of ceftriaxone should be administered.

These regimens provide coverage against frequent etiologic agents of PID; however, the optimal choice of a cephalosporin is unclear. Cefoxitin, a second-generation cephalosporin, has better anaerobic coverage than ceftriaxone, and, in combination with probenecid and doxycycline, has been effective in short-term clinical response among women with PID. Ceftriaxone has better coverage against *N. gonorrhoeae*. The addition of metronidazole to these regimens provides extended coverage against anaerobic organisms and will also effectively treat BV, which is frequently associated with PID.

Alternative Intramuscular or Oral Regimens

No data have been published regarding use of oral cephalosporins for treating PID. As a result of the emergence of quinolone-resistant *N. gonorrhoeae*, regimens that include a quinolone agent are not recommended for PID treatment. However, if the patient has cephalosporin allergy, the community prevalence and individual risk for gonorrhea are low, and follow-up is likely, alternative therapy can be considered. Use of either levofloxacin 500 mg orally once daily or moxifloxacin 400 mg orally once daily with metronidazole 500 mg orally 2 times/day for 14 days (*1179–1181*) or azithromycin 500 mg IV daily for 1–2 doses, followed by 250 mg orally daily in combination with metronidazole 500 mg 2 times/day for 12–14 days (*1178*), can be considered. Moxifloxacin is the preferred quinolone antimicrobial for *M. genitalium* infections; however, the importance of providing coverage for *M. genitalium* is unknown. Diagnostic tests for gonorrhea should be obtained before starting therapy, and persons should be managed as follows:

- If a culture for gonorrhea is positive, treatment should be based on results of antimicrobial susceptibility testing.
- If the isolate is determined to be quinolone-resistant *N. gonorrhoeae* or if antimicrobial susceptibility cannot be assessed (e.g., if only NAAT testing is available), consultation with an infectious disease specialist is recommended.

Other Management Considerations

To minimize disease transmission, women should be instructed to abstain from sexual intercourse until therapy is complete, symptoms have resolved, and sex partners have been treated (see Chlamydial Infections; Gonococcal Infections). All women who receive a diagnosis of PID should be tested for gonorrhea, chlamydia, HIV, and syphilis. The value of testing women with PID for *M. genitalium* is unknown (see *Mycoplasma genitalium)*. All contraceptive methods can be continued during treatment.

Follow-Up

Women should demonstrate clinical improvement (e.g., defervescence; reduction in direct or rebound abdominal tenderness; and reduction in uterine, adnexal, and cervical motion tenderness) <3 days after therapy initiation. If no clinical improvement has occurred <72 hours after outpatient IM or oral therapy, then hospitalization, assessment of the antimicrobial regimen, and additional diagnostics, including consideration of diagnostic laparoscopy for alternative diagnoses, are recommended. All women who have received a diagnosis of chlamydial or gonococcal PID should be retested 3 months after treatment, regardless of whether their sex partners have been treated (*753*). If retesting at 3 months is not possible, these women should be retested whenever they next seek medical care <12 months after treatment.

Management of Sex Partners

Persons who have had sexual contact with a partner with PID during the 60 days preceding symptom onset should be evaluated, tested, and presumptively treated for chlamydia and gonorrhea, regardless of the PID etiology or pathogens isolated. If the last sexual intercourse was >60 days before symptom onset or diagnosis, the most recent sex partner should be treated. Sex partners of persons who have PID caused by *C. trachomatis* or *N. gonorrhoeae* frequently are asymptomatic. Arrangements should be made to link sex partners to care. If linkage is delayed or unlikely, EPT is an alternative approach to treating sex partners who have chlamydial or gonococcal infection (*125*,*126*) (see Partner Services). Partners should be instructed to abstain from sexual intercourse until they

and their sex partners have been treated (i.e., until therapy is completed and symptoms have resolved, if originally present).

Special Considerations

Drug Allergy, Intolerance, and Adverse Reactions

The risk for penicillin cross-reactivity is highest with first-generation cephalosporins but is negligible between the majority of second-generation (e.g., cefoxitin) and all third-generation (e.g., ceftriaxone) cephalosporins (*619*,*631*,*653*,*656*) (see Management of Persons Who Have a History of Penicillin Allergy).

Pregnancy

Pregnant women suspected of having PID are at high risk for maternal morbidity and preterm delivery. These women should be hospitalized and treated with IV antimicrobials in consultation with an infectious disease specialist.

HIV Infection

Differences in PID clinical manifestations among women with HIV infection and those without have not been well delineated (*1182*). In early observational studies, women with HIV infection and PID were more likely to require surgical intervention. More comprehensive observational and controlled studies have demonstrated that women with HIV infection and PID coinfection have similar symptoms, compared with women without HIV (*1183–1185*), except they are more likely to have a tubo-ovarian abscess. Women with HIV responded equally well to recommended parenteral and IM or oral antibiotic regimens as women without HIV. The microbiologic findings for women with HIV and women without HIV were similar, except women with HIV had higher rates of concomitant *M. hominis* and streptococcal infections. These data are insufficient for determining whether women with HIV infection and PID coinfection require more aggressive management (e.g., hospitalization or IV antimicrobial regimens).

Intrauterine Devices

IUDs are one of the most effective contraceptive methods. Copper-containing and levonorgestrel-releasing IUDs are available in the United States. The risk for PID associated with IUD use is primarily confined to the first 3 weeks after insertion (*1186–1188*). If an IUD user receives a diagnosis of PID, the IUD does not need to be removed (*59*,*1189*). However, the woman should receive treatment according to these recommendations and should have close clinical follow-up. If no clinical improvement occurs within 48–72 hours of initiating treatment, providers should consider removing the IUD. A systematic review of evidence demonstrated that treatment outcomes did not differ between women with PID who retained the IUD and those who had the IUD removed (*1190*). These studies primarily included women using copper-containing or other nonhormonal IUDs. No studies are available regarding treatment outcomes among women using levonorgestrel-releasing IUDs.

Epididymitis

Acute epididymitis is a clinical syndrome causing pain, swelling, and inflammation of the epididymis and lasting <6 weeks (*1191*). Sometimes a testicle is also involved, a condition referred to as epididymo-orchitis. A high index of suspicion for spermatic cord (testicular) torsion should be maintained among men who have a sudden onset of symptoms associated with epididymitis because this condition is a surgical emergency.

Acute epididymitis can be caused by STIs (e.g., *C. trachomatis, N. gonorrhoeae,* or *M. genitalium*) or enteric organisms (i.e., *Escherichia coli*) (*1192*). Acute epididymitis caused by an STI is usually accompanied by urethritis, which is frequently asymptomatic. Acute epididymitis caused by sexually transmitted enteric organisms might also occur among men who are the insertive partner during anal sex. Nonsexually transmitted acute epididymitis caused by genitourinary pathogens typically occurs with bacteriuria secondary to bladder outlet obstruction (e.g., benign prostatic hyperplasia) (*1193*). Among older men, nonsexually transmitted acute epididymitis is also associated with prostate biopsy, urinary tract instrumentation or surgery, systemic disease, or immunosuppression. Uncommon infectious causes of nonsexually transmitted acute epididymitis (e.g., Fournier's gangrene) should be managed in consultation with a urologist.

Chronic epididymitis is characterized by a ≥6-week history of symptoms of discomfort or pain in the scrotum, testicle, or epididymis. Chronic infectious epididymitis is most frequently observed with conditions associated with a granulomatous reaction. *Mycobacterium tuberculosis* (TB) is the most common granulomatous disease affecting the epididymis and should be suspected, especially among men with a known history of or recent exposure to TB. The differential diagnosis of chronic noninfectious epididymitis, sometimes termed orchialgia or epididymalgia, is broad (e.g., trauma, cancer, autoimmune conditions, or idiopathic conditions). Men with this diagnosis should be referred to a urologist for clinical management (*1191*,*1192*).

Diagnostic Considerations

Men who have acute epididymitis typically have unilateral testicular pain and tenderness, hydrocele, and palpable swelling of the epididymis. Although inflammation and swelling usually begin in the tail of the epididymis, it can spread to the rest of the epididymis and testicle. The spermatic cord is usually tender and swollen. Spermatic cord (testicular) torsion, a surgical emergency, should be considered in all cases; however, it occurs more frequently among adolescents and men without evidence of inflammation or infection. For men with severe unilateral pain with sudden onset, those whose test results do not support a diagnosis of urethritis or urinary tract infection, or for whom diagnosis of acute epididymitis is questionable, immediate referral to a urologist for evaluation for testicular torsion is vital because testicular viability might be compromised.

Bilateral symptoms should increase suspicion of other causes of testicular pain. Radionuclide scanning of the scrotum is the most accurate method for diagnosing epididymitis but it is not routinely available. Ultrasound should be used primarily for ruling out torsion of the spermatic cord in cases of acute, unilateral, painful scrotal swelling. However, because partial spermatic cord torsion can mimic epididymitis on scrotal ultrasound, differentiation between spermatic cord torsion and epididymitis when torsion is not ruled out by ultrasound should be made on the basis of clinical evaluation. Although ultrasound can demonstrate epididymal hyperemia and swelling associated with epididymitis, it provides minimal diagnostic usefulness for men with a clinical presentation consistent with epididymitis. A negative ultrasound does not rule out epididymitis and thus does not alter clinical management. Ultrasound should be reserved for men if torsion of the spermatic cord is suspected or for those with scrotal pain who cannot receive an accurate diagnosis by history, physical examination, and objective laboratory findings.

All suspected cases of acute epididymitis should be evaluated for objective evidence of inflammation by one of the following POC tests:

- Gram, MB, or GV stain of urethral secretions demonstrating ≥2 WBCs per oil immersion field (*737*) (see Urethritis). These stains are preferred POC diagnostic tests for evaluating urethritis because they are highly sensitive and specific for documenting both urethral inflammation and presence or absence of gonococcal infection. Gonococcal infection is established by documenting the presence of WBC-containing intracellular gram-negative or purple diplococci on urethral Gram, MB, or GV stain, respectively.
- Positive leukocyte esterase test on first-void urine.
- Microscopic examination of sediment from a spun first-void urine demonstrating ≥10 WBCs/HPF.

All suspected cases of acute epididymitis should be tested for *C. trachomatis* and *N. gonorrhoeae* by NAAT. Urine is the preferred specimen for NAAT for men (*553*). Urine cultures for chlamydial and gonococcal epididymitis are insensitive and are not recommended. Urine bacterial cultures should also be performed for all men to evaluate for the presence of genitourinary organisms and to determine antibiotic susceptibility.

Treatment

To prevent complications and transmission of STIs, presumptive therapy for all sexually active men is indicated at the time of the visit before all laboratory test results are available. Selection of presumptive therapy is based on risk for chlamydial and gonococcal infections or enteric organisms. Treatment goals for acute epididymitis are 1) microbiologic infection cure, 2) improvement of signs and symptoms, 3) prevention of transmission of chlamydia and gonorrhea to others, and 4) decreased potential for chlamydial or gonococcal epididymitis complications (e.g., infertility or chronic pain). Although the majority of men with acute epididymitis can be treated on an outpatient basis, referral to a specialist and hospitalization should be considered when severe pain or fever indicates other diagnoses (e.g., torsion, testicular infarction, abscess, or necrotizing fasciitis) or when men are unable to comply with an antimicrobial regimen. Age, history of diabetes, fever, and elevated C-reactive protein can indicate more severe disease requiring hospitalization (*1193*).

Recommended Regimens for Epididymitis

For acute epididymitis most likely caused by chlamydia or gonorrhea:
Ceftriaxone 500 mg* IM in a single dose
plus
Doxycycline 100 mg orally 2 times/day for 10 days

For acute epididymitis most likely caused by chlamydia, gonorrhea, or enteric organisms (men who practice insertive anal sex):
Ceftriaxone 500 mg* IM in a single dose
plus
Levofloxacin 500 mg orally once daily for 10 days

For acute epididymitis most likely caused by enteric organisms only:
Levofloxacin 500 mg orally once daily for 10 days

* For persons weighing ≥150 kg, 1 g of ceftriaxone should be administered.

Levofloxacin monotherapy should be considered if the infection is most likely caused by enteric organisms only, and gonorrhea has been ruled out by Gram, MB, or GV stain. This includes men who have undergone prostate biopsy, vasectomy, and other urinary tract instrumentation procedures. Treatment

should be guided by bacterial cultures and antimicrobial susceptibilities. As an adjunct to therapy, bed rest, scrotal elevation, and nonsteroidal anti-inflammatory drugs are recommended until fever and local inflammation have subsided. Complete resolution of discomfort might not occur for a few weeks after completion of the antibiotic regimen.

Other Management Considerations

Men who have acute epididymitis confirmed or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* should be advised to abstain from sexual intercourse until they and their partners have been treated and symptoms have resolved. All men with acute epididymitis should be tested for HIV and syphilis.

Follow-Up

Men should be instructed to return to their health care providers if their symptoms do not improve <72 hours after treatment. Signs and symptoms of epididymitis that do not subside in <3 days require reevaluation of the diagnosis and therapy. Men who experience swelling and tenderness that persist after completion of antimicrobial therapy should be evaluated for alternative diagnoses, including tumor, abscess, infarction, testicular cancer, TB, and fungal epididymitis.

Management of Sex Partners

Men who have acute sexually transmitted epididymitis confirmed or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* should be instructed to refer all sex partners during the previous 60 days before symptom onset for evaluation, testing, and presumptive treatment (see Chlamydial Infections; Gonococcal Infections). If the last sexual intercourse was >60 days before onset of symptoms or diagnosis, the most recent sex partner should be evaluated and treated. Arrangements should be made to link sex partners to care. EPT is an effective strategy for treating sex partners of men who have or are suspected of having chlamydia or gonorrhea for whom linkage to care is anticipated to be delayed (*125*,*126*) (see Partner Services). Partners should be instructed to abstain from sexual intercourse until they and their sex partners are treated and symptoms have resolved.

Special Considerations

Drug Allergy, Intolerance, and Adverse Reactions

The risk for penicillin cross-reactivity is negligible between all third-generation cephalosporins (e.g., ceftriaxone) (*658*,*681*) (see Management of Persons Who Have a History of Penicillin Allergy). Alternative regimens have not been studied; therefore, clinicians should consult an infectious disease specialist if such regimens are required.

HIV Infection

Men with HIV infection who have uncomplicated acute epididymitis should receive the same treatment regimen as those who do not have HIV. Other etiologic agents have been implicated in acute epididymitis among men with HIV, including CMV, salmonella, toxoplasmosis, *U. urealyticum*, *Corynebacterium* species, *Mycoplasma* species, and *Mima polymorpha* (*1192*).

Human Papillomavirus Infections

Approximately 150 types of HPV have been identified, at least 40 of which infect the genital area (*1194*). The majority of HPV infections are self-limited and are asymptomatic or unrecognized. Sexually active persons are usually exposed to HPV during their lifetime (*838*,*1195*,*1196*). Oncogenic, high-risk HPV infection (e.g., HPV types 16 and 18) causes the majority of cervical, penile, vulvar, vaginal, anal, and oropharyngeal cancers and precancers (*1197*), whereas other HPV infection (e.g., HPV types 6 and 11) causes genital warts and recurrent respiratory papillomatosis. Persistent oncogenic HPV infection is the strongest risk factor for development of HPV-attributable precancers and cancers. A substantial proportion of cancers and anogenital warts are attributable to HPV in the United States. An estimated 34,800 new HPV-attributable cancers occurred every year during 2012–2016 (*1198*). Before HPV vaccines were introduced, approximately 355,000 new cases of anogenital warts occurred every year (*1199*).

Prevention

HPV Vaccines

Three HPV vaccines are licensed in the United States: Ceravrix, a 2-valent vaccine (2vHPV) that targets HPV types 16 and 18; Gardasil, a 4-valent vaccine (4vHPV) that targets HPV types 6, 11, 16, and 18; and Gardasil 9, a 9-valent vaccine (9vHPV) that targets HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. Types 16 and 18 account for 66% of all cervical cancers, whereas the five additional types targeted by the 9-valent vaccine account for 15%. Types 6 and 11 cause >90% of genital warts. Only 9vHPV vaccine is available in the United States.

ACIP recommendations for HPV vaccination (https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html) include the following:

- Routine HPV vaccination for all adolescents at age 11 or 12 years.
- Administering vaccine starting at age 9 years.
- Catch-up vaccination through age 26 years for those not vaccinated previously.
- Not using HPV vaccination for all adults aged >26 years. Instead, shared clinical decision-making between a patient and a provider regarding HPV vaccination is recommended for certain adults aged 27–45 years not vaccinated previously.
- A 2-dose vaccine schedule (at 0- and 6–12-month intervals) is recommended for persons who initiate vaccination before their 15th birthday.
- A 3-dose vaccine schedule (at 0-, 1–2-, and 6-month intervals) for immunocompromised persons regardless of age of initiation.

HPV vaccines are not recommended for use in pregnant women. HPV vaccines can be administered regardless of history of anogenital warts, abnormal Pap test or HPV test, or anogenital precancer. Women who have received HPV vaccine should continue routine cervical cancer screening (see Cervical Cancer). HPV vaccine is available for eligible children and adolescents aged <19 years through the Vaccines for Children (VFC) program (additional information is available at https://www.cdc.gov/vaccines/programs/vfc/index.html or by calling CDC INFO 800-232-4636). For uninsured persons aged <19 years, patient assistance programs are available from the vaccine manufacturers. Prelicensure and postlicensure safety evaluations have determined that the vaccine is well tolerated. With >120 million doses of HPV vaccines distributed in the United States, robust data demonstrate that HPV vaccines are safe (https://www.cdc.gov/vaccinesafety). Impact-monitoring studies in the United States have demonstrated reductions of genital warts as well as the HPV types contained within the quadrivalent vaccine (*1200–1203*). Settings that provide STI services should either administer the vaccine to eligible clients within the routine and catch-up age groups through age 26 years who have not started or completed the vaccine series, or link these persons to another facility equipped to provide the vaccine. Clinicians providing services to children, adolescents, and young adults should be knowledgeable about HPV and the vaccine (https://www.cdc.gov/vaccines/who/teens/for-hcp/hpv-resources.html). HPV vaccination has not been associated with initiation of sexual activity or sexual risk behaviors (*1204*,*1205*).

Abstaining from sexual activity is the most reliable method for preventing genital HPV infection. Persons can decrease their chances of infection by practicing consistent and correct condom use and limiting their number of sex partners. Although these interventions might not fully protect against HPV, they can decrease the chances of HPV acquisition and transmission.

Diagnostic Considerations

HPV tests are available for detecting oncogenic types of HPV infection and are used in the context of cervical cancer screening and management or follow-up of abnormal cervical cytology or histology (see Cervical Cancer). These tests should not be used for male partners of women with HPV or women aged <25 years, for diagnosis of genital warts, or as a general STI test.

Application of 3%–5% acetic acid, which might cause affected areas to turn white, has been used by certain providers to detect genital mucosa infected with HPV. The routine use of this procedure to detect mucosal changes attributed to HPV infection is not recommended because the results do not influence clinical management.

Treatment

Treatment is directed to the macroscopic (e.g., genital warts) or pathologic precancerous lesions caused by HPV. Subclinical genital HPV infection typically clears spontaneously; therefore, specific antiviral therapy is not recommended to eradicate HPV infection. Precancerous lesions are detected through cervical cancer screening; HPV-related precancer should be managed on the basis of existing guidance (see Cervical Cancer).

Counseling

Key Messages for Persons with Human Papillomavirus Infection

When counseling persons with anogenital HPV infection, the provider should discuss the following:

- Anogenital HPV infection is common. It usually infects the anogenital area but can infect other areas, including the mouth and throat. The majority of sexually active persons get HPV at some time during their lifetime, although most never know it.
- Partners tend to share HPV, and it is not possible to determine which partner transmitted the original infection. Having HPV does not mean that a person or his or her partner is having sex outside the relationship.
- Persons who acquire HPV usually clear the infection spontaneously, meaning that HPV becomes undetectable with no associated health problems.
- If HPV infection persists, genital warts, precancers, and cancers of the cervix, anus, penis, vulva, vagina, head, or neck might develop.
- Discussion of tobacco use, and provision of cessation counseling, is important because of its contribution to the progression of precancer and cancer.
- The types of HPV that cause genital warts are different from the types that can cause cancer.

- Many types of HPV are sexually transmitted through anogenital contact, mainly during vaginal and anal sex. HPV also might be transmitted during oral sex and genital-to-genital contact without penetration. In rare cases, a pregnant woman can transmit HPV to an infant during delivery.
- Treatments are available for the conditions caused by HPV but not for the virus itself.
- Having HPV does not make it harder for a woman to get pregnant or carry a pregnancy to term. However, certain precancers or cancers that HPV can cause, and the surgical procedures needed to treat them, can affect a woman's ability to get pregnant or carry a pregnancy to term.
- No HPV test can determine which HPV infection will become undetectable and which will persist or progress to disease. However, in certain circumstances, HPV tests can determine whether a woman is at increased risk for cervical cancer. These tests are not for detecting other HPV-related problems, nor are they useful for women aged<25 years or men of any age.

Prevention

- Three HPV vaccines can prevent diseases and cancers caused by HPV. The 2vHPV, 4vHPV, and 9vHPV vaccines protect against the majority of cervical cancer cases, although the 4vHPV and 9vHPV vaccines also protect against the majority of genital warts. Only 9vHPV vaccine is available in the United States. HPV vaccines are safe and effective and are recommended routinely for adolescents aged 11–12 years. Catch-up vaccination is also recommended for older adolescents and young adults through age 26 years (https://www.cdc.gov/hpv/hcp/index.html). Shared clinical decision-making is recommended regarding HPV vaccination for certain adults aged 27–45 years who are not adequately vaccinated per guidance (https://www.cdc.gov/mmwr/volumes/68/wr/pdfs/mm6832a3-H.pdf).
- Condoms used consistently and correctly can lower the chances of acquiring and transmitting HPV and developing HPV-related diseases (e.g., genital warts or cervical cancer). However, because HPV can infect areas not covered by a condom, condoms might not fully protect against HPV.
- Limiting the number of sex partners can reduce the risk for HPV. However, even persons with only one lifetime sex partner can get HPV.
- Abstaining from sexual activity is the most reliable method for preventing genital HPV infection.

Anogenital Warts

Anogenital warts are a common disease, and 90% are caused by nononcogenic HPV types 6 or 11. These types can be commonly identified before or at the same time anogenital warts are detected (*1206*). HPV types 16, 18, 31, 33, and 35 also are occasionally identified in anogenital warts (usually as infections with HPV 6 or 11) and can be associated with foci of high-grade squamous intraepithelial lesion (HSIL), particularly among persons who have HIV infection. In addition to anogenital warts, HPV types 6 and 11 have been associated with conjunctival, nasal, oral, and laryngeal warts.

Anogenital warts are usually asymptomatic; however, depending on the size and anatomic location, they can be painful or pruritic. They are usually flat, papular, or pedunculated growths on the genital mucosa. Anogenital warts occur commonly at certain anatomic sites, including around the vaginal introitus, under the foreskin of the uncircumcised penis, and on the shaft of the circumcised penis. Warts can also occur at multiple sites in the anogenital epithelium or within the anogenital tract (e.g., cervix, vagina, urethra, perineum, perianal skin, anus, or scrotum). Intra-anal warts are observed predominantly in persons who have had receptive anal intercourse; however, they also can occur among men and women who have not had a history of anal sexual contact.

Prevention

Anogenital warts have decreased among adolescents, young women, and heterosexual men with use of HPV vaccination in multiple countries, including the United States (*1203*,*1207–1216*).

Diagnostic Considerations

Diagnosis of anogenital warts is usually made by visual inspection but can be confirmed by biopsy, which is indicated if lesions are atypical (e.g., pigmented, indurated, affixed to underlying tissue, bleeding, or ulcerated lesions). Biopsy might also be indicated in the following circumstances, particularly if the patient is immunocompromised (including those with HIV infection): the diagnosis is uncertain, the lesions do not respond to standard therapy, or the disease worsens during therapy. HPV testing is not recommended for anogenital wart diagnosis because test results are not confirmatory and do not guide genital wart management. Some anogenital lesions can resemble anogenital warts (condyloma accuminata), but do not respond to anogenital wart treatment. Condyloma lata, a manifestation of secondary syphilis, can be diagnosed by serologic tests or through direct detection from serous fluid from the lesions (see Syphilis, Diagnostic Considerations).

Treatment

The aim of treatment is removal of the warts and amelioration of symptoms, if present. The appearance of warts also can result in considerable psychosocial distress, and removal can relieve cosmetic concerns. For most patients, treatment results in resolution of the warts. If left untreated, anogenital warts can resolve spontaneously, remain unchanged, or increase in size or number. Because warts might spontaneously resolve in <1 year, an acceptable alternative for certain persons is to forego treatment and wait for spontaneous resolution. Available therapies for anogenital warts might reduce, but probably do not eradicate, HPV infectivity. Whether reduction in HPV viral DNA resulting from treatment reduces future transmission remains unknown.

Treatment of anogenital warts should be guided by wart size, number, and anatomic site; patient preference; cost of treatment; convenience; adverse effects; and provider experience. No definitive evidence indicates that any one recommended treatment is superior to another, and no single treatment is ideal for all patients or all warts. Shared clinical decision-making between a patient and a provider regarding treatment algorithms has been associated with improved clinical outcomes and should be encouraged. Because all available treatments have shortcomings, clinicians sometimes use combination therapy (e.g., provider-administered cryotherapy with patient-applied topical therapy between visits to the provider). However, limited data exist regarding the efficacy or risk for complications associated with combination therapy. Treatment regimens are classified as either patient-applied or provider-administered modalities. Patient-applied modalities are preferred by certain persons because they can be administered in the privacy of their home. To ensure that patient-applied modalities are effective, instructions should be provided to patients while in the clinic, and all anogenital warts should be accessible and identified during the clinic visit. Follow-up visits after weeks of therapy enable providers to answer any questions about use of the medication, address any side effects experienced, and facilitate assessment of the response to treatment.

Recommended Regimens for External Anogenital Warts (i.e., Penis, Groin, Scrotum, Vulva, Perineum, External Anus, or Perianus)*

Patient-applied: Imiquimod 3.75% or 5% cream†
or
Podofilox 0.5% solution or gel
or
Sinecatechins 15% ointment†

Provider-administered: Cryotherapy with liquid nitrogen or cryoprobe
or
Surgical removal by tangential scissor excision, tangential shave excision, curettage, laser, or electrosurgery
or
Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution

* Persons with external anal or perianal warts might also have intra-anal warts. Thus, persons with external anal warts might benefit from an inspection of the anal canal by digital examination, standard anoscopy, or high-resolution anoscopy.
† Might weaken condoms and vaginal diaphragms.

Imiquimod is a patient-applied, topically active immune enhancer that stimulates production of interferon and other cytokines. Imiquimod 5% cream should be applied once at bedtime, 3 times/week for <16 weeks (*1217*). Similarly, imiquimod 3.75% cream should be applied once at bedtime every night for <8 weeks (*1218*). With either formulation, the treatment area should be washed with soap and water 6–10 hours after the application. Local inflammatory reactions, including redness, irritation, induration, ulceration or erosion, and vesicles might occur with using imiquimod, and hypopigmentation has also been described (*1219*). Limited case reports demonstrate an association between treatment with imiquimod cream and worsened inflammatory or autoimmune skin diseases (e.g., psoriasis, vitiligo, or lichenoid dermatoses) (*1220–1222*). Data from studies of human participants are limited regarding use of imiquimod during pregnancy; however, animal data indicate that this therapy poses low risk (*431*).

Podofilox (podophyllotoxin) is a patient-applied antimitotic drug that causes wart necrosis. Podofilox solution (using a cotton swab) or podofilox gel (using a finger) should be applied to anogenital warts 2 times/day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, for up to four cycles. The total wart area treated should not exceed 10 cm^2, and the total volume of podofilox should be limited to 0.5 mL/day. If possible, the health care provider should apply the initial treatment to demonstrate proper application technique and identify which warts should be treated. Mild to moderate pain or local irritation might develop after treatment. After each treatment, the gel or solution should be allowed to dry. Patients should wash their hands before and after each application. Podofilox is contraindicated during pregnancy (*431*).

Sinecatechins is a patient-applied, green-tea extract with an active product (catechins). Sinecatechins 15% ointment should be applied 3 times/day (0.5-cm strand of ointment to each wart) by using a finger to ensure coverage with a thin layer of ointment until complete clearance of warts is achieved. This product should not be continued for >16 weeks (*1223–1225*). The medication should not be washed off after use. Genital, anal, and oral sexual contact should be avoided while the ointment is on the skin. The most common side effects of sinecatechins are erythema, pruritus or burning, pain, ulceration, edema, induration, and vesicular

rash. This medication is not recommended for persons with HIV infection, other immunocompromised conditions, or genital herpes because the safety and efficacy of therapy has not been evaluated. The safety of sinecatechins during pregnancy is unknown.

Cryotherapy is a provider-administered therapy that destroys warts by thermal-induced cytolysis. Health care providers should be trained on the correct use of this therapy because overtreatment or undertreatment can result in complications or low efficacy. Pain during and after application of the liquid nitrogen, followed by necrosis and sometimes blistering, is common. Local anesthesia (topical or injected) might facilitate therapy if warts are present in many areas or if the area of warts is large. Surgical therapy has the advantage of eliminating the majority of warts at a single visit, although recurrence can occur. Surgical removal requires substantial clinical training, additional equipment, and sometimes a longer office visit. After local anesthesia is applied, anogenital warts can be physically destroyed by electrocautery, in which case no additional hemostasis is required. Care should be taken to control the depth of electrocautery to prevent scarring. Alternatively, the warts can be removed either by tangential excision with a pair of fine scissors or a scalpel, by CO_2 laser, or by curettage. Because most warts are exophytic, this procedure can be accomplished with a resulting wound that only extends into the upper dermis. Hemostasis can be achieved with an electrocautery unit or, in cases of minor bleeding, a chemical styptic (e.g., an aluminum chloride solution). Suturing is neither required nor indicated in the majority of cases. For patients with large or extensive warts, surgical therapy, including CO_2 laser, might be most beneficial; such therapy might also be useful for intraurethral warts, particularly for those persons whose warts have not responded to other treatments. Treatment of anogenital and oral warts should be performed in a ventilated room by using standard precautions (https://www.cdc.gov/infectioncontrol/guidelines/isolation/index.html/Isolation2007.pdf#page) and local exhaust ventilation (e.g., a smoke evacuator) (*1226*).

Trichloroacetic acid (TCA) and bichloroacetic acid (BCA) are provider-administered caustic agents that destroy warts by chemical coagulation of proteins. Although these preparations are widely used, they have not been investigated thoroughly. TCA solution has a low viscosity, comparable with that of water, and can spread rapidly and damage adjacent tissues if applied excessively. A small amount should be applied only to the warts and allowed to dry (i.e., develop white frost on tissue) before the patient sits or stands. If pain is intense or an excess amount of acid is applied, the area can be covered with sodium bicarbonate (i.e., baking soda), washed with liquid soap preparations, or be powdered with talc to neutralize the acid or remove unreacted acid. TCA or BCA treatment can be repeated weekly if necessary.

Alternative Regimens for External Genital Warts

Fewer data are available regarding the efficacy of alternative regimens for treating anogenital warts, which include podophyllin resin, intralesional interferon, photodynamic therapy, and topical cidofovir. Shared clinical decision-making between the patient and provider regarding benefits and risks of these regimens should be provided. In addition, alternative regimens might be associated with more side effects. Podophyllin resin is no longer a recommended regimen because of the number of safer regimens available, and severe systemic toxicity has been reported when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours (*1227–1229*). Podophyllin resin 10%–25% in a compound tincture of benzoin might be considered for provider-administered treatment under conditions of strict adherence to recommendations. Podophyllin should be applied to each wart and then allowed to air dry before the treated area comes into contact with clothing. Overapplication or failure to air dry can result in local irritation caused by spread of the compound to adjacent areas and possible systemic toxicity. The treatment can be repeated weekly, if necessary. To avoid the possibility of complications associated with systemic absorption and toxicity, application should be limited to <0.5 mL of podophyllin or an area of <10 cm^2 of warts per session; the area to which treatment is administered should not contain any open lesions, wounds, or friable tissue; and the preparation should be thoroughly washed off 1–4 hours after application. Podophyllin resin preparations differ in the concentration of active components and contaminants. Shelf life and stability of podophyllin preparations are unknown. The safety of podophyllin during pregnancy has not been established.

Recommended Regimens for Urethral Meatus Warts

Cryotherapy with liquid nitrogen
or
Surgical removal

Recommended Regimens for Vaginal Warts

Cryotherapy with liquid nitrogen

The use of a cryoprobe in the vagina is not recommended because of the risk for vaginal perforation and fistula formation.

or
Surgical removal
or
Trichloracetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution

Recommended Regimens for Cervical Warts

Cryotherapy with liquid nitrogen

or
Surgical removal
or
Trichloracetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution

Management of cervical warts should include consultation with a specialist. For women who have exophytic cervical warts, a biopsy evaluation to exclude HSIL should be performed before treatment is initiated.

Recommended Regimens for Intra-Anal Warts

Cryotherapy with liquid nitrogen
or
Surgical removal
or
Trichloracetic acid (TCA) or bichloroacetic acid (BCA) 80%–90% solution

Management of intra-anal warts should include consultation with a colorectal specialist.

Follow-Up

Anogenital warts typically respond within 3 months of therapy. Factors that might affect response to therapy include immunosuppression and treatment compliance. Warts located on moist surfaces or in intertriginous areas respond best to topical treatment. A new treatment modality should be selected when no substantial improvement is observed after a complete course of treatment or in the event of severe side effects; treatment response and therapy-associated side effects should be evaluated throughout the therapy course. Complications occur rarely when treatment is administered correctly. Persistent hypopigmentation or hyperpigmentation can occur with ablative modalities (e.g., cryotherapy and electrocautery) and have been described with immune modulating therapies (e.g., imiquimod cream). Depressed or hypertrophic scars are uncommon but can occur, especially if patients have insufficient time to heal between treatments. Rarely, treatment can result in chronic pain syndromes (e.g., vulvodynia and hyperesthesia of the treatment site) or, in the case of anal warts, painful defecation or fistulas.

Counseling

When counseling persons with anogenital warts, the provider should discuss the following:

- If left untreated, genital warts might resolve, stay the same, or increase in size or number. The types of HPV that cause genital warts are different from the types that can cause cancer.
- Women with genital warts do not need Pap tests more often than other women.
- Time of HPV acquisition cannot be definitively determined. Genital warts can develop months or years after acquiring HPV.
- HPV types that cause genital warts can be passed on to another person, even without visible signs of warts. Sex partners tend to share HPV, even though signs of HPV (e.g., warts) might occur in only one or neither partner.
- Although genital warts are common and benign, certain persons might experience considerable psychosocial impact after receiving this diagnosis.
- Although genital warts can be treated, such treatment does not cure the virus itself. For this reason, genital warts often recur after treatment, especially during the first 3 months.
- Because genital warts can be sexually transmitted, persons with genital warts benefit from testing for other STIs. HPV might remain present and can still be transmitted to partners even after the warts are gone.
- Condoms might lower the chances of transmitting genital warts if used consistently and correctly; however, HPV can infect areas that are not covered by a condom and might not fully protect against HPV.
- A vaccine is available for males and females to prevent genital warts (Gardasil 9) but it will not treat existing HPV or genital warts. This vaccine can prevent the majority of cases of genital warts among persons who have not yet been exposed to wart-causing types of HPV.

Management of Sex Partners

Persons should inform current partners about having genital warts because the types of HPV that cause warts can be passed on to partners. Partners should be counseled that they might already have HPV despite no visible signs of warts; therefore, HPV testing of sex partners of persons with genital warts is not recommended. Partners might benefit from a physical examination to detect genital warts and tests for other STIs. No recommendations can be made regarding informing future sex partners about a diagnosis of genital warts because the duration of viral persistence after warts have resolved is unknown.

Special Considerations

Pregnancy

Podofilox, podophyllin, and sinecatechins should not be used during pregnancy. Imiquimod appears to pose low risk but should be avoided until more data are available. Anogenital warts can proliferate and become friable during pregnancy. Although removal of warts during pregnancy can be considered, resolution might be incomplete or poor until pregnancy is complete. Rarely, HPV types 6 and 11 can cause respiratory papillomatosis among infants and children, although the route of transmission (i.e., transplacental, perinatal, or postnatal) is not completely understood. Whether cesarean delivery prevents respiratory papillomatosis among infants and children also

is unclear (*1230*); therefore, cesarean delivery should not be performed solely to prevent transmission of HPV infection to the newborn. Cesarean delivery is indicated for women with anogenital warts if the pelvic outlet is obstructed or if vaginal delivery would result in excessive bleeding. Pregnant women with anogenital warts should be counseled about the low risk for warts on the larynx of their infants or children (recurrent respiratory papillomatosis).

HIV and Other Causes of Immunosuppression

Persons with HIV infection or who are otherwise immunosuppressed are more likely to develop anogenital warts than those who do not have HIV (*1231*). Moreover, such persons can have larger or more numerous lesions, might not respond to therapy as well as those who are immunocompetent, and might have more frequent recurrences after treatment (*1231*,*1232*–*1234*). Despite these factors, data do not support altered approaches to treatment for persons with HIV infection. Squamous cell carcinomas arising in or resembling anogenital warts might occur more frequently among immunosuppressed persons, therefore requiring biopsy for confirmation of diagnosis for suspicious cases (*1235*–*1237*).

High-Grade Squamous Intraepithelial Lesions

Biopsy of an atypical wart might reveal HSIL or cancer of the anogenital tract. In this instance, referral to a specialist for treatment is recommended.

Cancers and Precancers Associated with Human Papillomavirus

Persistent infection with high-risk (oncogenic) types of HPV has a causal role in approximately all cervical cancers and in certain vulvar, vaginal, penile, anal, and oropharyngeal cancers (*1238*). However, cervical cancer is the only HPV-associated cancer for which routine screening is recommended.

Cervical Cancer

Screening Recommendations

Recommendations for cervical cancer screening in the United States are based on systematic evidence reviews by major medical and advocacy organizations, including USPSTF (*174*), ACS (*177*), and ACOG (*175*). Over time, general alignment across these organizations has emerged as to when to start and end cervical cancer screening as well as the periodicity of screening. Although no single guideline universally guides screening practices in the United States, the Patient Protection and Affordable Care Act required Medicaid and new private health insurance plans to provide coverage for preventive services graded A or B by USPSTF, which includes cervical cancer screening. In addition, the National Center for Quality Assurance provides a set of measures (the Healthcare Effectiveness Data and Information Set [HEDIS]) for up-to-date cervical cancer screening that aligns with USPSTF recommendations (https://www.ncqa.org/hedis/measures/cervical-cancer-screening). The Center for Medicaid and Medicare Services uses the same measure as HEDIS to measure cervical cancer screening performance.

USPSTF screening recommendations apply to persons with a cervix at average risk, defined as those with no previous cervical cancer or high-grade precancer, not currently under close follow-up for a recent abnormal result, not immunocompromised (e.g., persons with HIV), and who had no exposure to diethylstilbestrol in utero. Among these persons, screening should be performed starting at age 21 years and continue through age 65 years. Testing can be performed using either conventional or liquid-based cytologic tests (i.e., Pap tests). For persons aged ≥30 years, screening can include FDA-cleared tests for high-risk, oncogenic types of HPV. For cytopathologic testing, clinics should use CLIA-certified laboratories using acceptable terminology (Bethesda 2001 or LAST terminology) (*1239*).

Annual cervical cancer screening is not recommended for persons at average risk. Instead, cytology testing is recommended every 3 years for persons aged 21–29 years. For persons aged 30–65 years, a cytology test every 3 years, an HPV test alone every 5 years, or a cytology test plus an HPV test (cotest) every 5 years is recommended. Cotesting can be done by either collecting one sample for the cytology test and another for the HPV test or by using the remaining liquid cytology material for the HPV test. Cervical screening programs should screen those who have received HPV vaccination in the same manner as those that are unvaccinated. Screening is not recommended before age 21 years among those at average risk. For those aged 30–65 years, cytology alone or primary HPV testing is preferred by USPSTF; however, cotesting can be used as an alternative approach. ACOG (*1240*), ACS (*177*), and USPSTF (*174*) each have screening recommendations (*1241*) (Table 1).

Clinics should weigh the benefits of each screening strategy as well as their resources, such as time and cost, in deciding on which of the three possible screening strategies to implement. Decision analytic models (*1242*) estimating the benefits, harms, and costs (*1243*) of several different strategies might be useful in making this determination (*174*,*1244*,*1245*). Adopting recommended screening and follow-up procedures, including screening methods, results provision, and follow-up, can lead to success in implementing cervical cancer screening in clinics (*1246*).

Patients should be provided a copy of their test results; those with normal results should be provided information on follow-up visits and the importance of continued cervical

TABLE 1. Cervical cancer screening and surveillance recommendations

Population	Screening specifics	Guideline group, yr of recommendation		
		USPSTF, 2018	**ACOG, 2016**	**ACS, 2020**
Persons at average risk	Age to start screening	21 yrs	21 yrs	25 yrs
	Age to end screening	65 yrs	65 yrs	65 yrs
		If three consecutive negative cytology tests or two negative cytology plus HPV tests or two negative HPV tests (ACS) with the most recent within the previous 5 yrs and no abnormal tests within the previous 10 yrs (ACS) and no CIN 2 or CIN 3 within the previous 25 yrs		
	Screening test options and intervals	Aged 21–65 yrs: Cytology alone every 3 yrs ***or*** Aged 21–29 yrs: Cytology alone every 3 yrs Aged 30–65 yrs: Cytology plus HPV testing every 5 yrs ***or*** Aged 21–29 yrs: Cytology alone every 3 yrs Aged 30–65: HPV testing alone every 5 yrs*		HPV testing alone every 5 yrs ***or*** Cytology plus HPV testing every 5 yrs ***or*** Cytology alone every 3 yrs
	Preferred strategies	Cytology alone every 3 yrs and HPV testing alone every 5 yrs (equally preferred)	Cytology plus HPV testing every 5 yrs	HPV testing alone every 5 yrs
	Previous hysterectomy with removal of cervix	Screening not recommended after hysterectomy for benign indications Surveillance testing recommended for previous diagnosis of high-grade precancer, AIS, or cancer		
Persons with an immunocompromising medical condition† (e.g., HIV infection or solid organ transplantation)	Age to start screening	No specific recommendation	Within 1 yr of onset of sexual activity or, if already sexually active, within the first year after HIV or other immunocompromising medical condition diagnosis but no later than age 21 yrs	
	Age to end screening		None; lifelong screening recommended	
	Screening test options and intervals		Aged 21–65 yrs: Cytology every year; after three consecutive annual normal cytology test results, screening can be every 3 yrs ***or*** Aged 21–29 yrs: Cytology every year Aged 30–65 yrs: Cytology plus HPV testing every 3 yrs	
	Previous hysterectomy with removal of cervix		Not specified	
Persons with in utero exposure to diethylstilbestrol§	Age to start screening	No specific recommendation	Not specified	No specific recommendation
	Age to end screening		Not specified	
	Screening test options and intervals		Cytology alone annually	
	Previous hysterectomy with removal of cervix		Not specified	
Persons who have received HPV vaccination	No changes to the screening approaches above			
			ASCCP, 2019, and ACOG, 2020	
Persons with a diagnosis of CIN 2 or CIN 3 (histologic HSIL¶) within the previous 25 yrs	Age to start screening	Not applicable		
	Age to end screening	May end at age 65 yrs if CIN diagnosis ≥25 yrs ago and criteria for ending screening met, otherwise continue screening past age 65 yrs Continued screening for ≥25 yrs after diagnosis is acceptable if patient is in good health		
	Screening test options and intervals	**Initial surveillance:** HPV testing alone or cytology plus HPV testing at 6, 18, and 30 mos ***or*** Cytology at 6, 12, 18, 24, and 30 mos **Long-term surveillance:** HPV testing alone or cytology plus HPV testing every 3 yrs ***or*** Cytology alone annually Continue for ≥25 yrs from the initial CIN diagnosis, even if extends past age 65 yrs Routine screening can resume after the posttreatment surveillance period		
	Previous hysterectomy with removal of cervix	HPV testing alone or cytology plus HPV testing every 3 yrs ***or*** Cytology alone annually Continue for ≥25 yrs from the initial CIN diagnosis, even if extends past age 65 yrs		

Source: Perkins R, Guido R, Saraiya M, et al. Summary of current guidelines for cervical cancer screening and management of abnormal test results: 2016–2020. J Womens Health (Larchmt) 2021;30:5–13.

Abbreviations: ACS = American Cancer Society; ACOG = American College of Obstetricians and Gynecologists; AIS = adenocarcinoma in situ; ASCCP = American Society for Colposcopy and Cervical Pathology; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; USPSTF = U.S. Preventive Services Task Force.

* Considered an alternative screening strategy by ACOG.

† Panel for Opportunistic Infections, ACOG, 2016.

§ ACOG, 2016.

¶ Either by cytology or by histology; includes a persistent cytologic diagnosis of atypical squamous cells, cannot rule out HSIL.

cancer screening, if applicable. Those with abnormal screening tests should be managed per published guidelines. National consensus guidelines are available for the management of abnormal cervical cancer screening tests (*1247*). HPV testing or cotesting is preferred to cytology alone for surveillance after an abnormal screening test result. These guidelines base management recommendations on case-by-case assessment of risk considering past screening history and current results (see Follow-Up). Patients with abnormal cervical cancer screening test results should be counseled about those results (see Counseling Messages).

The following additional management considerations are associated with performing Pap tests and HPV tests:

- Cytology (Pap tests) and HPV tests should not be considered screening tests for STIs.
- All persons with a cervix should receive cervical cancer screening, regardless of sexual orientation or gender identity (i.e., those who identify as lesbian, bisexual, heterosexual, or transgender).
- A conventional cytology test (in which the sample is smeared onto a dry slide) should ideally be scheduled for 10–20 days after the first day of menses. Liquid-based cytology can be performed at any time during the menstrual cycle.
- If specific infections other than HPV (e.g., chlamydia or gonorrhea) are identified at the visit, a repeat cytology test after appropriate treatment for those infections might be indicated. However, in most instances (even in the presence of certain severe cervical infections), cytology tests will be reported as satisfactory for evaluation, and reliable final reports can be produced without the need to repeat the cytology test after treatment.
- The presence of a mucopurulent discharge should not postpone cytology testing. The test can be performed after removal of the discharge with a saline-soaked cotton swab.
- HPV testing can be performed either as a separate test or by using material from the liquid-based cytology specimen.
- In the absence of other indications, the presence of external genital warts does not warrant more frequent cervical cancer screening.
- The sequence of cytology testing in relation to collection of other endocervical specimens does not influence Pap test results or their interpretation (*600*). Typically, vaginal specimens are preferred for chlamydia and gonorrhea screening; however, during a pelvic examination, endocervical specimens for STI testing can be collected first.
- Persons who have had a total hysterectomy with removal of the cervix do not require screening unless cervical intraepithelial neoplasia (CIN) 2, CIN 3, or adenocarcinoma in situ was diagnosed within the previous 20 years (*175*,*1247*). If the cervix remains intact after a supracervical hysterectomy, regularly scheduled Pap tests should be performed as indicated (*1248–1250*).
- Health care facilities that train providers on cytology test collection and use simple quality assurance measures are more likely to obtain satisfactory test results (as determined by the laboratory).
- The use of instruments designed to sample the cervical transformation zone (e.g., cytobrushes) improves the accuracy of cytology tests (*1251*).
- Both liquid-based and conventional cytology are acceptable because they have similar test-performance characteristics.
- At an initial visit, providers should ask patients about their recent cytology test and HPV results and any history of evaluation and treatment (e.g., loop electrosurgical excision procedure and colposcopy) to assist with management; effort should be made to obtain copies of recent results. The importance and frequency of screening should be reinforced.

Counseling

Persons might believe the cytology (Pap test) or HPV test screens for conditions other than cervical cancer, or they might be confused by abnormal results (*1252–1254*). Health care providers, as trusted sources of information about HPV infections and abnormal cytology test results, have an important role in educating persons about HPV and can moderate the psychosocial impact of abnormal results (*1255*,*1256*). Persons should be counseled on the risks, uncertainties, and benefits of screening (*174*,*1257*).

An abnormal cytology test or a positive HPV test can cause short-term anxiety, stress, fear, and confusion, possibly decreasing the patient's ability to absorb and retain information and acting as a barrier to follow-up care (*1258–1261*). A positive HPV test might elicit concerns about partners, worries about disclosure, and feelings of guilt, anger, and stigmatization (*1260*). Providers should frame HPV positivity in a neutral, nonstigmatizing context and emphasize its common, asymptomatic, and transient nature. Providers also should emphasize that HPV infections often are shared between partners but it is often not possible to know the origin of an HPV infection; HPV tests might become positive many years after initial exposure due to reactivation of latent infections in both male and female partners. Having an HPV infection should not raise concerns about a male partner's health (*1262*). Providers should communicate the meaning of both the cytology and HPV test results to patients at screening.

Providers also should screen for tobacco use and perform cessation counseling (www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2011/09/

tobacco-use-and-womens-health). Smoking contributes to the progression of CIN, with both active and passive smoking associated with squamous cell carcinoma of the cervix in women with HPV 16 or 18 infection (*1263–1266*).

Promoting Cervical Cancer Screening

Clinics can use the evidence-based interventions in the *Community Preventive Services Task Force* guidelines to promote cervical cancer screening in their communities (https://www.thecommunityguide.org/findings/cancer-screening-multicomponent-interventions-cervical-cancer). Implementing interventions that increase community demand for screening (*1266*) (e.g., client reminders, client incentives, media, group education, or one-on-one education) together with those that increase community access to screening (e.g., reducing structural barriers and reducing client out-of-pocket costs) is effective in increasing cervical cancer screening coverage. These interventions are more effective if they are implemented with interventions to increase provider delivery of screening services (e.g., provider assessment and feedback, provider incentives, and provider reminders). Print materials and online resources are available at https://www.cdc.gov/cancer/cervical/basic_info/screening.htm and https://www.cdc.gov/std/hpv/facts-brochures.htm. Patient navigators can be effective in improving both screening and follow-up after abnormal results (*1267*).

Key Messages About Cervical Cancer Screening

When counseling persons about cervical cancer screening, the provider should discuss the following:

- Cervical cancer can be prevented with regular screening tests, like the Pap test (cytology) and HPV tests. Those at average risk should start getting cytology tests at age 21 years.
- The cytology test can find abnormal cervical cells, which could lead to cervical cancer over time, and an HPV test detects HPV infection of the cervix. The HPV test can be used alone for cervical cancer screening or at the same time as the cytology test (known as cotesting) for those aged ≥30 years to 65 years. The HPV test is also used after a cytology test result of atypical squamous cells of undetermined significance (ASC-US) among persons aged >25 years (known as reflex HPV testing).
- Positive cytology and HPV tests are markers of cervical precancerous lesions, which often do not cause symptoms until they become invasive. Appropriate follow-up is essential to ensure that cervical cancer does not develop.
- HPV is a common infection and is often controlled by the body without any medical interventions. A positive HPV test does not mean that a person has cancer.
- Providers should emphasize that HPV infections often are shared between partners, and it is often not possible to know the origin of an HPV infection; HPV tests might become positive many years after initial exposure due to reactivation of latent infections in both male and female partners.

Management of Sex Partners

The benefit of disclosing a positive HPV test to current and future sex partners is unclear. The following counseling messages can be communicated to sex partners:

- Sex partners do not need to be tested for HPV.
- Sex partners tend to share HPV. Sex partners of persons with HPV infection also are likely have an HPV infection.
- Female sex partners of men who disclose they had a previous female partner with HPV should be screened at the same intervals as women with average risk. No data are available to suggest that more frequent screening is of benefit.
- When used correctly and consistently, condoms might lower the risk for HPV infection and might decrease the time to clear in those with HPV infection. However, HPV can infect areas not covered by the condom, and condoms might not fully protect against HPV (*24*,*25*).

Additional messages for partners include the messages for persons with HPV (see Cervical Cancer Screening; Counseling Messages).

Screening Recommendations in Special Populations

Pregnancy

Persons who are pregnant should be screened at the same intervals as those who are not. A swab, Ayre's spatula, or cytobrush can be used for obtaining cytology test samples during pregnancy (*1268–1270*).

HIV Infection

Several studies have documented an increased risk for cervical precancers and cancers in individuals with HIV infection (*1271–1273*). Adolescents with HIV should be screened 1 year after onset of sexual activity but no later than age 21 years. Sexually active persons should be screened at the time of the initial HIV diagnosis. Conventional or liquid-based cytology (Pap test) should be used as primary HPV testing and is not recommended in individuals with HIV. Cotesting (cytology and HPV test) can be done in individuals aged ≥30 years with HIV. Annual screening is recommended for persons with HIV infection; after 3 years of consecutive normal cytology results or normal cotest (normal cytology and negative HPV test), the screening interval can be increased to every 3 years. Lifelong screening is recommended among persons with HIV infection.

Providers should defer to existing *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV* for guidance on cervical cancer screening and management of results in persons with HIV (*98*).

Adolescents

Prevalence of HPV infection is high among those aged <21 years (*174*); however, HPV infections and squamous intraepithelial lesions caused by HPV in adolescents are more likely to regress than those in older persons. For these reasons, cervical cancer screening and HPV testing are not recommended in immunocompetent adolescents. However, for adolescents with HIV infection, providers should screen 1 year after onset of sexual activity, regardless of age or mode of HIV acquisition (e.g., perinatally acquired or sexually acquired) (*98*); such screening is warranted because of the reported high rate of progression of abnormal cytology in adolescents with HIV.

Human Papillomavirus Tests for Cervical Cancer Screening

Clinical tests for HPV are used for the following: cervical cancer screening as a primary test, cervical cancer screening with a cytology test, triage of some abnormal cervical cytology results, follow-up after abnormal screening test results, follow-up after a colposcopy in which no CIN 2 or CIN 3 is found, and follow-up after treatment of cervical precancers. These tests are only FDA cleared for use with cervical specimens, not oral or anal specimens. Testing for nononcogenic HPV types (e.g., types 6 and 11) is not recommended (https://www.asccp.org/guidelines).

FDA-cleared HPV tests detect viral DNA or messenger RNA. Several FDA-cleared tests for HPV are available for use in the United States. The Cobas 4800 HPV test (Roche Molecular Diagnostics) and the Onclarity HPV test (Becton Dickinson) can detect the presence of 14 oncogenic HPV types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), as well as individual types 16 and 18, and are cleared for primary cervical cancer screening.

Other HPV tests are cleared for use in conjunction with a cytology test or to triage some abnormal cervical cytology results; they should not be used for primary HPV testing because they are not cleared for this purpose. These tests include the Hybrid Capture 2 High-Risk HPV DNA test (Qiagen), the Cervista HPV High-Risk DNA and HPV 16/18 DNA tests (Hologics), and the APTIMA HR HPV (Gen Probe) test. All HPV assays should be FDA cleared and used only for the appropriate indications (https://www.fda.gov/media/122799/download) (*158*).

HPV testing should not be performed in the following situations:

- Deciding whether to vaccinate against HPV
- Conducting HPV tests for low-risk (nononcogenic) HPV types (e.g., types 6 and 11)
- Providing care to persons with genital warts or their partners
- Testing persons aged <25 years as part of routine cervical cancer screening
- Testing oral or anal specimens

Unlike cytology, samples for HPV testing have the potential to be collected by the patient and mailed to health programs for analysis, thus self-collection might be one strategy for increasing screening rates among populations where screening rates are low. Self-collection for HPV testing is not cleared by FDA or recommended by U.S. medical organizations (*174*).

Follow-Up of Abnormal Cytology and Human Papillomavirus Test Results

If the result of the cytology (Pap test) is abnormal, follow-up care should be provided according to the *2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors* (*158*). Clinics that serve clients who might have difficulty adhering to follow-up recommendations and for whom linkage to care is unlikely should consider offering in-house colposcopy and biopsy services.

Consensus guidelines for management of abnormal cervical cancer screening tests combine patient-level risk data with clinical action thresholds to generate personalized management recommendations (Table 2). This framework allows management on the basis of risk for CIN 3, not specific test results. The guidelines were designed to identify persons at high risk who require colposcopy or expedited treatment and persons at low risk who might be able to safely defer invasive diagnostic procedures. The risk-based framework was designed to easily incorporate future revisions, such as the inclusion of new technologies for screening and management. Use of the guidelines can be facilitated by electronic technology that is continually updated, such as a smartphone application or the website (https://www.asccp.org/Default.aspx).

The following are highlights of the new management guidelines:

- Colposcopy can be deferred for patients at low risk.
  - If a patient has a minimally abnormal test result (i.e., negative for intraepithelial lesion or malignancy HPV positive, ASC-US HPV positive, LSIL, or HPV positive) that was preceded by a negative screening HPV test or cotest within the past 5 years, follow-up in 1 year instead of colposcopy is recommended (a negative HPV test or cotest performed during follow-up of abnormal results would not similarly reduce risk).
  - Referral to colposcopy is recommended if cytology test results are abnormal or the HPV test is positive at the 1-year follow-up visit.
- Treatment can be expedited for high-risk patients.

TABLE 2. Comparison of 2012 and 2019 consensus recommendations for management of common abnormalities — American Society for Colposcopy and Cervical Pathology

Current HPV result	Current Pap test result	Previous result	Management by 2012 guidelines	Management by 2019 guidelines
Negative	ASC-US	Unknown or HPV negative*	Repeat Pap plus HPV testing in 3 yrs	Repeat HPV test with or without concurrent Pap test in 3 yrs
Negative	LSIL	Unknown or HPV negative*	Repeat Pap plus HPV testing in 1 yr preferred, colposcopy acceptable	Repeat HPV test with or without concurrent Pap test in 1 yr
Negative	ASC-H	Noncontributory	Colposcopy	Colposcopy
Noncontributory	AGC	Noncontributory	Colposcopy	Colposcopy
Positive	NILM	Unknown or HPV negative*	Repeat Pap plus HPV testing in 1 yr	Repeat HPV test with or without concurrent Pap test in 1 yr
Positive	NILM	HPV positive†	Colposcopy	Colposcopy
Positive for genotype HPV 16, HPV 18, or both	NILM	Noncontributory	Colposcopy	Colposcopy
Positive for genotype HPV 16, HPV 18, or both	ASC-US or LSIL	Noncontributory	Not applicable, genotyping not recommended for ASC-US or LSIL in 2012	Colposcopy
Positive	ASC-US or LSIL	Unknown or HPV positive	Colposcopy	Colposcopy
Positive	ASC-US or LSIL	Negative screening results with HPV testing or HPV plus Pap testing within the previous 5 yrs	Colposcopy	Repeat HPV test with or without concurrent Pap test in 1 yr§
Positive	ASC-US or LSIL	Colposcopy confirming the absence of high-grade lesion within the past yr	Colposcopy	Repeat HPV test with or without concurrent Pap test in 1 yr§
Positive	ASC-H	Noncontributory	Colposcopy	Colposcopy or expedited treatment
Positive untyped, positive for genotype other than HPV 16, or negative	HSIL	Noncontributory	Colposcopy or expedited treatment	Colposcopy or expedited treatment
Positive for genotype HPV 16	HSIL	Noncontributory	Colposcopy or expedited treatment	Expedited treatment¶

Sources: Massad LS, Einstein MH, Huh WK, et al.; 2012 ASCCP Consensus Guidelines Conference. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Obstet Gynecol 2013;121:829–46; Perkins RB, Guido RS, Castle PE, et al; 2019 ASCCP Risk-Based Management Consensus Guidelines Committee. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis 2020;24:102–31; Perkins R, Guido R, Saraiya M, et al. Summary of current guidelines for cervical cancer screening and management of abnormal test results: 2016–2020. J Womens Health (Larchmt) 2021;30:5–13.

Abbreviations: AGC = atypical glandular cells; AIS = adenocarcinoma in situ; ASC-H = atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion; ASC-US = atypical squamous cells of undetermined significance; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; LSIL = low-grade squamous intraepithelial lesion; NILM = negative for intraepithelial lesion or malignancy; Pap = Papanicolaou.

* Colposcopy may be warranted for patients with a history of high-grade lesions (CIN 2 or CIN 3, histologic or cytologic HSIL, ASC-H, AGC, or AIS).

† Previous Pap test results do not modify the recommendation; colposcopy is always recommended for two consecutive HPV-positive tests.

§ Negative HPV test or cotest (HPV plus Pap test) results only reduce risk sufficiently to defer colposcopy if performed for screening purposes within the last 5 years. Colposcopy is still warranted if negative HPV test or cotest results occurred in the context of surveillance for a previous abnormal result.

¶ Expedited treatment is preferred for nonpregnant patients aged ≥25 years. Colposcopy with biopsy is an acceptable option if desired by patient after shared decision-making.

- If a patient has a high-grade cytology (Pap test) result (i.e., HSIL) and an HPV test that is positive for HPV type 16, then treatment with a loop electrosurgical excision procedure (LEEP) is preferred. A colposcopy with biopsy is not necessary to confirm the diagnosis first.
- If a patient who has not been screened in more than 5 years (i.e., rarely screened) has an HSIL cytology result and a positive HPV test (regardless of type), then treatment with LEEP is preferred. A colposcopy with biopsy is not necessary to confirm the diagnosis first.
- When considering treatment without confirmatory biopsy, shared decision-making with the patient is important. Considerations include age, concern about cancer, ability to follow up, financial concerns, and concerns about the potential effect of treatment on a future pregnancy.

- When primary HPV testing is used for screening, cytology testing should be performed for all positive HPV test results to help determine the next steps in management.
  - Ideally, cytology testing should be performed by the laboratory as a reflex test from the same specimen so the patient does not need to return to the clinic. Colposcopy is recommended if HPV genotyping is positive for types 16 or 18, and it can be considered if it is infeasible for the patient to return for cytology alone (*1274*).
  - HPV 16 is the highest-risk HPV type. Expedited treatment should be considered for HSIL cytology results, and colposcopy is recommended in all other cases, even if the cytology test is normal.

- HPV 18 has a relatively high association with cancer, and colposcopy is recommended in all cases, even if the cytology test is normal. Because of the association of HPV 18 with adenocarcinoma, endocervical sampling is acceptable at the time of colposcopy.
- If the HPV type is not HPV 16 or 18, and the cytology test is normal, return in 1 year is recommended in most cases.

- HPV testing or cotesting is preferred to cytology testing alone for follow-up after an abnormal test result.
  - Negative HPV testing or cotesting is less likely to miss disease than normal cytology testing alone. Therefore, cytology testing is recommended more often than HPV testing or cotesting for follow-up of abnormal results. Specifically, cytology testing is recommended annually when HPV testing or cotesting is recommended at 3-year intervals, and cytology testing is recommended at 6-month intervals when HPV testing or cotesting is recommended annually.
- After treatment for a high-grade precancer (moderate or severe dysplasia), surveillance should continue for at least 25 years.
  - Initial testing includes an HPV test or cotest at 6, 18, and 30 months. If cytology alone is used, testing should occur at 6, 12, 18, 24, and 30 months.
  - After completing initial testing, long-term surveillance includes testing at 3-year intervals if using HPV testing or cotesting, or annual testing if using cytology testing alone.
  - Surveillance should continue for at least 25 years after the initial treatment, even if this extends beyond age 65 years. If a woman undergoes hysterectomy during the surveillance period, vaginal screening should continue.

Anal Cancer

Anal cancer is rare in the general population (1–2 cases per 100,000 person-years); however, incidence is substantially higher among specific populations, including MSM with HIV infection (80–131 cases per 100,000 person-years), men with HIV infection (40–60 cases per 100,000 person-years), women with HIV infection (20–30 cases per 100,000 person-years), and MSM without HIV infection (14 cases per 100,000 person-years) (*1275–1279*). Incidence is variable among women with previous HPV-related gynecologic dysplasia and cancer (6–63 cases per 100,000 person-years) (*1280*,*1281*). Persistent HPV infection might be a risk factor for preventable HPV-associated second primary cancers among survivors of HPV-associated cancers (*1282*).

Data are insufficient to recommend routine anal cancer screening with anal cytology in persons with HIV infection, MSM without HIV infection, and the general population. An annual digital anorectal examination (DARE) might be useful to detect masses on palpation in persons with HIV infection and possibly in MSM without HIV with a history of receptive anal intercourse (*98*). More evidence is needed concerning the natural history of anal intraepithelial neoplasia, the best screening methods and target populations, the safety and response to treatments, and other programmatic considerations before screening can be routinely recommended.

Populations at High Risk and Digital Anorectal Examination

Providers should discuss anal cancer risk with their patients among specific populations to guide management. According to the HIV Opportunistic Infection guidelines and the International Anal Neoplasia Society, a DARE should be performed to detect early anal cancer in persons with HIV infection and MSM without HIV with a history of receptive anal intercourse (*98*,*1283*). DARE is acceptable to patients and has a low risk for adverse outcomes (*1284*,*1285*).

Data are insufficient to guide initiation of DARE at a defined age or optimal intervals for examination. Whereas anal HSIL is observed among young adults, cancer incidence begins to increase after the early 30s and continues to increase as a function of age.

Populations at High Risk and Anal Cytology

Data are insufficient to recommend routine anal cancer screening with anal cytology among populations at risk for anal cancer. Certain clinical centers perform anal cytology to screen for anal cancer among populations at high risk (e.g., persons with HIV infection, MSM, and those having receptive anal intercourse), followed by high-resolution anoscopy (HRA) for those with abnormal cytologic results (e.g., ACS-US, LSIL, or HSIL). Sensitivity and specificity of anal cytology to detect HSIL are limited (sensitivity 55%–89% and specificity 40%–67%) (*1286–1291*). Health centers that initiate a cytology-based screening program should only do so if referrals to HRA and biopsy are available.

HRA can be used for diagnosis of HSIL, to monitor response to therapy, or to conduct surveillance of HSIL for evidence of progression. HRA is the primary method used for diagnosis of superficially invasive squamous carcinoma, a very early form of anal cancer that is not palpable on DARE. However, data are insufficient to conclude whether use of HRA leads to reductions in anal cancer incidence or improves anal cancer morbidity and mortality. An ongoing clinical trial is investigating whether treatment of HSIL is effective in reducing the incidence of anal cancer among persons with HIV infection (NCT02135419).

Human Papillomavirus Testing

HPV tests (using high-risk HPV types) are not clinically useful for anal cancer screening because of a high prevalence

of anal HPV infection among populations at high risk, particularly MSM (*1278*,*1289*,*1290*). No standard HPV-based algorithms exist for anal cancer screening due to the high prevalence of high-risk HPV infection among groups at risk.

Treatment of Anal High-Grade Squamous Intraepithelial Lesion

Multiple office-based treatments exist for anal HSIL, including ablative methods (e.g., laser, electrocautery, or infrared coagulation) and topical patient-applied therapies (e.g., imiquimod). Recurrence rates with both provider-applied and patient-applied treatments are high, ranging from approximately 50% at 1 year to 77% after 3 years (*1289*,*1292*,*1293*). In addition, evidence exists that HSIL might spontaneously regress without treatment (*1294*,*1295*). Shared decision-making about treatment for anal HSIL is recommended because of limited data on the natural history of anal HSIL, including factors related to progression or regression of lesions.

Viral Hepatitis

Hepatitis A Virus Infection

HAV infection has an incubation period of approximately 28 days (range: 15–50 days) (*1296*). HAV replicates in the liver and is shed in high concentrations in feces from 2–3 weeks before to 1 week after the onset of clinical illness. HAV infection produces a self-limited disease that does not result in chronic infection or chronic liver disease. However, approximately 10% of patients experience a relapse of symptoms during the 6 months after acute illness. Acute liver failure from hepatitis A is rare (overall case-fatality rate: 0.5%). The risk for symptomatic infection is directly related to age, with approximately 70% of adults having symptoms compatible with acute viral hepatitis and the majority of children having either asymptomatic or unrecognized infection. Antibody produced in response to HAV infection persists for life and confers protection against reinfection (*1297*).

HAV infection is primarily transmitted by the fecal-oral route, by either person-to-person contact or through consumption of contaminated food or water (*1298*). Transmission of HAV during sexual activity probably results from fecal-oral contact. Although viremia occurs early during infection and can persist for weeks after symptom onset, bloodborne transmission of HAV is uncommon (*1299*). Transmission by saliva has not been demonstrated.

In the United States, of the hepatitis A cases accompanied by risk information, a particular risk was identified among only 23.8% (*13*,*372*). Among cases with a risk factor identified, a recognized foodborne or waterborne outbreak was the most commonly identified risk (49.6%). Other infection sources identified in the United States include MSM; persons who use injecting drugs; sexual and household contacts; those experiencing homelessness; international travelers; those with children attending a nursery, childcare, or preschool; and persons working in such settings (*13*,*372*).

Diagnostic Considerations

Diagnosis of HAV infection cannot be made on a clinical basis alone but requires serologic testing. Presence of IgM antibody to HAV is diagnostic of acute HAV infection. A positive test for total anti-HAV indicates immunity to HAV infection but does not differentiate current from previous HAV infection. Although usually not sensitive enough to detect the low level of protective antibody after vaccination, anti-HAV tests also might be positive after hepatitis A vaccination.

Treatment

Patients with acute HAV infection usually require only supportive care, with no restrictions in diet or activity. Hospitalization might be necessary for patients who become dehydrated because of nausea and vomiting and is crucial for patients with signs or symptoms of acute liver failure. Medications that might cause liver damage or are metabolized by the liver should be used with caution among persons with HAV infection.

Prevention

Vaccination is the most effective means of preventing HAV transmission among persons at risk for infection (e.g., MSM, injecting drug users, and persons with chronic liver disease) who did not receive hepatitis A vaccination during childhood. Hepatitis A vaccines are prepared from formalin-inactivated, cell-culture–derived HAV. Two monovalent vaccines (Havrix and Vaqta are approved by FDA for persons aged ≥12 months (Table 3). These vaccines are available for eligible children and adolescents aged <19 years through the VFC program (https://www.cdc.gov/vaccines/programs/vfc/index.html). Administered IM in a 2-dose series at 0 and 6–12 months, hepatitis A vaccines induce protective antibody levels among virtually all adults. By 1 month after the first dose, 94%–100% of adults have protective antibody levels, and after a second dose, 100% achieve protective levels (*1297*,*1300*,*1301*). Kinetic models of antibody decrease among adults indicate that protective levels persist for >40 years (*1302–1304*). A study of Alaska Natives demonstrated that seropositivity for hepatitis A persists for >20 years after completing 2-dose vaccination at age 12–21 months (*1302*). Anti-HAV persistence of >20 years was demonstrated among immunocompetent adults vaccinated

with a 2-dose hepatitis A schedule as adults (*1303*,*1305*). A combined hepatitis A and hepatitis B vaccine (Twinrix) has been developed and licensed for use as a 3-dose series for adults aged ≥18 years at risk for HAV or HBV infections. When administered IM on a 0-, 1-, and 6-month schedule, the vaccine has equivalent immunogenicity to that of the monovalent hepatitis A vaccines.

Pre-Exposure Vaccination

Persons at risk for HAV infection (Box 5) (*1297*) should be offered vaccine (Table 3). If persons are at risk for both HAV and HBV, the combined vaccine can be considered.

Prevaccination Serologic Testing

Among U.S.-born adults aged >20 years, HAV susceptibility prevalence (i.e., total antibody to HAV was negative) was 74.1% (95% CI: 72.9%–75.3%) during 2007–2016 (*1306*). Prevaccination serologic testing for HAV immunity before vaccination is not routinely recommended; however, it can be considered in specific settings to reduce costs by not vaccinating persons who are already immune. Prevaccination serologic testing should not be a barrier to vaccination of susceptible persons, especially for populations that are difficult to access. If prevaccination testing is performed, commercially available tests for total anti-HAV or IgG anti-HAV should be used (*1297*).

TABLE 3. Vaccines for preventing hepatitis A infection

Vaccine	Trade name (manufacturer)	Age group (yrs)	Dose	Route	Schedule	Booster
Hep A inactivated (2 doses)	Havrix (GlaxoSmithKline)	1–18	0.5 mL (720 ELISA units inactivated HAV)	IM	0, 6–12 mos	None
		≥19	1 mL (1,440 ELISA units inactivated HAV	IM	0, 6–12 mos	None
Hep A inactivated (2 doses)	Vaqta (Merck)	1–18	0.5 mL (25 units HAV antigen)	IM	0, 6–18 mos	None
		≥19	1 mL (50 units HAV antigen)	IM	0, 6–18 mos	None
Combined Hep A and Hep B* (3 doses)	Twinrix (GlaxoSmithKline)	≥18 (primary)	1 mL (720 ELISA units inactivated plus 20 μg HBsAg	IM	0, 1, 6 mos	None
		≥18 (accelerated)	1 mL (720 ELISA units inactivated plus 20 μg HBsAg	IM	0, 7, 21–30 days	12 mos

Source: Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Recomm Rep 2020;69(No. RR-5).
Abbreviations: ELISA = enzyme-linked immunosorbent assay; HAV = hepatitis A virus; HBsAg = hepatitis B surface antigen; Hep A = hepatitis A; Hep B = hepatitis B; IM= intramuscular.
* Combined Hep A and Hep B vaccine (Twinrix) should not be used as postexposure prophylaxis.

BOX 5. Populations recommended for hepatitis A vaccination — Advisory Committee on Immunization Practices, 2020

Children
- All children aged 12–23 months
- Unvaccinated children and adolescents aged 2–18 years

Persons at increased risk for hepatitis A virus (HAV) infection
- International travelers
- Men who have sex with men
- Persons who use injecting or noninjecting drugs (i.e., all those who use illegal drugs)
- Persons with occupational risk for exposure
- Persons who anticipate close personal contact with an international adoptee
- Persons experiencing homelessness

Persons at increased risk for severe disease from HAV infection
- Persons with chronic liver disease
- Persons with HIV infection

Other persons recommended for vaccination
- Pregnant women at risk for HAV infection or severe outcome from HAV infection
- Any persons who requests a vaccine

Vaccination during outbreaks
- Unvaccinated persons in outbreak settings who are at risk for HAV infection or at risk for severe disease from HAV

Implementation strategies for settings providing services to adults
- Persons in settings that provide services to adults where a high proportion of those persons have risk factors for HAV infection

Hepatitis A vaccination is no longer recommended by the Advisory Committee on Immunization Practices
- Persons who receive blood products for clotting disorders (e.g., hemophilia)

Source: Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Recomm Rep 2020;69(No. RR-5).

Persons for whom prevaccination testing will likely be most cost-effective include adults who were either born in or lived for extensive periods in geographic areas where HAV endemicity is high or intermediate (*1297*). Prevaccination serologic testing of children is not indicated because of the low prevalence of infection among that age group.

For populations who are expected to have high rates of previous HAV infection, vaccination history should be obtained when feasible before testing or vaccination. Vaccination should not be postponed if vaccination history cannot be obtained, records are unavailable, or prevaccination testing is infeasible. Vaccinating persons immune from natural infection carries no known risk, nor does giving extra doses of hepatitis A vaccine (*1307*). Vaccination of a person who is already immune is not harmful. Persons who have a documented history of ≥2 doses of hepatitis A vaccine do not need further vaccination or serologic testing.

Postvaccination Serologic Testing

Serologic testing for immunity is unnecessary after routine vaccination of infants, children, or adults (*1297*). Testing for anti-HAV antibody after vaccination is recommended for persons whose subsequent clinical management depends on knowledge of their immune status and persons for whom revaccination might be indicated (e.g., persons with HIV infection and other immunocompromising conditions).

Postexposure Prophylaxis

Persons who recently have been exposed to HAV and who previously have not received hepatitis A vaccine should be administered a single dose of monovalent hepatitis A vaccine or immunoglobulin (IG) (0.1 mL/kg body weight) as soon as possible, ideally <2 weeks after exposure because the efficacy of vaccine or IG when administered >2 weeks after exposure has not been established (*1297*). In most cases, monovalent hepatitis A vaccine at the age-appropriate dose is preferred over IG for PEP. Advantages of hepatitis A vaccine for PEP include induction of active immunity, longer-term protection, ease of administration, and better acceptability and availability. Decisions to use vaccine versus IG should be guided by patient characteristics associated with more severe manifestations of HAV infection (e.g., older age, immunocompromising conditions, and chronic liver disease) and the magnitude of the risk for HAV transmission resulting from the exposure (*1297*).

IG should be used for children aged <6 months, immunocompromised persons, persons with chronic liver disease, and persons for whom vaccine is contraindicated. IG can be administered to persons aged >40 years, in addition to hepatitis A vaccine (*1297*).

IG administered IM can provide PEP against HAV (Table 4). IG is a sterile solution of concentrated immunoglobulins prepared

TABLE 4. Recommendations for hepatitis A postexposure prophylaxis and pre-exposure protection, by age group and risk category — Advisory Committee on Immunization Practices, 2020

Indication and age group	Risk category and health status	Hepatitis A vaccine	IG*
Postexposure prophylaxis			
0–11 mos	Healthy	No	0.1 mL/kg body weight
12 mos to 40 yrs	Healthy	1 dose†	None
>40 yrs	Healthy	1 dose†	0.1 mL/kg body weight§
≥12 mos	Immunocompromised or chronic liver disease	1 dose†	0.1 mL/kg body weight¶
≥12 mos	Vaccine contraindicated**	No	0.1 mL/kg body weight
Pre-exposure protection (e.g., travel)††			
<6 mos	Healthy	No	0.1–0.2 mL/kg body weight§§
6–11 mos	Healthy	1 dose¶¶	None
12 mos to 40 yrs	Healthy	1 dose***	None
>40 yrs	Healthy	1 dose***	0.1–0.2 mL/kg body weight§§,†††
>6 mos	Immunocompromised or chronic liver disease	1 dose***	0.1–0.2 mL/kg body weight§§,†††
>6 mos	Persons who elect not to receive vaccine or for whom vaccine is contraindicated**	No	0.1–0.2 mL/kg body weight§§

Source: Nelson NP, Weng MK, Hofmeister MG, et al. Prevention of hepatitis A virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices, 2020. MMWR Recomm Rep 2020;69(No. RR-5).

Abbreviations: HAV = hepatitis A virus; IG = immune globulin.

* Measles, mumps, and rubella vaccine should not be administered for ≥2 weeks before and 6 months after administration of IG.

† A second dose of hepatitis A vaccine is not required for postexposure prophylaxis; however, for long-term immunity, the vaccination series should be completed with a second dose ≥6 months after the first dose.

§ The provider's risk assessment should determine the need for IG administration. If the provider's risk assessment determines that both vaccine and IG are warranted, hepatitis A vaccine and IG should be administered simultaneously at different anatomic sites (e.g., separate limbs).

¶ Vaccine and IG should be administered simultaneously at different anatomic sites (e.g., separate limbs).

** Life-threatening allergic reaction to a previous dose of hepatitis A vaccine or allergy to any vaccine component.

†† IG should be considered before travel for persons with special risk factors for either HAV infection or severe disease from HAV infection.

§§ 0.1 mL/kg body weight for travel ≤1 month; 0.2 mL/kg body weight for travel ≤2 months; 0.2 mL/kg every 2 months for travel of ≥2 months' duration.

¶¶ This dose should not be counted toward the routine 2-dose series, which should be initiated at age 12 months.

*** For persons not previously vaccinated with hepatitis A vaccine, administer dose as soon as travel is considered and complete the series according to routine schedule if the next dose is needed before travel.

††† Can be administered on the basis of the provider's risk assessment.

from pooled human plasma processed by cold ethanol fractionation. In the United States, IG is produced only from plasma that has tested negative for HBsAg, antibodies to HIV and HCV, and HIV and HCV RNA. In addition, the process used to manufacture IG inactivates viruses (e.g., HBV, HCV, and HIV). When administered IM <2 weeks after exposure to HAV, IG is >85% effective in preventing HAV infection (*1308*).

If IG is administered to persons for whom hepatitis A vaccine also is recommended, a dose of vaccine should be provided simultaneously with IG in different anatomic sites (e.g., different limbs) as soon as possible, and the second vaccine dose should be administered according to the licensed schedule to complete the series. The combined vaccine can be considered for persons among whom both hepatitis A and hepatitis B vaccine is recommended (*13*,*1297*,*1302–1304*).

Special Considerations

For persons with HIV infection, antibody response can be directly related to $CD4^+$ T-cell levels. Although persons with HIV who have lower $CD4^+$ T-cell counts or percentages might have a weaker response to the vaccine, vaccination should not be delayed for the $CD4^+$ T-cell count to exceed a certain threshold because of the prolonged risk for HAV exposure created by missed opportunities to vaccinate.

Hepatitis B Virus Infection

The incubation period for HBV infection from time of exposure to symptom onset ranges from 6 weeks to 6 months. The highest concentrations of HBV are located in blood, with lower concentrations in other body fluids including wound exudates, semen, vaginal secretions, and saliva (*1309*,*1310*). HBV is more infectious and more stable in the environment than other bloodborne pathogens (e.g., HCV or HIV).

HBV infection can be either self-limited or chronic. Among adults, approximately half of newly acquired HBV infections are symptomatic, and approximately 1% of reported cases result in acute liver failure and death (*1311*). Risk for chronic infection is inversely related to age at acquisition; approximately 90% of infected infants and 30% of infected children aged <5 years become chronically infected, compared with 2%–6% of persons who become infected as adults (*1312*). Among persons with chronic HBV infection, the risk for premature death from cirrhosis or hepatocellular carcinoma is 15%–25% (*1313*).

HBV is efficiently transmitted by percutaneous or mucous membrane exposure to HBV-infected blood or body fluids that contain HBV. The primary risk factors associated with infection among adolescents and adults are unprotected sex with an infected partner, having multiple partners, men having sex with men, having history of other STIs, and injecting drug use (*233*). In addition, studies have demonstrated other modes of HBV transmission, including premastication and lapses in health care infection control procedures, as less common sources of transmission (*1314–1317*).

CDC's national strategy for eliminating transmission of HBV infection includes prevention of perinatal infection through routine screening of all pregnant women for HBsAg and immunoprophylaxis of infants born to mothers with HBsAg or mothers whose HBsAg status is unknown, routine infant vaccination, vaccination of previously unvaccinated children and adolescents through age 18 years, and vaccination of previously unvaccinated adults at increased risk for infection (*12*). High vaccination coverage rates with subsequent decreases in acute HBV infection incidence have been achieved among infants and adolescents (*1318*). The vaccination of persons as children and adolescents likely has led to improved vaccination coverage among adults aged <30 years (*1319*) and corresponding lower rates of acute HBV infection among this group. In contrast, vaccination coverage among the majority of adult populations at high risk aged ≥30 years (e.g., persons with multiple sex partners, MSM, and injecting drug users) has remained low (*1320*,*1321*); these groups account for the highest rates of preventable acute infections (*12*,*1319*,*1322*). STD clinics and other health care settings providing STI services to adults at high risk for infection should administer hepatitis B vaccine to those who are unvaccinated.

Diagnosis

Diagnosis of acute or chronic HBV infection requires serologic testing (Table 5). Because HBsAg is present in both acute and chronic infection, presence of IgM antibody to hepatitis B core antigen (IgM anti-HBc) is diagnostic of acute or recently acquired HBV infection. Antibody to HBsAg (anti-HBs) is produced after a resolved infection and is the only HBV antibody marker present after vaccination. The presence of HBsAg and anti-HBc, with a negative test for IgM anti-HBc, indicates chronic HBV infection. The presence of total anti-HBc alone might indicate acute, resolved, or chronic infection or a false-positive result.

Treatment

No specific therapy is available for persons with acute HBV infection; treatment is supportive. Persons with chronic HBV infection should be referred for evaluation to a provider experienced in managing such infections. Therapeutic agents approved by FDA for treatment of chronic HBV infection can achieve sustained suppression of HBV replication and remission of liver disease (*1323*).

TABLE 5. Interpretation of serologic test results* for hepatitis B virus infection

Serologic marker				
HBSAG	Total anti-HBc	IgM anti-HBc	Anti-HBs	Interpretation
–	–	–	–	Never infected
+[†]	–	–	–	Early acute infection; transient (≤18 days) after vaccination
+	+	+	–	Acute infection
–	+	+	–	Acute resolving infection
–	+	–	+	Recovered from past infection and immune
+	+	–	–	Chronic infection
–	+	–	–	Past infection; low-level chronic infection[§]; passive transfer to infant born to HBsAg-positive mother; false positive (no infection)
–	–	–	+	Immune if concentration is >10 mIU/mL after vaccination, passive transfer after HBIG administration

Source: Adapted from Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67(No. RR-1).
Abbreviations: anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; HBIG = hepatitis B immune globulin; HBsAg = hepatitis B surface antigen; IgM = immunoglobulin M.
* – = negative test result; + = positive test result.
† To ensure that an HBsAg-positive test result is not false positive, samples with repeatedly reactive HBsAg results should be tested with a neutralizing confirmatory test cleared by the Food and Drug Administration.
§ Persons positive for only anti-HBc are unlikely to be infectious, except under unusual circumstances involving direct percutaneous exposure to large quantities of blood (e.g., blood transfusion or organ transplantation) or mutant HBsAg-related infection.

Prevention

Two products have been approved for HBV prevention: hepatitis B immune globulin (HBIG) for PEP and hepatitis B vaccine (*12*). HBIG provides temporary (i.e., 3–6 months) protection from HBV infection and is typically used as PEP as an adjunct to hepatitis B vaccination for previously unvaccinated persons or for persons who have not responded to vaccination. HBIG is prepared from plasma known to contain high concentrations of anti-HBs. The recommended dose of HBIG is 0.06 mL/kg body weight.

Hepatitis B vaccine contains HBsAg produced in yeast by recombinant DNA technology and provides protection from HBV infection when used for both pre-exposure vaccination and PEP. The three available monovalent hepatitis B vaccines for use in the United States are Recombivax HB, Engerix-B, and Heplisav-B. A combination hepatitis A and hepatitis B vaccine for use among persons aged ≥18 years, Twinrix, also is available.

When selecting a hepatitis B vaccination schedule, health care providers should consider the need to achieve completion of the vaccine series. The recommended HBV dose and schedule varies by product and age of recipient (Table 6). Three different 3-dose schedules for adolescents and adults have been approved for both monovalent hepatitis B vaccines (i.e., Engerix-B and Recombivax HB); these vaccines can be administered at 0, 1, and 6 months; 0, 1, and 4 months; or 0, 2, and 4 months. A 4-dose schedule of Engerix-B at 0, 1, 2, and 12 months is licensed for all age groups. A 2-dose schedule of Recombivax HB adult formulation (10 μg) is licensed for adolescents aged 11–15 years, with a 4-month minimal interval between doses. When scheduled to receive the second dose, adolescents aged 16–19 years should be switched to a 3-dose series, with doses 2 and 3 consisting of the pediatric formulation (5 μg) administered on a recommended schedule. Heplisav-B is a new single-antigen recombinant hepatitis B vaccine with a novel cytosine-phosphate-guanine 1018 oligodeoxynucleotide adjuvant for prevention of HBV infection among persons aged ≥18 years, administered as a 2-dose series at 0 and 1 month (>4 weeks apart) (*156*). Twinrix is a 3-dose schedule administered at 0, 1, and 6 months to persons aged ≥18 years at risk for both HAV and HBV infections.

Hepatitis B vaccine should be administered IM in the deltoid muscle and can be administered simultaneously with other vaccines. If the vaccine series is interrupted after the first or second dose of vaccine, the missed dose should be administered as soon as possible. The series does not need to be restarted after a missed dose. HBV vaccination is available for eligible children and adolescents aged <19 years through the VFC program (https://www.cdc.gov/vaccines/programs/vfc/contacts-state.html). When feasible, the same manufacturer's vaccines should be used to complete the series; however, vaccination should not be deferred when the manufacturer of the previously administered vaccine is unknown or when the vaccine from the same manufacturer is unavailable (*1324*).

Among adolescents and healthy adults aged <40 years, approximately 30%–55% achieve a protective antibody response (i.e., anti-HBs ≥10 mIU/mL) after the first single-antigen vaccine dose, 75% after the second, and >90% after the third. Recent clinical trials reported a protective antibody response achieved among approximately 90% of participants receiving Heplisav-B, compared with 70.5%–90.2% of participants receiving Engerix-B (*12*). Vaccine-induced immune memory has been demonstrated to persist for >30 years (*1325–1327*).

TABLE 6. Recommended doses of licensed formulations of hepatitis B vaccines

	Single-antigen vaccine						Combination vaccine	
	Recombivax HB		Engerix-B		Heplisav-B*		Twinrix†	
Age group (yrs)	Dose (μg)§	Volume (mL)	Dose (μg)§	Volume (mL)	Dose (μg)§	Volume (mL)	Dose (μg)§	Volume (mL)
Infants (<1)	5	0.5	10	0.5	—¶	—¶	NA	NA
Children (1–10)	5	0.5	10	0.5	—¶	—¶	NA	NA
Adolescents (11–15)	10**	1.0	NA	NA	—¶	—¶	NA	NA
Adolescents (11–19)	5	0.5	10	0.5	—¶	—¶	NA	NA
Adults (≥18)	—††	—††	—††	—††	20*	0.5	20†	1
Adults (≥20)	10	1.0	20	1.0	20†	0.5	20†	1
Hemodialysis patients and other immunocompromised persons (<20§§)	5	0.5	10	0.5	20	0.5	NA	NA
Hemodialysis patients and other immunocompromised persons (≥20)	40¶¶	1.0	40***	2.0	20	0.5	NA	NA

Source: Adapted from Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018;67(No. RR-1).
Abbreviation: NA = not applicable.
* Administered on a 2-dose schedule.
† Combined hepatitis A and B vaccines. This vaccine is recommended for persons aged ≥18 years who are at increased risk for both hepatitis B and hepatitis A virus infections.
§ Recombinant hepatitis B surface antigen protein dose.
¶ Heplisav-B should not be used for vaccination of infants, children, or adolescents because the safety and effectiveness of Heplisav-B has not been established in persons aged <8 years and is not approved for use in these populations.
** Adult formulation administered on a 2-dose schedule.
†† Engerix-B and Recombivax HB are approved for use in persons of all ages.
§§ Higher doses might be more immunogenic; however, no specific recommendations have been made.
¶¶ Dialysis formulation administered on a 3-dose schedule at 0, 1, and 6 months.
*** Two 1.0-mL doses administered at one site, on a 4-dose schedule at 0, 1, 2, and 6 months.

Periodic testing to determine antibody levels after routine vaccination among immunocompetent persons is unnecessary, and booster doses of vaccine are not recommended.

Hepatitis B vaccination is usually well tolerated by the majority of recipients. Pain at the injection site and low-grade fever are reported by a minority of recipients. For children and adolescents, a causal association exists between receipt of hepatitis B vaccination and anaphylaxis. For each 1.1 million doses of vaccine administered, approximately one recipient will experience this type of reaction (*1328*); however, no deaths have been reported among these patients (*1318*,*1328*). Vaccine is contraindicated for persons with a history of anaphylaxis after a previous dose of hepatitis B vaccine and persons with a known anaphylactic reaction to any vaccine component (*1329*). No other adverse events after administration of hepatitis B vaccine have been demonstrated.

Pre-Exposure Vaccination

Hepatitis B vaccination is recommended for all unvaccinated children and adolescents; all unvaccinated adults at risk for HBV infection, especially injecting drug users; MSM; adults with multiple sex partners; sex partners, needle-sharing contacts, or household contacts of persons with chronic hepatitis B; and persons with diabetes and all adults seeking protection from HBV infection (*1318*). For adults, acknowledgment of a specific risk factor is not a requirement for vaccination.

Hepatitis B vaccine should be routinely offered to all unvaccinated persons attending STD clinics and to all unvaccinated persons seeking evaluation or treatment for STIs in other settings, especially correctional facilities, facilities providing substance misuse treatment and prevention services, Federally Qualified Health Centers, and settings serving MSM (e.g., HIV infection care and prevention settings). If hepatitis B vaccine is unavailable at a particular facility, persons should be linked to a setting where they can receive vaccine. Persons with a reliable vaccination history (i.e., a written, dated record of each dose of a complete series) or reliable history of hepatitis B infection (i.e., a written record of infection and serologic results providing evidence of previous infection) do not require vaccination. In all settings, vaccination should be initiated at the initial visit, even if concerns about completion of the vaccine series exist.

Prevaccination Serologic Testing

Conducting prevaccination serologic testing for susceptibility just before the initial vaccine dose is administered can be considered for identifying persons with chronic HBV infection and, potentially, reducing the cost of completing the vaccination series for adult populations that have an expected high prevalence (20%–30%) of HBV infection (e.g., injecting drug users and MSM, especially those among older age groups, or persons born where HBV endemicity is moderate to high). In addition, prevaccination testing for susceptibility is

recommended for unvaccinated household, sexual, and needle-sharing contacts of HBsAg-positive persons (*1318*). Serologic testing should not be a barrier to vaccination. The first vaccine dose should be administered immediately after collection of the blood sample for serologic testing. Vaccination of persons who are immune to HBV infection because of current or previous infection or vaccination is not harmful and does not increase the risk for adverse events.

Prevaccination testing should be performed with HBsAg, anti-HBs, and total anti-HBc to define patients' HBV clinical status and deliver recommended care (*1330*). Persons who test HBsAg positive should receive prevention counseling and evaluation for antiviral treatment (see Management of Persons Who Are HBsAg Positive). Persons who test total anti-HBc positive and anti-HBs positive should be counseled that they have had previous HBV infection and are immune. Those persons with isolated anti-HBc (i.e., negative HBsAg and anti-HBs) need further assessment to rule out occult HBV infection, and they are at higher risk for reactivation if exposed to immunosuppressants. Persons who test negative to all three HBV seromarkers should receive the complete vaccination series, with the first vaccine dose administered immediately.

Postvaccination Serologic Testing for Response

Postvaccination serologic testing for immunity is unnecessary after routine vaccination of adolescents or adults. However, such testing is recommended for persons whose subsequent clinical management depends on knowledge of their immune status. Persons recommended to receive postvaccination serologic testing include health care personnel and public safety workers, persons with HIV infection, sex and needle-sharing partners of HBsAg-positive persons, hemodialysis patients and others who might require outpatient hemodialysis (e.g., predialysis, peritoneal dialysis, or home dialysis), and other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy) (*1318*).

If indicated, anti-HBs testing should be performed 1–2 months after administration of the last dose of the vaccine series. Persons determined to have anti-HBs levels of <10 mIU/mL after the primary vaccine series should be revaccinated with a 3-dose series and tested again for anti-HBs 1–2 months after the third dose. Persons who do not respond to revaccination should be tested for HBsAg and HBc. If HBsAg positive, persons should receive recommended management (see Management of Persons Who Are HBsAg Positive). If HBsAg negative, persons should be considered susceptible to HBV infection and counseled about precautions for preventing HBV infection and the need for HBIG PEP for any known exposure. If isolated anti-HBc positive (i.e., negative HBsAg and anti-HBs), persons will need further assessment to rule out occult HBV infection and are at higher risk for reactivation if exposed to immunosuppressants.

Postexposure Prophylaxis

Both passive and active PEP (simultaneous administration of HBIG [i.e., 0.06 mL/kg body weight] and hepatitis B vaccine at separate anatomic sites) and active PEP (administration of hepatitis B vaccination alone) have been demonstrated to be highly effective in preventing transmission after exposure to HBV (*12*). HBIG alone also has been demonstrated to be effective in preventing HBV transmission; however, with the availability of hepatitis B vaccine, HBIG typically is used as an adjunct to vaccination.

Exposure to a Source Who Is HBsAg Positive

Unvaccinated persons or persons known not to have responded to a complete hepatitis B vaccine series should receive both HBIG and hepatitis vaccine as soon as possible (preferably ≤24 hours) after a discrete, identifiable exposure to blood or body fluids that contain blood from a person with HBsAg (Table 7). Hepatitis B vaccine should be administered simultaneously with HBIG at a separate anatomic site, and the vaccine series should be completed by using the age-appropriate vaccine dose and schedule (Table 6). Exposed persons who are not fully vaccinated because they have not completed the vaccine series should receive HBIG (i.e., 0.06 mL/kg body weight) and complete the vaccine series. Persons who have written documentation of a complete hepatitis B vaccine series who did not receive postvaccination testing should receive a single vaccine booster dose. Exposed persons who are known to have responded to vaccination by postvaccination testing are considered protected; therefore, they need no additional doses of vaccine or HBIG. All persons with an occupational exposure to blood or body fluids that contain HBV should be managed according to guidelines (*12*).

Exposure to a Source with Unknown HBsAg Status

Unvaccinated persons and persons with previous nonresponse to hepatitis B vaccination who have a discrete, identifiable exposure to blood or body fluids containing blood from a person with unknown HBsAg status should receive the hepatitis B vaccine series, with the first dose initiated as soon as possible after exposure (preferably <24 hours) and the series completed according to the age-appropriate dose and schedule. Exposed persons who are not fully vaccinated but started the series should complete the vaccine series. Exposed persons with written documentation of a complete hepatitis B vaccine series who did not receive postvaccination testing require no further treatment.

TABLE 7. Guidelines for postexposure prophylaxis* of persons with nonoccupational exposure† to blood or body fluids that contain blood, by exposure type and hepatitis B vaccination status

Source of exposure	Unvaccinated person§	Previously vaccinated person¶
HBsAg-positive source Percutaneous (e.g., bite or needlestick) or mucosal exposure to HBsAg-positive blood or body fluids ***or*** Sex or needle-sharing contact with an HBsAg-positive person ***or*** Victim of sexual assault or abuse by an assailant who is HBsAg positive	Administer hepatitis B vaccine series and HBIG	Complete hepatitis B vaccine series and HBIG, if vaccine series not completed ***or*** Administer hepatitis B vaccine booster dose, if previous vaccination without testing**
Source with unknown HBsAg status Percutaneous (e.g., bite or needlestick) or mucosal exposure to potentially infectious blood or body fluids from a source with unknown HBsAg status ***or*** Sex or needle-sharing contact with person with unknown HBsAg status ***or*** Victim of sexual assault or abuse by a perpetrator with unknown HBsAg status	Administer hepatitis B vaccine series	Complete hepatitis B vaccine series

Sources: CDC. CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering postexposure management. MMWR Recomm Rep 2013;62(No. RR-10); CDC. Postexposure prophylaxis to prevent hepatitis B virus infection. MMWR Recomm Rep 2006;55(No. RR-16).
Abbreviations: HBIG = hepatitis B immune globulin; HBsAg = hepatitis B surface antigen.
* When indicated, immunoprophylaxis should be initiated as soon as possible, preferably within 24 hours. Studies are limited regarding the maximum interval after exposure during which postexposure prophylaxis is effective, but the interval is unlikely to exceed 7 days for percutaneous exposures or 14 days for sexual exposures. The hepatitis B vaccine series should be completed. These guidelines apply to nonoccupational exposures.
† These guidelines apply to nonoccupational exposures.
§ A person who is in the process of being vaccinated but who has not completed the vaccine series should complete the series and receive treatment for hepatitis B as indicated.
¶ A person who has written documentation of a complete hepatitis B vaccine series and who did not receive postvaccination testing.
** No booster dose is needed for persons who have written documentation of hepatitis B vaccine series with serologic response.

Other Management Considerations

All persons with HBV infection should be tested for HIV, syphilis, gonorrhea, and chlamydia.

Management of Persons Who Are HBsAg Positive

Recommendations for management of all persons with HBsAg include the following:

- All persons with HBsAg documented on laboratory results should be reported to the state or local health department.
- To verify the presence of chronic HBV infection, persons with HBsAg should be retested. The absence of IgM anti-HBc or the persistence of HBsAg for ≥6 months indicates chronic HBV infection.
- Persons with chronic HBV infection should be referred for evaluation to a specialist experienced in managing chronic hepatitis B infection.
- Household, sexual, and needle-sharing contacts of persons with chronic infection should be evaluated. Unvaccinated sex partners and household and needle-sharing contacts should be tested for susceptibility to HBV infection and receive the first dose of hepatitis B vaccine immediately after collection of the blood sample for serologic testing (see Prevaccination Serologic Testing). Susceptible persons should complete the vaccine series by using an age-appropriate vaccine dose and schedule.
- Sex partners of persons with HBsAg should be counseled to use latex condoms (*1331*) to protect themselves from sexual exposure to infectious body fluids (e.g., semen and vaginal secretions), unless they have been demonstrated to be immune after vaccination (anti-HBs ≥10 mIU/mL) or previously infected (anti-HBc positive).
- To prevent or reduce the risk for transmission to others in addition to vaccination, persons with HBsAg also should be advised to
  - use methods (e.g., condoms) to protect nonimmune sex partners from acquiring HBV infection from sexual activity until the partner can be vaccinated and immunity documented;
  - cover cuts and skin lesions to prevent spread by infectious secretions or blood;
  - refrain from donating blood, plasma, body organs, other tissue, or semen; and
  - refrain from sharing household articles (e.g., toothbrushes, razors, or personal injecting equipment) that could become contaminated with blood, and refrain from premastication of food.
- To protect the liver from further harm, persons with HBsAg should be advised to

- avoid or limit alcohol consumption because of the effects of alcohol on the liver;
- refrain from starting any new medicines, including over-the-counter and herbal medicines, without checking with their health care provider; and
- obtain vaccination against hepatitis A.

When seeking medical or dental care, persons who are HBsAg positive should be advised to inform their health care providers of their HBsAg status so that they can be evaluated and managed. The following are key counseling messages for persons with HBsAg:

- HBV is not usually spread by hugging, coughing, food or water, sharing eating utensils or drinking glasses, or casual contact.
- Persons should not be excluded from work, school, play, childcare, or other settings because they are infected with HBV.
- Involvement with a support group might help patients cope with chronic HBV infection.
- HBV infection is a chronic condition that can be treated, and patients should receive prevention counseling and be evaluated for antiviral treatment.

Special Considerations

Pregnancy

Regardless of whether they have been previously tested or vaccinated, all pregnant women should be tested for HBsAg at the first prenatal visit and again at delivery if at high risk for HBV infection (see STI Detection Among Special Populations). Pregnant women at risk for HBV infection and without documentation of a complete hepatitis B vaccine series should receive hepatitis B vaccination. All pregnant women with HBsAg should be reported to state and local perinatal hepatitis B prevention programs and referred to a specialist. Information about management of pregnant women with HBsAg and their infants is available at https://www.cdc.gov/hepatitis/hbv/perinatalxmtn.htm.

HIV Infection

HIV infection can impair the response to hepatitis B vaccination. Persons with HIV should be tested for anti-HBs 1–2 months after the third vaccine dose (see Postvaccination Serologic Testing). Modified dosing regimens, including a doubling of the standard antigen dose and administration of additional doses, might increase the response rate and should be managed in consultation with an infectious disease specialist. Additional recommendations for management of persons with HBsAg and HIV infection are available (*98*).

Hepatitis C Virus Infection

HCV infection is the most common chronic bloodborne infection in the United States, with an estimated 2.4 million persons living with chronic infection (*1332*). HCV is not efficiently transmitted through sex (*1333–1335*). Studies of HCV transmission between heterosexual couples and MSM have yielded mixed results; however, studies have reported either no or minimally increased rates of HCV infection among partners of persons with HCV infection compared with partners of those without HCV (*1334*,*1336–1338*). However, data indicate that sexual transmission of HCV can occur, especially among persons with HIV infection. Increasing incidence of acute HCV infection among MSM with HIV infection has been reported in multiple U.S. (*96*,*236*,*239*,*1339*) and European cities (*237*,*1340–1342*). A recent systematic review reported an HCV incidence of 6.35 per 1,000 person years among MSM with HIV infection (*1343*). An association exists with high-risk and traumatic sexual practices (e.g., condomless receptive anal intercourse or receptive fisting) and concurrent genital ulcerative disease or STI-related proctitis (*237*,*1342*). HCV transmission among MSM with HIV infection has also been associated with group sex and chemsex (i.e., using recreational drugs in a sexual context) (*1344–1348*). Shedding of HCV in the semen and in the rectum of men with HIV infection has been documented (*1349*,*1350*). Certain studies have revealed that risk increases commensurate with increasing numbers of sex partners among heterosexual persons (*1337*,*1338*,*1351–1353*) and MSM with HIV infection (*1349*,*1354–1357*), especially if their partners are also coinfected with HIV (*237*,*1340*,*1354–1356*,*1358*). More recently, acute HCV infections have been reported among MSM on PrEP, increasing concerns that certain MSM might be at increased risk for incident HCV infection through condomless sexual intercourse with MSM with HCV infection (*1359*,*1360*).

Persons newly infected with HCV typically are either asymptomatic or have a mild clinical illness. HCV RNA can be detected in blood within 1–3 weeks after exposure. The average time from exposure to antibody to HCV (anti-HCV) seroconversion is 4–10 weeks, and anti-HCV can be detected among approximately 97% of persons by 6 months after exposure (*1361–1364*) (https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section3).

Chronic HCV infection develops among 75%–85% of persons with HCV infection (*1365*,*1366*), and 10%–20% of persons with chronic infection develop cirrhosis in 20–30 years of active liver disease (*1367*). The majority of infected persons remain unaware of their infection because they are not clinically

ill. However, infected persons are a source of transmission to others and are at risk for cirrhosis and hepatocellular carcinoma decades after infection.

HCV is primarily transmitted parenterally, usually through shared drug-injecting needles and paraphernalia. HCV also can be transmitted through exposures in health care settings as a consequence of inadequate infection control practices (*1314*). Transmission after receipt of blood from donors and from transplantation of tissues and organs with HCV infection has occurred only rarely since 1992, when routine screening of these donated products was mandated in the United States (*1367*,*1369*). Tattoos applied in regulated settings have not been associated with HCV transmission, although those obtained in certain settings have been linked to such transmission (*1336*). Occupational and perinatal exposures also can result in transmission of HCV; however, such transmission is uncommon.

Acute HCV infection is a reportable condition in 49 states. Matching viral hepatitis and HIV surveillance registries, and molecular epidemiologic assessments, can facilitate early detection of social networks of HCV transmission among MSM with HIV infection.

CDC recommends hepatitis C screening at least once in a lifetime for all adults aged ≥18 years and for all women during each pregnancy, except in settings where the prevalence of HCV infection is <0.1% (*156*). One-time hepatitis C testing is also recommended regardless of age, setting, or recognized conditions or exposures (e.g., HIV infection, history of injecting drug use, or children born to women with HCV infection). Routine periodic HCV testing is recommended for persons with ongoing risk factors (e.g., injecting drug use or hemodialysis).

Diagnosis

Testing for HCV infection should include use of an FDA-cleared test for antibody to HCV (i.e., immunoassay, EIA, or enhanced CIA and, if recommended, a supplemental antibody test) followed by NAAT to detect HCV RNA for those with a positive antibody result (*1370*). Persons with HIV infection with low $CD4^+$ T-cell count might require further testing by NAAT because of the potential for a false-negative antibody assay.

Persons determined to have HCV infection (i.e., positive for HCV RNA) should be evaluated for treatment. Antibody to HCV remains positive after spontaneously resolving or successful treatment; therefore, subsequent testing for HCV reinfection among persons with ongoing risk factors should be limited to HCV RNA. Persons who have spontaneous resolution or who have undergone successful treatment are not immune to reinfection.

Treatment

HCV infection is curable, and persons with diagnosed HCV infection should be linked to care and treatment. Providers should consult existing guidelines to learn about the latest advances in treating HCV infection (https://www.hcvguidelines.org) and with hepatitis specialists, as needed. Persons at high risk for transmitting HCV to others should be treated both for individual benefit and to prevent HCV transmission.

Management of Sex Partners

Because incident HCV has not been demonstrated to occur among heterosexual couples followed over time (*1334*,*1371–1373*), condom use might not be necessary in such circumstances. Persons with HCV infection with one long-term, steady sex partner do not need to change their sexual practices. However, they should discuss the risk for transmission with their partner and discuss the need for testing (*234*) (https://www.cdc.gov/hepatitis/hcv/index.htm). Heterosexual persons and MSM with HCV infection and more than one partner, especially those with concurrent HIV infection, should protect their partners against HCV and HIV acquisition by using external latex condoms (*237*,*1358*,*1374*) and HIV PrEP. Partners of persons with HCV and HIV should be tested for both infections.

Other Management Considerations

All persons with HCV infection for whom HIV and HBV infection status is unknown should be tested for these infections. Those who have HIV or HBV infection should be referred for or provided with recommended care and treatment. Persons without previous exposure to HAV or HBV should be vaccinated.

Prevention

Reducing the burden of HCV infection and disease in the United States requires implementing both primary and secondary prevention activities. Primary prevention reduces or eliminates HCV transmission, whereas secondary prevention identifies persons through screening and then provides treatment to reduce chronic liver disease and other chronic diseases and HCV transmission. No vaccine for hepatitis C is available, and prophylaxis with IG is not effective in preventing HCV infection after exposure. PEP using direct-acting antivirals is not recommended.

Persons with HCV infection should be provided information about how to protect their liver from further harm (i.e., hepatotoxic agents); for instance, persons with HCV infection should be advised to avoid drinking alcohol and taking any new medicines, including over-the-counter or herbal medications, without checking with their clinician. In addition, a need for

hepatitis A and B vaccination should be determined; persons who are not immune should be vaccinated.

To reduce the risk for transmission to others, persons with HCV infection should be advised not to donate blood, body organs, other tissue, or semen; not to share any personal items that might have blood on them (e.g., toothbrushes or razors); and to cover cuts and sores on the skin to keep the virus from spreading by blood or secretions. Women with HCV infection do not need to avoid pregnancy or breastfeeding, although children born to women with HCV also should be tested for HCV.

Persons who use or inject drugs should be counseled about the importance of prevention and provided access to substance misuse treatment, including medication-assisted treatment, if indicated. Persons who inject drugs should be encouraged to take the following additional steps to reduce personal and public health risks:

- Never reuse or share syringes, water, or drug preparation equipment.
- Only use syringes obtained from a reliable source (e.g., a syringe services program or a pharmacy).
- Use a new, sterile syringe to prepare and inject drugs each time.
- If possible, use sterile water to prepare drugs; otherwise, use clean water from a reliable source (e.g., fresh tap water).
- Use a new or disinfected container (i.e., cooker) and a new filter (i.e., cotton) to prepare drugs.
- Clean the injection site with a new alcohol swab before injection.
- Safely dispose of syringes after one use.

Postexposure Follow-Up

No PEP has been demonstrated to be effective against HCV infection. Testing for HCV is recommended for health care workers after percutaneous or perimucosal exposures to HCV-positive blood. Prompt identification of acute infection is vital because outcomes are improved when treatment is initiated early during the illness course.

Special Considerations

Pregnancy

All pregnant women should be screened with each pregnancy for HCV antibodies at the first prenatal visit in settings where the HCV prevalence is >0.1% (https://www.cdc.gov/hepatitis/hcv/index.htm) (*154*,*155*). Although the rate of transmission is highly variable, more than six of every 100 infants born to women with HCV infection become infected; this infection occurs predominantly during or near delivery, and no treatment or delivery method (e.g., cesarean delivery) has been demonstrated to decrease this risk (*1375*). However, the risk is increased by the presence of maternal HCV viremia at delivery and is twofold to threefold greater if the woman has HIV infection. Although no recommendations are available for HCV treatment during pregnancy, discussion about the individual risks and benefits of postpartum treatment can be considered in accordance with existing guidance (https://www.hcvguidelines.org/unique-populations/pregnancy).

HCV has not been reported to be transmitted through breast milk, although mothers with HCV infection should consider abstaining from breastfeeding if their nipples are cracked or bleeding. Infants born to mothers with HCV infection should be tested for HCV infection; children should be tested for anti-HCV no sooner than age 18 months because anti-HCV from the mother might last until that age. If diagnosis is desired before the child reaches age 18 months, testing for HCV RNA can be performed at or after the infant's first well-child visit at age 1–2 months. HCV RNA testing can be repeated at a subsequent visit, independent of the initial HCV RNA test result (*1376*) (https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section3).

HIV Infection

All persons with HIV infection should undergo serologic screening for HCV at initial evaluation (*98*) (https://www.hcvguidelines.org). Providers should be aware of the likelihood that MSM with HIV infection can acquire HCV after initial screening. Because acute HCV infection acquisition among persons with HIV infection can occur, especially among MSM, and regular screening of those with HIV is cost-effective (*238*,*239*,*1377*), periodic HCV screening should be conducted (*1378–1380*). For persons with HIV infection, hepatitis C screening with HCV antibody assays (followed by HCV RNA if antibody positive) can be considered at least yearly, for those at high risk for infection, and more frequently depending on specific circumstances (e.g., community HCV infection prevalence and incidence, high-risk sexual behavior, and concomitant ulcerative STIs and proctitis). Antibody to HCV remains positive after spontaneously resolved infection or successful treatment; therefore, subsequent testing for potential HCV reinfection among persons with ongoing risk should be limited to HCV RNA testing only. Indirect testing (e.g., alanine aminotransferase [ALT]) is not recommended for detecting incident HCV infections because such testing, especially if performed once a year, can miss persons who have reverted after acute HCV infection to a normal ALT level at the time of testing (*239*) (https://www.hcvguidelines.org). Conversely, ALT can be elevated by antiretroviral and other medications, alcohol, and toxins. If ALT levels are being monitored, persons with HIV infection who experience new or unexplained increases in ALT should be tested for acute

HCV infection and evaluated for possible medication toxicity or excessive alcohol use.

Continued unprotected sexual contact between partners with HIV can facilitate spread of HCV infection because the virus can be recovered from the semen of men with HIV infection (*1349*,*1381*). Specific prevention practices (e.g., barrier precautions that limit contact with body fluids during sexual contact with other MSM) should be discussed.

Because a minimal percentage of persons with HIV infection do not develop HCV antibodies, HCV RNA testing should be performed for persons with HIV infection and unexplained liver disease who are anti-HCV negative. The course of liver disease is more rapid among persons with HIV and HCV, and the risk for cirrhosis is higher than that for persons with HCV infection alone.

Proctitis, Proctocolitis, and Enteritis

Sexually transmitted gastrointestinal syndromes include proctitis, proctocolitis, and enteritis. Evaluation for these syndromes should include recommended diagnostic procedures, including anoscopy or sigmoidoscopy, stool examination for WBCs, and microbiologic workup (e.g., gonorrhea, chlamydia [LGV PCR if available], herpes simplex NAAT, and syphilis serology). For those with enteritis, stool culture or LGV PCR also is recommended.

Proctitis is inflammation of the rectum (i.e., the distal 10–12 cm) that can be associated with anorectal pain, tenesmus, or rectal discharge. Fecal leukocytes are common. Proctitis occurs predominantly among persons who have receptive anal exposures (oral-anal, digital-anal, or genital-anal). *N. gonorrhoeae*, *C. trachomatis* (including LGV serovars), HSV, and *T. pallidum* are the most common STI pathogens. Genital HSV and LGV proctitis are more prevalent among persons with HIV infection (*545*,*556*,*1382*). *M. genitalium* has been detected in certain cases of proctitis and might be more common among persons with HIV infection (*937*,*1382*). *N. meningitidis* has been identified as an etiology of proctitis among MSM with HIV infection (*1383*).

Proctocolitis is associated with symptoms of proctitis, diarrhea or abdominal cramps, and inflammation of the colonic mucosa extending to 12 cm above the anus. Fecal leukocytes might be detected on stool examination, depending on the pathogen. Proctocolitis can be acquired through receptive anal intercourse or by oral-anal contact, depending on the pathogen.

Pathogenic organisms include *Campylobacter* species, *Shigella* species, *E. histolytica*, LGV serovars of *C. trachomatis,* and *T. pallidum*. Among immunosuppressed persons with HIV infection, CMV or other opportunistic agents should be considered. The clinical presentation can be mistaken for inflammatory bowel disease or malignancy, resulting in a delayed diagnosis (*1384*,*1385*).

Enteritis usually results in diarrhea and abdominal cramping without signs of proctitis or proctocolitis. Fecal leukocytes might be detected on stool examination, depending on the pathogen. When outbreaks of gastrointestinal illness occur among social or sexual networks of MSM, clinicians should consider sexual transmission as a mode of spread and provide counseling accordingly. Sexual practices that can facilitate transmission of enteric pathogens include oral-anal contact or, in certain instances, direct genital-anal contact. *G. lamblia* is the most frequently implicated parasite, and bacterial pathogens include *Shigella* species, *Salmonella*, *E. coli, Campylobacter* species, and *Cryptosporidium*. Outbreaks of *Shigella* species, *Campylobacter*, *Cryptosporidium*, and microsporidiosis have been reported among MSM (*259*,*274*,*1386*,*1387*). Multiple enteric pathogens and concurrent STIs have also been reported. Among immunosuppressed persons with HIV infection, CMV or other opportunistic pathogens should be considered.

Diagnostic and Treatment Considerations for Acute Proctitis

Diagnosis

Persons with symptoms of acute proctitis should be examined by anoscopy. A Gram-stained smear of any anorectal exudate from anoscopic or anal examination should be examined for polymorphonuclear leukocytes. All persons should be evaluated for herpes simplex (preferably by NAAT of rectal lesions), *N. gonorrhoeae* (NAAT or culture), *C. trachomatis* (NAAT), and *T. pallidum* (darkfield of lesion if available and serologic testing). If the *C. trachomatis* NAAT test is positive on a rectal swab and severe symptoms associated with LGV are present (including rectal ulcers, anal discharge, bleeding, ≥10 WBCs on Gram stain, and tenesmus), patients should be treated empirically for LGV. Molecular testing for LGV is not widely available or not FDA cleared, and results are not typically available in time for clinical decision-making. However, if available, molecular PCR testing for *C. trachomatis* serovars L1, L2, or L3 can be considered for confirming LGV (*553*).

The pathogenic role of *M. genitalium* in proctitis is unclear. For persons with persistent symptoms after standard treatment, providers should consider testing for *M. genitalium* with NAAT and treat if positive (see *Mycoplasma genitalium*).

Treatment

Acute proctitis among persons who have anal exposure through oral, genital, or digital contact is usually sexually acquired (*1382*,*1388*). Presumptive therapy should be

initiated while awaiting results of laboratory tests for persons with anorectal exudate detected on examination or polymorphonuclear leukocytes detected on a Gram-stained smear of anorectal exudate or secretions. Such therapy also should be initiated when anoscopy or Gram stain is not available and the clinical presentation is consistent with acute proctitis for persons reporting receptive anal exposures.

Recommended Regimen for Acute Proctitis
Ceftriaxone 500 mg* IM in a single dose *plus* **Doxycycline** 100 mg orally 2 times/day for 7 days†

* For persons weighing ≥150 kg, 1 g of ceftriaxone should be administered.
† Doxycycline course should be extended to 100 mg orally 2 times/day for 21 days in the presence of bloody discharge, perianal or mucosal ulcers, or tenesmus and a positive rectal chlamydia test.

Bloody discharge, perianal ulcers, or mucosal ulcers among persons with acute proctitis and rectal chlamydia (NAAT) should receive presumptive treatment for LGV with an extended course of doxycycline 100 mg orally 2 times/day for 3 weeks (*1389*,*1390*) (see Lymphogranuloma Venereum). If painful perianal ulcers are present or mucosal ulcers are detected on anoscopy, presumptive therapy should also include a regimen for genital herpes (see Genital Herpes).

Diagnostic and Treatment Considerations for Proctocolitis or Enteritis

Treatment for proctocolitis or enteritis should be directed to the specific enteric pathogen identified. Multiple stool examinations might be necessary for detecting *Giardia*, and special stool preparations are required for diagnosing cryptosporidiosis and microsporidiosis. Diagnostic and treatment recommendations for all enteric infections are beyond the scope of these guidelines. Providers should be aware of the potential for antimicrobial-resistant pathogens, particularly during outbreaks of *Shigella* and *Campylobacter* among sexual networks of MSM where increased resistance to azithromycin, fluoroquinolones, and isolates resistant to multiple antibiotics have been described (*266*,*272*,*273*,*1391*,*1392*).

Other Management Considerations

To minimize transmission and reinfection, patients treated for acute proctitis should be instructed to abstain from sexual intercourse until they and their partners have been treated (i.e., until completion of a 7-day regimen and symptoms have resolved). Studies have reported that behaviors that facilitate enteric pathogen transmission might be associated with acquisition of other STIs, including HIV infection. All persons with acute proctitis and concern for sexually transmitted proctocolitis or enteritis should be tested for HIV, syphilis, gonorrhea, and chlamydia (at other exposed sites). PEP should be considered for exposures that present a risk for HIV acquisition. For ongoing risk for HIV acquisition, PrEP should be considered.

Evidence-based interventions for preventing acquisition of sexually transmitted enteric pathogens are not available. However, extrapolating from general infection control practices for communicable diseases and established STI prevention practices, recommendations include avoiding contact with feces during sex, using barriers, and washing hands after handing materials that have been in contact with the anal area (i.e., barriers and sex toys) and after touching the anus or rectal area.

Follow-Up

Follow-up should be based on specific etiology and severity of clinical symptoms. For proctitis associated with gonorrhea or chlamydia, retesting for the respective pathogen should be performed 3 months after treatment.

Management of Sex Partners

Partners who have had sexual contact with persons treated for gonorrhea or chlamydia <60 days before the onset of the persons symptoms should be evaluated, tested, and presumptively treated for the respective infection. Partners of persons with proctitis should be evaluated for any diseases diagnosed in the index partner. Sex partners should abstain from sexual contact until they and their partners are treated. No specific recommendations are available for screening or treating sex partners of persons with diagnosed sexually transmitted enteric pathogens; however, partners should seek care if symptomatic.

Special Considerations

Drug Allergy, Intolerance, and Adverse Reactions

Allergic reactions with third-generation cephalosporins (e.g., ceftriaxone) are uncommon among persons with a history of penicillin allergy (*620*,*631*,*658*,*896*).

HIV Infection

Persons with HIV infection and acute proctitis might present with bloody discharge, painful perianal ulcers, or mucosal ulcers and LGV and herpes proctitis are more prevalent among this population. Presumptive treatment in such cases should include a regimen for genital herpes and LGV.

Ectoparasitic Infections

Pediculosis Pubis

Persons who have pediculosis pubis (i.e., pubic lice) usually seek medical attention because of pruritus or because they notice lice or nits on their pubic hair. Pediculosis pubis is caused by the parasite *Phthirus pubis* and is usually transmitted by sexual contact (*1393*).

Diagnosis

The clinical diagnosis is based on typical symptoms of itching in the pubic region. Lice and nits can be observed on pubic hair.

Treatment

Recommended Regimens for Pediculosis Pubis
Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes *or* **Pyrethrin with piperonyl butoxide** applied to the affected area and washed off after 10 minutes

Alternative Regimens
Malathion 0.5% lotion applied to affected areas and washed off after 8–12 hours *or* **Ivermectin** 250 μg/kg body weight orally, repeated in 7–14 days

Reported resistance to pediculcides (permethrin and pyrethrin) has been increasing and is widespread (*1394*,*1395*). Malathion can be used when treatment failure is believed to have occurred as a result of resistance. The odor and longer duration of application associated with malathion therapy make it a less attractive alternative compared with the recommended pediculicides. Ivermectin has limited ovicidal activity (*1396*). Ivermectin might not prevent recurrences from eggs at the time of treatment, and therefore treatment should be repeated in 7–14 days (*1397*,*1398*). Ivermectin should be taken with food because bioavailability is increased, thus increasing penetration of the drug into the epidermis. Adjustment of ivermectin dosage is not required for persons with renal impairment; however, the safety of multiple doses among persons with severe liver disease is unknown. Lindane is not recommended for treatment of pediculosis because of toxicity, contraindications for certain populations (pregnant and breastfeeding women, children aged <10 years, and those with extensive dermatitis), and complexity of administration.

Other Management Considerations

The recommended regimens should not be applied to the eyes. Pediculosis of the eyelashes should be treated by applying occlusive ophthalmic ointment or petroleum jelly to the eyelid margins 2 times/day for 10 days. Bedding and clothing should be decontaminated (i.e., machine washed and dried by using the heat cycle or dry cleaned) or removed from body contact for at least 72 hours. Fumigation of living areas is unnecessary. Pubic hair removal has been associated with atypical patterns of pubic lice infestation and decreasing incidence of infection (*537*,*1399*). Persons with pediculosis pubis should be evaluated for HIV, syphilis, chlamydia, and gonorrhea.

Follow-Up

Evaluation should be performed after 1 week if symptoms persist. Retreatment might be necessary if lice are found or if eggs are observed at the hair-skin junction. If no clinical response is achieved to one of the recommended regimens, retreatment with an alternative regimen is recommended.

Management of Sex Partners

Sex partners within the previous month should be treated. Sexual contact should be avoided until patients and partners have been treated, bedding and clothing decontaminated, and reevaluation performed to rule out persistent infection.

Special Considerations

Pregnancy

Existing data from human participants demonstrate that pregnant and lactating women should be treated with either permethrin or pyrethrin with piperonyl butoxide. Because no teratogenicity or toxicity attributable to ivermectin has been observed during human pregnancy experience, ivermectin is classified as "human data suggest low risk" during pregnancy and probably compatible with breastfeeding (*431*).

HIV Infection

Persons who have pediculosis pubis and HIV infection should receive the same treatment regimen as those who do not have HIV.

Scabies

Scabies is a skin infestation caused by the mite *Sarcoptes scabiei*, which causes pruritus. Sensitization to *S. scabiei* occurs before pruritus begins. The first time a person is infested with *S. scabiei*, sensitization takes weeks to develop. However, pruritus might occur <24 hours after a subsequent reinfestation. Scabies among adults frequently is sexually acquired, although scabies among children usually is not (*1400–1402*).

Diagnosis

Scabies diagnosis is made by identifying burrows, mites, eggs, or the mites' feces from affected areas. Skin scrapings can be examined under the microscope to identify organisms, although

this method has low sensitivity and is time consuming (*1403*). Alternatively, noninvasive examination of the affected skin by using videodermatoscopy, videomicroscopy, or dermoscopy can be used, each of which has high sensitivity and specificity, particularly when performed by experienced operators (*1404*). Low-technology strategies include the burrow ink test and the adhesive tape test.

Treatment

Recommended Regimens for Scabies
Permethrin 5% cream applied to all areas of the body from the neck down and washed off after 8–14 hours *or* **Ivermectin** 200 ug/kg body weight orally, repeated in 14 days* *or* **Ivermectin 1% lotion** applied to all areas of the body from the neck down and washed off after 8–14 hours; repeat treatment in 1 week if symptoms persist
* Oral ivermectin has limited ovicidal activity; a second dose is required for eradication.

Alternative Regimen
Lindane 1% 1 oz of lotion or 30 g of cream applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after 8 hours*
* Infants and children aged <10 years should not be treated with lindane.

Topical permethrin and oral and topical ivermectin have similar efficacy for cure of scabies (*1405–1410*). Choice of treatment might be based on patient preference for topical versus oral therapy, drug interactions with ivermectin (e.g., azithromycin, trimethoprim/sulfamethoxazole [Bactrim], or cetirizine [Zytrec]), and cost. Permethrin is safe and effective with a single application (*1411*). Ivermectin has limited ovicidal activity and might not prevent recurrences of eggs at the time of treatment; therefore, a second dose of ivermectin should be administered 14 days after the first dose (*1412*). Ivermectin should be taken with food because bioavailability is increased, thereby increasing penetration of the drug into the epidermis. Adjustments to ivermectin dosing are not required for patients with renal impairment; however, the safety of multiple doses among patients with severe liver disease is unknown.

Lindane is an alternative regimen because it can cause toxicity (*1413*); it should be used only if the patient cannot tolerate the recommended therapies or if these therapies have failed (*1414–1416*). Lindane is not recommended for pregnant and breastfeeding women, children aged <10 years, and persons with extensive dermatitis. Seizures have occurred when lindane was applied after a bath or used by patients who had extensive dermatitis. Aplastic anemia after lindane use also has been reported (*1413*). Lindane resistance has been reported in some areas of the world, including parts of the United States (*1413*).

Other Management Considerations

Bedding and clothing should be decontaminated (i.e., either machine washed and dried by using the heat cycle or dry cleaned) or removed from body contact for >72 hours. Fumigation of living areas is unnecessary. Persons with scabies should be advised to keep fingernails closely trimmed to reduce injury from excessive scratching (*1417*).

Crusted Scabies

Crusted scabies is an aggressive infestation that usually occurs among immunodeficient, debilitated, or malnourished persons, including persons receiving systemic or potent topical glucocorticoids, organ transplant recipients, persons with HIV infection or human T-lymphotrophic virus-1 infection, and persons with hematologic malignancies. Crusted scabies is transmitted more easily than scabies (*1418*). No controlled therapeutic studies for crusted scabies have been conducted, and a recommended treatment remains unclear. Substantial treatment failure might occur with a single-dose topical scabicide or with oral ivermectin treatment. Combination treatment is recommended with a topical scabicide, either 5% topical permethrin cream (full-body application to be repeated daily for 7 days then 2 times/week until cure) or 25% topical benzyl benzoate, and oral ivermectin 200 *u*g/kg body weight on days 1, 2, 8, 9, and 15. Additional ivermectin treatment on days 22 and 29 might be required for severe cases (*1419*). Lindane should be avoided because of the risks for neurotoxicity with heavy applications on denuded skin.

Follow-Up

The rash and pruritus of scabies might persist for <2 weeks after treatment. Symptoms or signs persisting for >2 weeks can be attributed to multiple factors. Treatment failure can occur as a result of resistance to medication or faulty application of topical scabicides. These medications do not easily penetrate into thick, scaly skin of persons with crusted scabies, perpetuating the harboring of mites in these difficult-to-penetrate layers. In the absence of recommended contact treatment and decontamination of bedding and clothing, persisting symptoms can be attributed to reinfection by family members or fomites. Finally, other household mites can cause symptoms to persist as a result of cross-reactivity between antigens. Even when treatment is successful, reinfection is avoided, and cross-reactivity does not occur, symptoms can persist or worsen as a result of allergic dermatitis.

Retreatment 2 weeks after the initial treatment regimen can be considered for those persons who are still symptomatic or when live mites are observed. Use of an alternative regimen is recommended for those persons who do not respond initially to the recommended treatment.

Management of Sex Partners and Household Contacts

Persons who have had sexual, close personal, or household contact with the patient within the month preceding scabies infestation should be examined. Those identified as being infested should be provided treatment.

Management of Outbreaks in Communities, Nursing Homes, and Other Institutional Settings

Scabies epidemics frequently occur in nursing homes, hospitals, residential facilities, and other communities (*1420*,*1421*). Control of an epidemic can only be achieved by treating the entire population at risk. Ivermectin can be considered in these settings, especially if treatment with topical scabicides fails. Mass treatment with oral ivermectin is highly effective in decreasing prevalence in settings where scabies is endemic (*1422*). Epidemics should be managed in consultation with a specialist.

Special Considerations

Infants, Young Children, and Pregnant or Lactating Women

Infants and young children should be treated with permethrin; the safety of ivermectin for children weighing <15 kg has not been determined. Infants and children aged <10 years should not be treated with lindane. Ivermectin likely poses a low risk to pregnant women and is likely compatible with breastfeeding; however, because of limited data regarding ivermectin use for pregnant and lactating women, permethrin is the preferred treatment (*431*) (see Pediculosis Pubis).

HIV Infection

Persons with HIV infection who have uncomplicated scabies should receive the same treatment regimens as those who do not have HIV. Persons with HIV infection and others who are immunosuppressed are at increased risk for crusted scabies and should be managed in consultation with a specialist.

Sexual Assault and Abuse and STIs

Adolescents and Adults

These guidelines are primarily limited to the identification, prophylaxis, and treatment of STIs and conditions among adolescent and adult female sexual assault survivors. However, some of the following guidelines might still apply to male sexual assault survivors. Documentation of findings, collection of nonmicrobiologic specimens for forensic purposes, and management of potential pregnancy or physical and psychological trauma are beyond the scope of these guidelines. Examinations of survivors of sexual assault should be conducted by an experienced clinician in a way that minimizes further trauma to the person. The decision to obtain genital or other specimens for STI diagnosis should be made on an individual basis. Care systems for survivors should be designed to ensure continuity, including timely review of test results, support adherence, and monitoring for adverse reactions to any prescribed therapeutic or prophylactic regimens. Laws in all 50 states limit the evidentiary use of a survivor's previous sexual history, including evidence of previously acquired STIs, as part of an effort to undermine the credibility of the survivor's testimony. Evidentiary privilege against revealing any aspect of the examination or treatment also is enforced in most states. Although it rarely occurs, STI diagnoses might later be accessed, and the survivor and clinician might opt to defer testing for this reason. Although collection of specimens at initial examination for laboratory STI diagnosis gives the survivor and clinician the option of deferring empiric prophylactic antimicrobial treatment, compliance with follow-up visits is typically poor (*1423*–*1425*). Among sexually active adults, identification of an STI might represent an infection acquired before the assault, and therefore might be more important for the medical management of the patient than for legal purposes.

Trichomoniasis, BV, gonorrhea, and chlamydia are the most frequently diagnosed infections among women who have been sexually assaulted. Such conditions are prevalent among the population, and detection of these infections after an assault does not necessarily imply acquisition during the assault. However, a postassault examination presents an important opportunity for identifying or preventing an STI. Chlamydial and gonococcal infections among women are of particular concern because of the possibility of ascending infection. In addition, HBV infection can be prevented through postexposure vaccination (see Hepatitis B Virus Infection). Because persons who have been sexually assaulted also are at risk for acquiring HPV infection, and the efficacy of the HPV vaccine is high (*1426*,*1427*), HPV vaccination is also recommended for females and males through age 26 years (https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html) (*11*). Reproductive-aged female survivors should be evaluated for pregnancy and offered emergency contraception.

Evaluating Adolescents and Adults for STIs

Initial Examination

Decisions to perform the following tests should be made on an individual basis. An initial examination after a sexual assault might include the following:

- NAATs for *C. trachomatis* and *N. gonorrhoeae* at the sites of penetration or attempted penetration should be performed (*553*). These tests are preferred for diagnostic evaluation of adolescent or adult sexual assault survivors.
- Females should be offered NAAT testing for *T. vaginalis* from a urine or vaginal specimen. POC or wet mount with measurement of vaginal pH and KOH application for the whiff test from vaginal secretions should be performed for evidence of BV and candidiasis, especially if vaginal discharge, malodor, or itching is present.
- MSM should be offered screening for *C. trachomatis* and *N. gonorrhoeae* if they report receptive oral or anal sex during the preceding year, regardless of whether sexual contact occurred at these anatomic sites during the assault. Anoscopy should be considered in instances of reported anal penetration.
- A serum sample should be performed for HIV, HBV, and syphilis infection.

Treatment

Compliance with follow-up visits is poor among survivors of sexual assault (*1423–1425*). Consequently, the following routine presumptive treatments after a sexual assault are recommended:

- An empiric antimicrobial regimen for chlamydia, gonorrhea, and trichomonas for women and chlamydia and gonorrhea for men.
- Emergency contraception should be considered when the assault could result in pregnancy (see Emergency Contraception).
- Postexposure hepatitis B vaccination (without HBIG) if the hepatitis status of the assailant is unknown and the survivor has not been previously vaccinated. If the assailant is known to be HBsAg positive, unvaccinated survivors should receive both hepatitis B vaccine and HBIG. The vaccine and HBIG, if indicated, should be administered to sexual assault survivors at the time of the initial examination, and follow-up doses of vaccine should be administered 1–2 and 4–6 months after the first dose. Survivors who were previously vaccinated but did not receive postvaccination testing should receive a single vaccine booster dose (see Hepatitis B Virus Infection).
- HPV vaccination for female and male survivors aged 9–26 years who have not been vaccinated or are incompletely vaccinated (*11*) (https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html). The vaccine should be administered to sexual assault survivors at the time of the initial examination, and follow-up doses should be administered at 1–2 months and 6 months after the first dose. A 2-dose schedule (0 and 6–12 months) is recommended for persons initiating vaccination before age 15 years.
- Recommendations for HIV PEP are made on a case-by-case basis according to risk (see Risk for Acquiring HIV Infection; Recommendations for Postexposure HIV Risk Assessment of Adolescents and Adults <72 Hours After Sexual Assault).

Recommended Regimen for Adolescent and Adult Female Sexual Assault Survivors
Ceftriaxone 500 mg* IM in a single dose *plus* **Doxycycline** 100 mg 2 times/day orally for 7 days *plus* **Metronidazole** 500 mg 2 times/day orally for 7 days
* For persons weighing ≥150 kg, 1 g of ceftriaxone should be administered.

Recommended Regimen for Adolescent and Adult Male Sexual Assault Survivors
Ceftriaxone 500 mg* IM in a single dose *plus* **Doxycycline** 100 mg 2 times/day orally for 7 days
* For persons weighing ≥150 kg, 1 g of ceftriaxone should be administered.

Clinicians should counsel persons regarding the possible benefits and toxicities associated with these treatment regimens; gastrointestinal side effects can occur with this combination. The efficacy of these regimens in preventing infections after sexual assault has not been evaluated. For those requiring alternative treatments, refer to the specific sections in this report relevant to the specific organisms.

Other Management Considerations

At the initial examination and, if indicated, at follow-up examinations, patients should be counseled regarding symptoms of STIs and the need for immediate examination if symptoms occur. Further, they should be instructed to abstain from sexual intercourse until STI prophylactic treatment is completed.

Follow-Up

After the initial postassault examination, follow-up examinations provide an opportunity to detect new infections acquired during or after the assault, complete hepatitis B and HPV vaccinations, if indicated, complete counseling and treatment for other STIs, and monitor side effects and adherence to PEP, if prescribed. If initial testing was performed, follow-up evaluation should be conducted in <1 week to ensure that results of positive tests can be discussed promptly with the survivor, treatment is provided if not administered at the initial visit, and any follow-up for infections can be arranged. If initial tests are negative and treatment was not provided,

examination for STIs can be repeated 1–2 weeks after the assault; repeat testing detects infectious organisms that might not have reached sufficient concentrations to produce positive test results at the time of initial examination. For survivors who are treated during the initial visit, regardless of whether testing was performed, posttreatment testing should be conducted only if the person reports having symptoms. If initial test results were negative and infection in the assailant cannot be ruled out, serologic tests for syphilis can be repeated at 4–6 weeks and 3 months; HIV testing can be repeated at 6 weeks and at 3 months by using methods to identify acute HIV infection.

Risk for Acquiring HIV Infection

HIV seroconversion has occurred among persons whose only known risk factor was sexual assault or sexual abuse; however, the frequency of this occurrence likely is low (*1428*,*1429*). In consensual sex, the per-act risk for HIV transmission from vaginal intercourse is 0.08%, and for receptive anal intercourse, 1.38% (*192*). The per-act risk for HIV transmission from oral sex is substantially lower. Specific circumstances of an assault (e.g., bleeding, which often accompanies trauma) might increase risk for HIV transmission in cases involving vaginal, anal, or oral penetration. Site of exposure to ejaculate, viral load in ejaculate, and the presence of an STI or genital lesions in the assailant or survivor also might increase risk for HIV acquisition.

PEP with a 28-day course of zidovudine was associated with an 81% reduction in risk for acquiring HIV in a study of health care workers who had percutaneous exposures to HIV-infected blood (*1430*). On the basis of these results and results from animal studies, PEP has been recommended for health care workers who have occupational exposures to HIV (*1431*). These findings have been extrapolated to nonoccupational injecting drug and sexual HIV exposures, including sexual assault. The possibility of HIV exposure from the assault should be assessed at the initial examination; survivors determined to be at risk for acquiring HIV should be informed about the possible benefit of PEP in preventing HIV infection. Initiation of PEP as soon as possible after the exposure increases the likelihood of prophylactic benefit.

Multiple factors affect the medical recommendation for PEP and affect the assault survivor's acceptance of that recommendation. These factors include the likelihood of the assailant having HIV, any exposure characteristics that might increase the risk for HIV transmission, the time elapsed after the event, and the potential benefits and risks associated with PEP (*1431*). Determination of the assailant's HIV status at the time of the postassault examination is usually not possible. Therefore, health care providers should assess any available information concerning the characteristics and HIV risk behaviors of the assailant (e.g., being an MSM or using injecting drugs), local epidemiology of HIV/AIDS, and exposure characteristics of the assault. When an assailant's HIV status is unknown, determinations about risk for HIV transmission to the survivor should be based on whether vaginal or anal penetration occurred; whether ejaculation occurred on mucous membranes; whether multiple assailants were involved; whether mucosal lesions were present in the assailant or survivor; and any other characteristics of the assault, survivor, or assailant that might increase risk for HIV transmission.

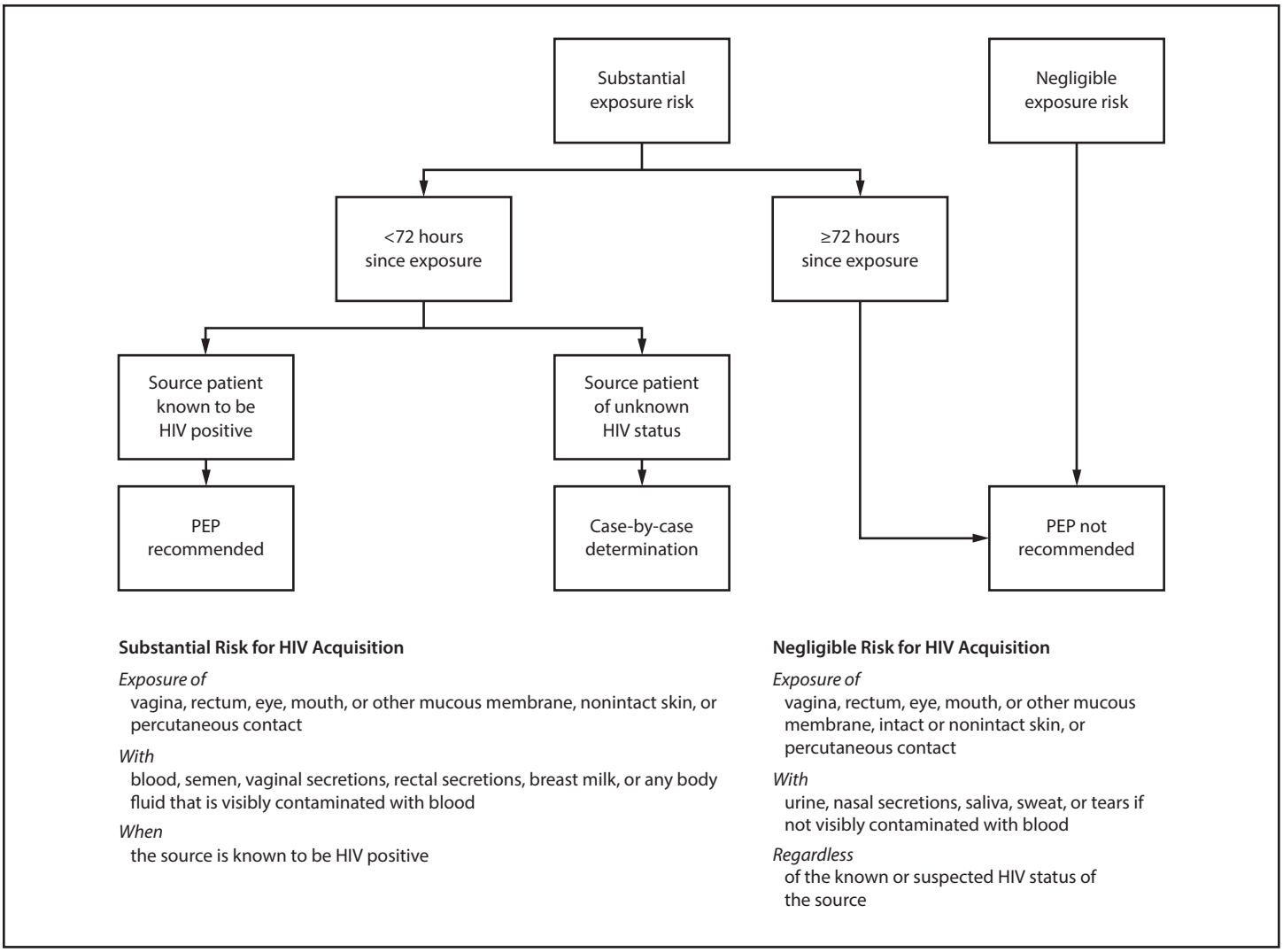
If PEP is offered, the following information should be discussed with the survivor: the necessity of early initiation of PEP to optimize potential benefits (i.e., as soon as possible after and <72 hours after the assault), the importance of close follow-up, the benefit of adherence to recommended dosing, and potential adverse effects of antiretroviral medications. Providers should emphasize that severe adverse effects are rare from PEP (*1431–1435*). Clinical management of the survivor should be implemented according to the HIV PEP guidelines and in collaboration with specialists (*1436*). Health care providers should provide an initial course of 3–7 days of medication (i.e., a starter pack) with a prescription for the remainder of the course, or, if starter packs are unavailable, they should provide a prescription for an entire 28-day course. Provision of the entire 28-day PEP medication supply at the initial visit has been reported to increase likelihood of adherence, especially when patients have difficulty returning for multiple follow-up visits (*1437*). Routinely providing starter packs or the entire 28-day course requires that health care providers stock PEP drugs in their practice setting or have an established agreement with a pharmacy to stock, package, and urgently dispense PEP drugs with required administration instructions. Uninsured patients or those with high copayments can be enrolled in a patient-assistance program to ensure access to PEP medications. An early follow-up visit should be scheduled at which health care providers can discuss the results of HIV and STI testing, provide additional counseling and support, provide indicated vaccines not administered at the initial evaluation, assess medication side effects and adherence, or provide an altered PEP medication regimen if indicated by side effects or laboratory test results.

Recommendations for Postexposure HIV Risk Assessment of Adolescents and Adults <72 Hours After Sexual Assault

Health care providers should do the following:

- Assess risk for HIV infection in the assailant, and test that person for HIV whenever possible.
- Use the algorithm to evaluate the survivor for the need for HIV PEP (Figure) (*1436*).

FIGURE. Algorithm to evaluate the need for nonoccupational HIV postexposure prophylaxis among adult and adolescent survivors of sexual assault



Source: Adapted from Announcement: updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV—United States, 2016. MMWR Morb Mortal Wkly Rep 2016;65:458.
Abbreviation: PEP = postexposure prophylaxis.

- Consult with a specialist in HIV treatment if PEP is being considered.
- If the survivor appears to be at risk for acquiring HIV from the assault, discuss PEP, including benefits and risks.
- If the survivor chooses to start PEP, provide an initial course of 3–7 days of medication (i.e., a starter pack) with a prescription for the remainder of the course or provide a prescription for an entire 28-day course. Schedule an early follow-up visit to discuss test results and provide additional counseling (*1438*).
- If PEP is started, obtain serum creatinine, AST, and alanine aminotransferase at baseline.
- Perform an HIV antibody test at original assessment; repeat at 6 weeks and 3 months.
- Counsel the survivor regarding ongoing risk for HIV acquisition and about HIV PrEP, and provide referrals to a PrEP provider.

Assistance with PEP-related decisions can be obtained by calling the National Clinician's Post Exposure Prophylaxis Hotline (PEP Line) (telephone: 888-448-4911).

Sexual Assault or Abuse of Children

These guidelines are limited to the identification and treatment of STIs in prepubertal children. Management of the psychosocial or legal aspects of the sexual assault or abuse of children is beyond the scope of these guidelines.

Identification of STIs in children past the neonatal period strongly indicates sexual abuse (*1438*). The importance of

identifying a sexually transmitted organism for such children as evidence of possible child sexual abuse varies by pathogen. Postnatally acquired gonorrhea, syphilis, chlamydia, and *T. vaginalis* infection and nontransfusion, nonperinatally acquired HIV infection are indicative of sexual abuse. Sexual abuse should be suspected when anogenital herpes or anogenital warts are diagnosed. Investigation of sexual abuse among children who have an infection that might have been transmitted sexually should be conducted in compliance with recommendations by clinicians who have experience and training in all elements of the evaluation of child abuse, neglect, and assault. The social significance of an infection that might have been acquired sexually varies by the specific organism, as does the threshold for reporting suspected child sexual abuse (Table 8). When any STI has been diagnosed in a child, efforts should be made in consultation with a specialist to evaluate the possibility of sexual abuse, including conducting a history and physical examination for evidence of abuse and diagnostic testing for other commonly occurring STIs (*1439–1441*).

The general rule that STIs beyond the neonatal period are evidence of sexual abuse has exceptions. For example, genital infection with *T. vaginalis* (*1442*) or rectal or genital infection with *C. trachomatis* among young children might be the result of perinatally acquired infection and has, in certain cases of chlamydial infection, persisted for as long as 2–3 years (*1443–1445*), although perinatal chlamydial infection is now uncommon because of prenatal screening and treatment of pregnant women. Genital warts have been diagnosed among children who have been sexually abused (*1426*) but also among children who have no other evidence of sexual abuse (*1446*,*1447*); lesions appearing for the first time in a child aged >5 years are more likely to have been caused by sexual transmission (*1448*). BV has been diagnosed among children who have been abused but its presence alone does not prove sexual abuse. The majority of HBV infections among children result from household exposure to persons who have chronic HBV infection rather than sexual abuse.

Reporting

All U.S. states and territories have laws that require reporting of child abuse. Although the exact requirements differ by state or territory, if a health care provider has reasonable cause to suspect child abuse, a report must be made (*1448*). Health care providers should contact their state or local child protection service agency regarding child abuse reporting requirements.

Evaluating Children for STIs

Evaluating children for sexual assault or abuse should be conducted in a manner designed to minimize pain and trauma to the child. Examinations and collection of vaginal specimens in prepubertal girls can be extremely uncomfortable and should be performed by an experienced clinician to avoid psychological and physical trauma to the child. The decision to obtain genital or other specimens from a child to evaluate for STIs should be made on an individual basis. However, children who received a diagnosis of one STI should be screened for other STIs. History and reported type of sexual contact might not be a reliable indicator, and urogenital, pharyngeal, and rectal testing should be considered for preverbal children and children who cannot verbalize details of the assault (*1438*,*1449*). Factors that should lead the physician to consider testing for STIs include the following (*1449*):

- The child has experienced penetration or has evidence of recent or healed penetrative injury to the genitals, anus, or oropharynx.
- The child has been abused by a stranger.

TABLE 8. Implications of commonly encountered sexually transmitted or sexually associated infections for diagnosis and reporting of sexual abuse among infants and prepubertal children

Infection	Evidence for sexual abuse	Recommended action
Gonorrhea*	Diagnostic	Report†
Syphilis*	Diagnostic	Report†
HIV§	Diagnostic	Report†
*Chlamydia trachomatis**	Diagnostic	Report†
*Trichomonas vaginalis**	Diagnostic	Report†
Anogenital herpes	Suspicious	Consider report†,¶
Condylomata acuminata (anogenital warts)*	Suspicious	Consider report†,¶,**
Anogenital molluscum contagiosum	Inconclusive	Medical follow-up
Bacterial vaginosis	Inconclusive	Medical follow-up

Sources: Adapted from Kellogg N; American Academy of Pediatrics Committee on Child Abuse and Neglect. The evaluation of child abuse in children. Pediatrics 2005;16:506–12; Adams JA, Farst KJ, Kellogg ND. Interpretation of medical findings in suspected child abuse: an update for 2018. J Pediatr Adolesc Gynecol 2018;31:225–31.

* If unlikely to have been perinatally acquired and vertical transmission, which is rare, is excluded.
† Reports should be made to the local or state agency mandated to receive reports of suspected child abuse or neglect.
§ If unlikely to have been acquired perinatally or through transfusion.
¶ Unless a clear history of autoinoculation exists.
** Report if evidence exists to suspect abuse, including history, physical examination, or other identified infections. Lesions appearing for the first time in a child aged >5 years are more likely to have been caused by sexual transmission.

- The child has been abused by an assailant known to be infected with an STI or at high risk for STIs (e.g., injecting drug user, MSM, person with multiple sex partners, or person with a history of STIs).
- The child has a sibling, other relative, or another person in the household with an STI.
- The child lives in an area with a high rate of STIs in the community.
- The child has signs or symptoms of STIs (e.g., vaginal discharge or pain, genital itching or odor, urinary symptoms, or genital lesions or ulcers).
- The child or parent requests STI testing.
- The child is unable to verbalize details of the assault.

If a child has symptoms, signs, or evidence of an infection that might be sexually transmitted, the child should be tested for common STIs before initiation of any treatment that might interfere with diagnosing other STIs. Because of the legal and psychosocial consequences of a false-positive diagnosis, only tests with high specificities should be used. The potential benefit to the child of a reliable STI diagnosis justifies deferring presumptive treatment until specimens for highly specific tests are obtained by providers with experience in evaluating sexually abused and assaulted children.

Evaluations should be performed on a case-by-case basis, according to history of assault or abuse and in a manner that minimizes the possibility for psychological trauma and social stigma. If the initial exposure was recent, the infectious organisms acquired through the exposure might not have produced sufficient concentrations to result in positive test results or examination findings (*1450*). Alternatively, positive test results after a recent exposure might represent the assailant's secretions (but would nonetheless be an indication for treatment of the child). A second visit approximately 2–6 weeks after the most recent sexual exposure should be scheduled to include a repeat physical examination and collection of additional specimens to identify any infection that might not have been detected at the time of initial evaluation. A single evaluation might be sufficient if the child was abused for an extended period and if a substantial amount of time elapsed between the last suspected episode of abuse and the medical evaluation. Compliance with follow-up appointments might be improved when law enforcement personnel or child protective services are involved.

Initial Examination

Visual inspection of the genital, perianal, and oral areas for genital discharge, odor, bleeding, irritation, warts, and ulcerative lesions should be performed during initial examination. The clinical manifestations of certain STIs are different for children than for adults. For example, typical vesicular lesions might be absent even in the presence of HSV infection. The following should be performed during the initial examination, if STI testing is indicated:

- Testing for *N. gonorrhoeae* and *C. trachomatis* can be performed from specimens collected from the pharynx and rectum, as well as the vagina for girls and urine for boys. Cervical specimens are not recommended for prepubertal girls. For boys with a urethral discharge, a meatal specimen discharge is an adequate substitute for an intraurethral swab specimen. Culture or NAAT can be used to test for *N. gonorrhoeae* and *C. trachomatis.* Although data regarding NAAT for children are more limited and performance is test dependent (*553*), no evidence demonstrates that performance of NAAT for detection of *N. gonorrhoea* or *C. trachomatis* among children differs from that among adults. Only FDA-cleared NAAT assays should be used. Consultation with an expert is necessary before using NAAT in this context, both to minimize the possibility of cross-reaction with nongonococcal *Neisseria* species and other commensals (e.g., *N. meningitidis*, *N. sicca*, *N. lactamica*, *N. cinerea*, or *M. catarrhalis*) and to ensure correct interpretation of results. Because of the implications of a diagnosis of *N. gonorrhoeae* or *C. trachomatis* infection in a child, only CLIA-validated, FDA-cleared NAATs should be used (*837*). If culture for the isolation of *N. gonorrhoeae* or *C. trachomatis* is performed, only standard culture procedures should be followed. Specimens from the vagina, urethra, pharynx, or rectum should be streaked onto selective media for isolation of *N. gonorrhoeae*, and all presumptive isolates of *N. gonorrhoeae* should be identified definitively by at least two tests that involve different approaches (e.g., biochemical, enzyme substrate, or molecular probes). Gram stains are inadequate for evaluating prepubertal children for gonorrhea and should not be used to diagnose or exclude gonorrhea. Specimens (either NAAT or culture, including any isolates) obtained before treatment should be preserved for further validation if needed. When a specimen is positive, the result should be confirmed either by retesting the original specimen or obtaining another. Because of the overall low prevalence of *N. gonorrhoeae* and *C. trachomatis* among children, false-positive results can occur, and all specimens that are initially positive should be confirmed.
- Testing for *T. vaginalis* should not be limited to girls with vaginal discharge if other indications for vaginal testing exist because evidence indicates that asymptomatic sexually abused children might be infected with *T. vaginalis* and might benefit from treatment (*1451*,*1452*). NAAT can be used as an alternative or in addition to culture and wet

mount, especially in settings where culture and wet mount of vaginal swab specimens are not obtainable. Data regarding use of NAATs for detection of *T. vaginalis* among children are limited; however, no evidence indicates that performance of NAAT for detection of *T. vaginalis* for children would differ from that for adults. Consultation with an expert is necessary before using NAAT in this context to ensure correct interpretation of results. Because of the implications of a diagnosis of *T. vaginalis* infection in a child, only CLIA-validated, FDA-cleared NAATs should be used (*837*). POC tests for *T. vaginalis* have not been validated for prepubertal children and should not be used. In the case of a positive specimen, the result should be confirmed either by retesting the original specimen or obtaining another. Because of the overall low prevalence of *T. vaginalis* among children, false-positive results can occur, and all specimens that are initially positive should be confirmed.

- HSV can be indicative of sexual abuse; therefore, specimens should be obtained from all vesicular or ulcerative genital or perianal lesions and sent for NAAT or viral culture.
- Wet mount can be used for a vaginal swab specimen for BV if discharge is present.
- Collection of serum samples should be evaluated, preserved for subsequent analysis, and used as a baseline for comparison with follow-up serologic tests. Sera can be tested for antibodies to *T. pallidum*, HIV, and HBV. Decisions regarding the infectious agents for which to perform serologic tests should be made on a case-by-case basis.

Treatment

The risk for a child acquiring an STI as a result of sexual abuse or assault has not been well studied. Presumptive treatment for children who have been sexually assaulted or abused is not recommended because the incidence of most STIs among children is low after abuse or assault, prepubertal girls appear to be at lower risk for ascending infection than adolescent or adult women, and regular follow-up of children usually can be ensured. However, certain children or their parent or guardian might be concerned about the possibility of infection with an STI, even if the health care provider has perceived the risk to be low. Such concerns might be an indication for presumptive treatment in certain settings and might be considered after all relevant specimens for diagnostic tests have been collected.

Other Management Considerations

Children who are survivors of sexual assault or abuse are at increased risk for future unsafe sexual practices that have been linked to higher risk for HPV acquisition (*1426*,*1453*) and are more likely to engage in these behaviors at an earlier age; therefore, ACIP recommends vaccination of these children at age ≥9 years if they have not initiated or completed HPV vaccination (see Human Papillomavirus Infections, Prevention) (https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hpv.html). Although HPV vaccine will not protect against progression of infection already acquired or promote clearance of the infection, the vaccine protects against HPV types not yet acquired.

Follow-Up

If no infections were identified at the initial examination after the last suspected sexual exposure, and if this exposure was recent, a follow-up evaluation approximately 2 weeks after the last exposure can be considered. Likewise, if no physical examination or diagnostic testing was performed at the initial visit, a complete examination can be scheduled approximately 2 weeks after the last exposure to identify any evidence of STIs. In circumstances in which transmission of syphilis, HIV, HBV, or HPV is a concern but baseline tests for syphilis, HIV, and HBV are negative and examinations for genital warts are negative, follow-up serologic testing and examination approximately 6 weeks and <3 months after the last suspected sexual exposure is recommended to allow time for antibodies to develop and signs of infection to appear. In addition, results of HBsAg testing should be interpreted carefully because HBV can be transmitted nonsexually. Decisions regarding which tests should be performed should be made on a case-by-case basis.

Risk for Acquiring HIV Infection

HIV has been reported among children for whom sexual abuse was the only known risk factor. Serologic testing for HIV should be considered for sexually abused children. The decision to test for HIV should involve the family, if possible, and be made on a case-by-case basis depending on the likelihood of infection in the assailant (*1448*,*1454*). Although data are insufficient concerning the efficacy of PEP among children, treatment is well tolerated by infants and children with and without HIV, and children have a minimal risk for serious adverse reactions because of the short period recommended for prophylaxis (*1455*).

Recommendations for Postexposure HIV Risk Assessment of Children <72 Hours After Sexual Assault

Providers should do the following:

- Review local HIV epidemiology, assess risk for HIV in the assailant, and test for HIV.

- Evaluate the circumstances of the assault or abuse that might affect risk for HIV transmission.
- Perform HIV antigen or antibody testing (or antibody testing, if antigen or antibody testing is unavailable) during the original assessment and again at follow-up visits, in accordance with CDC guidelines (https://stacks.cdc.gov/view/cdc/38856). In considering whether to offer PEP, health care providers should consider whether the child can be treated soon after the sexual exposure (i.e., <72 hours), the likelihood that the assailant has HIV infection, and the likelihood of high compliance with the prophylactic regimen (*1436*). Potential benefit of treating a sexually abused child should be weighed against the risk for adverse reactions.
- Consult with a provider specializing in evaluating or treating children with HIV infection to determine age-appropriate dosing and regimens and baseline laboratory testing, if PEP is being considered.
- Discuss PEP with the caregivers, including its toxicity, unknown efficacy, and possible benefits, for children determined to be at risk for HIV transmission from the assault or abuse.
- Provided adequate doses of medication, if PEP is begun, to last until the follow-up visit 3–7 days after the initial assessment, at which time the child should be reevaluated and tolerance of medication assessed (*139*).

Conflicts of Interest

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. Christina Muzny reports other support from CDC, during the conduct of the study; grants from the National Institutes of Health/National Institute of Allergy and Infectious Diseases and Lupin Pharmaceuticals; personal fees from Lupin Pharmaceuticals, PhagoMed, Cepheid, and Beckton Dickinson; and personal fees and other support from Roche Diagnostics, Abbott Molecular, and BioFire Diagnostics, outside the submitted work. Hilary Reno reports grants from Hologic, outside the submitted work. Christine Johnston reports other support from CDC, during the conduct of the study; received research funding from Sanofi-Pasteur; royalties from UpToDate; and personal fees from MedPace, Gilead, AbbVie, and UpToDate, outside the submitted work.

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STI Treatment Guidelines, 2021, Work Group Members

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Disclosure of Relationships

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