

Sexually Transmitted Diseases Treatment Guidelines, 2014

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Contents

| | |
|--|-----|
| Introduction | 3 |
| Methods | 4 |
| Clinical Prevention Guidance..... | 5 |
| STD/HIV Prevention Counseling..... | 6 |
| Prevention Methods..... | 9 |
| Partner Services | 15 |
| Reporting and Confidentiality | 17 |
| Special Populations | 18 |
| Pregnant Women | 18 |
| Adolescents..... | 21 |
| Children | 23 |
| Persons in Correctional Facilities | 24 |
| MSM..... | 25 |
| Women Who Have Sex with Women (WSW) | 28 |
| Transgender Men and Women | 30 |
| Emerging Issues | 31 |
| Hepatitis C | 31 |
| Mycoplasma genitalium | 36 |
| HIV Infection: Detection, Counseling, and Referral | 38 |
| Diseases Characterized by Genital, Anal, or Perianal Ulcers | 45 |
| Chancroid | 46 |
| Genital HSV Infections | 48 |
| Granuloma Inguinale (Donovanosis)..... | 60 |
| Lymphogranuloma Venereum..... | 62 |
| Syphilis | 64 |
| Syphilis in Pregnancy | 81 |
| Congenital Syphilis | 83 |
| Management of Persons Who Have a History of Penicillin Allergy | 92 |
| Diseases Characterized by Urethritis and Cervicitis | 96 |
| Urethritis..... | 96 |
| Nongonococcal Urethritis..... | 98 |
| Cervicitis..... | 100 |
| Chlamydial Infections | 103 |
| Gonococcal Infections..... | 114 |
| Diseases Characterized by Vaginal Discharge..... | 128 |

| | |
|--|-----|
| Bacterial Vaginosis..... | 129 |
| Trichomoniasis | 134 |
| Vulvovaginal Candidiasis..... | 140 |
| Pelvic Inflammatory Disease (PID)..... | 146 |
| Epididymitis | 155 |
| Human Papillomavirus (HPV) Infection..... | 160 |
| Genital Warts | 163 |
| HPV-Associated Cancers | 171 |
| Vaccine Preventable STDs | 177 |
| Hepatitis A..... | 177 |
| Hepatitis B | 180 |
| Proctitis, Proctocolitis, and Enteritis | 188 |
| Ectoparasitic Infections..... | 190 |
| Pediculosis Pubis | 190 |
| Scabies | 192 |
| Sexual Assault and STDs | 195 |
| References..... | 206 |
| Terms and Abbreviations Used in This Report..... | 261 |
| Consultants | 268 |

Sexually Transmitted Diseases Treatment Guidelines, 2014

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Summary

*These guidelines for the treatment of persons who have or are at risk for sexually transmitted diseases (STDs) were updated by CDC after consultation with a group of professionals knowledgeable in the field of STDs who met in Atlanta on April 30–May 2, 2013. The information in this report updates the Sexually Transmitted Diseases Treatment Guidelines, 2010 (MMWR 2010;59 [No. RR–12]). Included in these updated guidelines is new information regarding 1) alternative treatment regimens for *Neisseria gonorrhoeae*; 2) use of nucleic acid amplification tests for the diagnosis of trichomoniasis; 3) alternative treatment options for genital warts; 4) the role of *Mycoplasma genitalium* in urethritis/cervicitis and treatment-related implications; 5) 5 updated HPV counseling messages; 6) new section on the management of transgender individuals 7) annual testing for hepatitis C in persons with HIV infection; 8) updated recommendations for diagnostic evaluation of urethritis; and 9) retesting to detect repeat infection.*

Introduction

The term sexually transmitted diseases (STDs) is used to refer to a variety of clinical syndromes and infections caused by pathogens that can be acquired and transmitted through sexual activity. Physicians and other health-care providers play a critical role in preventing and treating STDs. These guidelines for the treatment of STDs are intended to assist with that effort. Although these guidelines emphasize treatment, prevention strategies and diagnostic recommendations also are discussed.

This document updates the CDC Sexually Transmitted Diseases Treatment Guidelines published in 2010¹. These recommendations should be regarded as a source of clinical guidance and not 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 individuals at risk for STDs, including family-planning clinics, HIV-care clinics, private physicians' offices, Federally Qualified Health Centers, and other primary-care facilities. These guidelines focus on the treatment and counseling of individuals and do not address other community services and interventions that are essential to STD/human immunodeficiency virus (HIV) prevention efforts.

Methods

These guidelines were developed by CDC staff and an independent workgroup selected on the basis of their expertise in the field of STDs. Members of the multidisciplinary workgroup included representation from federal, state, and local health departments, clinical and basic science researchers, and numerous professional organizations. (listed at the end of this document). All workgroup members provided conflict of interest form and several members of the workgroup acknowledged receiving financial support from companies performing clinical research. All potential conflicts of interest were disclosed and managed in accordance with the editorial standards of the journals that published the scientific reports.

Specifically in 2012, CDC staff and workgroup members were asked to identify key questions regarding STD treatment and clinical management that emerged since the 2010 STD Treatment Guidelines. Development of these key questions focused on four principal outcomes of STD therapy for each individual disease or infection: 1) treatment of infection based on microbiologic eradication; 2) alleviation of signs and symptoms; 3) prevention of sequelae; and 4) prevention of transmission, 5) cost-effectiveness and other advantages and disadvantages of specific regimens. Then, CDC staff members assigned workgroup members key questions to research, and with the assistance of CDC staff, conducted an extensive and systematic literature review using an extensive MEDLINE database evidence-based approach (e.g., published abstracts and peer-reviewed journal articles), focusing on these key questions, common STDs, and information that had become available since publication of the *Sexually Transmitted Diseases Treatment Guidelines, 2010*¹.

Workgroup members assigned to address key questions developed tables of evidence from peer-reviewed publications that summarized 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. . . This information was presented at an in-person meeting of invited experts (including public- and private-sector professionals knowledgeable in the treatment of persons with STDs) in April 2013. . . Each key question was discussed and relevant publications were reviewed in terms of strengths, weaknesses, and relevance to the particular key question. The workgroup evaluated the quality of evidence, provided answers to the key questions and then rated the recommendations based on the United Services Preventive Services Task Forces modified rating system. After the discussion, a recommendation was proposed and adopted for consideration by CDC. More detailed description of the search terms, key questions, systematic search, and review of the literature, evidence tables, quality of evidence and strength of the recommendations are available at www.cdc.gov/std.

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Following the in person meeting, the literature was searched periodically for subsequent

published articles for the workgroup to consider by email or conference calls.. Draft recommendations were then developed by CDC generated from the background materials and the senior author was responsible for the overall content To confirm that the the recommendations were evidence based , a second independent panel of public health and clinical experts reviewed the draft recommendations. The recommendations for STD screening during pregnancy and cervical cancer screening were developed after CDC staff reviewed the published recommendations from other professional organizations, including the American College of Obstetricians and Gynecologists (ACOG), United States Preventive Services Task Force (USPSTF), American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP) and the Advisory Committee on Immunization Practices (ACIP). The sections on hepatitis B (HBV) and hepatitis A (HAV) infections are based on previously published recommendations.²⁻⁴

Throughout this report, the evidence used as the basis for specific recommendations is discussed briefly. More comprehensive, annotated discussions of such evidence will appear in background papers that will be available in a supplement issue of the journal *Clinical Infectious Diseases* after publication of the treatment guidelines. When more than one therapeutic regimen is recommended, the sequence is alphabetized unless prioritized based on efficacy, tolerance, or costs. For infections with more than one recommended regimen, listed regimens have similar efficacy and similar rates of intolerance or toxicity unless otherwise specified. Recommended regimens should be used primarily; alternative regimens can be considered in instances of significant drug allergy or other medical contraindications to the recommended regimens.

Clinical Prevention Guidance

The prevention and control of STDs are based on the following five major strategies:

- accurate risk assessment, education and counseling of persons at risk on ways to avoid STDs through changes in sexual behaviors and use of recommended prevention services;
- pre-exposure vaccination of persons at risk for vaccine-preventable STDs;
- identification of asymptomatically infected persons and of persons with symptoms associated with STDs;
- effective diagnosis, treatment, counseling and follow up of infected persons; and
- evaluation, treatment, and counseling of sex partners of persons who are infected with an STD.

STD/HIV Risk Assessment:

Primary prevention of STDs includes performing a behavioral risk assessment (i.e., assessing the sexual behaviors that may place persons at risk for infection) as well as a biologic assessment of risk (i.e, testing for std risk markers for 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 in obtaining a sexual history is available on the CDC Division of STD Prevention resource page <http://www.cdc.gov/std/treatment/resources.htm> and in the curriculum provided by CDC's STD/HIV Prevention Training Centers <http://nnptc.org/clinical-ptcs/>. 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 to delivering prevention messages effectively. Key techniques that can be effective in facilitating rapport with patients include the use of 1) open-ended questions (e.g., "Tell me about any new sex partners you've had since your last visit," and "What's your experience with using condoms been like?"); 2) understandable, nonjudgmental language ("Are your sex partners men, women or both?" "Have you ever had a sore or scab on your penis?"); and 3) normalizing language ("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 concerning five key areas of interest (Box 1). Additional information about gaining cultural competency when working with certain populations (e.g., gay, bisexual or other men who have sex with men, women who have sex with women, or transgender men and women) can be found in the respective chapters in this document.

In addition to obtaining a behavioral risk assessment described above, a comprehensive STD/HIV risk assessment should include STD screening because STDs are biological markers of risk especially for MSM. . STD screening is an essential and underutilized component of an STD/HIV risk assessment in most clinical settings. Persons seeking treatment or evaluation for a particular STD should be screened for HIV, and possibly other STDs as indicated by community prevalence and individual risk factors (see section on repeat testing, and sections on individual STDs). Individuals should be informed about all the STDs for which they are being tested and notified about tests for common STDs (e.g., genital herpes, HPV) that are available but not being performed. Efforts should be made to ensure that all persons receive care regardless of individual circumstances (e.g., ability to pay, citizenship or immigration status, language spoken, or specific sex practices).

STD/HIV Prevention Counseling

After obtaining a sexual history from their patients and all providers should encourage risk-reduction through prevention counseling using various strategies, including prevention methods outlined below. Prevention counseling is most effective if provided in a nonjudgmental and empathetic manner appropriate to the patient's culture, language, gender, sexual orientation, age, and developmental level. Prevention counseling for STD/HIV should be offered to all sexually active adolescents and to adults, who are diagnosed with an STD, have had an STD in the past year, or have multiple sexual partners.

Box 1. The Five P's: Partners, Prevention of Pregnancy, Protection from STDs, Practices, and Past History of STDs

1. Partners

- “Do you have sex with men, women, or both?”
- “In the past 2 months, how many partners have you had sex with?”
- “In the past 12 months, how many partners have you had sex with?”

- “Is it possible that any of your sex partners in the past 12 months had sex with someone else while they were still in a sexual relationship with you?”

2. Practices

- “To understand your risks for STDs, I need to understand the kind of sex you have had recently.”
- “Have you had vaginal sex, meaning ‘penis in vagina sex’?”
If yes, “Do you use condoms: never, sometimes, or always?”
- “Have you had anal sex, meaning ‘penis in rectum/anus sex’?” If yes, “Do you use condoms: never, sometimes, or always?”
- “Have you had oral sex, meaning ‘mouth on penis/vagina’?”

3. Prevention of pregnancy

- “What are you doing to prevent pregnancy?”

4. Protection from STDs

- “What do you do to protect yourself from STDs and HIV?”

For condom answers:

- If “never:” “Why don’t you use condoms?”
- If “sometimes:” “In what situations (or with whom) do you

use condoms?”

5. Past history of STDs

- “Have you ever had an STD?”
- “Have any of your partners had an STD?”

Additional questions to identify HIV and viral hepatitis risk include:

- “Have you or any of your partners ever injected drugs?”
- “Have any of your partners exchanged money or drugs for sex?”
- “Is there anything else about your sexual practices that I need to know about?”

USPSTF recommends high-intensity behavioral counseling for all sexually active adolescents and for adults at increased risk for STDs and HIV ^{5,6}Such interactive counseling is directed at an individual’s personal risk, the situations in which risk occurs, and the use of personalized goal-setting strategies, but are resource intensive. One such approach, known as client-centered STD/HIV prevention counseling, involves tailoring a discussion of risk reduction to the individual situation. While one large study in STD clinics (Project RESPECT) demonstrated that this approach was associated with lower acquisition of curable STDs, including trichomoniasis, chlamydia, gonorrhea, and syphilis⁷, another study 10 years later in the same settings (Project AWARE) did not replicate this result.⁸ Briefer provider-delivered prevention messages have been shown to be feasible and to decrease subsequent STDs in HIV primary care settings.⁹ 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 <http://effectiveinterventions.org>. Training in client-centered counseling is available through the CDC STD/HIV National Network of Prevention Training Centers (<http://nnptc.org>).

In addition to individual STD/HIV prevention counseling, videos and large group presentations can provide explicit information concerning STDs and reducing disease transmission (e.g., how to use condoms correctly, routine screening). Group-based strategies have been effective in reducing the occurrence of additional STDs among persons at risk, including those attending STD clinics¹⁰.

Because the incidence of some STDs, notably syphilis, is higher in persons with HIV infection, the use of client-centered STD counseling for persons with HIV infection continues to be strongly encouraged by public health agencies and other health organizations. Consensus guidelines issued by CDC, the Health Resources and Services Administration, the HIV Medicine Association of the Infectious Diseases Society of America, and the National Institutes of Health emphasize that STD/HIV risk assessment, STD screening, and client-centered risk reduction counseling should be provided routinely to persons with HIV infection¹¹. Briefer risk reduction counseling delivered by medical providers during HIV primary care visits coupled with routine STD screening has been shown to reduce STD incidence in persons with HIV infection⁹. Several other specific methods have been designed for the HIV care setting¹²⁻¹⁴, and additional information regarding these approaches is available at <http://effectiveinterventions.org>.

Prevention Methods

Abstinence and Reduction of Number of Sex Partners

The most reliable way to avoid transmission of STDs is to abstain from oral, vaginal, and anal sex or to be in a long-term, mutually monogamous relationship with a partner known to be uninfected. For persons who are being treated for an STD other than HIV (or whose partners are undergoing treatment), counseling that encourages abstinence from sexual intercourse until completion of the entire course of medication is crucial. A recent trial conducted among women on the effectiveness of counseling messages demonstrated that women with condom experience may benefit from a hierarchical message that includes condoms, whereas women without such experience may benefit more from an abstinence only message.¹⁵ A more comprehensive discussion of abstinence and other sexual practices that can help persons reduce their risk for STDs is available in *Contraceptive Technology, 20th Edition*¹⁶.

Pre-exposure Vaccination

Pre-exposure vaccination is one of the most effective methods for preventing transmission of human papillomavirus (HPV), Hepatitis A, and Hepatitis B virus. Two HPV vaccines are available and others are being evaluated. HPV vaccination is recommended routinely for boys and girls aged 11 or 12 years. Either bivalent or quadrivalent HPV vaccine is recommended for females, and quadrivalent vaccine is recommended for males^{17,18,19}. Vaccination is recommended through age 26 years for females and through age 21 years for males that have not received any or all of the vaccine doses. For persons with HIV infection and for men who have sex with men, vaccination is recommended through age 26. Further details regarding HPV vaccination are available in the HPV section and at www.cdc.gov/std/hpv.

Hepatitis B vaccination is recommended for all unvaccinated, uninfected persons, including those being evaluated or treated for an STD^{3,4}. In addition, hepatitis A and B vaccines are recommended for men who have sex with men (MSM), injection-drug users (IDUs), persons with chronic liver disease and persons with HIV infection who have not yet been infected with one or both types of hepatitis virus.^{3,4,20}. Details regarding hepatitis A and B vaccination are available at <http://www.cdc.gov/hepatitis>.

Male Condoms

When used consistently and correctly, male latex condoms are highly effective in preventing the sexual transmission of HIV infection. In heterosexual HIV serodiscordant relationships (i.e., those involving one infected and one uninfected partner) in which condoms were consistently used, HIV-negative partners were 80% less likely to become infected with HIV compared with persons in similar relationships in which condoms were not used²¹.

Moreover, studies show consistent condom use reduces the risk for other STDs, including chlamydia, gonorrhea, and trichomoniasis.^{22,23 24} By limiting lower genital tract infections, condoms also might reduce the risk of developing pelvic inflammatory disease (PID) in women²⁵. 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 covered²⁶⁻³⁰. Additional information is available at www.cdc.gov/condomeffectiveness/latex.htm and www.factsaboutcondoms.com/professional.php

Condoms are regulated as medical devices and are subject to random sampling and testing by the U.S. Food and Drug Administration (FDA). Each latex condom manufactured in the United States is tested electronically for holes before packaging. Rates of condom breakage during sexual intercourse and withdrawal are approximately two broken condoms per 100 condoms used in the United States. During anal intercourse, rates of breakage and slippage may be slightly higher.³¹ }Richters 2000,{Silverman, 1997 #2075}, Hernandex-romieu, d"anna lh)The failure of condoms to protect against STD or unintended pregnancy usually results from inconsistent or incorrect use rather than condom breakage³¹.

Male condoms made of materials other than latex are available in the United States. Two general categories of nonlatex condoms exist. The first type is made of polyurethane or other synthetic material and provides comparable protection against STDs/HIV and pregnancy to that of latex condoms^{16,24}. These can be substituted for latex condoms by persons with latex allergy, and are generally more resistant to deterioration and are compatible with use of both oil-based and water-based lubricants. The effectiveness of synthetic male condoms to prevent sexually transmitted infections has not been extensively studied, and FDA-labeling restricts their recommended use to latex-sensitive or allergic persons.

The second type is natural membrane condoms (frequently called "natural skin" condoms or, incorrectly, "lambskin" condoms). These 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 viral STD transmission can occur with natural membrane condoms.¹⁶ While natural membrane condoms are recommended for pregnancy prevention, they are not recommended for prevention of STDs and HIV.

Providers should advise their patients that condoms must be used consistently and correctly to be effective in preventing STDs and HIV infection; providing instructions about the correct use

of condoms can be useful. Communicating the following recommendations can help ensure that patients use male 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 lubricants (e.g., K-Y Jelly, Astroglide, AquaLube, and glycerin) with latex condoms. Oil-based lubricants (e.g., petroleum jelly, shortening, mineral oil, massage oils, body lotions, and cooking oil) can weaken latex and should not be used; however, oil-based lubricants can generally be used with synthetic condoms.
- Ensure adequate lubrication during vaginal and anal sex, which might require the use of exogenous water-based lubricants.
- To prevent the condom from slipping off, hold the condom firmly against the base of the penis during withdrawal, and withdraw while the penis is still erect.

Further information may be found at <http://www.cdc.gov/condomeffectiveness/latex.htm>

Female Condoms

Several female condoms are globally available including the FC2, Reddy condom, Cupid condom and Woman's condom³². Use of female condoms can provide protection from acquisition and transmission of sexually transmitted infections, although data are limited³². Although female condoms are more costly compared with male condoms, they offer the advantage of being a female-controlled STD/HIV prevention method and the newer versions may be acceptable to both men and women. Although the female condom also has been used during receptive anal intercourse its efficacy remains unknown³³. Further information may be found at www.ashasexualhealth.org/sexual-health/condoms/female-condoms.html

Cervical Diaphragms

In observational studies, diaphragm use has been demonstrated to protect against cervical gonorrhea, chlamydia, and trichomoniasis³⁴. However a trial that examined the effect of use of a diaphragm plus lubricant on HIV acquisition in women in Africa showed 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 STD or HIV infection.

Nonbarrier Contraception, Surgical Sterilization, and Hysterectomy

Contraceptive methods that are not mechanical barriers offer no protection against HIV or other STDs. Sexually active women who use hormonal contraception (i.e., oral contraceptives, patch, ring, implants, injectables or intrauterine hormonal methods), have non-hormonal intrauterine devices (IUDs), have been surgically sterilized, or have had hysterectomies should be counseled to use condoms to reduce the risk for STDs, including HIV infection.

The issue of whether hormonal contraception raises a woman's risk of acquiring HIV or another STD is unclear. A systematic review of epidemiologic evidence found that most studies showed no association between use of oral contraceptives and HIV acquisition among women. Studies were mixed on an association between progestin-only injectables and HIV acquisition, with some studies showing a higher risk of acquisition among women using depot medroxyprogesterone acetate (DMPA) while other studies did not³⁷. The WHO and CDC reviewed the evidence on hormonal contraception and HIV acquisition and concluded that data were insufficient to recommend that women modify their hormonal contraceptive practices, but that women using progestin-only injectables should be strongly advised to also use condoms as an HIV prevention strategy^{38 39}.

Topical Microbicides and Spermicides

Nonspecific topical microbicides for the prevention of HIV are ineffective^{40 41 42-44}. Spermicides containing N-9 may disrupt genital or rectal epithelium and have been associated with an increased risk of HIV infection. Condoms with N-9 are no more effective than condoms without N-9. Therefore N-9 alone or in a condom should not be recommended for STD or HIV prevention⁴⁰.

There are also no proven topical antiretroviral agents for the prevention of HIV, though trials are underway to evaluate several candidates for vaginal and rectal microbicides using tenofovir and other antiretroviral drugs.

Male Circumcision

Male circumcision reduces the risk for HIV and some STDs in 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 reduced the risk for HIV acquisition among men by 50%–60%⁴⁷⁻⁴⁹. In these trials, circumcision was also protective against other STDs, including high-risk genital HPV infection and genital herpes⁵⁰⁻⁵². Follow up studies have demonstrated sustained benefit of circumcision for HIV prevention⁵³ and that the effect is not mediated solely through a reduction in HSV-2 infection or genital ulcer disease⁵⁴.

The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) have recommended that male circumcision be scaled up as an effective intervention for the prevention of heterosexually acquired HIV infection⁵⁵. These organizations also recommend that countries with hyperendemic and generalized HIV epidemics and low

prevalence of male circumcision expand access to safe male circumcision services within the context of ensuring universal access to comprehensive HIV prevention, treatment, care, and support. In the United States, The American Academy of Pediatrics (AAP) recommends that newborn male circumcision be available to families that desire it, as the benefits of the procedure, including prevention of penile cancers, urinary tract infections, genital ulcer disease and HIV, outweigh the risks⁵⁶. The American College of Obstetricians and Gynecologists has also endorsed the AAP's policy statement⁵⁶. The American Urological Association states that male circumcision should be presented as an option for health benefits among other strategies for risk reduction.⁵⁷

No definitive data exist to answer the question of whether male circumcision reduces HIV and acquisition in MSM, , although one randomized trial is ongoing in China.⁵⁸ A review found a modest protective effect among men who were the insertive partner for anal intercourse, but the evidence was rated as poor. Further higher quality studies are needed to confirm any potential benefit of male circumcision for this population⁵⁸.

Emergency Contraception (EC)

Unprotected intercourse exposes women to risks of both STDs and unplanned pregnancy. Providers managing such women should offer counseling about the option of EC if pregnancy is not desired. The options for EC in the United States include the copper IUD and emergency contraceptive pills (ECPs).⁵⁹ ECPs are available in the following formulations: ulipristal acetate in a single dose (30 mg), levonorgestrel in a single dose (1.5 mg) or as a split dose (0.75 mg each taken 12 hours apart), or combined estrogen and progestin (Yuzpe regimen). Some ECPs can be obtained over the counter; ECPs can also be provided through advance prescription or supply from providers.^{60,61} Emergency insertion of a copper IUD up to 5 days after sex can reduce pregnancy risk by more than 99%⁶². ECPs are most efficacious when initiated as soon as possible after unprotected sex but have some efficacy as long as 5 days later. ECPs are ineffective (but not harmful) if the woman is already pregnant⁶³. A recent Cochrane review summarized the efficacy, safety, and convenience of various methods of emergency contraception⁶³. More information about EC is available in the 20th edition of *Contraceptive Technology*¹⁶ or <http://www.arhp.org/topics/emergency-contraception>.

Postexposure Prophylaxis (PEP) for HIV and STD

Guidelines for the use of PEP aimed at preventing HIV infection as a result of sexual exposure are discussed in another section of this report (see Sexual Assault and STDs). Genital hygiene methods (e.g., vaginal washing and douching) after sexual exposure are ineffective in protecting against HIV and STD and might increase the risk for bacterial vaginosis, some STDs, and HIV infection⁶⁴.

Antiretroviral Treatment of Persons with HIV Infection to Prevent Infection in Uninfected Partners

The randomized controlled trial HPTN 052 demonstrated that in HIV serodiscordant, heterosexual couples in that early HIV antiretroviral therapy in the infected partner decreases the risk of transmission to the uninfected partner by 96%⁶⁵. Antiretroviral therapy therefore not only provides benefit for the individual health of HIV-infected persons, but also reduces the risk of onward transmission. For these reasons, treatment should be offered to all HIV-infected persons. Detailed guidance for prescribing antiretroviral regimens can be found in the US Department of Health and Human services HIV Treatment guidelines⁶⁶.

Preexposure Prophylaxis (PrEP) for HIV and STD

Several large randomized placebo controlled trials have demonstrated safety⁶⁷ and a substantial reduction in the rate of HIV acquisition for MSM⁶⁸, men and women in heterosexual HIV-discordant couples⁶⁹, and heterosexual men and women recruited as individuals⁷⁰ who were prescribed daily oral antiretroviral preexposure prophylaxis (PrEP) with a fixed-dose combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC). In addition, one clinical trial among persons who inject drugs⁷¹ and one among men and women in heterosexual HIV-discordant couples⁶⁹ have demonstrated substantial efficacy and safety of daily oral PrEP with TDF alone. The demonstrated efficacy of PrEP was in addition to the effects of repeated condom provision, sexual risk-reduction counseling, and the diagnosis and treatment of sexually transmitted infection were provided to all trial participants. High adherence to oral PrEP with tenofovir disoproxil fumarate (TDF) alone or in a fixed-dose combination with emtricitabine (FTC) was strongly associated with protection from infection. Data suggest that when TDF is orally administered it has lower levels in vaginal than rectal tissue, potentially explaining why high levels of adherence were needed to see benefit in women in these trials⁷². Despite initial concerns about PrEP fostering antiretroviral resistance among persons who become infected, emergence of resistance was detected **by standard tests** in these studies only in persons inadvertently started on PrEP during acute HIV infection, and not in initially uninfected persons who later became infected while taking PrEP medication⁷³.

On the basis of these trial results and the FDA **approval of an** indication for the use of TDF/FTC for pre-exposure prophylaxis, the U.S. Public Health Service recommends that clinicians evaluate HIV-negative men and women who are sexually active or who are injecting illicit drugs and consider PrEP as one prevention option to those whose sexual or injection behaviors and epidemiologic context place them at substantial risk of acquiring HIV infection. Comprehensive guidance for the use of daily PrEP to reduce the risk of acquiring HIV infection can be found at <http://www.cdc.gov/hiv/prevention/research/prep/index.html>.

HSV Treatment

Providing HSV treatment to persons dually infected with HIV and HSV has demonstrated no benefit in reducing HIV transmission or acquisition. A large RCT evaluated 3408 serodiscordant heterosexual couples enrolled at 14 Africa sites in which the partner with HIV infection was also seropositive for HSV-2. The dually infected partner was randomized to either placebo or acyclovir 400mg bid, and the primary outcome was HIV transmission to the uninfected partner. Use of acyclovir had no impact on HIV transmission⁷⁴. This is consistent with a prior large trial

that found no benefit of acyclovir in preventing HIV-1 acquisition in people who were seropositive for HSV-2⁷⁵.

HIV Seroadaptation Strategies

Seroadaptive strategies for HIV prevention have largely originated within communities of MSM. They are predicated on knowledge of self and partner HIV-infection 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 only with HIV serodiscordant partners. Another practice is seropositioning, in which in serodiscordant couples, the individual with HIV infection is the receptive partner for anal intercourse.

Observational studies have consistently found that serosorting confers greater risk of HIV infection than consistent condom use, but is lower risk compared to anal intercourse without condoms and without serosorting⁷⁹⁻⁸¹. Serosorting practices have been associated with increased risk of STDs including chlamydia and gonorrhea^{82,83}.

Serosorting is not recommended because: (1) too many MSM who have HIV do not know they are infected because they have not been tested for HIV recently, (2) men's assumptions about the HIV status of their partners may be wrong, and (3) some men with HIV infection may not tell or may misrepresent their HIV status. All of these factors increase the risk that serosorting could lead to HIV infection. Additional information can be found at <http://www.cdc.gov/msmhealth/serosorting.htm> or http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en/

Retesting After Treatment to Detect Repeat Infections

Retesting several months after a diagnosis of chlamydia, gonorrhea or trichomoniasis can detect repeat infection and potentially can be used to enhance population-based prevention.^{84,85} Any patient who tests positive for chlamydia or gonorrhea should be rescreened three months after treatment. Women who test positive for trichomonas should be rescreened at three months. Any patient diagnosed with syphilis should undergo follow up serologic syphilis testing per current recommendations. Further details on retesting can be found in the specific sections on chlamydia, gonorrhea, and trichomonas within this report.

Partner Services

Partner services refer to a continuum of clinical evaluation, counseling, diagnostic testing, and treatment designed to increase the number of infected persons brought to treatment and disrupt transmission networks. This continuum includes efforts undertaken by health departments, medical providers and patients themselves. Public health partner services refer to efforts by public health departments to identify the sex- and needle-sharing partners of infected persons to assure their medical evaluation and treatment.

Clinicians can provide partner services by directly evaluating and treating sex partners, by cooperating with state and local health departments, or by counseling persons and providing

them with written information and/or medication to give to their partners. Providers' efforts to ensure the treatment of a patient's sex partners can reduce the risk of reinfection and potentially diminish the ongoing transmission of STDs⁸⁶. Therefore, providers should encourage all persons with STDs to notify their sex partners and urge them to seek medical evaluation and treatment. Time spent with index patients to counsel them on the importance of notifying partners is associated with improved notification outcomes⁸⁷. When possible, providers who ask persons to return to their practice for treatment should advise them to bring a partner with them and should concurrently treat both persons. While this approach can be effective^{88,89}, it is not a practical approach for persons with more than one sex partner. Also, some evidence suggests that providing patients with written information to give to their sex partners can increase partner treatment.

The types and comprehensiveness of public health partner services and the specific STDs for which they are offered vary by provider, public health agency, and geographic area. In most areas of the U.S., health departments routinely attempt to provide partner services to all persons with early syphilis, and an increasing number of departments routinely provide such services to persons with newly diagnosed HIV infection. In contrast, relatively few U.S. health departments routinely provide partner services to persons with gonorrhea, chlamydial infection, trichomonas or other STDs.⁹⁰ Clinicians should familiarize themselves with public health practices in their area, but in most instances providers should anticipate that responsibility for ensuring the treatment of partners of persons with STDs other than syphilis and HIV rests with the diagnosing provider and the patient.

Expedited Partner Therapy

Unless prohibited by law or other regulation, medical providers should routinely offer expedited partner therapy (EPT) to heterosexual patients with gonorrhea or chlamydial infection when the provider cannot confidently assure that all of a patient's sex partners from the prior 60 days will be treated. If the patient has not had sex in the 60 days prior to diagnosis, providers should attempt to treat a patient's most recent sex partner. EPT, also termed patient-delivered partner therapy (PDPT), is now legal in most U.S. states. Providers should visit www.cdc.gov/std/ept to obtain updated information for their state. Providing patients with appropriately packaged medication is the preferred approach to PDPT, since data on the efficacy of PDPT using prescriptions is very limited, and many persons do not fill prescriptions given to them by a sex partner. Medication or prescriptions provided for PDPT should be accompanied by treatment instructions, appropriate warnings about taking medications (if the partner is pregnant or has an allergy to the medication), general health counseling, and a statement advising that partners seek a medical evaluation. These instructions should emphasize the importance of medical evaluations for any symptoms of STD, particularly PID.

The evidence supporting PDPT is based on three clinical trials conducted in the U.S. that included heterosexual men and women with chlamydia or gonorrhea⁹¹⁻⁹³. All three trials reported that more partners were treated when patients were offered PDPT, two reported statistically significant declines in the rate of reinfection and one observed a lower risk of persistent or recurrent infection that was nonsignificant. A fourth trial in the U.K. did not observe a difference in the risk of reinfection or in the numbers of partners treated between

persons offered PDPT and those advised to notify their sex partners⁹⁴. The U.S. trials and a meta-analysis of PDPT revealed that the magnitude of reduction in reinfection of index case-patients compared with patient referral differed according to the STD and the sex of the index case-patient^{86,91-93}. However, across trials, reductions in chlamydia prevalence at follow-up were approximately 20%; reductions in gonorrhea at follow-up were approximately 50%. Existing data suggest that PDPT also might have a role in partner management for trichomoniasis; however, no single partner management intervention has been shown to be more effective than any other in reducing reinfection rates^{95,96}. The risk of concurrent gonorrhea or chlamydial infection in the sex partners of persons with trichomoniasis is approximately 10%, thus clinicians should attempt to test such partners for chlamydia and gonorrhea when possible.⁹⁷ No data support the use of PDPT in the routine management of patients with syphilis. Data on the use of PDPT for gonorrhea or chlamydial infection among MSM are very limited^{98,99}, and published studies suggest that over 5% of MSM without a prior HIV diagnosis who are evaluated as contacts to partners with gonorrhea or chlamydial infection are newly diagnosed with HIV infection when tested^{97,100}. As a result, PDPT should not be used routinely in MSM. All persons diagnosed with bacterial STDs as well as their sex partners, particularly MSM, should be tested for HIV infection.

Many health departments now use the internet to notify the sex partners of persons with STDs¹⁰¹, especially among MSM and in cases where no other identifying information is available (<http://www.ncsddc.org/upload/wysiwyg/documents/NGuidelinesforInternet.htm>). Clinical providers are unlikely to participate directly in internet partner notification. However, internet sites allowing patients to send anonymous email or text messages advising partners of their exposure to an STD are now operational in some areas. The extent to which these sites increase, decrease or have no effect on partner notification and treatment is uncertain. Patients should be encouraged to notify their partners in-person or over the telephone, or to allow a medical provider or public health professional do so for them. However, anonymous notification via the internet is superior to no notification at all and may be an option in some instances.

Reporting and Confidentiality

The accurate and timely reporting of STDs is integral to efforts to assess morbidity trends, allocate limited resources, and assist local health authorities in partner notification and treatment. STD/HIV and acquired immunodeficiency syndrome (AIDS) cases should be reported in accordance with state and local statutory requirements. Syphilis (including congenital syphilis), gonorrhea, chlamydia, chancroid, HIV infection, and AIDS are reportable diseases in every state. Because the requirements for reporting other STDs differ by state, clinicians should be familiar with the reporting requirements applicable within their jurisdictions.

Reporting can be provider- or laboratory-based or both. Clinicians who are unsure of state and local reporting requirements should seek advice from state or local health departments or STD programs. STDs and HIV reports are kept strictly confidential. In most jurisdictions, such reports are protected by statute or regulation. Before conducting a follow-up of a positive STD-test result, public health professionals should consult the patient's health-care provider if possible to verify the diagnosis and to determine the treatments being received.

Special Populations

Pregnant Women

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

Recommendations to screen pregnant women for STDs are based on disease severity and sequelae, prevalence in the population, costs, medicolegal considerations (e.g., state laws), and other factors. The screening recommendations in this report are generally broader (i.e., if followed, more women will be screened for more STDs than would by following other screening recommendations) and are also consistent with other CDC guidelines.

Recommended Screening Tests

- All pregnant women in the United States should be screened for HIV infection as early in pregnancy as possible^{102 103}. Screening should be conducted after the woman is notified that she will be screened for HIV as part of the routine panel of prenatal tests, unless she declines (i.e., opt-out screening). For women who decline HIV testing, providers should address their objections, and when appropriate, continue to encourage testing strongly. Women who decline testing because they have had a previous negative HIV test should be informed of the importance of retesting during each pregnancy. Testing pregnant women and treating those who are infected are vital not only to maintain the health of the woman, but to reduce perinatal transmission of HIV through available antiretroviral and obstetrical interventions. Retesting in the third trimester (preferably before 36 weeks' gestation) is recommended for women at high risk for acquiring HIV infection (e.g., women who use illicit drugs, have STDs during pregnancy, have multiple sex partners during pregnancy, live in areas with high HIV prevalence, or have partners with HIV infection). Rapid HIV screening should be performed on any woman in labor who has an undocumented HIV status unless she declines. If a rapid HIV test result is positive in these women, antiretroviral prophylaxis should be administered without waiting for the results of the confirmatory test¹⁰⁴
- A serologic test for syphilis should be performed on all pregnant women at the first prenatal visit.¹⁰⁵ In populations in which the amount of prenatal care delivered is not optimal, rapid plasma reagin (RPR) card test screening (and treatment, if that test is reactive) should be performed at the time that a pregnancy is confirmed. Women who are at high risk for syphilis, live in areas of high syphilis morbidity, or are previously untested should be screened again early in the third trimester (at approximately 28 weeks' gestation) and at delivery. Some states require all women to be screened at delivery. Neonates should not be discharged from the hospital unless the syphilis serologic status of the mother has been determined at least one time during pregnancy and preferably again at delivery. Any woman who delivers a stillborn infant should be tested for syphilis.

- All pregnant women should be routinely tested for hepatitis B surface antigen (HBsAg) during an early prenatal visit (i.e., a visit during the first trimester), even if they have been previously vaccinated or tested ¹⁰⁶. 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 in the previous 6 months, evaluation or treatment for an STD, recent or current injection-drug use, and an HBsAg-positive sex partner) and those with clinical hepatitis should be retested at the time of admission to the hospital for delivery. Pregnant women at risk for HBV infection also should be vaccinated. 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 use an FDA-cleared HBsAg test and perform testing according to the manufacturer's labeling, including testing of 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 ¹⁰⁶.
- All pregnant women should be routinely screened for *Chlamydia trachomatis* (see Chlamydia Infections, Diagnostic Considerations) during the first prenatal visit ¹⁰⁷. Women aged <25 years and those at increased risk for chlamydia (e.g., women who have a new or more than one sex partner) also should be retested during the third trimester to prevent maternal postnatal complications and chlamydial infection in the infant. Women found to have chlamydial infection during the first trimester should be retested within approximately 3–6 months, preferably in the third trimester. ¹⁰⁸ Screening during the first trimester might prevent the adverse effects of chlamydia during pregnancy, but supportive evidence for such screening is lacking.
- All pregnant women at risk for gonorrhea or living in an area in which the prevalence of *Neisseria gonorrhoeae* is high should be screened at the first prenatal visit for *N. gonorrhoeae*. ¹⁰⁹ Women aged <25 years are at highest risk for gonorrhea infection. Other risk factors for gonorrhea include a previous gonorrhea infection, other STDs, new or multiple sex partners, inconsistent condom use, commercial sex work, and drug use. Pregnant women found to have gonococcal infection during the first trimester should be retested within approximately 3–6 months, preferably in the third trimester. Uninfected pregnant women who remain at high risk for gonococcal infection also should be retested during the third trimester.
- All pregnant women at high risk for hepatitis C virus (HCV) infection should be screened for hepatitis C antibodies (see Hepatitis C, Diagnostic Considerations) at the first prenatal visit. The most important risk factor for HCV infection is past or current injection drug use. ¹¹⁰ Additional risk factors include intranasal drug use, a history of blood transfusion or organ transplantation before 1992 and other percutaneous exposures.
- Pregnant women should undergo a Papanicolaou (Pap) test at the same frequency as nonpregnant women, although recommendations for their management differ. ¹¹¹

Other Tests

- Evidence does not support routine testing for bacterial vaginosis (BV) in pregnancy. For asymptomatic pregnant women at high risk for preterm delivery, evidence is insufficient to assess the balance of benefits and harms of screening for BV.¹¹² Symptomatic women should be evaluated and treated (see Bacterial Vaginosis).
- Evidence does not support routine screening for *Trichomonas vaginalis* in asymptomatic pregnant women. Women who report symptoms should be evaluated and treated appropriately (see Trichomonas).
- Evidence does not support routine HSV-2 serologic screening among previously undiagnosed women during pregnancy.

Other Concerns

- 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 appropriate prophylaxis is provided for their infants. Information concerning the pregnant woman's HBsAg status should be provided to the hospital in which delivery is planned and to the health-care provider who will care for the newborn. In addition, household and sex contacts of women who are HBsAg positive should be vaccinated.
- Women who are HBsAg positive should be provided with, or referred for, appropriate counseling and medical management. Pregnant women who are HBsAg positive should receive information regarding hepatitis B that addresses:
 - Modes of transmission;
 - Perinatal concerns (e.g., breastfeeding is not contraindicated);
 - Prevention of HBV transmission, including the importance of postexposure prophylaxis for the newborn infant and hepatitis B vaccination for household contacts and sex partners; and
 - Evaluation for and treatment of chronic HBV infection.
- There is no established treatment for pregnant women infected with hepatitis C virus (HCV). However, all women with HCV infection should receive appropriate counseling and supportive care as needed (see Hepatitis C, Prevention). No vaccine is available to prevent HCV transmission.
- In the absence of lesions during the third trimester, routine serial cultures for herpes simplex virus (HSV) are not indicated for women who have a history of recurrent genital herpes. Prophylactic cesarean delivery is not indicated for women who do not have active genital lesions at the time of delivery.

- The presence of genital warts is not an indication for cesarean delivery.

For a more detailed discussion of STD testing and treatment among pregnant women, refer to the following references: *Screening for HIV in Pregnant Women: Systematic Review to Update the 2005 U.S. Preventive Services Task Force Recommendation*¹⁰²; *Screening for HIV: US Preventive Services Task Force Recommendation Statement*¹⁰³; *Guidelines for Perinatal Care*¹¹³; *Rapid HIV Antibody Testing During Labor and Delivery for Women of Unknown HIV Status: A Practical Guide and Model Protocol*¹¹⁴; *Viral Hepatitis in Pregnancy*¹¹⁵; *Hepatitis B Virus: A Comprehensive Strategy for Eliminating Transmission in the United States — Recommendations of the Immunization Practices Advisory Committee (ACIP)*⁴; *Screening for Chlamydial Infection: U.S. Preventive Services Task Force Recommendation Statement*¹⁰⁷; *Canadian guidelines on sexually transmitted infections*¹¹⁶; *USPSTF recommendations for STI screening*¹¹⁷; and *Screening for Bacterial Vaginosis in Pregnancy to Prevent Preterm Delivery: U.S. Preventive Services Task Force Recommendation Statement*¹¹².

Adolescents

In the United States, prevalence rates of many sexually acquired infections are highest among adolescents.^{118,119} For example, the reported rates of chlamydia and gonorrhea are highest among females aged 15–24 years, and many persons acquire HPV infection during their adolescent and young adult years.

Persons who initiate sex early in adolescence are at higher risk for STDs, along with persons residing in detention facilities, attending STD clinics, young men having sex with men (YMSM), and youth who use injection drugs. Factors contributing to this increased risk during adolescence include having multiple sexual partners concurrently, having sequential sexual partnerships of limited duration, failing to use barrier protection consistently and correctly, having increased biologic susceptibility to infection, and experiencing multiple obstacles to accessing health care¹¹⁹

All 50 states and the District of Columbia explicitly allow minors to consent for their own health services for STDs. No state requires parental consent for STD care or requires that providers notify parents that an adolescent minor has received STD services, except in limited or unusual circumstances.

Protecting confidentiality for such care, particularly for adolescents enrolled in private health insurance plans, presents multiple problems. After a claim has been reported, 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 benefit [EOB]¹²⁰). In addition, federal laws obligate notices to beneficiaries when claims are denied, including alerting consumers who need to pay for care until the allowable deductible is reached. For STD detection- and treatment-related care, an EOB or medical bill that is received by a parent might disclose services provided and list any laboratory tests performed. Despite the high rates of infections documented in the adolescent population, providers frequently fail to inquire about sexual behaviors, assess STD risks, provide risk reduction counseling, and ultimately, fail to screen for asymptomatic infections during

clinical encounters. Discussions concerning sexual behavior should be appropriate for the patient's developmental level and should be aimed at identifying risk behaviors (e.g., unprotected oral, anal, or vaginal sex and drug-use behaviors). Careful, nonjudgmental, and thorough counseling is particularly vital for adolescents who might not feel comfortable acknowledging their engagement in behaviors that place them at high risk for STDs.

Screening Recommendations

Routine laboratory screening for common STDs is indicated for sexually active adolescents. The following screening recommendations summarize published federal agency and medical professional organizations' clinical guidelines for sexually active adolescents:

- Routine screening for *C. trachomatis* of all sexually active females aged <25 years is recommended annually¹⁰⁷. Evidence is insufficient to recommend routine screening for *C. trachomatis* in sexually active young men based on feasibility, efficacy, and cost-effectiveness. However, screening of sexually active young males should be considered in clinical settings associated with high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, and STD clinics) and should be offered to YMSM (see MSM section)^{107,121}.
- Routine screening for *N. gonorrhoeae* in all sexually active females at risk for infection is recommended annually¹⁰⁹. Females aged <25 years are at highest risk for gonorrhea infection. Other risk factors that place females at increased risk include a previous gonorrhea infection, the presence of other STDs, new or multiple sex partners, inconsistent condom use, commercial sex work, and drug use. Screening should be offered to YMSM (see MSM section).
- HIV screening should be discussed and offered to all adolescents. Frequency of repeat screenings of those who are at risk for HIV infection should be based on level of risk^{122,123}. Persons who test positive for HIV should receive prevention counseling and referral to care before leaving the testing site.
- The routine screening of adolescents who are asymptomatic for certain STDs (e.g., syphilis, trichomoniasis, BV, HSV, HPV, HAV, and HBV) is not recommended. However, YMSM and pregnant adolescent females might require more thorough evaluation for all STDs.
- Guidelines from USPSTF, ACOG, and the American Cancer Society recommend that cervical cancer screening begin at age 21 years¹²⁴⁻¹²⁶ a recommendation based on the low incidence of cervical cancer and limited utility of screening for adolescents¹²⁷.

Primary Prevention Recommendations

Primary prevention and anticipatory guidance to recognize symptoms and behaviors associated with STDs are strategies that can be incorporated into any or all types of health-care visits. The following recommendations for primary prevention of STDs (i.e., vaccination and counseling) are based on published federal agency and medical professional organizations' clinical guidelines for sexually active adolescents:

- The HPV vaccine, either bivalent or quadrivalent, is recommended routinely for females aged 11 and 12 years^{17,19}. Vaccination is also recommended for females aged 13–26 years who have not yet received all doses, or completed the vaccine series. The quadrivalent HPV vaccine is recommended routinely for males aged 11 or 12 years¹⁸. Vaccination with quadrivalent HPV vaccine is recommended for males aged 13–21 years who have not yet received all doses, or completed the vaccine series; males aged 22 through 26 years may be vaccinated. For HIV-infected persons and for men who have sex with men, vaccination is recommended through age 26.
- The HBV vaccination series is recommended for all adolescents. Adolescents who have not previously received hepatitis B vaccine should be vaccinated routinely at any age with an appropriate dose and schedule^{3,4}
- The HAV vaccination series should be offered to adolescents and young adults who have not previously received the HAV vaccine series or for those at increased risk for infection or who live in areas that target older children for HAV vaccine²
- Information regarding HIV infection, testing, transmission, 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 health care¹²²
- Health-care providers who care for children and adolescents should integrate sexuality education into clinical practice. Providers should counsel adolescents about the sexual behaviors that are associated with risk for acquiring STDs and should educate patients regarding evidence-based prevention strategies, all of which include a discussion about abstinence and other risk-reduction behaviors (e.g., consistent and correct condom use). Interactive counseling approaches, such as high-intensity behavioral counseling (HIBC) and motivational interviewing, are effective STD/HIV prevention strategies. USPSTF recommends high-intensity behavioral counseling to prevent STIs* for all sexually active adolescents⁶. Educational materials, such as handouts, pamphlets, or videos, should be available to reinforce office-based educational efforts.

Children

Management of children who have STDs requires close cooperation between clinicians, laboratorians, and child-protection authorities. Official investigations, when indicated, should be initiated promptly. Certain diseases (e.g., gonorrhea, syphilis, and chlamydia), if acquired after the neonatal period, are virtually 100% indicative of sexual contact. For other diseases (e.g., HPV infections and vaginitis), the association with sexual contact is not as clear (see Sexual Assault and STDs).

* STI is the term used by USPSTF to describe the syndromes caused by various pathogens that can be acquired and transmitted through sexual activity.

Persons in Correctional Facilities

Multiple studies have demonstrated that persons entering correctional facilities have high rates of STDs (including HIV) and viral hepatitis (www.cdc.gov/hepatitis/Settings/corrections.htm), especially those aged ≤ 35 years¹¹⁹. Incarcerated persons are more likely to have low socioeconomic status, live in urban areas, and be ethnic and racial minorities. Risk behaviors for contracting STDs (e.g., having unprotected sex; having multiple sexual partners; using drugs and alcohol; engaging in commercial, survival, or coerced sex) are common among incarcerated populations. Before incarceration, many have had limited access to medical care, especially to community-based clinical prevention services.

Although no comprehensive national guidelines regarding STD care and management have been developed for correctional populations, there is growing evidence of the utility of expanded STD services in correctional settings. For example, in jurisdictions with comprehensive, targeted jail screening, more chlamydial infections among females (and males if males are screened) are detected in the jails, and subsequently treated, than at any other single reporting source^{119,128} and may even represent the majority of reported cases in certain jurisdictions¹²⁹.

Both men and women ≤ 35 years of age in juvenile and adult detention facilities have been reported to have higher rates of chlamydia¹³⁰ and gonorrhea¹¹⁹ than their non-incarcerated counterparts in the community, and across many studies, rates have been consistently higher among women than men. Syphilis seroprevalence rates, which can indicate previous or current infection, are considerably higher among adult men and women than in adolescents, consistent with the overall national syphilis trends¹³¹. Moreover, due to higher levels of sexual risk behavior among detainees, detection and treatment of early syphilis in correctional facilities may have greater impact on transmission than cases detected elsewhere¹³².

The provision of STD services in short-term facilities, including jails and juvenile detention facilities (often housing entrants for < 1 year) is complicated by the fact that up to half of all entrants are released back in the community within 48 hours. As a result, treatment completion rates for those screened and diagnosed with STDs in short-term facilities may 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 may be considerable¹³³. Moreover, treatment completion rates $\geq 95\%$ can be achieved by offering screening at or shortly after intake, shortening the time it takes the laboratory to provide test results, and follow-up of untreated individuals through public health outreach¹²⁹.

While universal screening for chlamydia in women ≤ 35 years entering juvenile and adult correctional facilities has been a long-standing recommendation, no such recommendation existed for men. In 2006, CDC convened a consultation on male chlamydia screening¹²¹, resulting in recommendations to screen men < 30 years for chlamydia at intake into jails.

Chlamydia and Gonorrhea Screening

Women ≤ 35 and men < 30 years in correctional facilities should be screened for chlamydia and gonorrhea.

Syphilis Screening

Universal screening should be conducted on the basis of the local area and institutional prevalence of early (primary, secondary, and early latent) infectious syphilis

Trichomoniasis Screening

Screening for trichomoniasis should be considered among incarcerated individuals due to the high prevalence of infection¹³⁴⁻¹³⁶.

MSM

The term “men who have sex with men (MSM)” describes a heterogeneous group of men who have varied behaviors, identities, and health care needs¹³⁷. Some MSM are at high risk for HIV infection and other viral and bacterial STDs, because of the unique susceptibility of the rectal mucosa to certain STD pathogens, and having multiple partners. The frequency of unsafe sexual practices and the reported rates of bacterial STDs and incident HIV infection declined substantially in MSM from the 1980s through the mid-1990s. However, since that time, increased rates of early syphilis (primary, secondary, or early latent), gonorrhea, and chlamydial infection and higher rates of sexual risk behaviors have been documented among MSM in the United States and virtually all industrialized countries.

At present, about 2/3 of the cases of primary and secondary syphilis in the U.S. are diagnosed in MSM¹¹⁹, particularly in ethnic minority MSM¹³⁸. Between 2004 and 2008, primary and secondary syphilis diagnoses increased 70% in Black MSM aged 13-24¹³⁹. One study has demonstrated increasing syphilis screening in MSM resulting in a doubling of early syphilis detection, however 71% of the syphilis cases were still diagnosed when persons sought care for symptoms¹⁴⁰. HIV incidence in HIV-uninfected MSM after a new syphilis diagnosis was 10.5% per year in one series¹⁴¹. One California study found that 19.2% of MSM who were newly diagnosed with syphilis reported methamphetamine use, and 36.4% met sex partners online¹⁴². These data suggest a need to increase the rate of syphilis screening for sexually active MSM, particularly if they have HIV infection, use recreational drugs (especially crystal methamphetamine), and/or meet casual partners on the internet.

Gonococcal infection in MSM has been associated with various risk factors including meeting partners on line, and substance use, particularly crystal methamphetamine use¹⁴³. Insertive oral sex has been associated with urethral gonorrhea acquisition¹⁴⁴, and the prevalence of pharyngeal gonorrhea was 7.3% and pharyngeal *C. trachomatis*, 2.3% in one study¹⁴⁵. In a multi-city study, rectal gonorrhea prevalence was 5.4% and rectal chlamydia prevalence was 8.9% in MSM¹⁴⁶. Recurrent rectal gonorrhea or chlamydia infection has been associated with an increased risk for HIV seroconversion among MSM^{147 148}. Rectal gonorrhea and chlamydia screening in MSM may offer a cost-effective intervention in certain urban settings¹⁴⁹.

Rectal gonococcal rates are increasing among MSM with HIV infection, underscoring the importance of an accurate sexual history on an ongoing basis, and to inquire about correlates of increased risk, including anonymous sex, and substance use¹⁵⁰. Newly diagnosed MSM with HIV infection were more likely than HIV-uninfected MSM to be diagnosed with asymptomatic gonorrhea (25.9% vs 10.9%, $p<0.001$) and chlamydia (18.5% vs 7.8%, $p<0.001$) than HIV-uninfected MSM¹⁵¹

MSM remain at disproportionate risk for HIV acquisition and transmission, with substantial numbers of MSM unaware of their serostatus (up to 44% in one recent survey focusing on younger men of color).¹⁵² Moreover, HIV prevalence is sufficiently high (19%), particularly among MSM from racial and ethnic minority communities, that any sex act without a condom with a new partner could expose the individual to a high risk of HIV infection. Behaviors that increase the risk for HIV infection in MSM include either receptive or insertive anal sex without a condom, having another STD, having sex with anonymous partners without a condom, using methamphetamines or sexual performance enhancing drugs¹⁵³. Individuals who report any of these behaviors should be screened for HIV and other STDs and should undergo counseling and repeat testing every 3 to 6 months, if these risks persist. Unfortunately, many MSM are not asked about their sexual risks, nor undergo routine testing with providers, often because of discomfort in discussing their sexual behavior with their care givers¹⁵⁴. In recent years, medical educational materials have been developed in print¹⁵⁵ and through electronic media (www.lgbthealtheducation.org) to increase the knowledge base of primary care providers, and to train them to be culturally competent in the diagnosis and management of STDs and other clinical conditions.

Because many MSM meet partners on line and may seek health information from websites, increased use of the internet for STD control may be warranted. MSM have indicated that they are amenable to receive HIV and STD risk reduction messages online¹⁵⁶ and to respond to requests for partner identification from public health authorities through the internet¹⁵⁷.

All MSM with HIV infection entering care should be screened for syphilis, as well as gonorrhea and chlamydia at appropriate anatomical sites of exposure.²⁰ The frequency of follow-up testing may be dictated by subsequent behavior, but recent studies suggest that for many MSM with HIV infection, screening every 3 to 6 months may be beneficial¹³⁷. Data from 557 adults in a recent study of adults with HIV infection engaged in primary care in 4 US cities found that 13% had an STD at enrollment and 7% incident STD at 6 months; among MSM with HIV infection the STD incidence was 20%⁹. Excluding trichomoniasis, 94% of incident STDs were diagnosed in MSM. STD screening rates in HIV clinics have been suboptimal. In one 8 city US study, although HIV providers tested the majority of MSM with HIV infection for syphilis, less than 10% were screened for extra-genitourinary gonorrhea or chlamydia, and less than 1 in 5 provided urine or urethral specimens¹⁵⁸. In addition to screening at risk MSM for bacterial STDs, HIV care providers should use the opportunity to provide evidence-based counseling on safer sex, using interventions that have been demonstrated to decrease STD incidence in clinical care settings⁹.

Clinicians also should routinely ask sexually active MSM about symptoms consistent with common STDs, including urethral discharge, dysuria, genital and perianal ulcers, regional

lymphadenopathy, skin rash, and anorectal symptoms consistent with proctitis, including discharge and pain on defecation or during anal intercourse. However, many infections are asymptomatic, and thus clinicians should perform appropriate diagnostic testing for sexually active MSM.

The following screening tests should be performed at least annually for sexually active MSM:

- HIV serology, if HIV negative **and who themselves or whose sex partners have had more than one sex partner since most recent HIV test**;
- syphilis serology, with a confirmatory test to establish whether persons with reactive serologies have incident untreated syphilis, have partially treated syphilis, or are manifesting a slow serologic response to appropriate prior therapy;
- a test for urethral infection with *N. gonorrhoeae* and *C. trachomatis* in men who have had insertive intercourse[†] during the preceding year; testing of the urine using nucleic acid amplification[†] testing (NAAT) is the preferred approach;
- a test for rectal infection[§] with *N. gonorrhoeae* and *C. trachomatis* in men who have had receptive anal intercourse* during the preceding year (NAAT of a rectal swab is the preferred approach); and
- a test for pharyngeal infection[§] with *N. gonorrhoeae* in men who have had receptive oral intercourse[†] during the preceding year (NAAT is the preferred approach). Testing for *C. trachomatis* pharyngeal infection is not recommended.

More frequent STD screening (i.e., at 3–6-month intervals) is indicated for MSM who themselves or whose sexual partners had had multiple partners.

Evaluation for HSV-2 infection with type-specific serologic tests also can be considered if infection status is unknown in persons with previously undiagnosed genital tract infection.

Human papillomavirus (HPV) infection and HPV-associated conditions such as anogenital warts and anal squamous intraepithelial lesions are highly prevalent among MSM. The quadrivalent vaccine is recommended routinely for MSM through age 26 years.^{159,160} The efficacy of this vaccine in preventing HPV associated diseases in men older than 26 years is unknown.

Data are insufficient to recommend routine anal cancer screening with anal cytology in persons with HIV infection or HIV-negative MSM. 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. However, some clinical centers perform anal cytology to screen for anal cancer among high-risk populations (e.g persons with HIV infection, MSM), followed by high-resolution

[†] Regardless of condom use during exposure.

[§] Commercially available NAATS are not not FDA cleared for these indications, but they can be used by laboratories that have met all regulatory requirements for an off-label procedure.

anoscopy for those with abnormal cytologic results (e.g. ASC-US).

All MSM should be tested for HBsAg to detect HBV infection. Prompt identification of chronic infection with HBV is essential to ensure necessary care and services to prevent transmission to others¹⁶¹. HBsAg testing should be made available in STD treatment settings. In addition, screening among past or current drug users should include HCV and HBV testing.

Vaccination against hepatitis A and B is recommended for all MSM in whom previous infection or vaccination cannot be documented^{2,3}. Preimmunization serologic testing might be considered to reduce the cost of vaccinating MSM who are already immune to these infections, but this testing should not delay vaccination. Vaccinating persons who are immune to HAV or HBV infection because of previous infection or vaccination does not increase the risk for vaccine-related adverse events (see Hepatitis B, Prevacination Antibody Screening).

Sexual transmission of HCV can occur, especially among MSM with HIV infection. Serologic screening for HCV is recommended at initial evaluation of newly diagnosed persons with HIV infection. Because of accumulating evidence of acute HCV infection acquisition among persons with HIV infection, especially MSM with HIV infection^{162,163 164 165; 166; 167} and cost-effectiveness of regular screening for HCV infection^{168,169} MSM with HIV infection should be regularly screened for HCV. Repetitive screening should be performed at least yearly and more frequently depending on local circumstances (HCV prevalence and incidence, high-risk sexual behavior, or concomitant ulcerative STDs). Screening should be performed using HCV antibody assays followed by HCV RNA testing for those with a positive antibody result {CDC, 2013 #1913

Women Who Have Sex with Women (WSW)

Few data are available on the risk of STDs conferred by sex between women, but transmission risk probably varies by the specific STD and sexual practice (e.g., oral-genital sex, vaginal or anal sex using hands, fingers, or penetrative sex items, and oral-anal sex)^{170,171}. 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^{172,173} and HIV transmitted sexually between women by concordant drug resistance genotype testing and by phylogenetic linkage analysis.^{174,175} There is also a high prevalence of BV among monogamous WSW¹⁷¹ However, the majority of self-identified WSW (53%–97%) have had sex with men in the past and might continue this practice, with 5%-28% of WSW reporting male partners within the past year.^{171,176-178}

Transmission of HPV can occur with skin-to-skin or skin-to-mucosa contact, which can occur during sex between women. Data now strongly support that HPV infections are common among WSW and that sexual transmission of HPV likely occurs between women¹⁷⁹⁻¹⁸¹ HPV DNA has been detected through polymerase chain reaction (PCR)-based methods from the cervix, vagina, and vulva in 13%–30% of WSW.^{179,180} Among WSW who reported never having had a male sexual partner, 26% had antibodies to HPV-16 and 42% had antibodies to HPV-6.¹⁷⁹ High- and low-grade squamous intraepithelial lesions (SIL) have been detected on Pap tests in

WSW who reported no previous sex with men.^{179,180,182,183} Women who have sex with women are at risk from acquiring HPV from both their female partners and from current or prior male partners, and thus are at risk for cervical cancer. Therefore, routine cervical cancer screening should be offered to all women, regardless of sexual preference or sexual practices, and women should be offered HPV vaccine as per current guidelines.

HSV-2 genital transmission between female sex partners is probably inefficient but can occur. A US population based survey among women aged 18-59 demonstrated an HSV-2 seroprevalence of 30% among women reporting same sex partners in the past year, 36% among women reporting same sex partners in their lifetime, and 24% among women reporting no lifetime same sex behavior.¹⁷⁷ HSV-2 seroprevalence among women self-identifying as “homosexual or lesbian” was 8%, similar to a prior clinic based study of WSW.^{177,178} The relatively frequent practice of orogenital sex among WSW might place them at higher risk for genital infection with HSV-1. This hypothesis is supported by the recognized association between HSV-1 seropositivity and previous number of female partners among WSW. Sexual transmission of HSV-1 and HSV-2 can occur between female sex partners, and this information should be included in the counseling and evaluation of women’s sexual health.

Less is known regarding transmission of bacterial pathogens 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* between women is unknown, infection may also be acquired from past or current male partners. More recent data suggests that *C. trachomatis* infection among WSW may be more common than previously thought.^{184,185} Report of same sex behavior in women should not deter providers from considering and performing screening for sexually transmitted infections, including *Chlamydia*, in their clients according to current guidelines.

Bacterial vaginosis (BV) is common among women in general and even more so among women with female partners.^{186,187} Sexual behaviors that facilitate the transfer of vaginal fluid and/ or bacteria between partners may be involved in the pathogenesis of BV. A study including monogamous couples demonstrated that female sex partners frequently share identical genital *Lactobacillus* strains.¹⁸⁸ Within a cohort of community based WSW, extrvaginal (oral, rectal) reservoirs of BV-associated bacteria were a risk factor for incident BV.¹⁸⁹ Several new studies have examined the impact of specific sexual practices on the vaginal microflora¹⁹⁰⁻¹⁹² and on recurrent¹⁹³ or incident^{194,195} BV among WSW and non-WSW. These studies have continued to support, though have not proven, the hypothesis that sexual behaviors, specific BV-associated bacteria, and possibly exchange of vaginal or extrvaginal microbiota (for example, oral bacterial communities) between partners may be involved in the pathogenesis of BV in WSW.

Although BV is common in WSW, routine screening for BV is not currently recommended. Results of a randomized trial utilizing a behavioral intervention to reduce persistent BV among WSW through reduced sharing of vaginal fluid on hands or sex toys has been published¹⁹⁶. Despite the fact that women randomized to the intervention were 50% less likely to report receptive digital-vaginal contact without gloves than controls and that shared sex toy use was infrequent, there was no reduction in persistent BV at one month post-treatment or incident episodes of recurrent BV among women randomized to the intervention. To date there

have been no reported trials examining the potential benefits of treating female partners of women with BV, and thus no data on which to base a recommendation for partner therapy in WSW. Encouraging awareness of signs and symptoms of bacterial vaginosis in women and encouraging healthy sexual practices (avoiding shared sex toys, cleaning shared sex toys, barrier use) may be helpful to women and their partners

Women who have sex with women are a diverse group with variations in sexual identity, sexual behaviors, sexual practices, and risk behaviors. Recent studies indicate that some WSW, particularly adolescents and young women as well as women with both male and female partners may be at increased risk for STDs and HIV based on reported risk behaviors^{185,197-200}. Several recent studies have highlighted the wide diversity of sexual practices and examined use of protective/ risk reduction strategies among populations of WSW.²⁰¹⁻²⁰³ Use of barrier protection with female partners (gloves during digital-genital sex, condoms with sex toys, latex or plastic barriers, also known as dental dams for oral-genital sex) was infrequent in all studies. Despite this, few comprehensive and reliable resources of sexual health information for WSW are available.²⁰⁴

Women who have sex with women are at risk of acquiring bacterial, viral, and protozoal STDs from current and prior partners, both male and female. Women who have sex with women should not be presumed to be at low or no risk for STDs based on sexual orientation. Report of same sex behavior in women should not deter providers from considering and performing screening for STDs and cervical cancer in their clients according to current guidelines. Effective screening requires a comprehensive and open discussion of sexual and behavioral risks, beyond sexual identity, between care providers and their female clients.

Transgender Men and Women

Transgender individuals have a gender identity that differs from that which they were assigned at birth. Transgender men (also referred to as trans men or transgender female to male) identify as men but were assigned female sex at birth based on their anatomy. Similarly transgender women (also referred to as trans women or transgender male to female) identify as women but were assigned male sex at birth. However, transgender individuals are diverse, and may use different and often fluid terminology to refer to themselves through their life course. Gender identity is independent from sexual orientation. A transgender person may have sex with men, women or both, and consider themselves as heterosexual, gay, lesbian, or bisexual. Prevalence studies of transgender people in the overall population have been limited and often based on small, convenience samples.

Transgender Women

Although the transgender population is relatively small, studies of HIV among transgender women suggest that the prevalence of HIV is the highest among subpopulation groups in the United States: 27.7% among all transgender women, and 56.3% among African American transgender women²⁰⁵. Data also suggests high rates of HIV among transgender women globally²⁰⁶. Bacterial STD prevalence varies among transgender women, but is based largely on convenience samples. In order to appropriately counsel transgender women about STD and HIV

prevention, it is important to learn about their current anatomy and patterns of sexual behavior with others²⁰⁷. A majority of transgender women have not undergone genital affirmation surgery and may retain a functional penis^{208 209,210}. In this case they may engage in insertive oral, vaginal or anal sex with other men and women.

Transgender Men

There are fewer studies of HIV prevalence and incidence in transgender men, and they appear to suggest that some transgender men engage in risky behaviors but have a lower prevalence of HIV than transgender women²¹¹. When counseling patients it is important to consider the great diversity among transgender men regarding their anatomy, as many transgender men may still have a vagina and a cervix putting them at risk for bacterial STDs, as well as cervical HPV and cervical cancer²¹².

Recommendations

Clinicians should assess STD and HIV related risks of transgender individuals, including an assessment about risk and behavior. Given the diversity of transgender individuals, their choices regarding surgical affirming procedures and hormone use, and their patterns of sexual behavior, it will be important to assess for symptoms consistent with common STDs, and to screen for asymptomatic STDs based on their behavioral histories (refer to MSM and WSW sections).

Emerging Issues

Hepatitis C

Hepatitis C virus (HCV) infection is the most common chronic bloodborne infection in the United States, with an estimated 2.7 million persons with chronic infection {Denniston, 2014 #2068}. HCV is mainly a parenterally transmitted virus, usually from shared drug injection needles and paraphernalia. HCV is not efficiently transmitted sexually^{162 213}, but reports are accumulating that sexually active men with HIV infection who are having sex with one another (“serosorting”) are acquiring acute HCV infection; these men usually engage in high-risk and traumatic sexual practices and have concurrent genital ulcerative disease^{214, 162 215}. These persons with HIV infection as well as those at risk for infection through injection-drug use might seek care in facilities that treat sexually transmitted infections, HIV counseling and testing facilities, correctional facilities, drug treatment facilities, and other public health settings where STD and HIV prevention and control services are available.

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 8–9 weeks, and anti-HCV can be detected in >97% of persons by 6 months after exposure. Chronic HCV infection develops in 70%–85% of HCV-infected persons; 60%–70% of chronically infected persons develop evidence of active liver disease. Most infected persons remain unaware of their infection because they are not clinically ill. However, infected persons serve as a source of transmission to others and are at

risk for chronic liver disease (CLD) and other HCV-related chronic diseases decades after infection.

HCV is transmitted through parenteral exposures to contaminated blood, usually through use of injection drugs (sharing of needles or works) and to a lesser extent through exposures in health-care settings as a consequence of inadequate infection-control practices²¹⁶. Transmission rarely follows receipt of blood, tissues, and organs from donors with HCV infection who were not identified during routine screening activities, which have been mandated in the United States since 1992. Tattoos applied in regulated settings have not been associated with HCV transmission, although tattoos received in unregulated settings have been linked to HCV transmission²¹⁷. Occupational and perinatal exposures also can result in transmission of HCV, but are uncommon.

Sexual transmission of HCV had been considered to occur rarely. Specific studies of HCV transmission between heterosexual or homosexual couples have yielded mixed results, but generally have found either no or very low increased rates of HCV infection in partners of persons with HCV infection compared with those whose partners are not HCV-infected^{217 213,218-223}. However, recent data indicate that sexual transmission of HCV can occur, especially among persons with HIV infection. Several studies have revealed that risk increases commensurate with increasing numbers of sex partners among heterosexual persons with HIV infection^{218,219,224-226} and MSM²²⁷⁻²³⁰, especially if those partners are also coinfecting with HIV^{215,227-232}.

Apparent sexual transmission of HCV has been reported among MSM with HIV infection in multiple European cities^{214,215,232}. In this country, increasing incidence of acute HCV infection among MSM with HIV infection has been reported in New York City^{233 234} and Boston^{167,169}. Common practices associated with these clusters of infection include ‘serosorting’ (i.e., men with HIV infection having sex with one another), group sex, and the use of cocaine and other non-intravenous drugs during sex.

All persons with HIV infection should undergo serologic testing for HCV at initial evaluation^{20,235}. Because of accumulating evidence of acute HCV infection acquisition in persons with HIV infection, especially MSM with HIV infection, and cost-effectiveness of regular screening^{168,169}, periodic HCV screening should be considered¹⁶²⁻¹⁶⁷. HCV testing in persons with HIV infection testing can be considered at least yearly in those at high risk for infection and more frequently depending on local circumstances (HCV prevalence and incidence, resources,). The USPSTF found no evidence on the frequency of screening in persons at risk for HCV infection¹¹⁰. Screening should be performed using HCV antibody assays. Indirect testing such as by alanine aminotransferase (ALT) is not recommended for detecting incident HCV infections, because ALT testing, especially if performed once a year, can miss many persons who have reverted after acute HCV infection to a normal ALT level at the time of test; and many incident infections may be missed^{167,169}. A converse problem—lack of test specificity—is that ALT can be elevated by antiretroviral medications, alcohol, various medicines and toxins. If ALT levels are being monitored, persons with HIV infection with new and unexplained increases in ALT should be tested for acute HCV infection as well as evaluated for possible medication toxicity or excessive alcohol use.

Acute hepatitis C is a reportable condition in 49 states, and matching viral hepatitis and HIV surveillance registries can facilitate early detection of social networks of HCV transmission among MSM with HIV infection. Suspected clusters of acute HCV infection should be reported to the appropriate public health authorities. Unprotected sexual contact between partners with HIV infection can facilitate spread of HCV, as the virus can be recovered from the semen of men with HIV²³⁶. Specific prevention practices (e.g., barrier precautions that limit contact with body fluids during sexual contact with other MSM) should be discussed.

Diagnosis and Treatment

HCV testing is recommended by CDC and USPSTF for all persons born during 1945-1965 and others based on their risk for infection or on a recognized exposure, including past or current injection drug use, receiving a blood transfusion before 1992, long-term hemodialysis, being born to a mother with HCV infection, intranasal drug use, receipt of an unregulated tattoo, and other percutaneous exposures^{110,237-217} (see Hepatitis C, Prevention). Testing for HCV infection should include the use of an FDA-cleared test for antibody to HCV (i.e., immunoassay, EIA, or enhanced chemiluminescence immunoassay and, if recommended, a supplemental antibody test) followed by HCV RNA testing for those with a positive antibody result²³⁸.

Persons determined to be anti-HCV positive should be evaluated (by referral or consultation, if appropriate) for the presence of active infection, presence or development of CLD, and possible treatment. Nucleic acid testing, including reverse transcriptase polymerase chain reaction (RT-PCR) to detect HCV RNA, is necessary to confirm the diagnosis of current HCV infection, and an elevated ALT level is biochemical evidence of CLD. Providers should consult with specialists knowledgeable about management of hepatitis C infection and refer to existing guidelines that reflect the latest advances in the management of hepatitis C (www.hcvguidelines.org).

Prevention

Reducing the burden of HCV infection and disease in the United States requires implementation of both primary and secondary prevention activities. Primary prevention reduces or eliminates HCV transmission, whereas secondary prevention activities are aimed at reducing CLD and other chronic diseases in persons with HCV infection by first identifying them and then providing medical management and antiviral therapy, if appropriate. No vaccine for hepatitis C is available, and prophylaxis with immune globulin is not effective in preventing HCV infection after exposure.

Most scientific evidence demonstrates that although HCV can be transmitted sexually, such transmission happens rarely. Because incident HCV has not been demonstrated to occur in heterosexual partner-pairs followed over time²¹³⁻²²⁰⁻²²², condom use might not be necessary in such circumstances. However, heterosexual and homosexual persons, especially those with concurrent HIV infection or with more than one partner, should protect themselves and their partners against transmission of HCV, HBV, HIV, and other pathogens by use of male latex condoms. Condom use is especially important for men with HIV infection, who might spread HCV to other men through unprotected sexual activity^{215,232,233}.

Providers in STD clinics and other primary-care settings should identify those persons who should be offered HCV testing. In STD clinics and other settings that serve large numbers of persons at high risk for bloodborne infections (e.g., correctional settings), the major risk factor necessitating screening for HCV infection is past or current injection drug use¹¹⁰. Other risk factors for which routine HCV testing is recommended include:

- having had a blood transfusion before July 1992;
- receipt of an unregulated tattoo;
- having been on long-term hemodialysis;
- intranasal drug use; and
- other percutaneous exposures

Persons with HIV infection who test negative for anti-HCV who had an exposure more than 12 months previously should be reassured that they are not infected; persons with HIV infection with low CD4-positive cell count may require further testing by nucleic acid testing (for HCV RNA) because of the potential for a false negative antibody assay. Those who test positive for anti-HCV and are confirmed infected by nucleic acid testing (see Diagnosis and Treatment) should be provided information regarding how to protect their liver from further harm; for instance, persons with HCV infection should be advised to avoid drinking alcohol and taking any new medicines (including OTC and herbals) without checking with their clinician.

To reduce the risk for transmission to others, persons with HCV infection should be advised to 1) not donate blood, body organs, other tissue, or semen; 2) not share any personal items that might have blood on them (e.g., toothbrushes and razors); and 3) cover cuts and sores on the skin to keep the virus from spreading by blood or secretions. Persons with HCV infection with one long-term, steady sex partner do not need to change their sexual practices. They should discuss the low but present risk for transmission with their partner and discuss the need for testing^{162,237}. HCV-positive women do not need to avoid pregnancy or breastfeeding.

Persons with HCV infection should be evaluated (by referral or consultation, if appropriate) to detect current HCV infection and the presence of chronic liver disease. Evaluation should involve testing for liver function, additional assessment of the severity of liver disease, possible treatment, and the determination for the need of hepatitis A and B vaccination.

Regardless of test results, persons who use or inject drugs should be counseled to stop using and injecting drugs and provided assistance to enter and complete substance abuse treatment (including relapse prevention). Persons who continue to inject drugs despite counseling should be encouraged to take the following 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., pharmacies);
- use a new, sterile syringe to prepare and inject drugs;

- 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 before injection with a new alcohol swab;
- safely dispose of syringes after one use;
- get vaccinated for hepatitis A and B if nonimmune; and
- get tested for HIV infection.

Postexposure Follow-Up

No post exposure prophylaxis has been demonstrated to be effective against HCV. Testing to determine whether HCV infection has developed is recommended for health-care workers after percutaneous or permucosal exposures to HCV-positive blood. Children born to women with HCV infection also should be tested for HCV. Prompt identification of acute infection is important, because outcomes are improved when treatment is initiated earlier in the course of illness.

Special Considerations

Pregnancy

Routine testing for HCV infection is not recommended for all pregnant women. Pregnant women with a known risk factor for HCV infection should be offered testing. While the rate of transmission is highly variable, up to six of every 100 infants born to HCV-infected woman become infected; this infection occurs predominantly during or near delivery, and no treatment or delivery method—such as caesarian section—has been demonstrated to decrease this risk²³⁹. The risk is increased, however, by the presence of maternal HCV viremia at delivery and also is greater (2–3 times) if the woman is coinfecting with HIV. HCV has not been shown 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(<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6218a5.htm>; because maternal antibody is present for the first 18 months and before the infant mounts an immunologic response, nucleic acid testing is recommended.

HIV Infection

Because of the high prevalence of HIV/HCV coinfection and because of critical clinical management issues for coinfecting persons, all persons with HIV infection should undergo initial and repetitive serologic testing for HCV. Providers should be aware of the likelihood that MSM

with HIV infection will acquire HCV after initial screening. HCV antibody tests should be serially monitored, at least yearly and more frequently depending on local circumstances (HCV prevalence, incidence, resources, and other factors), to detect conversion from HCV-antibody-negative to positive. Persons with new and unexplained increases in ALT should also be tested for acute HCV infection, as well as evaluated for hepatitis viruses A and B, alcohol use, and antiretroviral and other medication toxicity.

Because a small percentage of persons with HIV infection fail to develop HCV antibodies, HCV RNA testing should be performed in persons with unexplained liver disease who are anti-HCV negative. The course of liver disease is more rapid in HIV/HCV coinfecting persons, and the risk for cirrhosis is nearly twice that of persons with HCV infection alone. Coinfecting persons receiving HIV antiviral regimens are now being treated for HCV after their CD4+ cell counts increase, optimizing their immune response.

Mycoplasma genitalium

Mycoplasma genitalium was first identified in the early 1980's²⁴⁰ and has become recognized as a cause of male urethritis. It is responsible for approximately 15-20% of non-gonococcal urethritis (NGU) cases, 20-25% of non-chlamydial NGU, and approximately 30% of persistent or recurrent urethritis²⁴¹. In most settings it is more common than *Neisseria gonorrhoeae* but less common than *Chlamydia trachomatis*. While *M. genitalium* is often the sole pathogen detected, coinfection with *C. trachomatis* is not uncommon in selected areas²⁴²⁻²⁴⁴.

Although strong and consistent evidence has linked *M. genitalium* to urethritis in men, it remains unknown whether it can cause male infertility or other male anogenital tract disease syndromes. The organism has been detected in men with epididymitis in a limited number of cases, but this has not been extensively studied. Similarly, *M. genitalium* has been found in the rectum, but detection is infrequently accompanied by rectal symptoms and it does not appear to cause a syndrome of clinical proctitis.

The pathogenic role of *M. genitalium* is less definitive in women than it is in men. *M. genitalium* can be found in the vagina, cervix, and endometrium and, like chlamydial and gonococcal infections, *M. genitalium* infections in women are commonly asymptomatic. It can be detected in 10-30% of women with clinical cervicitis and most²⁴⁴⁻²⁵⁰, but not all studies have found that *M. genitalium* is more common among women with cervicitis than in women without the syndrome^{242,251,252}.

M. genitalium is found in the cervix and/or endometrium of women with pelvic inflammatory disease (PID) more often than in women without PID²⁵³⁻²⁶² and endosalpingitis develops in non-human primates after inoculation with *M. genitalium*, suggesting that it can cause PID. It has been detected in 2-22% of PID cases (median 10%) depending on the setting, but the frequency with which *M. genitalium*-infected women experience PID has been little studied. While one study in Sweden reported a substantial increase in risk for post-abortion PID among women with *M. genitalium*²⁵³, the proportion of *M. genitalium*-positive women who subsequently experienced PID in two other studies was relatively low (<5%)^{263,264} and evidence from serologic studies assessing the association of PID with antibody to *M. genitalium* is inconsistent. Overall,

current evidence suggests that *M. genitalium* can cause PID, but that this occurs less frequently than it does with *C. trachomatis*^{262, 264}.

A small number of seroepidemiologic studies have found that women with tubal factor infertility are more likely to have antibodies to *M. genitalium* than fertile women, suggesting it may cause female infertility. However, more research is needed on this subject. Based on very few reports, *M. genitalium* does not appear to be common in women who experience adverse pregnancy outcomes, but was associated with increased risk for preterm delivery in one well-conducted study in the US and one in Peru^{265,266}. Very little data exist on *M. genitalium* and ectopic pregnancy.

Diagnostic Considerations

M. genitalium is a very slow-growing organism, culture can take up to 6 months, and only a few laboratories in the world are able to recover clinical isolates. Therefore, culture is not a viable diagnostic option and nucleic acid amplification testing (NAAT) is the preferred method to detect *M. genitalium*. In research settings, an *M. genitalium* diagnosis is obtained by NAAT testing of urine, urethral, vaginal and cervical swabs, and endometrial biopsies, typically using in-house PCR or research-use only assays. Some large medical centers and commercial laboratories have developed in-house PCR assays for *M. genitalium*, but there is currently no commercially available diagnostic test cleared by the FDA for use in the U.S. Diagnosis of *M. genitalium* infection is further complicated by the lack of a characteristic clinical syndrome. In the absence of validated tests, *M. genitalium* should be suspected in cases of persistent or recurrent urethritis, and may be considered in persistent or recurrent cases of cervicitis and PID.

Treatment

M. genitalium lacks a cell wall and antibiotics that target cell-wall biosynthesis are ineffective (e.g., beta-lactams including penicillins and cephalosporins). Given the diagnostic challenges, treatment of most *M. genitalium* infections will occur in the context of syndromic management for STD syndromes.

Urethritis and cervicitis

The 7-day doxycycline regimen recommended for treatment of urethritis is largely ineffective against *M. genitalium* with a median cure rate of approximately 31%.²⁶⁷⁻²⁶⁹ The 1 gram single dose of azithromycin was significantly more effective against *M. genitalium* than doxycycline in two randomized trials,^{267,268} and is preferred over doxycycline. However, resistance to azithromycin appears to be rapidly emerging. The median cure rate for both men and women is approximately 85%, but was only 40% in the most recent trial²⁶⁹. Individuals with treatment failures after the 1g azithromycin regimen frequently have macrolide resistant strains suggesting that single dose azithromycin therapy may select for resistance. A longer course of azithromycin (500mg once plus 250mg daily for 4 days) may be marginally superior to the single dose regimen and theoretically might prevent the development of resistance.²⁷⁰⁻²⁷² However, in some settings, as many as 50% of all *M. genitalium* infections are caused by organisms that are already

resistant to azithromycin²⁷³ and persons failing the 1g azithromycin regimen generally do not benefit from retreatment with the extended dose regimen.

Moxifloxacin (400mg x 7, 10 or 14 days) has been successfully used to treat *M. genitalium* treatment failures in men and women, with cure rates of 100% in initial reports^{271,274}. However, moxifloxacin has been used in a relatively small number of cases and the drug has not been tested in clinical trials. While generally considered effective, recent studies in Japan, Australia, and the US have reported moxifloxacin treatment failures after the 7 day regimen^{275 276 277,278}

PID

Currently recommended PID treatment regimens are based on antibiotics that are not effective against *M. genitalium*. Therefore, clinicians may consider *M. genitalium* in cases that fail to respond to therapy within 7-10 days. Where validated *M. genitalium* testing is available, clinicians may test women diagnosed with PID for *M. genitalium*. When *M. genitalium* is detected, a regimen of moxifloxacin 400mg/day x 14 days has been effective in eradicating the organism²⁷⁹. Nevertheless, there are no published data assessing the benefits of testing women with PID for *M. genitalium* and the importance of directing treatment against this organism is currently unknown.

Follow-up

In settings where validated *M. genitalium* testing is available, persons with persistent urethritis, cervicitis, or PID accompanied by persistent detection of *M. genitalium* may be treated with moxifloxacin. However, routine tests-of-cure in asymptomatic individuals are not recommended.

Management of sex partners

Management of sex partners should follow guidelines for patients with NGU, cervicitis and PID. In settings with access to validated *M. genitalium* tests, partner testing and treatment of identified infections may be considered.

Special considerations

HIV infection

Patients who have an *M. genitalium* infection and HIV infection should receive the same treatment regimen as those who are HIV negative.

HIV Infection: Detection, Counseling, and Referral

HIV infection typically begins with a brief acute retroviral syndrome, then transitions to a multiyear chronic illness that progressively depletes CD4 T- lymphocytes critical for maintenance of effective immune function, and ends with symptomatic, life-threatening immunodeficiency. This late stage of infection, known as acquired immunodeficiency syndrome

(AIDS), develops over months to years with an estimated median time of approximately 11 years²⁸⁰. In the absence of treatment, virtually all persons with AIDS will die; however with antiretroviral therapy, persons provided early effective treatment can expect to live a near normal lifespan²⁸¹⁻²⁸³. Early diagnosis of HIV infection and linkage to care are essential not only for individuals own health but also to reduce their risk of transmitting HIV to others. As of March 2012, U.S. guidelines recommend all persons diagnosed with HIV infection be offered effective antiretroviral therapy⁶⁶.

CDC estimates that as of 2011, approximately 16% of the estimated 1.2 million persons with HIV infection in the United States are unaware of their infection http://www.cdc.gov/hiv/pdf/2011_Monitoring_HIV_Indicators_HSSR_FINAL.pdf. Knowing that a patient is infected with HIV has important clinical implications because HIV infection alters the immune system and thereby affects the diagnosis, evaluation, treatment, and follow-up of some other STDs. Diagnosing HIV infection during the acute phase is particularly important (see acute HIV infection). Persons with HIV infection are most infectious because HIV concentrations are extremely high in plasma and genital secretions²⁸⁴⁻²⁸⁷, but tests for HIV antibodies are negative. Persons believing they are uninfected might unknowingly continue to engage in behaviors associated with HIV transmission. Providers serving individuals at risk for STDs are in a particularly good position to diagnose HIV infection in persons during the acute phase because they might present for assessment or treatment of a concomitantly acquired STD. Also, 50-90% of persons with acute HIV infection are symptomatic and many seek medical care^{288 289}.

Despite the availability of effective antiretroviral therapy, many cases of HIV infection continue to be diagnosed when it is already advanced (as evidenced by low CD4 cell counts). Nationally, the proportion of patients diagnosed with AIDS at or within 12 months of their HIV diagnosis in 2010 was 32%²⁹⁰). Since 2006, CDC has recommended efforts to increase HIV testing by streamlining the consent process and expanding opt-out testing to STD clinics and all settings serving those at risk for STDs¹²². HIV testing facilitates early diagnosis, which reduces the spread of disease, extends life expectancy, and reduces costs of care. However, rates of testing remain low: CDC estimates that in 2008, only 45% of adults aged 18-64 years had ever been tested²⁹¹, and that from 2006-2009 approximately 41% of persons with newly diagnosed HIV infection had never been previously tested²⁹².

Comprehensive HIV treatment services are usually not available in facilities focusing primarily on STD treatment (e.g., STD clinics). In such settings, patients with a new diagnosis of HIV infection, or with an existing diagnosis of HIV infection who are not engaged in regular on-going care, should be linked promptly to a health-care provider or facility experienced in caring for HIV-infected patients⁶⁶. Providers working in STD-treatment facilities should be knowledgeable about the treatment options available in their communities, educate HIV-infected persons about the illness, and link these patients to HIV-related care and support services. Provision of care should also include behavioral and psychosocial services, especially for alcohol and drug addiction and for mental health problems.

A detailed discussion of the complex issues required for the management of HIV infection is beyond the scope of this report; however this information is available in other

published resources^{20,66,235}. These HIV care resources are updated frequently and the most current versions are available on line (see URLs accompanying each reference). These resources provide additional information about the diagnosis and medical management of HIV infection, counseling of HIV-infected patients, referral for support services, and management of sex and injection-drug partners in STD-treatment facilities. In addition, subsequent sections of this report briefly discuss HIV infection during pregnancy and among infants and children.

Detection of HIV Infection: Screening

All persons who seek evaluation and treatment for STDs should be screened for HIV infection. Screening should be routine, regardless of whether the patient reports any specific behavioral risks for HIV infection.

CDC recommends HIV screening for patients aged 13–64 years in all health-care settings¹²². Persons should be notified that testing will be performed, unless they decline or defer testing (an opt-out approach)²⁹³. Consent for HIV screening should be incorporated into the general informed consent for medical care on the same basis as are other screening or diagnostic tests. A separate consent form for HIV testing is not recommended.

Providing prevention counseling in conjunction with HIV diagnostic testing or as part of HIV screening programs should not be required in health-care settings. However, some patients might be more likely to think about HIV and consider their risk-related behavior when undergoing an HIV test. HIV testing presents an excellent opportunity to provide prevention counseling and risk-reduction messages. High-intensity counseling with multiple sessions delivered to individuals or groups has been shown effective for reducing subsequent STD incidence⁶.

Establishing the Diagnosis of HIV Infection

HIV infection can be diagnosed by serologic tests that detect antibodies against HIV-1 and HIV-2 and by virologic tests that can detect HIV antigens or ribonucleic acid (RNA). Testing begins with a sensitive screening test, usually an antigen/antibody combination or antibody immunoassay (IA). Currently available serologic tests are both highly sensitive and specific and can detect all known subtypes of HIV-1. Most can also detect HIV-2 and uncommon variants of HIV-1 (e.g., group O and group N). Rapid HIV tests enable clinicians to make a preliminary diagnosis of HIV infection within half an hour. However, most rapid antibody assays become reactive later than conventional laboratory-based antibody or combination antigen/antibody serologic assays, and thus produce negative results in recently infection persons.

The recommended diagnostic algorithm for HIV infection consists of performing a laboratory-based immunoassay, which if repeatedly reactive is followed by a supplemental test such as an HIV-1/HIV-2 antibody differentiation assay, Western blot, or indirect immunofluorescence assay. However, currently available FDA-cleared HIV laboratory antigen/antibody immunoassay detect HIV infection earlier than the assays traditionally used as HIV supplemental tests, such as Western blots. Therefore, during very early HIV infection,

discordant HIV test results (reactive immunoassay results and negative supplemental test results) have been erroneously interpreted as negative.²⁹⁴ The recommended algorithm minimizes this problem begins with a combination HIV-1/HIV-2 antigen-antibody (Ag/Ab) combination immunoassay, which if reactive, is followed by an HIV-1/HIV-2 antibody differentiation assay²⁹⁵. This algorithm confers an additional advantage by testing all specimens reactive on the initial immunoassay for HIV-2 antibodies. RNA testing is performed on all specimens with reactive immunoassay but negative supplemental antibody test results to determine if the discordance represents acute HIV infection. Although HIV-2 is uncommon in the United States, accurate identification is important because monitoring and therapy for HIV-2 differs from that for HIV-1²⁹⁶

The following are specific recommendations that apply to testing for HIV infection:

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| <p>Key considerations when establishing an HIV diagnosis</p> |
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| <ul style="list-style-type: none"> • HIV screening is recommended for all persons who seek evaluation or treatment for STDs. • HIV testing must be voluntary and free from coercion. Patients must 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. • Specific signed consent for HIV testing should not be required. General informed consent for medical care is considered sufficient to encompass informed consent for HIV testing. • Use of Ag/Ab combination tests is encouraged unless persons are unlikely to receive their HIV test results. • Preliminary positive screening tests for HIV infection must be followed by additional testing to definitively establish the diagnosis. • Providers should be alert to the possibility of acute HIV infection and perform an antigen/antibody immunoassay or HIV RNA in conjunction with an antibody test. Persons suspected of recently acquired HIV infection should be referred immediately to an HIV clinical care provider. |
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Acute HIV Infection

Health-care providers should be knowledgeable about the symptoms and signs of acute retroviral syndrome, which develops in 50%–90% of persons within the first few weeks after they become infected with HIV²⁸⁹. Acute retroviral syndrome is characterized by non-specific symptoms, including fever, malaise, lymphadenopathy, and skin rash. Suspicion of acute

retroviral syndrome should prompt urgent assessment with an antigen/antibody IA or HIV RNA in conjunction with an antibody test. If IA are negative or indeterminate then testing for HIV RNA should follow. Clinicians should not assume that a laboratory report of a negative HIV antibody test result indicates that the necessary RNA screening for acute HIV infection has been conducted. Available HIV home kits only detect HIV antibodies and therefore will not detect acute HIV infection.

Persons with acute HIV infection are highly infectious during this stage of infection because the concentration of virus in plasma and genital secretions is extremely elevated^{285,297}. Antiretroviral therapy during acute HIV infection is recommended because it substantially reduces infectiousness to others, improves laboratory markers of disease, may decrease severity of acute disease, lowers viral set-point, reduces the size of the viral reservoir, decreases rate of viral mutation by suppressing replication, and preserves immune function⁶⁶. Persons diagnosed with acute HIV infection should be referred immediately to an HIV clinical-care provider, provided prevention counseling (e.g., reduce number of partners, use condoms correctly and consistently), and screened for STDs. Information should be provided on the availability of post-exposure prophylaxis for sexual and needle-sharing partners not known to have HIV infection if the most recent contact was within the 72 hours preceding HIV diagnosis (www.cdc.gov/hiv)

After establishing a New HIV Diagnosis

Persons with newly diagnosed HIV infection should be informed of the importance of promptly initiating medical care for their own health and to reduce further transmission of HIV, the effectiveness of HIV treatments, and about what to expect as they enter medical care for HIV infection.⁶⁶ They should be linked promptly to a health care provider or facility experienced in caring for patients with HIV. Persons with symptoms or signs that suggest advanced HIV infection (e.g., fever, weight loss, diarrhea, cough, shortness of breath, and oral candidiasis) should be evaluated or referred for evaluation immediately. Persons experiencing psychological distress should be referred accordingly (see Counseling for Persons with HIV Infection and Referral to Support Services). Detailed and regularly updated recommendation for the initial management of persons with HIV infection can be found in other published resources^{20,66,235}

Counseling for Persons with HIV Infection and Referral to Support Services

Providers should expect persons to be distressed when first informed of a positive HIV test result. Such persons face multiple major adaptive challenges, including coping with the reactions of others to a stigmatizing illness, developing and adopting strategies for maintaining physical and emotional health, initiating changes in behavior to prevent HIV transmission to others, and reducing the risk for acquiring additional STDs. Many persons will require assistance with making reproductive choices, gaining access to health services, and coping with changes in personal relationships. Therefore, behavioral and psychosocial services are an integral part of health care for persons with HIV infection.

Persons testing positive for HIV infection have unique needs. Some individuals may require referral for specific behavioral interventions (e.g., a substance abuse program), mental health disorders (e.g., depression), emotional distress, while others might require assistance with

securing and maintaining employment and housing. Women should be counseled or appropriately referred regarding reproductive choices and contraceptive options, and persons with multiple psychosocial problems might be candidates for comprehensive risk-reduction counseling and services.

The following are specific recommendations for HIV counseling and linkage to services that should be offered before leaving the testing site:

- Persons who test positive for HIV should be counseled, either on site or through referral, concerning the behavioral, psychosocial, and medical implications of HIV infection.
- Health-care providers should be alert for medical or psychosocial conditions that require immediate attention.
- Providers should assess the needs of newly diagnosed persons for immediate medical care or support and should link them to services provided by health-care personnel experienced in the management of HIV infection. Additional services that may be needed include substance abuse 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 as well as what to expect.

Several successful, innovative interventions to assist persons with HIV infection reduce the possibility of transmission to others have been developed for diverse at-risk populations, and these can be locally replicated or adapted^{14,298-302}. Involvement of nongovernment organizations and community-based organizations might complement such efforts in the clinical setting.

Management of Sex Partners and Injection-Drug Partners

Clinicians providing services to persons with HIV infection should determine whether any partners should be notified concerning possible exposure to HIV^{122,303}. In the context of HIV management, “partner” includes sex partners and persons with whom they share syringes or other injection equipment. Partner notification is an important component of disease management, because early diagnosis and treatment of HIV infection reduces risk of onward HIV transmission, decreases individual morbidity and mortality risk, and provides the opportunity to modify risk behaviors. Partner notification for HIV infection should be confidential. Specific guidance regarding spousal notification varies by jurisdiction. Detailed recommendations concerning identification, notification, diagnosis, and treatment of exposed partners are available in Recommendations for Partner Services Programs for HIV Infection, Syphilis, Gonorrhea, and Chlamydial Infections³⁰³.

The following are specific recommendations for implementing partner-notification procedures:

- Health care providers should inform persons with HIV infection about partner services including processes, benefits, and risks.
- Persons with HIV infection should be encouraged to notify their partners and to refer them for counseling and testing.
- Health-care providers should assist in this process, either directly or by referral to health department partner-notification programs which may attempt to contact them.
- If persons with HIV infection are unwilling to notify their partners or if they cannot ensure that their partners will seek counseling, HIV care staff or health department personnel should use confidential partner notification procedures. Importantly, health department staff are trained to locate hard-to-reach individuals through field investigation, while most clinical providers do not have the time or expertise in this type of partner notification.
- Partners who have been reached and are not known to have HIV infection and were exposed (to genital secretions or blood of a partner with HIV infection through sex or injection-drug use) within the preceding 72 hours should be offered post-exposure prophylaxis with combination antiretrovirals³⁰⁴

STD Testing during HIV Care:

During the course of HIV care, providers should test all sexually active persons with HIV infection for curable STDs (e.g., syphilis, gonorrhea, and chlamydia) at least annually¹¹. Specific testing includes syphilis serology, and testing for *N gonorrhoeae* and *C trachomatis* at the site of exposure, using nucleic acid amplification tests as the preferred approach. More frequent STD screening might be appropriate depending on individual risk behaviors, the local epidemiology of STDs, and whether STDs are detected initially. Many STDs are asymptomatic and their diagnosis may indicate risk behavior that should prompt referral for partner services and prevention counseling.⁹ Women should be screened for cervical cancer precursor lesions by cervical Pap tests per existing guidelines.²³⁵

Special Considerations

Pregnancy

All pregnant women should be tested for HIV infection as early during pregnancy as possible. A second test during the third trimester, preferably at <36 weeks' gestation, should be considered for all pregnant women and is recommended for the following women: those known to be at high risk for acquiring HIV, those who receive health care in jurisdictions with elevated incidence of HIV or AIDS among women, and women living in facilities in which prenatal screening identifies at least one HIV-infected pregnant woman per 1,000 women screened¹²². An RNA test should be used in conjunction with an HIV antibody test for women who have signs or symptoms consistent with acute HIV infection. The women should be informed that she will be tested for HIV infection as part of the panel of prenatal tests, unless she declines^{102,122}. For women who decline, providers should address concerns that pose obstacles to testing and encourage testing at subsequent prenatal visits. Women who decline testing because they have had a previous negative HIV test 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 particularly important not only to maintain the health of the patient, but because interventions (i.e., antiretroviral and obstetrical) can substantially reduce the risk for perinatal transmission of HIV.

After a pregnant woman has been identified as having HIV infection, she should be educated about the benefits of antiretroviral treatment for her health and for reducing the risk of transmission to her infant. In the absence of antiretroviral treatment, a mother's risk transmitting HIV to her neonate is approximately 30% but can be reduced to <2% with antiretroviral treatment, obstetrical interventions (i.e., elective cesarean section at 38 weeks of pregnancy), and by avoiding breastfeeding³⁰⁵. Pregnant women who have HIV infection should be linked to an HIV care provider, given appropriate antenatal and post-partum treatment and advice.

HIV Infection Among Neonates, Infants and Children

Diagnosis of HIV infection in a pregnant woman indicates the need to evaluate and manage the HIV-exposed neonate and consider whether the woman's other children might be infected. Detailed recommendations regarding diagnosis and management of HIV in neonates of mothers with HIV infection are beyond the scope of this report. Exposed neonates should be referred to physicians with expertise.

Diseases Characterized by Genital, Anal, or Perianal Ulcers

In the United States, most 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 a genital, anal, or perianal ulcer. Less common infectious causes of genital, anal, or perianal ulcers include chancroid and donovanosis. Genital herpes, syphilis, and chancroid have been associated with an increased risk for HIV transmission, and genital, anal, or perianal lesions can also be associated with infectious and not infectious conditions that are not sexually transmitted (e.g., yeast, trauma, carcinoma, aphthae, fixed drug eruption, and psoriasis).

A diagnosis based only on the patient's medical history and physical examination frequently is inaccurate. Therefore, all patients who have genital, anal, or perianal ulcers should be evaluated with a serologic test for syphilis and a diagnostic evaluation for genital herpes; in settings where chancroid is prevalent, a test for *Haemophilus ducreyi* should also be performed. Specific tests for evaluation of genital, anal, or perianal ulcers include 1) syphilis serology and darkfield examination; 2) culture or PCR testing for genital herpes; and 3) serologic testing for type-specific HSV antibody.

No FDA-cleared PCR test to diagnose syphilis is available in the United States but there are currently two FDA-cleared tests for the diagnosis of HSV1 & 2 in genital specimens. Some clinical laboratories have developed their own syphilis and HSV tests and have conducted a Clinical Laboratory Improvement Amendment (CLIA) verification study. Type-specific serology for HSV-2 might be helpful in identifying persons with genital herpes (see Genital Herpes, Type-

Specific Serologic Tests). In addition, biopsy of genital, anal, or perianal ulcers 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 with genital, anal, or perianal ulcers who are not known to have HIV infection (see Diagnostic Considerations, sections on Syphilis, Chancroid, and Genital Herpes Simplex Virus).

Because early treatment decreases the possibility of ongoing transmission, public health standards require health-care providers to presumptively treat any suspected cases of infectious syphilis at the initial visit, even before test results are available. Presumptive treatment of a suspected first episode of genital herpes is recommended because successful treatment depends on prompt initiation of therapy. The clinician should choose the presumptive treatment on the basis of clinical presentation (i.e., HSV lesions begin as vesicles and primary syphilis as a papule) and epidemiologic circumstances such as high incidence of disease among populations and communities. For example, syphilis is so common in MSM that any genital ulcer should be presumptively treated for syphilis. Even after complete diagnostic evaluation, at least 25% of patients who have genital ulcers have no laboratory-confirmed diagnosis.³⁰⁶

Chancroid

The prevalence of chancroid has declined in the United States¹¹⁹. When infection does occur, it is usually associated with sporadic outbreaks. Worldwide, chancroid appears to have declined as well, although infection might still occur in some regions of Africa and the Caribbean. Chancroid, as well as genital herpes and syphilis, is a risk factor in the transmission of HIV infection³⁰⁷

A definitive diagnosis of chancroid requires the identification of *H. ducreyi* on special culture media that is not widely available from commercial sources; even when these media are used, sensitivity is <80%³⁰⁸. No FDA-cleared PCR test for *H. ducreyi* is available in the United States, but such testing can be performed by clinical laboratories that have developed their own PCR test and have conducted a CLIA verification study.

The combination of a painful genital ulcer and tender suppurative inguinal adenopathy suggests the diagnosis of chancroid³⁰⁹. A probable diagnosis of chancroid, for both clinical and surveillance purposes, can be made if all of the following 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 of ulcer exudate or by a serologic test for syphilis performed at least 7 days after onset of ulcers; and 4) a PCR test for HSV performed on the ulcer exudate is negative.

Treatment

Successful treatment for chancroid cures the infection, resolves the clinical symptoms, and prevents transmission to others. In advanced cases, scarring can result, despite successful therapy.

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| <i>Recommended Regimens</i> |
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Azithromycin 1 g orally in a single dose

OR

Ceftriaxone 250 mg intramuscularly (IM) in a single dose

OR

Ciprofloxacin 500 mg orally twice a day for 3 days

OR

Erythromycin base 500 mg orally three times a day for 7 days

Azithromycin and ceftriaxone offer the advantage of single-dose therapy. Worldwide, several isolates with intermediate resistance to either ciprofloxacin or erythromycin have been reported. However, because cultures are not routinely performed, data are limited regarding the current prevalence of antimicrobial resistance.

Other Management Considerations

Men who are uncircumcised and patients with HIV infection do not respond as well to treatment as persons who are circumcised or HIV-negative. Patients should be tested for HIV infection at the time chancroid is diagnosed. If the initial test results were negative, a serologic test for syphilis and HIV infection should be performed 3 months after the diagnosis of chancroid.

Follow-Up

Patients should be re-examined 3–7 days after initiation of therapy. 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 must consider whether 1) the diagnosis is correct, 2) the patient is coinfecting with another STD, 3) the patient is infected with HIV, 4) the treatment was not used as instructed, or 5) 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 is slower for some 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 symptoms of the disease are present, sex partners of patients who have chancroid should be examined and treated if they had sexual contact with the patient during the 10 days preceding the patient's onset of symptoms.

Special Considerations

Pregnancy

Human data suggest ciprofloxacin presents a low risk to the fetus during pregnancy, with a potential for toxicity during breastfeeding.³¹⁰ Alternate drugs should be used during pregnancy and lactation. No adverse effects of chancroid on pregnancy outcome have been reported.

HIV Infection

Persons with HIV infection who have chancroid should be monitored closely because, as a group, they are more likely to experience treatment failure and to have ulcers that heal more slowly. Persons with HIV infection might require repeated or longer courses of therapy than those recommended for HIV-negative patients, and treatment failures can occur with any regimen. Because data are limited concerning the therapeutic efficacy of the recommended single dose azithromycin and ceftriaxone regimens in persons with HIV infection, these regimens should be used for such patients only if follow-up can be ensured.

Genital HSV Infections

Genital herpes is a chronic, life-long 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 at least 50 million persons in the United States are infected with this type of genital herpes³¹¹. However, an increasing proportion of ano-genital herpetic infections have been attributed to HSV-1 infection, which is especially prominent among young women and men who have sex with men.^{312,313 314}

Most persons infected with HSV-2 have not been diagnosed with genital herpes. Many such persons have mild or unrecognized infections but shed virus intermittently in the anogenital area. As a result, the majority of 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 disease and go beyond the treatment of acute episodes of genital lesions.

Diagnosis of HSV Infection

The clinical diagnosis of genital herpes is both insensitive and nonspecific. The classical painful multiple vesicular or ulcerative lesions are absent in many infected persons. Recurrences and subclinical shedding are much more frequent for genital HSV2 infection than for genital HSV-1 infection^{315,316}. A patient's prognosis and the type of counseling needed depends on the type of genital herpes (HSV-1 or HSV-2) causing the infection; therefore, the clinical diagnosis of genital herpes should be confirmed by type-specific laboratory testing^{317 314}. Both type-specific virologic and type-specific serologic tests for HSV should be available in clinical settings that provide care for persons diagnosed with or at risk for STDs.

Virologic Tests

Cell culture and PCR are the preferred HSV tests for persons who seek medical treatment for genital ulcers or other mucocutaneous lesions. The sensitivity of viral culture is low, especially for recurrent lesions, and declines rapidly as lesions begin to heal. Nucleic acid amplification methods, including PCR assays for HSV DNA are more sensitive and are increasingly available^{318,319 320}. PCR is the test of choice for diagnosing CNS HSV infections, and systemic infections such as meningitis, encephalitis and neonatal herpes. Viral culture isolates and PCR amplicons should be typed to determine which type of HSV is causing the infection. Failure to detect HSV by culture or PCR, especially in the absence of active lesions, does not indicate an absence of HSV infection, because viral shedding is intermittent. The use of cytologic detection of cellular changes of HSV infection is an insensitive and nonspecific method of diagnosis, both for genital lesions (i.e., Tzanck preparation) and for cervical Pap smears and therefore should not be relied upon.

Type-Specific Serologic Tests

Both type-specific and type-common antibodies to HSV develop during the first several weeks after infection and persist indefinitely. Accurate type-specific HSV serologic assays are based on the HSV-specific glycoprotein G2 (HSV-2) and glycoprotein G1 (HSV-1). Providers should only request type-specific glycoprotein G (gG)-based serologic assays when serology is performed for their patients.³²¹⁻³²³

Both laboratory-based assays and point-of-care tests that provide results for HSV-2 antibodies from capillary blood or serum during a clinic visit are available. The sensitivities of these glycoprotein G type-specific tests for the detection of HSV-2 antibody vary from 80-98% and false negative results might be more frequent at early stages of infection^{322,324,325}. The most commonly used test, HerpeSelect HSV-2 Elisa may be falsely positive at low index values (1.1-3.5)³²⁶⁻³²⁸. Such low values should be confirmed with another test, such as Biokit or the Western blot^{326 327}. Of note, HerpeSelect Immunoblot should not be used for confirmation as it uses the same antigen as the Elisa. Repeat testing is also indicated if recent acquisition of genital herpes is suspected. The HerpeSelect HSV-1 Elisa is insensitive for detection of HSV-1 antibody. IgM testing for HSV 1 or 2 is not useful, because the IgM tests are not type-specific and might be positive during recurrent genital or oral episodes of herpes³²⁹.

Because nearly all HSV-2 infections are sexually acquired, the presence of type-specific HSV-2 antibody implies anogenital infection. In this instance, education and counseling appropriate for persons with genital herpes should be provided. The presence of HSV-1 antibody alone is more difficult to interpret. Many persons with HSV-1 antibody have oral HSV infection acquired during childhood, which might be asymptomatic. However, acquisition of genital HSV-1 is increasing, and genital HSV-1 also can be asymptomatic^{312,313,330 311,314}. Lack of symptoms in an HSV-1 seropositive person does not distinguish anogenital from orolabial or cutaneous infection, and regardless of site of infection, these persons remain at risk for acquiring HSV-2.

Type-specific HSV serologic assays might be useful in the following scenarios: 1) recurrent genital symptoms or atypical symptoms with negative HSV PCR or culture. ; 2) a clinical diagnosis of genital herpes without laboratory confirmation; or 3) a patient whose partner has genital herpes. HSV serologic testing should be considered for persons presenting for an STD evaluation (especially for those persons with multiple sex partners), persons with HIV infection, and MSM at increased risk for HIV acquisition. Screening for HSV-1 and HSV-2 in the general population is not indicated.

Management of Genital Herpes

Antiviral chemotherapy offers clinical benefits to most symptomatic patients and is the mainstay of management. Counseling regarding the natural history of genital herpes, sexual and perinatal transmission, and methods to reduce transmission is 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 antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir³³¹⁻³³⁹. Valacyclovir is the valine ester of acyclovir and has enhanced absorption after oral administration. Famciclovir also has high oral bioavailability. Topical therapy with antiviral drugs offers minimal clinical benefit, and its use 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 develop severe or prolonged symptoms. Therefore, all patients with first episodes of genital herpes should receive antiviral therapy.

Recommended Regimens*

Acyclovir 400 mg orally three times a day for 7–10 days

OR

Acyclovir 200 mg orally five times a day for 7–10 days

OR

Valacyclovir 1 g orally twice a day for 7–10 days

OR

Famciclovir 250 mg orally three times a day for 7–10 days

*Treatment can be extended if healing is incomplete after 10 days of therapy.

Established HSV-2 Infection

Almost all persons with symptomatic first-episode genital HSV-2 infection subsequently experience recurrent episodes of genital lesions; recurrences are less frequent after initial genital HSV-1 infection. Intermittent asymptomatic shedding occurs in persons with genital HSV-2 infection, even in those with longstanding or 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. Some persons, including those with mild or infrequent recurrent outbreaks, benefit from antiviral therapy; therefore, options for treatment should be discussed. Many persons might prefer suppressive therapy, which has the additional advantage of decreasing the risk for genital HSV-2 transmission to susceptible partners^{340,341}.

Suppressive Therapy for Recurrent Genital Herpes

Suppressive therapy reduces the frequency of genital herpes recurrences by 70%–80% in patients who have frequent recurrences³³⁷⁻³⁴⁰; many persons receiving such therapy report having experienced no symptomatic outbreaks. Treatment also is effective in patients with less frequent recurrences. Safety and efficacy have been documented among patients receiving daily therapy with acyclovir for as long as 6 years and with valacyclovir or famciclovir for 1 year^{342,343}. Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment.

The frequency of genital herpes recurrences diminishes over time in many persons, and the psychological adjustment to the disease might change. Therefore, periodically during suppressive treatment (e.g., once a year), providers should discuss the need to continue therapy. However, stopping treatment or laboratory monitoring in a healthy person is not necessary.

Treatment with valacyclovir 500 mg daily decreases the rate of HSV-2 transmission in discordant, heterosexual couples in which the source partner has a history of genital HSV-2 infection³⁴¹. Such couples should be encouraged to consider suppressive antiviral therapy as part of a strategy to prevent transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Suppressive antiviral therapy also is likely to reduce transmission when used by persons who have multiple partners (including MSM) and by those who are HSV-2 seropositive without a history of genital herpes.

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| <i>Recommended Regimens</i> |
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Acyclovir 400 mg orally twice a day

OR

Valacyclovir 500 mg orally once a day*

OR

Valacyclovir 1 g orally once a day

OR

Famciclovir 250 mg orally twice a day

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

Acyclovir, famciclovir, and valacyclovir appear equally effective for episodic treatment of genital herpes³³⁴⁻³³⁸, but famciclovir appears somewhat less effective for suppression of viral shedding³⁴⁴. Ease of administration and cost also are important considerations for prolonged treatment.

Episodic Therapy for Recurrent Genital Herpes

Effective episodic treatment of recurrent herpes requires initiation of therapy 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.

Recommended Regimens

Acyclovir 400 mg orally three times a day for 5 days

OR

Acyclovir 800 mg orally twice a day for 5 days

OR

Acyclovir 800 mg orally three times a day for 2 days

OR

Valacyclovir 500 mg orally twice a day for 3 days

OR

Valacyclovir 1 g orally once a day for 5 days

OR

Famciclovir 125 mg orally twice daily for 5 days

OR

Famciclovir 1000 mg orally twice daily for 1 day

OR

Famciclovir 500 mg once, followed by 250 mg twice daily for 2 days

Severe Disease

Intravenous (IV) acyclovir therapy 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., meningoencephalitis). The recommended regimen is acyclovir 5–10 mg/kg IV every 8 hours for 2–7 days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days of total therapy. HSV encephalitis requires 21 days of intravenous therapy. Acyclovir dose adjustment is recommended for impaired renal function.

Counseling

Counseling of infected persons and their sex partners is critical to the management of genital herpes. The goals of counseling include 1) helping patients cope with the infection and 2) preventing sexual and perinatal transmission. Although initial counseling can be provided at the first visit, many patients benefit from learning about the chronic aspects of the disease after the acute illness subsides. Multiple resources, including websites (<http://www.ashstd.org>) and printed materials, are available to assist patients, their partners, and clinicians who become involved in counseling^{345,346}.

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^{347,348}, some HSV-infected persons 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 regarding genital herpes include the severity of initial clinical manifestations, recurrent episodes, sexual relationships and transmission to sex partners, and ability to bear healthy children. The misconception that HSV causes cancer should be dispelled.

The following recommendations apply to counseling of persons with genital HSV infection:

- Persons who have genital herpes should be educated concerning the natural history of the disease, with emphasis on the potential for recurrent episodes, asymptomatic viral shedding, and the attendant risks of sexual transmission.
- Persons experiencing a first episode of genital herpes should be advised that suppressive therapy is available and effective in preventing symptomatic recurrent episodes and that episodic therapy often is useful in shortening the duration of recurrent episodes.
- All persons with genital HSV infection should be encouraged to inform their current sex partners that they have genital herpes and to inform future partners before initiating a sexual relationship.
- Sexual transmission of HSV can occur during asymptomatic periods. Asymptomatic viral shedding is more frequent in genital HSV-2 infection than genital HSV-1 infection and is most frequent during the first 12 months after acquiring HSV-2.
- All persons with genital herpes should remain abstinent from sexual activity with uninfected partners when lesions or prodromal symptoms are present.
- The risk for HSV-2 sexual transmission can be decreased by the daily use of valacyclovir by the infected person. Episodic therapy does not reduce the risk for transmission and its use should be discouraged for this purpose among persons whose partners might be at risk for HSV-2 acquisition.
- Infected persons should be informed that male latex condoms, when used consistently and correctly, reduces but does not eliminate the risk for genital herpes transmission^{27,349,350}.

- Sex partners of infected persons should be advised that they might be infected even if they have no symptoms. Type-specific serologic testing of the asymptomatic partners of persons with genital herpes is recommended to determine whether such partners are already HSV seropositive or whether risk for acquiring HSV exists.
- The risk for neonatal HSV infection should be explained to all persons, including men. Pregnant women and women of childbearing age who have genital herpes should inform their providers who care for them during pregnancy and those who will care for their newborn infant about their infection. Pregnant women who are not known to be infected with HSV-2 should be advised to abstain from intercourse with men who have genital herpes during the third trimester of pregnancy. Similarly, pregnant women who are not known to be infected with HSV-1 should be counseled to avoid genital exposure to HSV-1 during the third trimester (e.g., oral sex with a partner with oral herpes and vaginal intercourse with a partner with genital HSV-1 infection).
- Asymptomatic persons diagnosed with HSV-2 infection by type-specific serologic testing should receive the same counseling messages as persons with symptomatic infection. In addition, such persons should be educated about the clinical manifestations of genital herpes.
- When exposed to HIV, HSV-2 seropositive persons are at increased risk for HIV acquisition. Suppressive antiviral therapy does not reduce the increased risk for HIV acquisition associated with HSV-2 infection^{75,351}.

Management of Sex Partners

The sex partners of persons who have genital herpes can benefit from evaluation and counseling. Symptomatic sex partners should be evaluated and treated in the same manner as patients who have genital herpes. Asymptomatic sex partners of patients who have genital herpes should be questioned concerning histories of genital lesions and offered type-specific serologic testing for HSV infection.

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Allergic and other adverse reactions to oral acyclovir, valacyclovir, and famciclovir are rare. Desensitization to acyclovir has been described³⁵².

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. HSV shedding is increased in persons with HIV infection. Whereas antiretroviral therapy reduces the severity and frequency of symptomatic genital herpes, frequent subclinical shedding still occurs^{353 354}. Clinical manifestations of genital herpes might

worsen during immune reconstitution early after initiation of antiretroviral therapy.

Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV among persons with HIV infection³⁵⁵⁻³⁵⁷. HSV type-specific serologic testing can be offered to persons with HIV infection during their initial evaluation if infection status is unknown, and suppressive antiviral therapy can be considered in those who have HSV-2 infection. Suppressive anti-HSV therapy in persons with HIV infections does not reduce the risk of HIV transmission or HSV-2 transmission to susceptible sex partners^{74,358 358}

Recommended Regimens for Daily Suppressive Therapy in Persons with HIV

Acyclovir 400–800 mg orally twice to three times a day

OR

Valacyclovir 500 mg orally twice a day

OR

Famciclovir 500 mg orally twice a day

Recommended Regimens for Episodic Infection in Persons with HIV

Acyclovir 400 mg orally three times a day for 5–10 days

OR

Valacyclovir 1 g orally twice a day for 5–10 days

OR

Famciclovir 500 mg orally twice a day for 5–10 days

Acyclovir, valacyclovir, and famciclovir are safe for use in immunocompromised patients in the doses recommended for treatment of genital herpes. For severe HSV disease, initiating therapy with acyclovir 5–10 mg/kg IV every 8 hours might be necessary.

Antiviral resistant HSV

If lesions persist or recur in a patient receiving antiviral treatment, HSV resistance should be suspected and a viral isolate should be obtained for sensitivity testing³⁵⁹. Such persons should be managed in consultation with an Infectious Disease specialist, and alternate therapy should be administered. All acyclovir-resistant strains are resistant to valacyclovir, and the majority are resistant to famciclovir. Foscarnet, 40-80 mg/kg IV every 8 hours until clinical resolution is attained, is frequently effective for treatment of acyclovir-resistant genital herpes^{360,361}. Intravenous cidofovir 5 mg/kg once weekly might also be effective. Imiquimod is a topical alternative³⁶², as is topical cidofovir gel 1%, however cidofovir must be compounded at a pharmacy³⁶³. These topical preparations should be applied to the lesions once daily for 5 consecutive days.

Clinical management of antiviral resistance remains challenging among HIV-infected patients, and other preventative approaches might be necessary. However, experience with another group of immunocompromised persons (hematopoietic stem-cell recipients) demonstrated that persons receiving daily suppressive antiviral therapy were less likely to develop acyclovir-resistant HSV compared with those who received episodic therapy for outbreaks³⁶⁴.

Genital Herpes in Pregnancy

Most mothers of newborns who acquire neonatal herpes lack histories of clinically evident genital herpes^{365 366}. 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 HSV during the first half of pregnancy^{367 367,368}.

Prevention of neonatal herpes depends both on preventing acquisition of genital HSV infection during late pregnancy and avoiding exposure of the neonate to herpetic lesions and viral shedding during delivery. Because the risk for herpes is highest in newborn infants of women who acquire genital HSV during late pregnancy, these women should be managed in consultation with maternal-fetal medicine and infectious disease specialists.

Women without known genital herpes should be counseled to abstain from intercourse during the third trimester with partners known or suspected of having genital herpes. In addition, pregnant women without known orolabial herpes should be advised to abstain from receptive

oral sex during the third trimester with partners known or suspected to have orolabial herpes. Type-specific serologic tests may be useful to identify pregnant women at risk for HSV infection and to guide counseling regarding the risk for acquiring genital herpes during pregnancy. For example, such testing may be offered to uninfected women whose sex partner has HSV infection. However, the effectiveness of antiviral therapy to decrease the risk for HSV transmission to pregnant women by infected partners has not been studied.

All pregnant women should be asked whether they have a history of genital herpes. At the onset of labor, all women should be questioned carefully about symptoms of genital herpes, including prodromal symptoms, and all women should be examined carefully for herpetic lesions. Women without symptoms or signs of genital herpes or its prodrome can deliver vaginally. Although cesarean delivery does not completely eliminate the risk for HSV transmission to the neonate, women with recurrent genital herpetic lesions at the onset of labor should deliver by cesarean delivery to prevent neonatal HSV infection.

Because no adverse effects in the fetus or newborn attributable to the use of acyclovir during pregnancy have been reported, and over 7500 infants are exposed each year, acyclovir should be compatible in all stages of pregnancy and in breastfeeding women.^{310, 369} While data regarding prenatal exposure to valacyclovir and famciclovir are limited, animal data suggest these drugs are also low risk in pregnant women. Acyclovir can be administered orally to pregnant women with first episode genital herpes or severe recurrent herpes and should be administered IV to pregnant women with severe HSV infection. Suppressive acyclovir treatment late in pregnancy reduces the frequency of cesarean delivery among women who have recurrent genital herpes by diminishing the frequency of recurrences at term³⁷⁰⁻³⁷². However, such treatment may not protect against transmission, and there remains a risk that neonates may become infected during delivery.³⁷³ No data support the use of antiviral therapy among HSV seropositive women without a history of genital herpes.

| Recommended regimen for treatment of women with recurrent genital herpes * |
|--|
| Acyclovir 400 mg orally three times a day |
| OR |
| Valacyclovir 500 mg orally twice a day |

*Treatment recommended starting at 36 weeks of gestation³⁷⁴

Neonatal Herpes

Newborn infants exposed to HSV during birth, as documented by maternal virologic testing or presumed by observation of maternal lesions, should be followed carefully in consultation with a pediatric infectious disease specialist. There is guidance on management of neonates who are delivered vaginally in the presence of maternal genital HSV lesions.³⁷⁵

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 initiation of treatment. In addition, administration of acyclovir might be considered for infants born to women who acquired HSV near term because the risk for neonatal herpes is high for these infants. All 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 IV every 8 hours for 14 days if disease limited to the skin and mucous membranes, or for 21 days for disseminated and CNS disease.

Granuloma Inguinale (Donovanosis)

Granuloma inguinale 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, although it is endemic in some tropical and developing areas, including India; Papua, New Guinea; the Caribbean; central Australia; and southern Africa³⁷⁶⁻³⁷⁸. Clinically, the disease is commonly characterized as painless, slowly progressive ulcerative lesions on the genitals or perineum without regional lymphadenopathy; subcutaneous granulomas (pseudobuboes) might also occur. The lesions are highly vascular (i.e., beefy red appearance) and bleed. Extragenital infection can occur with extension of infection to the pelvis, or it can disseminate to intraabdominal organs, bones, or the mouth. The lesions also can develop secondary bacterial infection and can coexist with other sexually transmitted pathogens.

The causative organism is difficult to culture, and diagnosis requires visualization of dark-staining Donovan bodies on tissue crush preparation or biopsy. No FDA-cleared molecular tests for the detection of *K. granulomatis* DNA exist, but such an assay might be useful when undertaken by laboratories that have conducted a CLIA verification study.

Treatment

Several antimicrobial regimens have been effective, but only a limited number of controlled trials have been published³⁷⁶. Treatment has been shown 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

Azithromycin 1 g orally once per week or 500 mg daily for at least 3 weeks and until all lesions have completely healed

| |
|------------------------------------|
| <i>Alternative Regimens</i> |
|------------------------------------|

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|--|
| Doxycycline* 100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed |
|--|

OR

| |
|--|
| Ciprofloxacin* 750 mg orally twice a day for at least 3 weeks and until all lesions have completely healed |
|--|

OR

| |
|--|
| Erythromycin base 500 mg orally four times a day for at least 3 weeks and until all lesions have completely healed |
|--|

OR

| |
|--|
| Trimethoprim-sulfamethoxazole* one double-strength (160 mg/800 mg) tablet orally twice a day for at least 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. Aminoglycoside treatment is an option (gentamicin 1 mg/kg IV every 8 hours).

Follow-Up

Patients should be followed clinically until signs and symptoms have resolved.

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 as above. However, the value of empiric therapy in the absence of clinical signs and symptoms has not been established.

Special Considerations

Pregnancy

Doxycycline should be avoided in the second and third trimester of pregnancy due to the risk of discoloration of teeth and bones, but is compatible with breastfeeding.³¹⁰ Human data suggest that ciprofloxacin is low risk in pregnant women, but animal data raise concerns about cartilage damage.³¹⁰ Sulfonamides are associated with rare but serious kernicterus in those with G6PD deficiency, and should be avoided in third trimester and breastfeeding.³¹⁰ For these reasons, pregnant and lactating women should be treated with a macrolide regimen (erythromycin or azithromycin), and consideration should be given to the addition of another antibiotic if improvement is not evident within the first few days of therapy. Aminoglycoside treatment is an option (gentamicin 1 mg/kg IV every 8 hours).

HIV Infection

Persons with both granuloma inguinale and HIV infection should receive the same regimens as those who do not have HIV infection. The addition of another antibiotic can be considered if improvement is not evident within the first few days of therapy. Aminoglycoside treatment is an option (gentamicin 1 mg/kg IV every 8 hours).

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is caused by *C. trachomatis* serovars L1, L2, or L3^{379,380}. The most common clinical manifestation of LGV among heterosexuals is tender inguinal and/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 patients seek care, the lesions have often disappeared. Rectal exposure in women or MSM can result in proctocolitis mimicking inflammatory bowel disease and findings may include mucoid and/or hemorrhagic rectal discharge, anal pain, constipation, fever, and/or tenesmus^{381,382}. LGV is often an invasive, systemic infection, and if it is not treated early, LGV proctocolitis can lead to chronic, colorectal fistulas and strictures. Reactive arthropathy has also been reported. However, there are recent reports that rectal LGV can be asymptomatic.³⁸³ Genital and colorectal LGV lesions can also develop secondary bacterial infection or can be coinfecting with other sexually and nonsexually transmitted pathogens.

Diagnosis is based on clinical suspicion, epidemiologic information, and the exclusion of other etiologies for proctocolitis, inguinal lymphadenopathy, or genital or rectal ulcers. Genital lesions, rectal specimens and lymph node specimens (i.e., lesion swab or bubo aspirate) can be tested for *C. trachomatis* by culture, direct immunofluorescence, or nucleic acid detection³⁸⁴. NAATs for *C. trachomatis* perform well on rectal specimens, but are not FDA-cleared for this purpose. Many laboratories have performed the CLIA validation studies that are needed to provide results from rectal specimens for clinical management. Additional molecular procedures (e.g., PCR-based genotyping) can be used to differentiate LGV from non-LGV *C. trachomatis*, but these are not widely available, and results are often not timely enough to influence treatment. Chlamydia serology (complement fixation titers $\geq 1:64$ or microimmunofluorescence titers $>$

1:256) may support the diagnosis of LGV in the appropriate clinical context. Comparative data between types of serologic tests are lacking, and the diagnostic utility of these older serologic methods procedures has not been established. Serologic test interpretation for LGV is not standardized, tests have not been validated for clinical proctitis presentations, and *C. trachomatis* serovar-specific serologic tests are not widely available.

In the absence of specific chlamydia diagnostic testing, patients with a clinical syndrome consistent with LGV, including proctocolitis or genital ulcer disease with lymphadenopathy, should be presumptively treated for LGV as described below.

Treatment

Treatment cures infection and prevents ongoing tissue damage, although tissue reaction to the infection can result in scarring. Buboec might require aspiration through intact skin or incision and drainage to prevent the formation of inguinal/femoral ulcerations.

Recommended Regimen

Doxycycline 100 mg orally twice a day for 21 days

Alternative Regimen

Erythromycin base 500 mg orally four times a day for 21 days

Although clinical data are lacking, azithromycin 1 g orally once weekly for 3 weeks is probably effective based on its chlamydial antimicrobial activity. Fluoroquinolone-based treatments might also be effective, but extended treatment intervals are likely required.

Follow-Up

Patients should be followed clinically until signs and symptoms have resolved.

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 examined, tested for urethral or cervical chlamydial infection, and presumptively treated with a chlamydia regimen (azithromycin 1 gm orally single dose or doxycycline 100 mg orally twice a day for 7 days).

Special Considerations

Pregnancy

Pregnant and lactating women should be treated with erythromycin. Azithromycin might prove useful for treatment of LGV in pregnancy, but no published data are available regarding its safety and efficacy. Doxycycline should be avoided in the second and third trimester of pregnancy due to the risk of discoloration of teeth and bones, but is compatible with breastfeeding.³¹⁰

HIV Infection

Persons with both LGV and HIV infection should receive the same regimens as those who are HIV negative. Prolonged therapy might be required, and delay in resolution of symptoms might occur.

Syphilis

Syphilis is a systemic disease caused by *Treponema pallidum*. On the basis of clinical findings, the disease has been divided into stages, which are used to help guide treatment and follow-up. Persons who have syphilis might seek treatment for signs or symptoms of primary syphilis infection (i.e., ulcers or chancre at the infection site), secondary syphilis (i.e., manifestations that include, but are not limited to, skin rash, mucocutaneous lesions, and lymphadenopathy), or tertiary syphilis (i.e., cardiac or gummatous lesions). 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 late latent syphilis. Neurosyphilis is a site of infection and can occur at any stage of syphilis. Early neurologic clinical manifestations (i.e., cranial nerve dysfunction, meningitis, stroke, acute altered mental status, and auditory or ophthalmic abnormalities), are usually present within first few months or years of infection. Late neurologic manifestations (i.e., tertiary syphilis) occur 10-30 years after infection. Treatment for late latent syphilis, latent syph of unknown duration and tertiary syphilis require a longer duration of therapy because organisms might be dividing more slowly; however, the validity of this concept has not been assessed.

Diagnostic Considerations

Darkfield examinations and tests to detect *T. pallidum* directly from lesion exudate or tissue are the definitive methods for diagnosing early syphilis³⁸⁵. Although no *T. pallidum* detection tests are commercially available, some laboratories provide locally developed and validated PCR tests for the detection of *T. pallidum* DNA. A presumptive diagnosis of syphilis is possible with the use of two types of serologic tests: 1) nontreponemal tests (e.g., Venereal Disease Research Laboratory [VDRL] and RPR) and 2) treponemal tests (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] tests, the *T. pallidum* passive particle agglutination [TP-PA] assay, various enzyme immunoassays [EIAs], chemiluminescence immunoassays, immunoblots and rapid treponemal assays). Although there are many treponemal based tests that are now commercially

available, only a few are approved for use in the U.S. The use of only one type of serologic test is insufficient for diagnosis and can result in false negative tests in the primary stage and false-positive test non-treponemal results in persons without syphilis. False-positive nontreponemal test results can be associated with various medical conditions unrelated to syphilis, including infections, HIV, autoimmune conditions, immunizations, pregnancy, injection-drug use and older age.^{386,387} Therefore, persons with a reactive nontreponemal test should always receive a treponemal test to confirm the diagnosis of syphilis.

Nontreponemal test antibody titers may correlate with disease activity and are used to follow treatment response. 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 to demonstrate a clinically significant difference between two nontreponemal test results that were obtained using the same serologic test. Sequential serologic tests in individual patients should be performed using the same testing method (e.g., VDRL or RPR), preferably by the same laboratory. The VDRL and RPR are equally valid assays, but quantitative results from the two tests cannot be compared directly because RPR titers frequently are slightly higher than VDRL titers. Nontreponemal test titers usually decline after treatment and might become nonreactive with time; however, in some persons, nontreponemal antibodies can persist for a long period of time — a response referred to as the “serofast reaction.” Most patients who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of treatment or disease activity. However, 15%–25% of patients treated during the primary stage revert to being serologically nonreactive after 2–3 years³⁸⁸. Treponemal antibody titers do not predict treatment response and so should not be used.

Some clinical laboratories are screening samples using treponemal tests, typically by EIA or chemiluminescence immunoassays.^{389,390} This reverse screening algorithm for syphilis testing can identify persons with previous treatment for syphilis, persons with untreated or incompletely treated syphilis, as well as persons with false-positive results such as those with a low likelihood of infection.

Persons with a positive treponemal screening test should have a standard nontreponemal test with titer performed reflexively by the laboratory to guide patient management decisions. If the nontreponemal test is negative, then the laboratory should perform a different treponemal test (preferably one based on different antigens than the original test) to confirm the results of the initial test. If a second treponemal test is positive, persons with a history of previous treatment will require no further management unless sexual history suggests likelihood of re-exposure. In this instance, a repeat non-treponemal test in 2–4 weeks is recommended to evaluate for early infection. Those without a history of treatment for syphilis should be offered treatment. Unless history or results of a physical examination suggest a recent infection, previously untreated persons should be treated for late latent syphilis. If the second treponemal test is negative, and the epidemiological risk and clinical probability for syphilis are low, further evaluation or treatment is not indicated. Low positive index values (i.e., low optical density on EIA) might provide additional information that in these low risk situations, treatment is not indicated³⁹¹

For most persons with HIV infection, serologic tests are accurate and reliable for the diagnosis of syphilis and for following a patient’s response to treatment. However, atypical non-

treponemal serologic test results (i.e., unusually high, unusually low, or fluctuating titers) may occur in either persons with HIV infection or HIV-uninfected persons. When serologic tests do not correspond with clinical findings suggestive of early syphilis, presumptive treatment is recommended and use of other tests (e.g., biopsy, PCR) should be considered.

Persons with clinical signs of neurosyphilis (e.g., cranial nerve dysfunction, auditory or ophthalmic abnormalities, meningitis, stroke, acute or chronic altered mental status, and loss of vibration sense) warrant further investigation. Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis in all instances. The diagnosis of neurosyphilis depends on a combination of CSF tests (CSF cell count or protein, and a reactive CSF-VDRL) in the setting of reactive serologic test results and neurologic signs and symptoms. Cerebrospinal fluid (CSF) laboratory abnormalities are common in persons with early syphilis and are of unknown significance in the absence of neurologic signs or symptoms³⁹². The VDRL in cerebrospinal fluid (CSF-VDRL), is highly specific but insensitive. In a person with neurologic signs or symptoms, a reactive CSF-VDRL (in a specimen not contaminated with blood), is considered diagnostic of neurosyphilis. If the CSF-VDRL is negative and clinical signs of neurosyphilis are present, but serologic test results are reactive, abnormal CSF cell count or protein are present, treatment for neurosyphilis should be considered. In this instance, additional evaluation using FTA-ABS testing on CSF can be considered. The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive; in the absence of specific neurological signs and symptoms, neurosyphilis is highly unlikely with a negative CSF FTA-ABS test³⁹³.

Among persons with HIV infection, the CSF leukocyte count usually is elevated (>5 white blood cell count [WBC]/mm³); using a higher cutoff (>20 WBC/mm³) might improve the specificity of neurosyphilis diagnosis³⁹⁴.

Treatment

Penicillin G, administered parenterally, is the preferred drug for treating all stages of syphilis. The preparation used (i.e., benzathine, aqueous procaine, or aqueous crystalline), the dosage, and the length of treatment depend on the stage and clinical manifestations of the disease. 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 some forms of penicillin. Combinations of benzathine penicillin, procaine penicillin, and oral penicillin preparations are not considered appropriate for the treatment of syphilis. Reports have indicated that practitioners have inadvertently prescribed combination benzathine-procaine penicillin (Bicillin C-R) instead of the standard benzathine penicillin product (Bicillin L-A) widely used in the United States. Practitioners, pharmacists, and purchasing agents should be aware of the similar names of these two products to avoid using the inappropriate combination therapy agent for treating syphilis³⁹⁵.

The effectiveness of penicillin for the treatment of syphilis was well established through clinical experience even before the value of randomized controlled clinical trials was recognized. Therefore, nearly all the recommendations for the treatment of syphilis are based not only on clinical trials and observational studies, but approximately 50 years of clinical experience.

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

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, myalgia, fever, and other symptoms that can occur within the first 24 hours after the initiation of any therapy for syphilis. The Jarisch-Herxheimer reaction occurs most frequently among persons who have early syphilis, presumably because bacterial burdens are higher during these stages. Antipyretics can be used to manage symptoms, but they have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction might induce early labor or cause fetal distress in pregnant women, but this should not prevent or delay therapy (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 sexually to a person especially who has primary, secondary, or early latent syphilis should be evaluated clinically and serologically and treated with a recommended regimen, according to the following recommendations:

- Persons who were exposed within the 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner might be infected even if seronegative; therefore, such persons should be treated presumptively for early syphilis.
- Persons who were exposed >90 days before the diagnosis of primary, secondary, or early latent syphilis in a sex partner should be treated presumptively if serologic test results are not available immediately 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 as described above.
- Of note in some areas with high rates of syphilis, health departments recommend to notify and presumptively treat persons exposed to individuals with latent syphilis who have high nontreponemal serologic test titers (i.e., >1:32) as high titers may be indicative of early syphilis. These persons should be managed as if the index case had early syphilis.
- Long-term sex partners of persons who have latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation findings.

Sexual partners of infected persons considered at risk of being infected who should be confidentially notified of the exposure and need for evaluation include partners who have had sexual contact within 3 months plus the duration of symptoms for persons diagnosed with primary syphilis, 6 months plus duration of symptoms for those with secondary syphilis, and 1 year for persons with early latent syphilis.

Primary and Secondary Syphilis

Treatment

Parenteral penicillin G has been used effectively for more than 50 years to achieve clinical resolution (i.e., the healing of lesions and prevention of sexual transmission) and to prevent late sequelae. However, no high quality comparative trials have been conducted to guide the selection of an optimal penicillin regimen. Substantially fewer data are available for nonpenicillin regimens.

Recommended Regimen for Adults*

Benzathine penicillin G 2.4 million units IM in a single dose

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

Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in primary and secondary syphilis do not enhance efficacy, regardless of HIV status^{396,397}.

Recommended Regimen for Infants and Children

Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose

Infants and children aged ≥ 1 month with acquired primary and secondary syphilis should be evaluated for sexual abuse (e.g., through consultation with child-protection services) (see Sexual Assault or Abuse of Children).

Other Management Considerations

All persons who have primary and secondary syphilis should be tested for HIV infection. In geographic areas in which the prevalence of HIV is high, persons who have primary or secondary syphilis should be retested for acute HIV in 3 months if the first HIV test result was negative.

Persons who have syphilis and symptoms or signs suggesting neurologic disease (e.g., cranial nerve dysfunction, meningitis, stroke and hearing loss) or ophthalmic disease (e.g., uveitis, iritis, neuroretinitis, and optic neuritis) should have an evaluation that includes CSF analysis, ocular slit-lamp ophthalmologic examination, and otologic examination. Treatment should be guided by the results of this evaluation.

Invasion of CSF by *T. pallidum* accompanied by CSF laboratory abnormalities is common among adults who have primary or secondary syphilis³⁹². In the absence of clinical neurologic findings, no evidence exists to support variation from the recommended treatment regimen for primary and secondary syphilis. It is very uncommon that symptomatic neurosyphilis develops in persons after treatment with the penicillin regimens recommended for primary and secondary syphilis. Therefore, unless clinical signs or symptoms of neurologic or ophthalmic involvement are present or treatment failure is documented, routine CSF analysis is not recommended for persons who have primary or secondary syphilis.

Follow-Up

Clinical and serologic evaluation should be performed 6 months and 12 months after treatment; more frequent evaluation might be prudent if follow-up is uncertain or if repeat infection is a concern. Serologic response (ie, titer) should be compared to the titer at the time of treatment. However, assessing serological response to treatment frequently can be difficult, and definitive criteria for cure or failure have not been well established. In addition, nontreponemal test titers might decline more slowly for persons previously treated for syphilis^{398 399}

Persons who have signs or symptoms that persist or recur, or who have a sustained fourfold increase in nontreponemal test titer (i.e., a four-fold increase or greater in titer that is sustained for more than 2 weeks), probably failed treatment or were re-infected. These persons should be retreated and reevaluated for HIV infection. Because treatment failure usually cannot be reliably distinguished from reinfection with *T. pallidum*, a CSF analysis also should be performed, and treatment should be based on CSF findings.

Failure of nontreponemal test titers to decline fourfold within 6–12 months after therapy for primary or secondary syphilis might be indicative of treatment failure. However, clinical trial data have demonstrated that 15-20% of persons with primary and secondary syphilis treated with the recommended therapy will not achieve the fourfold decline in nontreponemal titer used to define response at 6 months after treatment^{396,399}. Serological response to treatment appears to be associated with several factors including the person's stage of syphilis (earlier stages are more likely to decline fourfold and become negative) and initial non-treponemal antibody titers (lower titers are less likely to decline fourfold than higher titers)³⁹⁹. Optimal management of persons who have less than a four-fold decline in titers after treatment of syphilis is unclear. At a minimum, these persons should receive additional clinical and serologic follow-up. 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 such situations.

For retreatment, weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks is recommended, unless CSF examination indicates that neurosyphilis is present (see

Neurosyphilis). Serologic titers may not decline despite a negative CSF examination and a repeated course of therapy⁴⁰⁰. In these circumstances, the need for additional therapy or repeated CSF examinations is unclear, but is not generally recommended.

Management of Sex Partners

See Management of Sex Partners above.

Special Considerations

Penicillin Allergy

Data to support the use of alternatives to penicillin in the treatment of primary and secondary syphilis are limited. However, several therapies might be effective in nonpregnant, penicillin-allergic persons who have primary or secondary syphilis. Doxycycline 100 mg orally twice daily for 14 days^{401,402} and tetracycline (500 mg four times daily for 14 days) are regimens that have been used for many years. Compliance is likely to be better with doxycycline than tetracycline, because tetracycline can cause gastrointestinal side effects and dosing is more frequent. Although limited clinical studies, along with biologic and pharmacologic evidence, suggest that ceftriaxone (1-2 g daily either IM or IV for 10–14 days) is effective for treating primary and secondary syphilis, the optimal dose and duration of ceftriaxone therapy have not been defined⁴⁰³. Azithromycin as a single 2-g oral dose has been effective for treating primary and secondary syphilis in some populations⁴⁰⁴⁻⁴⁰⁶. However, *T. pallidum* chromosomal mutations associated with azithromycin (and other macrolide) resistance and treatment failures have been documented in multiple geographical areas in the United States⁴⁰⁷⁻⁴⁰⁹. Accordingly, azithromycin should not be used as first-line treatment for syphilis, and should be used with caution only when treatment with penicillin or doxycycline is not feasible. Azithromycin should not be used in MSM, persons with HIV, or pregnant women. Careful clinical and serologic follow-up of persons receiving any alternative therapies 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. Skin testing for penicillin allergy might be useful in some circumstances in which the reagents and expertise are available to perform 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 (see Management of Persons Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

Persons with HIV infection who have primary or secondary syphilis should be treated as described above. (See Syphilis in Persons with HIV infection)

Latent Syphilis

Latent syphilis is defined as syphilis characterized by seroreactivity without other evidence of disease. Persons who have latent syphilis and who acquired syphilis during the preceding year are classified as having early latent syphilis. Patients can be diagnosed with early latent syphilis if, during the year preceding the diagnosis, they had 1) a documented seroconversion or a sustained for more than 2 weeks fourfold or greater increase in titer of a nontreponemal test; 2) unequivocal symptoms of primary or secondary syphilis; or 3) 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, an asymptomatic person should be considered to have late latent syphilis. Nontreponemal serologic titers usually are higher during early latent syphilis than late latent syphilis. However, early latent syphilis cannot be reliably distinguished from late latent syphilis solely on the basis of nontreponemal titers. All persons with latent syphilis should have careful examination of all accessible mucosal surfaces (i.e., the oral cavity, perianal area, perineum and vagina in women, and underneath the foreskin in uncircumcised men) to evaluate for internal mucosal lesions.

Treatment

Because latent syphilis is not transmitted sexually (except in persons with early latent syphilis who relapse into the secondary stage), the objective of treating persons with this stage of disease is to prevent complications and transmission from a pregnant woman to her fetus. Although clinical experience supports the effectiveness of penicillin in achieving this goal, limited evidence is available to guide choice of specific regimens or duration.

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| <i>Recommended Regimens for Adults*</i> |
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|-------------------------------------|
| <i>Early Latent Syphilis</i> |
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| Benzathine penicillin G 2.4 million units IM in a single dose |
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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 infection^{396,397}.

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|------------------------------------|
| <i>Late Latent Syphilis</i> |
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| Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals |
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* Recommendations for treating syphilis in persons with HIV infection and pregnant women are discussed later in this report (see Syphilis in Persons with HIV infection and Syphilis in Pregnancy).

Recommended Regimens for Infants and Children

Early Latent Syphilis

Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose

Late Latent Syphilis

Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units, administered as 3 doses at 1-week intervals (total 150,000 units/kg up to the adult total dose of 7.2 million units)

Infants and children aged ≥ 1 month who have been diagnosed with latent syphilis should have a CSF examination to exclude neurosyphilis. In addition, birth and maternal medical records should be reviewed to assess whether they have congenital or acquired syphilis (see Congenital Syphilis). Those with acquired latent syphilis should be evaluated as described for adults (see Sexual Assault or Abuse of Children). These regimens are for penicillin nonallergic children who have acquired syphilis and who have normal CSF examination results.

Other Management Considerations

All persons who have latent syphilis should be tested for HIV infection. Persons diagnosed with latent syphilis who demonstrate any of the following criteria should have a prompt CSF examination:

- Neurologic signs and symptoms (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis or stroke)

- Evidence of active tertiary syphilis (e.g., aortitis and gumma); or
- Serologic treatment failure.

If a person misses a dose of penicillin in a course of weekly therapy for latent syphilis, the appropriate course of action is unclear. Clinical experience suggests that an interval of 10–14 days (i.e. if dose 1 is given on day 0, dose 2 is given between days 10 and 14) between doses of benzathine penicillin for late latent syphilis or syphilis of unknown duration might be acceptable before restarting the sequence of injections. Pharmacologic considerations suggest that an interval of 7 to 9 days between doses, if feasible, may be more optimal⁴¹⁰⁻⁴¹². Missed doses are not acceptable for pregnant women receiving therapy for late latent syphilis⁴¹³. Pregnant women who miss any dose of therapy must repeat the full course of therapy.

Follow-Up

Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months. A CSF examination should be performed if 1) a sustained for more than 2 weeks fourfold increase or greater in titer, 2) an initially high titer ($\geq 1:32$) fails to decline at least fourfold within 12–24 months of therapy, or 3) signs or symptoms attributable to syphilis develop. In such circumstances, patients with CSF abnormalities should be treated for neurosyphilis. Even if the CSF examination is negative, retreatment for latent syphilis should be administered. In rare instances, despite a negative CSF examination and a repeated course of therapy, serologic titers might fail to decline. In these circumstances, the need for additional therapy or repeated CSF examinations is unclear but is generally not recommended. Serologic and clinical monitoring should be offered.

Management of Sex Partners

See Management of Sex Partners.

Special Considerations

Penicillin Allergy

The effectiveness of alternatives to penicillin in the treatment of 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 the treatment of primary and secondary syphilis (see Primary and Secondary Syphilis, Treatment). The only acceptable alternatives for the treatment of late latent syphilis are doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times daily), each for 28 days. The efficacy of these alternative regimens in 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 in persons with HIV infection. Based on biologic plausibility and pharmacologic properties, ceftriaxone might be effective for treating late latent syphilis. However, the optimal dose and duration of ceftriaxone therapy have not been defined, and 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. Skin testing for penicillin allergy might be useful in some circumstances in which the reagents and expertise are available to perform 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 (see Management of Persons Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

Persons with HIV infection with latent syphilis should be treated as described above (see Syphilis in Persons with HIV Infection).

Tertiary Syphilis

Tertiary syphilis as described refers only to gummas and cardiovascular syphilis. Guidelines for all forms of neurosyphilis are discussed in Neurosyphilis, below. Persons who are not allergic to penicillin and have no evidence of neurosyphilis should be treated with the following regimen.

Recommended Regimen

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 be tested for HIV infection. Persons who have tertiary syphilis should have a CSF examination and HIV testing before therapy is initiated. Some providers treat all persons who have cardiovascular syphilis with a neurosyphilis regimen. These patients should be managed in consultation with an infectious diseases specialist.

Follow-Up

Limited information is available concerning clinical response and follow-up of persons who have tertiary syphilis.

Management of Sex Partners

See Management of Sex Partners, above.

Special Considerations

Penicillin Allergy

Persons 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 (see Management of Persons Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

Persons with HIV infection with tertiary syphilis should be treated as described above. (see Syphilis in Persons with HIV Infection)

Neurosyphilis

Treatment

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

Syphilitic uveitis or other ocular manifestations (e.g., neuroretinitis, optic neuritis) can be associated with neurosyphilis. A CSF examination should be performed in all instances of ocular syphilis even in the absence of clinical neurologic findings. Ocular syphilis should be managed in collaboration with an ophthalmologist and according to the treatment and other recommendations for neurosyphilis, even if a CSF examination is normal. In instances of ocular syphilis and abnormal CSF test results, follow-up CSF examinations should be performed to assess treatment response as discussed below.

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| <i>Recommended Regimen</i> |
| <i>Neurosyphilis</i> <hr/> |

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.

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|-----------------------------------|
| <i>Alternative Regimen</i> |
|-----------------------------------|

Procaine penicillin G 2.4 million units IM once daily

PLUS

Probenecid 500 mg orally four times a 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 late latent syphilis. Therefore, benzathine penicillin, 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

Other Management Considerations

Other considerations in the management of persons who have neurosyphilis are as follows:

- All persons who have neurosyphilis should be tested for HIV.
- Although systemic steroids are used frequently as adjunctive therapy for otologic syphilis, such drugs have not been proven to be beneficial.

Follow-Up

If CSF pleocytosis was present initially, a CSF examination should be repeated every 6 months until the cell count is normal. Follow-up CSF examinations also can be used to evaluate changes in the CSF-VDRL or CSF protein after therapy; however, changes in these two parameters occur more slowly than cell counts, and persistent abnormalities might be less important^{414,415}. The leukocyte count is a sensitive measure of the effectiveness of therapy. If the cell count has not decreased after 6 months, or if the CSF cell count or protein is not normal after 2 years, retreatment should be considered. Limited data suggest that, in immunocompetent persons and persons with HIV infection on highly active antiretroviral therapy, normalization of

the serum RPR titer predicts normalization of CSF parameters following neurosyphilis treatment⁴¹⁵.

Management of Sex Partners

See Management of Sex Partners, above.

Special Considerations

Penicillin Allergy

Limited data suggest that ceftriaxone 2 g daily either IM or IV for 10–14 days can be used as an alternative treatment for persons with neurosyphilis^{416,417}. The possibility of cross-sensitivity between ceftriaxone and penicillin exists, however the risk of penicillin cross-reactivity between third- generation cephalosporins is negligible⁴¹⁸⁻⁴²¹. . (see Management of Persons Who Have a History of Penicillin Allergy) If concern exists regarding the safety of ceftriaxone for a patient with neurosyphilis, skin testing should be performed (if available) to confirm penicillin allergy and, if necessary, desensitization in consultation with a specialist. 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 (see Syphilis During Pregnancy).

HIV Infection

Persons with HIV infection with neurosyphilis should be treated as described above. (See Syphilis in Persons with HIV infection).

Persons with HIV Infection

Diagnostic Considerations

Interpretation of treponemal and nontreponemal serologic tests for syphilis persons with HIV infection is the same as for the HIV-uninfected patient. Although rare, unusual serologic responses have been observed among persons with HIV infection who have syphilis, most such reports have involved post- treatment serologic titers that were higher than expected (high serofast) or fluctuating, but false-negative serologic test results and delayed appearance of seroreactivity have also been reported⁴²².

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

Treatment

Persons with HIV infection who have early syphilis might be at increased risk for neurologic complications⁴²³ and might have higher rates of serologic treatment failure with currently recommended regimens. The magnitude of these risks is not defined precisely, but is likely small. Although long-term comparative data of greater than 1 year are lacking, no treatment regimens for syphilis have been demonstrated to be more effective in preventing neurosyphilis in persons with HIV infection than the syphilis regimens recommended for persons without HIV infection³⁹⁶. Careful follow-up after therapy is essential. The use of antiretroviral therapy as per current guidelines might improve clinical outcomes in persons with HIV infection and syphilis^{415,424,425}.

Primary and Secondary Syphilis

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| <i>Recommended Regimen Persons with HIV infection</i> |
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| Benzathine penicillin G, 2.4 million units IM in a single dose. |
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Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early syphilis do not result in enhanced efficacy^{396,397}.

Other Management Considerations

Most persons with HIV infection respond appropriately to the recommended benzathine penicillin treatment regimen for primary and secondary syphilis. CSF abnormalities (e.g., mononuclear pleocytosis and elevated protein levels) are common in persons with HIV infection, even in those without syphilis. The clinical and prognostic significance of such CSF laboratory abnormalities with primary and secondary syphilis in persons without neurological symptoms is unknown. Several studies have demonstrated that among persons with HIV infection and syphilis, CSF abnormalities consistent with neurosyphilis are associated with a CD4 count of ≤ 350 cells/mL and/or an RPR titer of $\geq 1:32$ ^{394,426,427}; however, unless neurologic signs and symptoms are present, the value of CSF examination in this is not known. All persons with HIV infection and syphilis should have a careful neurologic exam.^{415,424,425}.

Follow-Up

Persons with HIV infection should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy.

Persons with HIV infection who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or persons who have a sustained for more than 2 weeks fourfold increase or greater in titer) should be managed in the same manner as HIV-negative patients (i.e., a CSF examination and retreatment guided by CSF findings). Additionally, CSF examination and retreatment can be considered for persons whose nontreponemal test titers do not decrease fourfold within 12-24 months of therapy. If CSF examination is normal, treatment with

benzathine penicillin G administered as 2.4 million units IM each at weekly intervals for 3 weeks is recommended. Serologic titers may not decline despite a negative CSF examination and a repeated course of therapy.⁴⁰⁰ In these circumstances, the need for additional therapy or repeated CSF examinations is unclear, but is not generally recommended.

Management of Sex Partners

See Management of Sex Partners, above.

Special Considerations

Penicillin Allergy, Persons with HIV infection who are penicillin-allergic who have primary or secondary syphilis should be managed according to the recommendations for penicillin-allergic, HIV-negative persons. In those persons with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin (see Management of Persons Who Have a History of Penicillin Allergy). The use of alternatives to penicillin has not been well studied in persons with HIV infection. These therapies should be used only in conjunction with close serologic and clinical follow-up.

Latent Syphilis

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| <i>Latent Syphilis</i> |
| <i>Recommended Regimen for Early Latent Syphilis in Persons with HIV infection</i> |
| Benzathine penicillin G, 2.4 million units IM in a single dose. |
| <i>Recommended Regimen for Late Latent Syphilis Among Persons with HIV infection</i> |
| Benzathine penicillin G, at weekly doses of 2.4 million units for 3 weeks. |

Other Management Considerations

All persons with HIV infection and syphilis should undergo a careful neurologic examination; those with neurologic symptoms or signs should undergo immediate CSF examination. Unless neurologic symptoms are present, CSF examination in this setting has not been associated with improved clinical outcomes, and is not recommended.

Follow-Up

Patients should be evaluated clinically and serologically at 6, 12, 18, and 24 months after

therapy. If, at any time, clinical symptoms develop or nontreponemal titers rise fourfold (sustained for greater than 2 weeks), a CSF examination should be performed and treatment administered accordingly. If the nontreponemal titer does not decline fourfold after 24 months, CSF examination can be considered and treatment administered accordingly, although initial low titers (<1:8) may remain serofast.

Management of Sex Partners

See Management of Sex Partners.

Special Considerations

Penicillin Allergy. The efficacy of alternative nonpenicillin regimens in persons 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 therapy or follow-up cannot be ensured should be desensitized and treated with penicillin (see Management of Persons Who Have a History of Penicillin Allergy).

Neurosyphilis Among Persons with HIV Infection

All persons with HIV infection and syphilis should have a careful neurologic examination.

Treatment

Persons with HIV infection and neurosyphilis should be treated according to the recommendations for HIV-negative persons with neurosyphilis (see Neurosyphilis).

Follow Up

Persons with HIV infection and neurosyphilis should be managed according to the recommendations for HIV negative persons with neurosyphilis. (see Neurosyphilis). Limited data suggest that changes in CSF parameters might occur more slowly in persons with HIV infection, especially those with more advanced immunosuppression^{414,424}.

Management of Sex Partners

See Management of Sex Partners, above.

Special Considerations

Penicillin Allergy. Persons with HIV infection who are penicillin-allergic and have have neurosyphilis should be managed according to the recommendations for penicillin-allergic, HIV-negative patients with neurosyphilis (See neurosyphilis). Several small observational studies conducted in persons with HIV infection with neurosyphilis suggest that ceftriaxone 1–2 g IV daily for 10-14 days might be effective as an alternate agent⁴²⁸⁻⁴³⁰. The possibility of cross-sensitivity between ceftriaxone and penicillin exists, however the risk of penicillin cross-

reactivity between third- generation cephalosporins is negligible⁴¹⁸⁻⁴²¹ (see Management of Persons Who Have a History of Penicillin Allergy). If concern exists regarding the safety of ceftriaxone for a person with HIV infection and neurosyphilis, skin testing should be performed (if available) to confirm penicillin allergy and, if necessary, desensitization in consultation with a specialist. Other regimens have not been adequately evaluated for treatment of neurosyphilis.

Syphilis in Pregnancy

All women should be screened serologically for syphilis early in pregnancy¹⁰⁵. Most states mandate screening at the first prenatal visit for all women⁴³¹. In populations in which use of prenatal care is not optimal, RPR test screening and treatment (if the RPR test is reactive) should be performed at the time that pregnancy is confirmed⁴³².

Antepartum screening by nontreponemal antibody testing is typical, but in some settings, treponemal antibody testing is being used. Pregnant women with reactive treponemal screening tests should have additional quantitative nontreponemal testing because titers are essential for monitoring treatment response.

For communities and populations in which the prevalence of syphilis is high and for women at high risk of infection, serologic testing should also be performed twice during the third trimester (ideally at 28–32 weeks' gestation) and at delivery. 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 the maternal serologic status having been determined at least once during pregnancy.

Diagnostic Considerations

Seropositive pregnant women should be considered infected unless an adequate treatment history is documented clearly in the medical records and sequential serologic antibody titers have declined appropriately for the stage of syphilis. In general, the risk of antepartum fetal infection or congenital syphilis at delivery is related to the stage of syphilis during pregnancy and the *T. pallidum* bacteremia with the highest risk at the primary and secondary stage. Quantitative maternal nontreponemal titer, especially if it is greater than or equal to 1:8 may be a marker of early infection and bacteremia. However, risk of fetal infection is still significant in pregnant women with late latent syphilis and low titers. Stable serofast low antibody titers might not require treatment in previously treated women; however, rising or persistently high antibody titers might indicate reinfection or treatment failure, and treatment should be considered.

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

1. If the second treponemal test is positive, then current or past syphilis infection is confirmed. For women with a history of adequately treated syphilis who do not have

ongoing risk, no further treatment is necessary. Women without a prior history of treatment should be staged and treated accordingly with a recommended penicillin regimen.

2. If the second treponemal test is negative, then the positive EIA/CIA is more likely to be a false positive test result³⁹¹. If the woman is at low risk for syphilis, without signs or symptoms of primary syphilis, her partner is without clinical or serologic evidence of syphilis and follow up is likely, then repeat serologic testing within 4 weeks can be considered to see if the EIA/CIA remains positive or if the the RPR/VDRL or the TP-PA becomes positive. Otherwise treat according to the stage of syphilis. If both the RPR and TP-PA remain negative, then no further treatment is necessary.

Treatment

Penicillin G is the only known effective antimicrobial for preventing maternal transmission to the fetus and for treating fetal infection⁴³³. Evidence is insufficient to determine optimal, recommended penicillin regimens⁴³⁴.

Recommended Regimen

Pregnant women should be treated with the penicillin regimen appropriate for their stage of infection.

Other Management Considerations

Some evidence suggests that additional therapy can be beneficial for pregnant women in some settings (e.g., a second dose of benzathine penicillin 2.4 million units IM administered 1 week after the initial dose for women who have primary, secondary, or early latent syphilis)⁴³⁵⁻⁴³⁷.

When syphilis is diagnosed during the second half of pregnancy, management should include a sonographic fetal evaluation for congenital syphilis, but this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis (i.e., hepatomegaly, ascites, hydrops, fetal anemia, or a thickened placenta) indicate a greater risk for fetal treatment failure⁴³⁸; such cases should be managed in consultation with obstetric specialists. Evidence is insufficient to recommend specific regimens for these situations.

Women treated for syphilis during the second half of pregnancy are at risk for premature labor and/or fetal distress if the treatment precipitates the Jarisch-Herxheimer reaction⁴³⁹. 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, but concern for this complication should not delay necessary treatment. There is no data that corticosteroid treatment alters the risk of complications of treatment in pregnancy.

All patients who have syphilis should be offered testing for HIV infection.

Follow-Up

Coordinated prenatal care and treatment are vital. At a minimum, serologic titers should be repeated at 28–32 weeks' gestation and at delivery. Serologic titers can be checked monthly in women at high risk for reinfection or in geographic areas in which the prevalence of syphilis is high. Providers should ensure that the clinical and antibody responses are appropriate for the patient's stage of disease, although most women will deliver before their serologic response to treatment can be assessed definitively. Inadequate maternal treatment is likely if delivery occurs within 30 days of therapy, if clinical signs of infection are present at delivery, or if the maternal antibody titer at delivery is fourfold higher than the pretreatment titer.

Management of Sex Partners

See Management of Sex Partners, above.

Special Considerations

Penicillin Allergy

For treatment of syphilis during pregnancy, no proven alternatives to penicillin exist. Pregnant women who have a history of penicillin allergy should be desensitized and treated with penicillin. 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 contraindicated in the second and third trimester of pregnancy.³¹⁰ Erythromycin and azithromycin should not be used, because neither reliably cures maternal infection or treats an infected fetus⁴³⁴. Data are insufficient to recommend ceftriaxone for treatment of maternal infection and prevention of congenital syphilis.

HIV Infection

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

Congenital Syphilis

Effective prevention and detection of congenital syphilis depends on the identification of syphilis in pregnant women and, therefore, on the routine serologic screening of pregnant women during the first prenatal visit and at 28 weeks' gestation and delivery (if increase in community or individual risk)^{432,440}. Moreover, as part of the management of pregnant women who have syphilis, information concerning ongoing risk behaviors and the treatment of sex partners should be obtained to assess the risk for reinfection.

Routine screening of newborn sera or umbilical cord blood is not recommended and is too late to prevent symptomatic congenital syphilis in some newborns. Serologic testing of the mother's serum is preferred because the serologic tests performed on the neonate's serum can be nonreactive if the mother's serologic test result is of low titer or the mother was infected late in pregnancy (see Diagnostic Considerations and Use of Serologic Tests). No mother or newborn infant should leave the hospital unless maternal serologic status has been documented at least once during pregnancy; in communities and populations in which the risk for congenital syphilis is high, documentation of maternal serologic testing should also occur at delivery.

Evaluation and Treatment of Neonates (Infants < 30 days of age)

The diagnosis of congenital syphilis is complicated by the transplacental transfer of maternal nontreponemal and treponemal IgG antibodies to the fetus, which can complicate the interpretation of reactive serologic tests for syphilis in neonates. Therefore, treatment decisions frequently must be made on the basis of 1) identification of syphilis in the mother; 2) adequacy of maternal treatment; 3) presence of clinical, laboratory, or radiographic evidence of syphilis in the neonate; and 4) comparison of maternal (at delivery) and neonatal nontreponemal serologic titers 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 infection.

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 Warton jelly can yield a false negative result. Conducting a treponemal test (i.e., TP-PA, FTA-ABS, EIA, or CIA) on neonatal serum is not necessary and difficult to interpret. No commercially available immunoglobulin (IgM) test can be recommended. These neonates should also be test for HIV.

All neonates born to women who have reactive serologic tests for syphilis should be examined thoroughly for evidence of congenital syphilis (e.g., nonimmune hydrops, jaundice, hepatosplenomegaly, rhinitis, skin rash, and 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 validated test according to CLIA regulations should be considered; DFA-TP reagents are not currently available. Darkfield microscopic examination or PCR testing of suspicious lesions or body fluids (e.g., bullous rash, nasal discharge) also should be performed. In addition to these tests, for stillborn infants, skeletal survey demonstrating typical osseous lesions may aid in the diagnosis of congenital syphilis.

The following scenarios describe the evaluation and treatment of infants for congenital syphilis. In all situations, the maternal history of infection with *T. pallidum* and treatment for syphilis must be considered when evaluating and treating the neonate.

Scenario 1: Proven or highly probable congenital syphilis

Any neonate with:

1. an abnormal physical examination that is consistent with congenital syphilis;

OR

2. a serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer;[¶]

OR

3. a positive darkfield test or PCR of lesions or body fluid(s).

Recommended Evaluation

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

Recommended Regimens

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

OR

Procaine penicillin G 50,000 units/kg/dose IM in a single daily dose for 10 days

If more than 1 day of therapy is missed, the entire course should be restarted. Data are insufficient regarding the 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

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

**CSF test results obtained during the neonatal period can be difficult to interpret; normal values differ by gestational age and are higher in preterm infants. Values as high as 25 white blood cells (WBCs) /mm³ and/or protein of 150 mg/dL might occur among normal neonates; Lower values (i.e., 5 WBCs/mm³ and protein of 40 mg/dL) might be considered the upper limits of normal. Other causes of elevated values should be considered when an infant is being evaluated for congenital syphilis.

sepsis. The use of agents other than penicillin requires close serologic follow-up to assess adequacy of therapy.

Scenario 2: Possible Congenital Syphilis

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer and one of the following:

1. mother was not treated, inadequately treated, or has no documentation of having received treatment;

OR

2. mother was treated with erythromycin or another a regimen other than those recommended in these guidelines;^{††}

OR

3. mother received recommended treatment <4 weeks before delivery.

Recommended Evaluation

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

A complete evaluation is not necessary if 10 days 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 bone radiographs) can be performed to further support a diagnosis of congenital syphilis.

Recommended Regimens

Aqueous crystalline penicillin G 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days.

OR

Procaine penicillin G 50,000 units/kg/dose IM in

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

a single daily dose for 10 days

OR

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

Before using the single dose benzathine penicillin G regimen, the complete evaluation (i.e., CSF examination, long-bone radiographs, and CBC with platelets) must be normal, and follow-up must be certain. If any part of the infant's evaluation is abnormal or not performed or if the CSF analysis is uninterpretable because of contamination with blood, then 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 of untreated syphilis is low, treatment of the neonate with a single IM dose of benzathine penicillin G 50,000 units/kg for possible incubating syphilis without an evaluation can be considered.

If the mother has untreated early syphilis at the time of delivery, then risk of congenital syphilis is higher and the 10-day course of penicillin G may be considered even if 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 the same or less than fourfold the maternal titer and **both** of the following are true:

1. mother was treated during pregnancy, treatment was appropriate for the stage of infection, and treatment was administered >4 weeks before delivery and
2. mother has no evidence of reinfection or relapse.

Recommended Evaluation

No evaluation is recommended.

| <i>Recommended Regimen</i> |
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| <p>Benzathine penicillin G 50,000 units/kg/dose IM in a single dose*</p> |
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| <p>* Another approach involves not treating the infant, but rather providing close serologic follow-up every 2-3 months for 6 months in those whose mother's nontreponemal titers decreased fourfold after appropriate therapy for early syphilis or remained stable or low for late syphilis (e.g.; VDRL <1:2; RPR <1:4).</p> |
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Scenario 4: Congenital Syphilis unlikely

Any neonate who has a normal physical examination and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer and **both** of the following are true:

1. mother's treatment was adequate before pregnancy and
2. mother's nontreponemal serologic titer remained low and stable before and during pregnancy and at delivery (VDRL <1:2; RPR <1:4).

Recommended Evaluation

No evaluation is recommended.

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| <i>Recommended Regimen</i> |
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| No treatment is required but infants with reactive nontreponemal tests should be followed serologically to ensure the nontreponemal test returns to negative (See follow-up below); however, benzathine penicillin G 50,000 units/kg as a single IM injection might be considered, particularly if follow-up is uncertain and the neonate has a reactive nontreponemal test. |
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Follow-Up

All neonates with reactive nontreponemal tests should receive careful follow-up examinations and serologic testing (i.e., a nontreponemal test) every 2–3 months until the test becomes nonreactive. In the neonate that was not treated because congenital syphilis was less likely or unlikely, nontreponemal antibody titers should decline by age 3 months and should be nonreactive by age 6 months (i.e., the reactive test result was caused by passive transfer of maternal IgG antibody). At 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 to be infected and should be treated. Treated neonates with persistent nontreponemal test titers by 6–12 months should be re-evaluated including a CSF examination and managed in consultation with an expert. Retreatment with a 10 day course of a penicillin G regimen may be indicated. Neonates with a negative nontreponemal test at birth and whose mothers were seroreactive at delivery should be retested at 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 may persist for at least 15 months.

Neonates whose initial CSF evaluations are abnormal should undergo a repeat lumbar puncture approximately every 6 months until the results are normal. A reactive CSF VDRL test or abnormal CSF indices that cannot be attributed to other ongoing illness requires retreatment for possible neurosyphilis and should be managed in consultation with an expert.

Special Considerations

Penicillin Shortage

During periods when the availability of aqueous crystalline penicillin G is compromised, the following is recommended (see <http://www.cdc.gov/nchstp/dstd/penicillinG.htm>).

1. For neonates with clinical evidence of congenital syphilis (Scenario 1), check local sources for aqueous crystalline penicillin G (potassium or sodium). If IV penicillin G is limited, substitute some or all daily doses with procaine penicillin G (50,000 U/kg/dose IM a day in a single daily dose for 10 days).

If aqueous or procaine penicillin G is not available, ceftriaxone (in doses appropriate for birth weight) can be considered with careful clinical and serologic follow-up and in consultation with an expert as evidence is insufficient to support the use of ceftriaxone for the treatment of congenital syphilis. Management may include a repeat CSF examination at age 6 months if the initial examination was abnormal. Ceftriaxone must be used with caution in infants with jaundice.

2. For neonates without any clinical evidence of congenital syphilis (Scenario 2 and Scenario 3), use

a. procaine penicillin G, 50,000 U/kg/dose IM a day in a single dose for 10 days;

or

b. benzathine penicillin G, 50,000 U/kg IM as a single dose.

If any part of the evaluation for congenital syphilis is abnormal, CSF examination is not interpretable, CSF examination was not performed, or follow-up is uncertain, procaine penicillin G is recommended. A single dose of ceftriaxone is inadequate therapy.

3. For premature infants who have no clinical evidence of congenital syphilis (Scenario 2 and Scenario 3) and might not tolerate IM injections because of decreased muscle mass, IV ceftriaxone can be considered with careful clinical and serologic follow-up. Ceftriaxone dosing must be adjusted according to birth weight.

HIV Infection

Evidence is insufficient to determine whether neonates who have congenital syphilis and whose mothers have HIV infection require different evaluation, therapy, or follow-up for syphilis

than is recommended for all neonates.

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 should have maternal serology and records reviewed to assess whether they have congenital or acquired syphilis (see Primary and Secondary Syphilis and Latent Syphilis, Sexual Assault or Abuse of Children). Any infant or child at risk for congenital should receive a full evaluation and testing for HIV infection.

Recommended Evaluation

- 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).

| <i>Recommended Regimen</i> |
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| <p>Aqueous crystalline penicillin G 200,000–300,000 units/kg/day IV, administered as 50,000 units/kg every 4–6 hours for 10 days</p> |
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If the infant or child has no clinical manifestations of disease, the CSF examination is normal, and the CSF VDRL test result is negative, treatment with up to 3 weekly doses of benzathine penicillin G, 50,000 U/kg IM can be considered. Any child who is suspected of having congenital syphilis or who has neurologic involvement should be treated with aqueous penicillin G IV for 10 days. A single dose of benzathine penicillin G, 50,000 units/kg IM after the 10-day course of IV aqueous penicillin can be considered to provide more comparable duration of treatment in those who have no clinical manifestations and normal CSF. All of the above treatment regimens also would be adequate for children who might have other treponemal infections.

Follow-Up

Careful follow-up examinations and serologic testing (i.e., a nontreponemal test) of infants and children treated for congenital syphilis after the neonatal period (30 days of age) 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. Treponemal tests should not be used to evaluate treatment response, because the results are qualitative, persist after treatment and passive transfer of maternal IgG treponemal antibody may persist for at least 15 months. If these titers increase at any point for more than 2 weeks or do not decrease fourfold after 12–18 months, the infant or child should be evaluated (e.g., CSF

examination) and treated with a 10-day course of parenteral penicillin G and managed in consultation with an expert.

Infants or children whose initial CSF evaluations are abnormal should undergo a repeat lumbar puncture approximately every 6 months until the results are normal. After 2 years of follow-up, a reactive CSF VDRL test or abnormal CSF indices that cannot be attributed to other ongoing illness requires retreatment 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 then treated with penicillin (see Management of Persons With a History of Penicillin Allergy). Skin testing has not been standardized for infants and children so is not available. Data are insufficient regarding the use of other antimicrobial agents (e.g., ampicillin or ceftriaxone) for congenital syphilis in infants and children. If a non-penicillin G agent is used, close serologic and CSF follow-up is required.

Penicillin Shortage

During periods when the availability of penicillin is compromised, the following is recommended (see <http://www.cdc.gov/nchstp/dstd/penicillinG.htm>).

1. For infants with clinical evidence of congenital syphilis, check local sources for aqueous crystalline penicillin G (potassium or sodium). If IV penicillin G is limited, substitute some or all daily doses with procaine penicillin G (50,000 U/kg/dose IM a day in a single daily dose for 10 days).

If aqueous or procaine penicillin G is not available, ceftriaxone (in doses appropriate for age and weight) can be considered with careful clinical and serologic follow-up and managed in consultation with an expert as evidence is insufficient to support the use of ceftriaxone for the treatment of congenital syphilis in infants or children. Management may include a repeat CSF examination at age 6 months if the initial examination was abnormal. For infants aged ≥ 30 days, use 75 mg/kg IV/IM of ceftriaxone a day in a single daily dose for 10–14 days; however, dose adjustment might be necessary based on current weight. For children, the dose should be 100 mg/kg of ceftriaxone a day in a single daily dose.

2. For infants without any clinical evidence of infection (Scenario 2 and Scenario 3), use

- a. procaine penicillin G, 50,000 U/kg/dose IM a day in a single dose for 10 days;

or

b. benzathine penicillin G, 50,000 U/kg IM as a single dose.

If any part of the evaluation for congenital syphilis is abnormal, CSF examination is not interpretable, CSF examination was not performed, or follow-up is uncertain, procaine penicillin G is recommended. A single dose of ceftriaxone is inadequate therapy.

HIV Infection

Evidence is insufficient to determine whether infants and children who have congenital syphilis and whose mothers have HIV infection require different evaluation, therapy, or follow-up for syphilis than is recommended for all infants.

Management of Persons Who Have a History of Penicillin Allergy

No proven alternatives to penicillin are available for treating neurosyphilis, congenital syphilis, or syphilis in pregnant women. Penicillin also is recommended for use, whenever possible, in persons with HIV infection. The prevalence of reported penicillin allergy in the United States is about 8-10%⁴⁴¹⁻⁴⁴³. The prevalence may be higher in hospitalized persons⁴⁴⁴. The prevalence of reported penicillin allergy in developing countries is unknown, however limited data has shown that penicillin is one of the most frequently reported allergies in some developing countries^{445,446}. Of those that report penicillin allergy about 10-15% have a positive skin test suggesting that they are penicillin allergic and at risk for an immunoglobulin E (IgE)-mediated allergic response to penicillin such as urticaria, angioedema, or anaphylaxis (i.e., upper airway obstruction, bronchospasm, or hypotension).^{418-420,447,448} Thus, many persons with a reported history of penicillin allergy likely have had other types of adverse drug reactions or lost their sensitivity to penicillin over time and can safely be treated with penicillin. Re-administration of penicillin to patients with a history of IgE-mediated hypersensitivity reactions can cause severe, immediate reactions. Because anaphylactic reactions to penicillin can be fatal, every effort should be made to avoid administering penicillin to penicillin-allergic persons, unless they undergo induction of drug tolerance, also known as, desensitization to temporarily eliminate IgE-mediated hypersensitivity.

Penicillin skin testing with the major and minor determinants of penicillin can reliably identify persons at high risk for IgE-mediated reactions to penicillin.^{448,449} Although the testing reagents are easily generated and have been available for more than 30 years, only benzylpenicilloyl poly-L-lysine (Pre-Pen [i.e., the major determinant]) and penicillin G have been available commercially. These two tests identify an estimated 90%–99% of the currently allergic patients. However, because skin testing without the minor determinants would still miss 1%–10% of allergic persons and because serious or fatal reactions can occur among these minor-determinant-positive persons, caution should be exercised when the full battery of skin-test reagents is not available (Box 2).⁴⁴⁷⁻⁴⁵⁰ Manufacturers are working to achieve availability of the minor determinant mixture as a FDA-cleared product. Penicillin skin testing has been used in a variety of settings to improve antibiotic utilization.^{443,451-453}

There has been concern regarding the use of cephalosporins in persons with a history of penicillin allergy as older studies reported cross-reactivity rates as high as 10%. In more recent studies, the cross reactivity between penicillins and cephalosporins has been found to be low

(<2.5%).^{418-421,454}. The risk is highest with first generation cephalosporins and cephalosporins that have similar R-group side chains to specific penicillins^{455,456}. The risk of penicillin cross-reactivity between most second- generation (cefoxitin) and all third generation cephalosporins (cefixime, ceftriaxone) is negligible⁴¹⁸⁻⁴²¹.

Recommendations

Persons with histories of severe non-IgE-mediated reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, and hemolytic anemia, are not candidates for skin testing or challenge and should avoid penicillins indefinitely. If the full battery of skin-test reagents is available, including both major and minor determinants (see Penicillin Allergy Skin Testing), persons who report a history of penicillin reaction and who are skin-test negative can receive conventional penicillin therapy. Skin-test positive persons should be desensitized before initiating treatment.

If the full battery of skin-test reagents, including the minor determinants, is not available, skin testing should be conducted using benzylpenicilloyl poly-L-lysine (i.e., the major determinant) and penicillin G. Those persons who have positive test results should be desensitized. For persons with negative skin tests, a subsequent observed challenge to the penicillin of choice is recommended. Additionally, for persons with a history of severe or recent suspected IgE-mediated reactions to penicillin with negative skin testing, the penicillin of choice should be given by graded challenge. If the major determinant (benzylpenicilloyl poly-L-lysine) is not available for skin testing, all persons with a history suggesting IgE-mediated reactions to penicillin (e.g., anaphylaxis, angioedema, bronchospasm, or urticaria) should be desensitized in a hospital setting. In persons with reactions not likely to be IgE-mediated, outpatient-monitored graded challenges can be considered.

Penicillin Allergy Skin Testing

Persons at high risk for anaphylaxis, including those who 1) have a history of penicillin-related anaphylaxis, asthma, or other diseases that would make anaphylaxis more dangerous or 2) are being treated with beta-adrenergic blocking agents, should be tested with 100-fold dilutions of the full-strength skin-test reagents before being tested with full-strength reagents. In these situations, testing should be performed in a monitored setting in which treatment for an anaphylactic reaction is available. If possible, antihistamines (chlorpheniramine maleate, fexofenadine, diphenhydramine HCL, or hydroxyzine) should not have been taken within the 5 days prior to skin testing.

Procedures

Dilute the antigens in saline either 100-fold for preliminary testing (if the patient has had a life-threatening reaction to penicillin) or 10-fold (if the patient has had another type of immediate, generalized reaction to penicillin within the preceding year). The major determinant (penicilloyl polylysine [Pre-Pen] is provided full-strength [6×10^{-5} meq penicilloyl] in a single dose ampoule. Penicillin G is diluted to 10,000 IU/ml in saline and aliquoted in sterile vials which appear to be stable for at least 6 months if frozen.

Epicutaneous (Prick) Tests

Duplicate drops of skin-test reagent are placed on the volar surface of the forearm. The underlying epidermis is pierced with a 26-gauge needle without drawing blood. An epicutaneous test is positive if the average wheal diameter after 15 minutes is ≥ 4 mm larger than that of negative controls; otherwise, the test is negative. The histamine controls should be positive to ensure that results are not falsely negative because of the effect of antihistaminic drugs.

Intradermal Test

If epicutaneous tests are negative, duplicate 0.02-mL intradermal injections of negative control and antigen solutions are made into the volar surface of the forearm by using a 26- or 27-gauge needle on a syringe. The margins of the wheals induced by the injections should be marked with a ball point pen. An intradermal test is positive if the average wheal diameter 15 minutes after injection is >2 mm larger than the initial wheal size and also is >2 mm larger than the negative histamine controls. Otherwise, the tests are negative. If the duplicates are discordant, a second set of duplicate tests can be used to resolve the ambiguity.

Desensitization

Persons who have a positive skin test to one of the penicillin determinants can be desensitized (Table 1). This is a straightforward, relatively safe procedure that can be performed orally or intravenously. Modified protocols may be considered based on an individual's symptoms, drug of choice, and route of administration⁴⁵⁷⁻⁴⁵⁹. Although the two approaches have not been compared, oral desensitization is regarded as safer and easier to perform. Desensitization should occur in a hospital setting because serious IgE-mediated allergic reactions can occur, and can usually be completed in approximately 4–12 hours, after which time the first dose of penicillin is administered. After desensitization, penicillin should be maintained continuously for the duration of the course of therapy. Once the course is completed and if penicillin is required in the future, the desensitization procedure would need to be repeated.

TABLE 1. Oral desensitization protocol for persons with a positive skin test*

| Penicillin V suspension dose† | Amount§ (units/mL) | mL | Units | Cumulative dose (units) |
|-------------------------------|--------------------|-----|--------|-------------------------|
| 1 | 1,000 | 0.1 | 100 | 100 |
| 2 | 1,000 | 0.2 | 200 | 300 |
| 3 | 1,000 | 0.4 | 400 | 700 |
| 4 | 1,000 | 0.8 | 800 | 1,500 |
| 5 | 1,000 | 1.6 | 1,600 | 3,100 |
| 6 | 1,000 | 3.2 | 3,200 | 6,300 |
| 7 | 1,000 | 6.4 | 6,400 | 12,700 |
| 8 | 10,000 | 1.2 | 12,000 | 24,700 |
| 9 | 10,000 | 2.4 | 24,000 | 48,700 |
| 10 | 10,000 | 4.8 | 48,000 | 96,700 |
| 11 | 80,000 | 1.0 | 80,000 | 176,700 |

| | | | | |
|----|--------|-----|---------|-----------|
| 12 | 80,000 | 2.0 | 160,000 | 336,700 |
| 13 | 80,000 | 4.0 | 320,000 | 656,700 |
| 14 | 80,000 | 8.0 | 640,000 | 1,296,700 |

Note: Observation period was 30 minutes before parenteral administration of penicillin.

* Reprinted with permission from the New England Journal of Medicine (Wendel GO, Jr, Stark BJ, Jamison RB, Melina RD, Sullivan TJ. Penicillin allergy and desensitization in serious infections during pregnancy. N Engl J Med 1985; 312:1229–32.).

† Interval between doses, 15–30 minutes; elapsed time, 4–8 hours; cumulative dose, 1.3 million units.

§ The specific amount of drug was diluted in approximately 30 mL of water and then administered orally.

Box 2. Skin-test reagents for identifying persons at risk for adverse reactions to penicillin*

Major Determinant

- Benzylpenicilloyl poly-L-lysine (PrePen) (AllerQuest, Plainville Connecticut) (6 x 10⁻⁵M).

Minor Determinant Precursors†

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

Positive Control

- Commercial histamine for intradermal skin testing (1.0 mg/mL)

Negative Control

- Diluent (usually saline) or allergen diluent

* Adapted from Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to

beta-lactam antibiotics. Ann Intern Med 1987;107:204–15. Reprinted with permission from G.N. Beall and *Annals of Internal Medicine*.

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

Diseases Characterized by Urethritis and Cervicitis

Urethritis

Urethritis, as characterized by urethral inflammation, can result from infectious and noninfectious conditions. Symptoms, if present, include dysuria, urethral pruritis, or mucoid, mucopurulent, or purulent discharge. Signs of urethral discharge on examination can also be present in persons without symptoms. Although *N. gonorrhoeae* and *C. trachomatis* are well established as clinically important infectious causes of urethritis, *Mycoplasma genitalium* has also been associated with urethritis and, less commonly, prostatitis^{460-463 464}. If point-of-care diagnostic tools (e.g., Gram, methylene blue or gram gram stain microscopy, first void urine with microscopy, or leukocyte esterase) are not available, drug regimens effective against both gonorrhea and chlamydia should be administered. Further testing to determine the specific etiology is recommended to prevent complications, re-infection and onward transmission because a specific diagnosis might improve compliance with treatment, risk reduction interventions, and partner notification. Both chlamydia and gonorrhea are reportable to health departments. NAATs are preferred for the detection of *C. trachomatis* and *N. gonorrhoeae*, and urine is the preferred specimen in males³⁸⁵. Although they are not FDA-cleared, NAAT-based tests are available for the diagnosis of *T. vaginalis* in men only in laboratories that have performed the appropriate validation studies⁴⁶⁵ according to CLIA regulations.

Etiology

Several organisms can cause infectious urethritis. The presence of Gram-negative intracellular diplococci (GNID) on urethral smear is indicative of presumed gonorrhea infection, which is frequently accompanied by chlamydial infection. Nongonococcal urethritis (NGU), which is diagnosed when microscopy of urethral secretions indicates inflammation without GNID, is caused by *C. trachomatis* in 15%–40% of cases; however, prevalence varies by age group, with a lower burden of disease occurring among older men⁴⁶⁶. Documentation of chlamydial infection as the etiology of NGU is essential because of the need for partner referral for evaluation and treatment to prevent complications of chlamydia especially in female partners. Complications of NGU among males caused by *C. trachomatis* include epididymitis, prostatitis, and reactive arthritis (i.e.; Reiter's syndrome).

M. genitalium, which can be sexually transmitted, is associated with both symptoms of urethritis and urethral inflammation and accounts for 15%–25% of NGU cases in the United States⁴⁶⁰⁻⁴⁶³. However, FDA-cleared diagnostic tests for *M. genitalium* are not available.

T. vaginalis can cause NGU in heterosexual men, but the prevalence varies substantially by

region of the U.S. and within specific subpopulations. In some instances, NGU may be acquired by fellatio, sometimes due to specific pathogens such as HSV, Epstein Barr Virus, and adenovirus. Data supporting other *Mycoplasma* species and *Ureaplasma* as etiologic agents are inconsistent.⁴⁶⁶ Diagnostic and treatment procedures for these organisms are reserved for situations in which these infections are suspected (e.g., urethral lesions, or severe dysuria and meatitis, which might suggest genital herpes) or when NGU is not responsive to recommended therapy. Enteric bacteria have been identified as an uncommon cause of NGU and might be associated with insertive anal intercourse⁴⁶⁶. The importance of NGU not caused by defined pathogens is uncertain; neither complications (urethral stricture, epididymitis) nor adverse outcomes in sex partners have been identified.

Diagnosis of Urethritis

Clinicians should attempt to obtain objective evidence of urethral inflammation. However, if point-of-care diagnostic tests (e.g., Gram, methylene blue or gram stain microscopy) are not available, all men should be tested using NAATS and treated with drug regimens effective against both gonorrhea and chlamydia.

In the setting of compatible symptoms, clinical 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 of urethral secretions demonstrating ≥ 2 WBC per oil immersion field⁴⁶⁷. The Gram stain is a point-of-care diagnostic test for evaluating urethritis that is highly sensitive and specific for documenting both urethritis and the presence or absence of gonococcal infection. Methylene Blue or Gentian Violet (MB/GV) smear is an alternative point-of-care diagnostic test with performance characteristics similar to gram stain and the cutoff number for WBC per oil immersion field should be the same⁴⁶⁸. Presumed gonococcal infection is established by documenting the presence of WBC containing GNID in Gram stain or intracellular purple diplococci in MB/GV smears and men should be presumptively treated and managed accordingly for GC infection (see GC section).
- Positive leukocyte esterase test on first-void urine
- Microscopic examination of first-void urine sediment demonstrating ≥ 10 WBC per high-power field.

If symptoms but no evidence of urethral inflammation, NAAT testing for *C. trachomatis* and *N. gonorrhoeae* in the absence of intracellular Gram negative or purple diplococci might identify infections.⁴⁶⁹ *T. vaginalis* testing could also be considered in areas or populations of high prevalence. If the results demonstrate infection with these pathogens, the appropriate treatment should be given and sex partners referred for evaluation and treatment. If none of these clinical criteria are present, empiric treatment of symptomatic men is recommended only for those men 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

Diagnostic Considerations

NGU is a nonspecific diagnosis that can have many infectious etiologies. NGU is confirmed in symptomatic men when staining of urethral secretions indicates inflammation without Gram negative or purple diplococci. All men who have confirmed NGU should be tested for chlamydia and gonorrhea even if point-of-care tests are negative for evidence of GC. NAATs for chlamydia and gonorrhea are recommended because of the high sensitivity and specificity and a specific diagnosis might reduce complications, re-infection and onward transmission. *T. vaginalis* testing could be considered in areas or populations of high prevalence.

Treatment

Presumptive treatment should be initiated at the time of NGU diagnosis. Azithromycin and doxycycline are highly effective for chlamydial urethritis. NGU associated with *M. genitalium* respond better to azithromycin than doxycycline, however azithromycin efficacy may be declining (See, *Mycoplasma genitalium*). Single-dose regimens have the advantage of improved compliance and directly observed treatment. To maximize compliance with recommended therapies, medications should be dispensed on-site in the clinic, and the first dose should be directly observed.

Recommended Regimens

Azithromycin 1 g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

Alternative Regimens

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

OR

Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days

OR

Levofloxacin 500 mg orally once daily for 7 days

OR

Ofloxacin 300 mg orally twice a day for 7 days

To minimize onward transmission and reinfection, men treated for NGU should be instructed to abstain from sexual intercourse until they and their partner(s) have been adequately treated (i.e.; for 7 days after single-dose therapy or until completion of a 7-day regimen, and symptoms have resolved.

Men diagnosed with NGU should be tested for HIV and syphilis.

Follow-Up

Men should be instructed to return for evaluation if symptoms persist or recur after completion of therapy. Symptoms alone, without documentation of signs or laboratory evidence of urethral inflammation, are not a sufficient basis for retreatment. Providers should be alert to the possible diagnosis of chronic prostatitis/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. Men should be provided results of the testing obtained as part of the NGU evaluation. Men with a specific diagnosis of CT, GC or trichomonias 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^{108, 470} (see Chlamydia and gonorrhea follow-up sections).

Management of Sex partners

All sex partners of men with NGU within the preceding 60 days should be referred for evaluation, testing, and presumptive treatment with a drug regimen effective against chlamydia. To avoid reinfection, sex partners should abstain from sexual intercourse until they and their partner(s) are adequately treated (see definition of adequate therapy). Expedited partner treatment is an alternative approach to treating female partners for CT if there are no symptoms

of PID⁹³. If the NAAT results are positive for gonorrhea or *T. vaginalis* or, then all partners should be evaluated and treated according to the management section for their respective pathogen.

Persistent and Recurrent NGU

The objective diagnosis of persistent or recurrent NGU should be made before considering additional antimicrobial therapy. In 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. Men who have persistent or recurrent NGU can be retreated with the initial regimen if they did not comply with the treatment regimen or if they were reexposed to an untreated sex partner.

Recent studies have shown that the most common cause of persistent or recurrent NGU is *M. genitalium*, especially following doxycycline therapy^{268,269}. Azithromycin 1 gram orally in single dose should be given to men initially treated with doxycycline. Several observational studies have shown that moxifloxacin 400 mg orally once daily for 7 days is highly effective against *M. genitalium*. Therefore, men who fail a regimen of azithromycin should be retreated with moxifloxacin 400 mg orally once daily for 7 days. There is no evidence that higher doses of azithromycin are effective for *M. genitalium* in this circumstance.

T. vaginalis is also known to cause urethritis in men who have sex with women but is not covered by the treatment regimens listed above for first episodes of NGU; While there is no FDA-cleared NAAT for *T. vaginalis* detection in men in the U.S., several large reference laboratories have performed the necessary CLIA validation of a urine-based *T. vaginalis* NAAT for men for clinical use. Trichomonas NAAT testing is more sensitive than culture⁴⁶⁵. In areas where *T. vaginalis* is highly prevalent, men who have sex with women and have persistent or recurrent urethritis should be presumptively treated with metronidazole 2 g orally in a single dose or tinidazole 2 g orally in a single dose. Persistent or recurrent NGU after presumptive treatment for *M. genitalium* or *T. vaginalis* should be referred to a urologist.

Special Considerations

HIV Infection

NGU might facilitate HIV transmission. Persons with NGU and HIV should receive the same treatment regimen as those who are HIV negative.

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 or 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, but some women complain of an abnormal vaginal discharge and intermenstrual vaginal bleeding (e.g., after sexual

intercourse). A finding of leukorrhea (>10 WBC per high-power field on microscopic examination of vaginal fluid) has been associated with chlamydial and gonococcal infection of the cervix. In the absence of the major diagnostic signs of inflammatory vaginitis, leukorrhea might be a sensitive indicator of cervical inflammation with a high negative predictive value (i.e.; cervicitis is unlikely in the absence of leukorrhea)^{471,472}. The criterion of using an increased number of WBCs on endocervical Gram stain in the diagnosis of cervicitis has not been standardized so is not helpful. In addition, it has a low positive-predictive value (PPV) for infection with *C. trachomatis* and *N. gonorrhoeae* and is not available in most clinical settings. Finally, although the presence of gram negative intracellular diplococci on Gram stain of endocervical fluid may be specific for the diagnosis of gonococcal cervical infection when evaluated by an experienced laboratorian, it is not a sensitive indicator of infection.

Etiology

When an etiologic organism is isolated in the presence of cervicitis, it is typically *C. trachomatis* or *N. gonorrhoeae*. Cervicitis also can accompany trichomoniasis and genital herpes (especially primary HSV-2 infection). However, in most cases of cervicitis, no organism is isolated, especially in women at relatively low risk for recent acquisition of these STDs (e.g., women aged >30 years⁴⁷³). Limited data indicate that BV infection with *M. genitalium* and BV and frequent douching might cause cervicitis^{248-250,252,256,474-476}. For reasons that are unclear, cervicitis can persist despite repeated courses of antimicrobial therapy. Because most persistent cases of cervicitis are not caused by recurrent or reinfection with *C. trachomatis* or *N. gonorrhoeae*, other factors (e.g., persistent abnormality of vaginal flora, douching [or exposure to other types of chemical irritants], or idiopathic inflammation in the zone of ectopy) might be involved.

Diagnosis

Because cervicitis might be a sign of upper-genital-tract infection (endometritis), women with a new episode of cervicitis should be assessed for signs of PID and should be tested for *C. trachomatis* and for *N. gonorrhoeae* with a NAAT which can be performed on either vaginal, cervical, or urine samples³⁸⁵ (see CT diagnostic considerations section). Women with cervicitis also should be evaluated for the presence of bacterial vaginosis and trichomoniasis, and if these organisms are detected, they should be treated. Because the sensitivity of microscopy to detect *T. vaginalis* is relatively low (approximately 50%), symptomatic women with cervicitis and negative microscopy for trichomonads should receive further testing (i.e., culture, NAAT or other FDA approved diagnostic test, if available) (see trich diagnostic considerations section). A finding of >10 WBC in vaginal fluid, in the absence of trichomoniasis, might indicate endocervical inflammation caused specifically by *C. trachomatis* or *N. gonorrhoeae*^{477,478}. Although HSV-2 infection has been associated with cervicitis, the utility of specific testing (i.e., PCR, culture or serologic testing) for HSV-2 in this setting is unknown. FDA-cleared diagnostic tests for *M. genitalium* are not commercially available.

Treatment

Several factors should affect the decision to provide presumptive therapy for cervicitis. Treatment with antibiotics for *C. trachomatis* should be provided for those women at increased

risk for this common STD (e.g., those aged <25 years, those with new or multiple sex partners or partners with concurrent partners), especially if follow-up cannot be ensured or if a NAAT testing is not possible. Concurrent therapy for *N. gonorrhoeae* is indicated for women at risk for GC¹⁰⁹ (e.g., age <25 years, those with new or multiple sex partners, previous gonorrhea infection other STDs) or who live in communities with high prevalence of GC (see GC section). Trichomoniasis and BV should also be treated if detected (see BV and Trich section). Presumptive treatment of clinically significant cervicitis where symptoms are clearly attributed to cervicitis may also be considered.

For women at lower risk of STDs deferring treatment until results of diagnostic tests are available is an option. If treatment is deferred and NAATS for CT and GC are negative, then a follow-up visit to see if the cervicitis has resolved can be considered.

Recommended Regimens for Presumptive Treatment*

Azithromycin 1 g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

* Consider concurrent treatment for gonococcal infection if prevalence of gonorrhea is high in the population under assessment.

To minimize onward transmission and reinfection, women treated for cervicitis should be instructed to abstain from sexual intercourse until they and their partner (s) have been adequately treated (i.e., for 7 days after single-dose therapy or until completion of a 7-day regimen, and symptoms have resolved

Women diagnosed with cervicitis should be tested for HIV and syphilis.

Follow-Up

Women should return after treatment so that a determination can be made regarding whether cervicitis has resolved and women who are not treated should be provided results of the testing obtained as part of the cervicitis evaluation. Follow-up should be conducted as recommended for the infections identified. If symptoms persist, women should be instructed to return for re-evaluation. Women with a specific diagnosis of CT, GC or trichomonas 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 treated¹⁰⁸.

Management of Sex Partners

Management of sex partners of women treated for cervicitis should be appropriate for the identified STD. All sex partners in the past 60 days should be notified and examined if chlamydia, gonorrhea, or trichomoniasis was identified or suspected in the index patient; these partners should then be treated for the STDs for which the index patient received treatment. To avoid reinfection, sex partners should abstain from sexual intercourse until they and their partner (s) are adequately treated (see definition of adequate therapy). Expedited partner treatment or other effective partner referral strategies (see Partner Services) are alternative approaches to treating male partners of women who have chlamydia or gonococcal infections⁹¹⁻⁹³.

Persistent or Recurrent Cervicitis

Women with persistent or recurrent cervicitis and who were treated should be reevaluated for possible reexposure or treatment failure to gonorrhea or chlamydia. If relapse and/or reinfection with a specific STD have been excluded, BV is not present, and sex partners have been evaluated and treated, management options for persistent cervicitis are undefined; in addition, the utility of repeated or prolonged administration of antibiotic therapy for persistent symptomatic cervicitis remains unknown. The etiology of persistent cervicitis including the potential role of *M. genitalium*⁴⁷⁹ is unclear. *M. genitalium* may be considered for cases of clinically significant cervicitis that persist after azithromycin or doxycycline therapy in which reexposure to an infected partner or medical nonadherence is unlikely. In settings with validated assays, women with persistent cervicitis should be tested for *M. genitalium* with the decision to treat with moxifloxacin based on results of diagnostic testing⁴⁸⁰. In treated women with persistent symptoms that are clearly attributable to cervicitis, referral to a gynecologic specialist can be considered.

Special Considerations

HIV Infection

Women with cervicitis and HIV infection should receive the same treatment regimen as those who are HIV negative. Cervicitis increases cervical HIV shedding. Treatment of cervicitis in women with HIV infection reduces HIV shedding from the cervix and might reduce HIV transmission to susceptible sex partners⁴⁸¹⁻⁴⁸⁵.

Pregnancy

Diagnosis and treatment of cervicitis in pregnant women does not differ from that in women that are not pregnant.

Chlamydial Infections

Chlamydial Infections in Adolescents and Adults

Urogenital chlamydial infection is the most frequently reported infectious disease in the

United States, and prevalence is highest in persons aged 24 and younger¹¹⁹. Several important sequelae can result from *C. trachomatis* infection in women, the most serious of which include PID, ectopic pregnancy, and infertility. Some women who have uncomplicated cervical infection already have subclinical upper-reproductive-tract infection upon diagnosis.

Asymptomatic infection is common among both men and women. To detect chlamydial infections, 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 with risk factors (e.g., those who have a new sex partner or multiple sex partners, and those reporting their sex partner may have a concurrent sex partner)^{107,486 487}. While CT incidence may be higher in some women 25 years of age and older in some communities, over all the largest burden of infection is among women < 25 years.

Chlamydia screening programs have been demonstrated to reduce the rates of PID in women^{488,489}. Although evidence is insufficient to recommend routine screening for *C. trachomatis* in sexually active young men because of several factors (including feasibility, efficacy, and cost-effectiveness)¹²¹, the screening of sexually active young men should be considered in clinical settings with a high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, and STD clinics) or in populations with high burden of infection (MSM). Among women, the primary focus of chlamydia screening efforts should be to detect chlamydia, prevent complications and test and treat their partners, whereas targeted chlamydia screening in men should only be considered when resources permit, prevalence is high, and it does not hinder chlamydia screening efforts in women^{490,491}. More frequent screening for some women (see adolescents) or certain men (see MSM) might be indicated.

Diagnostic Considerations

C. trachomatis urogenital infection in women can be diagnosed by testing first catch urine or by collecting swab specimens from the endocervix or vagina. Diagnosis of *C. trachomatis* urethral infection in men can be made by testing a urethral swab or first catch urine specimen. NAATs are the most sensitive tests for these specimens and are the recommended tests for *C. trachomatis* detection³⁸⁴. NAATs that are FDA-cleared for use with vaginal swab specimens, can be collected by a provider or self-collected by a patient. Self-collected vaginal swab specimens are equivalent in sensitivity and specificity to those collected by a clinician using NAATs^{492,493} and women find this screening strategy highly acceptable^{494,495}. Based on ease of collection and having *C. trachomatis* detection rates comparable to other specimens, optimal urogenital specimen types for chlamydia screening using NAATs include first catch urine from men and vaginal swabs from women. Rectal and oropharyngeal *C. trachomatis* infection in persons engaging in receptive anal or oral intercourse can be diagnosed by testing at the anatomic site of exposure. The clinical significance of oropharyngeal *C. trachomatis* infection is unclear and thus routine oropharyngeal screening for CT is not recommended (see MSM). NAATs are not FDA-cleared for use with rectal or oropharyngeal swab specimens. However, NAATs have been demonstrated to have improved sensitivity and specificity compared with culture for the detection of *C. trachomatis* at rectal sites⁴⁹⁶⁻⁴⁹⁸ and at oropharyngeal sites among men⁴⁹⁶⁻⁴⁹⁹. Some laboratories have established performance specifications when evaluating rectal and oropharyngeal swab specimens for *C. trachomatis* to meet CLIA regulatory requirements as

applicable prior to reporting results for clinical management. There is good evidence that performance of NAATs on self-collected rectal swabs is comparable to clinician-collected rectal swabs, and patients find this specimen collection strategy for rectal *C. trachomatis* screening highly acceptable⁵⁰⁰⁻⁵⁰². Self-collected rectal swabs are a reasonable alternative to clinician-collected rectal swabs for *C. trachomatis* screening by NAATs, especially when rectal exam is not feasible or when patients prefer self collection over clinician collection. Previous evidence suggests that the liquid-based cytology specimens collected for Pap smears might be acceptable specimens for NAAT testing, although test sensitivity using these specimens might be lower than those resulting from the use of cervical or vaginal swab specimens⁵⁰³; regardless, certain NAATs have been FDA-cleared for use on liquid-based cytology specimens.

Treatment

Treatment prevents adverse reproductive health complications and sexual transmission of *C. trachomatis*, and treating sex partners for chlamydia can prevent reinfection of the index patient and infection of other partners. Treating pregnant women usually prevents transmission of *C. trachomatis* to infants during birth. Chlamydia treatment should be provided promptly for all persons testing positive for infection; delays in receiving chlamydia treatment have been associated with complications (e.g., PID) in a limited proportion of chlamydia-infected women⁵⁰⁴. The following recommended treatment regimens and alternative regimens cure infection and usually relieve symptoms.

Recommended Regimens

Azithromycin 1 g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

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| <h3><i>Alternative Regimens</i></h3> <hr/> |
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Erythromycin base 500 mg orally four times a day for 7 days

OR

Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days

OR

Levofloxacin 500 mg orally once daily for 7 days

OR

Ofloxacin 300 mg orally twice a day for 7 days

A meta-analysis of 12 randomized clinical trials of azithromycin versus doxycycline for the treatment of urogenital chlamydial infection demonstrated that the treatments were equally efficacious, with microbial cure rates of 97% and 98%, respectively⁵⁰⁵. These studies were conducted primarily in populations with urethral and cervical infection in which follow-up was encouraged, adherence to a 7-day regimen was effective, and culture or EIA (rather than the more sensitive NAAT) was used for determining microbiological outcome. More recent retrospective studies have raised concern about the efficacy of azithromycin for rectal *C. trachomatis* infection^{506,507}, however these studies have limitations and prospective clinical trials comparing azithromycin versus doxycycline regimens for rectal *C. trachomatis* infection are needed. On-site, directly observed therapy with azithromycin should always be available to treat patients for whom adherence with multiday dosing is a concern. Most persons with *C. trachomatis* detected at oropharyngeal sites do not have oropharyngeal symptoms. The clinical significance of *C. trachomatis* detected at oropharyngeal sites is unclear, therefore routine *C. trachomatis* screening at oropharyngeal sites is not recommended. However, when gonorrhea testing is performed at the oropharyngeal site, chlamydia test results are often reported as well due to dual platform NAAT testing. Available evidence suggests oropharyngeal *C. trachomatis* can be sexually transmitted to genital sites^{508,509}, therefore detection of *C. trachomatis* from an oropharyngeal specimen should be treated with azithromycin or doxycycline. The efficacy of alternative antimicrobial regimens in resolving oropharyngeal chlamydia remains unknown.

In persons who have erratic health-care-seeking and follow-up behavior, or poor treatment adherence, azithromycin might be more cost-effective in treating chlamydia because it enables the provision of a single-dose of directly observed therapy⁵⁰⁵. In a double-blinded randomized control trial, a doxycycline delayed-release 200 mg tablet administered daily for 7 days was as effective as generic doxycycline 100 mg twice daily for 7 days for treatment of urogenital *C. trachomatis* infection in men and women and had a lower frequency of gastrointestinal side effects, but is more costly⁵¹⁰. Delayed-release doxycycline (Doryx ®) 200 mg daily for 7 days may be an alternative regimen to the doxycycline 100 mg twice daily for 7 days for treatment of

urogenital *C. trachomatis* infection. Erythromycin might be less efficacious than either azithromycin or doxycycline, mainly because of the frequent occurrence of gastrointestinal side effects that can lead to nonadherence with treatment. Levofloxacin and ofloxacin are effective treatment alternatives but are more expensive and offer no advantage in the dosage regimen. Other quinolones either are not reliably effective against chlamydial infection or have not been evaluated adequately.

To maximize adherence with recommended therapies, medications for chlamydial infections should be dispensed on site, and the first dose should be directly observed. 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. To minimize the risk for reinfection, patients also should be instructed to abstain from sexual intercourse until all of their sex partners are treated.

Follow-Up

Test-of-cure (i.e., repeat testing 3–4 weeks after completing therapy) is not advised for persons treated with the recommended or alternative regimens, unless therapeutic adherence is in question, symptoms persist, or reinfection is suspected. Moreover, the use of chlamydial NAAT testing at <3 weeks after completion of therapy is not recommended because false-positive results might occur due to the continued presence of nonviable organisms^{385,511}.

A high prevalence of *C. trachomatis* infection has been observed in women and men who were treated for chlamydial infection during the preceding several months^{108,470,512-514}. Most post-treatment infections result from reinfection caused by failure of sex partners to receive treatment or the initiation of sexual activity with a new infected partner rather than treatment failure. Repeat infections confer an elevated risk for PID and other complications in women. Men and women who have been treated for chlamydia should be retested approximately 3 months after treatment, regardless of whether they believe that their sex partners were treated^{108,470}. If retesting at 3 months is not possible, clinicians should retest whenever persons next present for medical care in the 1-12 months following initial treatment.

Persons who are diagnosed with chlamydia should be tested for other STDs, especially HIV, GC, and syphilis.

Management of Sex Partners

Sexual 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 defined for the identification of at-risk sex partners are based on limited data, the most recent sex partner should be evaluated and treated, if the time of the last sexual contact was >60 days before symptom onset or diagnosis.

Among heterosexual patients, if health department partner management strategies are impractical or not available (e.g., DIS) for persons with chlamydia and concerns exist that sex partners are unable to seek these evaluation and treatment services in a timely fashion, patient

delivery of antibiotic therapy to their partners can be considered as permitted by law (see Partner Services). Compared with standard patient referral of partners, this approach, patient delivered partner therapy, has been associated with a trend toward a decrease in rates of persistent or recurrent chlamydia⁹¹⁻⁹³. Patients or providers should provide written materials about chlamydia in general, the fact they have been exposed, the importance of treatment, and advice to seek care if allergies to the medications or for any symptoms suggestive of complications (e.g., testicular pain in men and pelvic or abdominal pain in women). Due to limited data, patient-delivered partner therapy is not routinely recommended for MSM with chlamydia because of a high risk for coexisting infections (especially undiagnosed HIV) in their partners and the efficacy of patient-delivered partner therapy has not been evaluated in MSM.

Partners should be instructed to abstain from sexual intercourse until they and their own sex partners have completed treatment. Abstinence should be continued until 7 days after a single-dose regimen or after completion of a multiple-dose regimen.

Special Considerations

Pregnancy

Doxycycline is contraindicated in the second and third trimesters of pregnancy. Human data suggest ofloxacin and levofloxacin present a low risk to the fetus during pregnancy, with a potential for toxicity during breastfeeding.³¹⁰ However, clinical experience and published studies suggest that azithromycin is safe and effective⁵¹⁵⁻⁵¹⁷. Due to concerns about chlamydia persistence following exposure to penicillin-class antibiotics that has been demonstrated in animal and in vitro studies, amoxicillin should be considered an alternative therapy for *C trachomatis* in pregnant women^{518,519}. Test of cure to document chlamydial eradication (preferably by NAAT) 3-4 weeks after completion of therapy with the regimens listed below is recommended for all pregnant women to ensure therapeutic cure, considering the severe sequelae that might occur in mothers and neonates if the infection persists. Detection of *C trachomatis* infection at repeat screening during the third semester is not uncommon in adolescent and young adult women, including in those without *C trachomatis* detected at the time of initial prenatal screening^{520,521}. Women aged <25 years and those at increased risk for chlamydia (e.g., women who have a new or more than one sex partner or who report their partner has a concurrent partner) therefore should be rescreened during the third trimester to prevent maternal postnatal complications and chlamydial infection in the infant¹⁰⁷. Pregnant women diagnosed with a chlamydial infection during the first trimester should not only receive a test to document chlamydial eradication, but be retested 3 months after treatment.

Recommended Regimens

Azithromycin 1 g orally in a single dose

Alternative Regimens

Amoxicillin 500 mg orally three times a day for 7 days

OR

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

OR

Erythromycin base 250 mg orally four times a day for 14 days

OR

Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days

OR

Erythromycin ethylsuccinate 400 mg orally four times a day for 14 days

The frequent gastrointestinal side effects associated with erythromycin can result in nonadherence with the alternative regimens. The lower dose 14-day erythromycin regimens can be considered if gastrointestinal tolerance is a concern. Erythromycin estolate is contraindicated during pregnancy because of drug-related hepatotoxicity.

HIV Infection

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

Chlamydial Infections 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. Although the efficacy of neonatal ocular prophylaxis with erythromycin ophthalmic ointments to prevent chlamydia ophthalmia is not clear, ocular prophylaxis with these agents does prevent gonococcal ophthalmia and therefore should be administered (see Ophthalmia Neonatorum caused by *N. gonorrhoeae*).

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 in 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 because of the institution of widespread prenatal screening and treatment of pregnant women.

Ophthalmia Neonatorum Caused by *C. trachomatis*

A chlamydial etiology should be considered for all infants aged ≤ 30 days who have conjunctivitis, especially if the mother has a history of chlamydia infection.

Diagnostic Considerations

Sensitive and specific methods used to diagnose chlamydial ophthalmia in the neonate include both tissue culture and nonculture tests (e.g., direct fluorescence antibody [DFA] tests, EIA, and NAAT). DFA is the only nonculture FDA-cleared test for the detection of chlamydia from conjunctival swabs; NAATs are not FDA-cleared for the detection of chlamydia from conjunctival swabs, and clinical laboratories must verify the procedure according to CLIA regulations. Specimens for culture isolation and nonculture tests should be obtained from the everted eyelid using a dacron-tipped swab or the swab specified by the manufacturer's test kit, and (for culture and DFA) they 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*).

Recommended Regimen

Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days*

OR

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

* An association between oral erythromycin and infantile hypertrophic pyloric stenosis (IHPS) has been reported in infants aged < 6 weeks who were treated with this drug. Infants treated with erythromycin should be followed for signs and symptoms of IHPS.

Data on the use of azithromycin for the treatment of neonatal chlamydia infection is limited but a short course of therapy, might be effective⁵²². Topical antibiotic therapy alone is inadequate for treatment for ophthalmia neonatorum caused by chlamydia and is unnecessary when systemic treatment is administered.

Follow-Up

The efficacy of erythromycin treatment for ophthalmia neonatorum is approximately 80% and a second course of therapy might be required⁵²³. There is limited data on the efficacy of azithromycin for ophthalmia neonatorum. Therefore, follow-up of infants is recommended to determine whether 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

The 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 in Adolescents and Adults).

Infant Pneumonia Caused by *C. trachomatis*

Characteristic signs of chlamydial pneumonia in infants include 1) a repetitive staccato cough with tachypnea and 2) hyperinflation and bilateral diffuse infiltrates on a chest radiograph. In addition, peripheral eosinophilia (≥ 400 cells/mm³) occurs frequently. Wheezing is rare, and infants are typically afebrile. Because clinical presentations differ, initial diagnostic tests and treatment should include *C. trachomatis* for all infants aged 1–3 months who are suspected of having pneumonia (especially those whose mothers have a history of chlamydial infection).

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, NAAT) can be used, although DFA of nasopharyngeal specimens have a lower sensitivity and specificity than culture. DFA is the only nonculture FDA-cleared test for the detection of *C. trachomatis* from nasopharyngeal specimens; NAATs are not FDA-cleared for the detection of chlamydia from nasopharyngeal specimens, and clinical laboratories must verify the procedure according to CLIA specifications. Tracheal aspirates and lung biopsy specimens, if collected, should be tested for *C. trachomatis*.

Because test results for chlamydia often are not available in a timely manner, the decision to provide treatment for *C. trachomatis* pneumonia must frequently be based on clinical and radiologic findings. The results of tests for chlamydial infection assist in the management of an infant's illness.

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| <h3><i>Recommended Regimen</i></h3> |
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Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days

OR

Azithromycin 20 mg/kg/day orally, 1 dose daily for three days

Follow-Up

The effectiveness of erythromycin in treating pneumonia caused by *C. trachomatis* is approximately 80%, as such a second course of therapy might be required⁵²⁴. Data on the effectiveness of azithromycin in treating chlamydial pneumonia is limited. Follow-up of infants is recommended to determine whether the pneumonia has resolved, although some infants with chlamydial pneumonia continue to have abnormal pulmonary function tests later in childhood.

Management of Mothers and Their Sex Partners

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

Neonates Born to Mothers Who Have Chlamydial Infection

Neonates born to mothers who have untreated chlamydia are at high risk for infection; however, prophylactic antibiotic treatment is not indicated, and the efficacy of such treatment is unknown. Infants should be monitored to ensure appropriate treatment if symptoms develop.

Chlamydial Infections Among Children

Sexual abuse must be considered a cause of chlamydial infection in preadolescent children, although perinatally transmitted *C. trachomatis* infection of the nasopharynx, urogenital tract, and rectum might persist for >1 year (see Sexual Assault or Abuse of Children).

Diagnostic Considerations

NAATs can be used for vaginal and urine specimens from girls (see Sexual Assault or Abuse of Children), however there are insufficient data to recommend the use of NAATs for use in boys and extragenital sites (rectum and pharynx) in boys and girls³⁸⁴. Culture is still the preferred method for detection of *C. trachomatis* at those sites. Other nonculture tests such as the DFA are not recommended because of specificity concerns.

| |
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| <i>Recommended Regimen for Children Who</i> |
|--|

Weigh <45 kg

Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days

Data is limited on the effectiveness and optimal dose of erythromycin or azithromycin for the treatment of chlamydial infection in children who weigh less than 45 kg.

Recommended Regimen for Children Who Weigh ≥ 45 kg but Who Are Aged <8 Years

Azithromycin 1 g orally in a single dose

Recommended Regimens for Children Aged ≥ 8 years

Azithromycin 1 g orally in a single dose

OR

Doxycycline 100 mg orally twice a day for 7 days

Other Management Considerations

See Sexual Assault or Abuse of Children.

Follow-Up

Follow-up test of cure cultures approximately two weeks after treatment are necessary to ensure that treatment has been effective.

Gonococcal Infections

Gonococcal Infections in Adolescents and Adults

In the United States, an estimated 820,000 new *N. gonorrhoeae* infections occur each year⁵²⁵. Gonorrhea is the second most commonly reported communicable disease¹¹⁹. Urethral infections caused by *N. gonorrhoeae* among men produce symptoms 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.

The prevalence of gonorrhea varies widely among communities and populations; health-care providers should consider local gonorrhea epidemiology when making screening decisions. For sexually active women, including those who are pregnant, USPSTF recommends that clinicians provide gonorrhea screening only to those at increased risk for infection.¹⁰⁹ Women aged <25 years are at highest risk of infection. Other women at increased risk of infection include women with new or multiple sex partners, previous gonorrhea infection, and other STDs, those who engage in commercial sex work and illicit drug use; women in certain demographic groups; and those living in communities with a high prevalence of disease. Subgroups of MSM are at high risk for gonorrhea infection and should be screened at sites of exposure (see MSM). USPSTF does not recommend screening for gonorrhea in men and women who are at low risk for infection¹⁰⁹.

Diagnostic Considerations

Specific microbiologic diagnosis of infection with *N. gonorrhoeae* should be performed in all persons at risk or suspected to have gonorrhea. Culture and NAATs are available for the detection of genitourinary infection with *N. gonorrhoeae*³⁸⁵. Culture requires female endocervical or male urethral swab specimens. NAATs allow testing of the widest variety of FDA-cleared specimen types including endocervical swabs, vaginal swabs, urethral swabs (men), and urine (from both men and women). However, product inserts for each NAAT manufacturer must be carefully examined, because collection methods and specimen types vary by NAAT test. NAAT tests are not FDA-cleared for with rectal, oropharyngeal, and conjunctival specimens; however, some laboratories have met CLIA requirements and established performance specifications for using NAAT with rectal and oropharyngeal swab specimens, thereby allowing results to be used for clinical management. Certain NAATs that have been demonstrated to detect commensal *Neisseria* species in urogenital specimens might have comparable low specificity when testing oropharyngeal specimens for *N. gonorrhoeae*⁵²⁶. The sensitivity of NAATs for the detection of *N. gonorrhoeae* in urogenital and nongenital anatomic sites is superior to culture but varies by NAAT type^{385,496-499}.

In cases of suspected or documented treatment failure, clinicians should perform both culture and antimicrobial susceptibility testing because nonculture tests cannot provide antimicrobial susceptibility results. *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 incubated in an increased CO₂ environment as soon as possible⁵²⁶. Several nonnutritive swab transport systems are available, and transport systems might maintain gonococcal viability for up to 48 hours in ambient temperatures⁵²⁷⁻⁵²⁹.

Because of its high specificity (>99%) and sensitivity (>95%), a Gram stain of urethral secretions that demonstrates polymorphonuclear leukocytes with intra-cellular Gram-negative diplococci can be considered diagnostic for infection with *N. gonorrhoeae* in symptomatic men. However, because of lower sensitivity, a negative Gram stain should not be considered sufficient for ruling out infection in asymptomatic men. In addition, Gram stain of endocervical specimens, pharyngeal, or rectal specimens also are not sufficient to detect infection, and therefore are not recommended.

All persons diagnosed with gonorrhea should be tested for other STDs, including chlamydia, syphilis, and HIV.

Dual Therapy for Gonococcal Infections

Based on experience with other microbes that have developed antimicrobial resistance rapidly, a theoretical basis exists for combination therapy using two antimicrobials with different mechanisms of action, such as a cephalosporin plus azithromycin to improve treatment efficacy and potentially slow the emergence and spread of resistance to cephalosporins. The use of azithromycin as the second antimicrobial is preferred to doxycycline because of the convenience and compliance advantages of single-dose therapy and the substantially higher prevalence of gonococcal resistance to tetracycline than to azithromycin among Gonococcal Isolate Surveillance Project (GISP) isolates, particularly in strains with elevated cefixime MICs^{119 530}. In addition, clinical trials have demonstrated the efficacy of azithromycin 1 gram for the treatment of uncomplicated urogenital GC^{531,532}.

Limited data suggest that dual treatment with azithromycin might enhance treatment efficacy for pharyngeal infection when using oral cephalosporins^{533,534}. In addition, persons infected with *N. gonorrhoeae* frequently are coinfecting with *C. trachomatis*; this finding has led to the longstanding recommendation that persons treated for gonococcal infection also be treated routinely with a regimen that is effective against uncomplicated genital *C. trachomatis* infection, further supporting the routine use of dual therapy that includes azithromycin⁵³⁵.

Antimicrobial-Resistant *N. gonorrhoeae*

Gonorrhea treatment is complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobial therapies⁵³⁶. In 2007, emergence of fluoroquinolone-resistant *N. gonorrhoeae* in the United States prompted CDC to no longer recommend fluoroquinolones for treatment of gonorrhea, leaving cephalosporins as the only remaining class of antimicrobials available for treatment of gonorrhea in the United States⁵³⁷. 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 treatment⁵³⁸. However, from 2006 to 2011, the minimum concentrations of cefixime needed to inhibit the growth in vitro of *N. gonorrhoeae*

strains circulating in the United States and many other countries increased, suggesting that the effectiveness of cefixime might be waning^{119,530}. In addition, recent reports from Europe, South Africa, and Canada have described patients with uncomplicated urogenital gonorrhea infection not cured by treatment with cefixime 400 mg orally^{539, 540, 541, 542, 543, 544}. As a result, CDC no longer recommends the routine use of cefixime as a first-line regimen for treatment of gonorrhea in the United States⁵³⁰. In addition, gonococcal strains in the United States with elevated MICs to cefixime are also likely to be resistant to tetracyclines but susceptible to azithromycin⁵³⁰. Consequently, only one regimen, dual treatment with ceftriaxone and azithromycin, is recommended for treatment of gonorrhea in the United States. The CDC website (<http://www.cdc.gov/std/gisp>) and state health departments can provide the most current information on 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 $\mu\text{g/mL}$ are considered to have decreased susceptibility⁵⁴⁵. In the United States, the proportion of isolates in CDC's Gonococcal Isolate Surveillance Project (GISP) demonstrating decreased susceptibility to ceftriaxone or cefixime has remained low; one (0.02%) isolate with decreased susceptibility to ceftriaxone (MIC = 0.5 $\mu\text{g/mL}$), and three (0.05%) isolates with decreased susceptibility to cefixime (two with MICs of 0.5 $\mu\text{g/mL}$ and one with MIC of 1.0 $\mu\text{g/mL}$) were identified in 2012¹¹⁹. Because increasing MICs may predict the emergence of resistance, lower cephalosporin MIC breakpoints were established by GISP for surveillance purposes to provide greater sensitivity in detecting declining gonococcal susceptibility than breakpoints defined by CLSI. The percentage of isolates with cefixime MICs ≥ 0.25 $\mu\text{g/mL}$ increased from 0.1% in 2006 to 1.4% in 2011^{119,530}, and declined to 1.0% in 2012¹¹⁹. The percentage of isolates with ceftriaxone MICs ≥ 0.125 $\mu\text{g/mL}$ increased from <0.1% in 2006 to 0.4% in 2011, and decreased slightly to 0.3% in 2012.

Globally, treatment failures with cefixime or other oral cephalosporins have been reported in Asia^{546 547 548 549}, Europe^{542 541 540 539,550}, South Africa⁵⁴³ and Canada^{551 544}. Ceftriaxone treatment failures for pharyngeal infections have been reported in Australia^{552 553}, Japan⁵⁵⁴, and Europe^{555,556}. Isolates with high-level cefixime and ceftriaxone MICs (cefixime MICs 1.5–8 $\mu\text{g/mL}$, ceftriaxone MICs 1.5–4 $\mu\text{g/mL}$) have been identified in Japan⁵⁵⁴, France⁵⁵⁰, and Spain^{557,558}.

Decreased susceptibility of *N. gonorrhoeae* to cephalosporins and other antimicrobials is expected to continue to spread; therefore, state and local surveillance for antimicrobial resistance is crucial for guiding local therapy recommendations⁵³⁶. GISP, which samples approximately 3% of all U.S. men who have gonococcal infections, is a mainstay of surveillance. However, surveillance by clinicians also is critical. Clinicians who diagnose *N. gonorrhoeae* infection in a patient with suspected cephalosporin treatment failure should perform culture and antimicrobial susceptibility testing (AST) of relevant clinical specimens, consult an infectious diseases specialist for guidance in clinical management, and report the case to CDC through state and local public health authorities. Isolates should be saved and sent to CDC through local and state public health laboratory mechanisms. Health departments should prioritize partner notification and culture evaluation of partner of persons with *N. gonorrhoeae* infection thought to be associated with cephalosporin treatment failure or associated with persons whose isolates

demonstrate decreased susceptibility to cephalosporin.

Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum

| <i>Recommended Regimen</i> |
|---|
| Ceftriaxone 250 mg in a single intramuscular dose |
| PLUS |
| Azithromycin 1g orally in a single dose |

As dual therapy, ceftriaxone and azithromycin should be administered together on the same day, preferably simultaneously and under direct observation. Ceftriaxone in a single injection of 250 mg provides sustained, high bactericidal levels in the blood. Extensive clinical experience indicates that ceftriaxone is safe and effective for the treatment of uncomplicated gonorrhea at all anatomic sites, curing 99.2% of uncomplicated urogenital and anorectal and 98.9% of pharyngeal infections in older clinical trials^{559,560}. There are no clinical data to support use of doses of ceftriaxone >250 mg.

Single-dose injectible cephalosporin regimens (other than ceftriaxone 250 mg IM) that are safe and generally effective against uncomplicated urogenital and anorectal gonococcal infections include ceftizoxime (500 mg IM), cefoxitin (2 g IM with probenecid 1 g orally), and cefotaxime (500 mg IM). None of the injectible cephalosporins offer any advantage over ceftriaxone for urogenital infection, and efficacy for pharyngeal infection is less certain^{559,560}.

| Alternative Regimens |
|--|
| If ceftriaxone is not available: |
| Cefixime 400 mg in a single oral dose |
| PLUS |
| Azithromycin 1 g orally in a single dose |

Several other antimicrobials are active against *N. gonorrhoeae*, but none have substantial advantages over the recommended regimen, and they should not be used if pharyngeal infection is suspected. A 400-mg oral dose of cefixime should be considered as an alternative cephalosporin regimen because it does not provide as high, nor as sustained, bactericidal blood levels as a 250-mg dose of ceftriaxone, and demonstrates limited efficacy for treatment of pharyngeal gonorrhea^{559,560}. The increase in the prevalence of US GISP isolates with elevated cefixime MICs might indicate early stages of development of clinically significant gonococcal resistance to cephalosporins. CDC anticipates that rising cefixime MICs soon will result in declining effectiveness of cefixime for the treatment of urogenital gonorrhea. Furthermore, as cefixime becomes less effective, continued use of cefixime might hasten the development of resistance to ceftriaxone, a safe, well-tolerated, injectable cephalosporin and the last

antimicrobial that is known to be highly effective in a single dose for treatment of gonorrhea at all anatomic sites of infection. Other oral cephalosporins such as cefpodoxime or cefuroxime are not recommended because of inferior efficacy and less favorable pharmacodynamics.

Because of the high prevalence of tetracycline resistance among GISP isolates, particularly those with elevated cefixime MICs, the use of azithromycin as the second antimicrobial is preferred. However, when there is an allergy to azithromycin, doxycycline (100 mg orally twice a day for 7 days) can be used as an alternative second antimicrobial in place of azithromycin when used in combination with cefixime.

A recent clinical trial demonstrated that dual treatment with single doses of oral gemifloxacin 320 mg plus oral azithromycin 2 g, or dual treatment with single doses of intramuscular gentamicin 240 mg plus oral azithromycin 2 g, are effective regimens for uncomplicated urogenital gonorrhea, with cure rates of 99.5% (lower one-sided 95% CI bound = 97.6%) and 100% (lower one-sided 95% CI bound = 98.5%), respectively⁵⁶¹. This trial was not powered to provide reliable estimates of the efficacy of these regimens for treatment of rectal or pharyngeal infection, but both regimens cured the few extra-genital infections among study participants. Either of these regimens may be considered as alternative treatment options in the setting of a cephalosporin allergy. However, gastrointestinal adverse events may limit their use: 7.7% of patients treated with gemifloxacin plus azithromycin and 3.3% of patients treated with gentamicin plus azithromycin vomited within 1 hour and required retreatment with a ceftriaxone and azithromycin.

Monotherapy with azithromycin 2 g orally as a single dose has been demonstrated to be effective against uncomplicated urogenital gonorrhea (99.2% efficacy; 95% CI = 97.3%–99.9%)⁵⁶⁰. However, monotherapy is no longer recommended because of, concerns over the ease with which *N. gonorrhoeae* can develop resistance to macrolides and because several studies have documented azithromycin treatment failures^{562 541,563-565}. *N. gonorrhoeae* in the United States is not adequately susceptible to penicillins, tetracyclines, and older macrolides (e.g., erythromycin) for these antimicrobials to be recommended.

Uncomplicated Gonococcal Infections of the Pharynx

Most gonococcal infections of the pharynx are asymptomatic and can be relatively common in some populations^{496,497,566,567}. Gonococcal infections of the pharynx are more difficult to eradicate than infections at urogenital and anorectal sites⁵⁵¹. Few antimicrobial regimens, including those involving oral cephalosporins, can reliably cure >90% of gonococcal pharyngeal infections^{559,560}. Providers should ask their patients with urogenital or rectal gonococcal about oral sexual exposure; if reported, patients should be treated with a regimen with acceptable efficacy against pharyngeal gonorrhea infection.

| |
|-----------------------------------|
| <i>Recommended Regimen</i> |
|-----------------------------------|

Ceftriaxone 250 mg in a single intramuscular dose

PLUS

Azithromycin 1 g orally in a single dose

Follow-Up

Persons diagnosed with uncomplicated urogenital or rectal gonorrhea who are treated with any of the recommended or alternative regimens do not need a test-of-cure. However, any person with pharyngeal gonorrhea who is treated with an alternative regimen should return 14 days after treatment for a test-of cure, using either culture or NAAT. If the NAAT is positive, every effort should be made to perform a confirmatory culture. All positive cultures for test-of cure should undergo antimicrobial susceptibility testing.

Persons with symptoms that persist after treatment should be evaluated by culture for *N. gonorrhoeae* (with or without simultaneous NAAT), and any gonococci isolated should be tested for antimicrobial susceptibility. Persistent urethritis, cervicitis, or proctitis also might be caused by other organisms (see urethritis, cervicitis, or proctitis).

A high prevalence of *N. gonorrhoeae* infection has been observed among men and women who were treated for gonorrhea in the preceding several months^{85,108,470,568}. Most 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, rather than treatment failure, indicating a need for improved patient education and treatment of sex partners. Providers should perform repeat testing at 3 months after treatment in recently infected women and men and conduct partner services at the time of treatment, regardless of whether their sex partners were treated. If retesting is unlikely because of unpredictable follow-up, providers should retest whenever they next seek medical care within 1 to 12 months following treatment.

Management of Sex Partners

Sex partners should be referred for evaluation, testing, and presumptive dual treatment if they have had sexual contact with a partner within 60 days before the patient's onset of symptoms or gonorrhea diagnosis. If the last potential sexual exposure was >60 days before onset of symptoms or diagnosis, the most recent sex partner should be treated. Partners should be instructed to abstain from sexual intercourse for seven days.

For heterosexual men and women with gonorrhea, if a provider cannot assure that the partner of an infected person will be promptly linked to clinical evaluation and treatment, then expedited partner therapy (EPT) with cefixime 400 mg and azithromycin 1 g, to be delivered to the partner by the patient, a disease investigation specialist, or through a collaborating pharmacy, should be considered (see Partner Services). Use of this approach^{91,93} should always be accompanied by efforts to educate partners (e.g., written materials that accompany the drugs) about symptoms and to encourage partners to seek clinical evaluation. For male patients

informing female partners, educational materials should include information about the importance of seeking medical evaluation for PID (especially if symptomatic). Possible undertreatment of PID in female partners and missed opportunities to diagnose other STDs are of concern and have not been evaluated for patient-delivered therapy in comparison with partner referral. This approach should not be considered a routine partner management strategy in MSM because of the high risk for coexisting undiagnosed STDs or HIV infection, and there is no data on the efficacy of patient delivered partner therapy in this population.

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Allergic reactions to first generation cephalosporins occur in approximately <2.5% of persons with a history of penicillin allergy and are uncommon with third-generation cephalosporins, such as ceftriaxone or cefixime^{418,420,454}. In those persons with a history of an IgE mediated penicillin allergy (anaphylaxis, Stevens Johnson syndrome, or toxic epidermal necrolysis), the use of ceftriaxone or cefixime is contraindicated^{418,421}.

Data are limited regarding alternative regimens for treating gonorrhea among persons who have either a cephalosporin or IgE mediated penicillin allergy. Potential therapeutic options are dual treatment with single doses of oral gemifloxacin 320 mg plus oral azithromycin 2 g or dual treatment with single doses of intramuscular gentamicin 240 mg plus oral azithromycin 2 g⁵⁶¹. Providers treating persons with cephalosporin or IgE mediated penicillin allergy should consult an infectious diseases specialist.

Pregnancy

Pregnant women infected with *N. gonorrhoeae* should be treated with dual therapy with ceftriaxone 250 mg in a single intramuscular dose and azithromycin 1 g orally as a single dose. When cephalosporin allergy or other considerations preclude treatment with this regimen, consultation with an infectious disease specialist is recommended.

HIV Infection

Persons who have gonorrhea and HIV infection should receive the same treatment regimen as those who are HIV negative.

Suspected Cephalosporin Treatment Failure or Resistance

Cephalosporin treatment failure is the persistence of *N. gonorrhoeae* infection despite appropriate cephalosporin treatment, and could indicate infection with cephalosporin resistant gonorrhea. Treatment failure due to cephalosporin resistant gonorrhea should be considered in 1) persons whose symptoms do not resolve within 3-5 days after appropriate treatment and report no sexual contact during the post treatment follow-up period, 2) persons with a positive test of cure (positive culture ≥ 72 hours or positive nucleic acid amplification test ≥ 7 days after appropriate treatment) when no sexual contact is reported during the post-treatment follow-up period, 3) persons with a positive *N. gonorrhoeae* culture within 30-60 days (but ≥ 72 hours) after treatment for

gonorrhea who are found to have elevated cephalosporin MICs on antimicrobial susceptibility testing, regardless of whether sexual contact is reported during the post-treatment follow-up period⁵⁶⁹.

Suspected treatment failure has been reported among persons receiving oral and injectable cephalosporins^{541 546-549,553 551 542 540 554 550,556 570 543 552 544}. Because the majority of suspected treatment failures in the United States are likely to be re-infections rather than actual treatment failures, retreatment with the recommended regimen should be given in most cases. However, because of the threat of resistant gonorrhea in the United States, prior to retreatment in cases where reinfection is unlikely and treatment failure is suspected, relevant clinical specimens should be obtained for culture, preferably with simultaneous NAAT. Antimicrobial susceptibility testing should be performed if *N. gonorrhoeae* is isolated. Phenotypic antimicrobial susceptibility testing should be performed using disk diffusion, Etest (BioMérieux, Durham, NC), or agar dilution. Data are limited on the use of DNA amplification and sequencing for detection of genetic mutations associated with gonococcal antimicrobial resistance. The laboratory should retain the isolate for possible further testing and sent to CDC for antimicrobial susceptibility testing by agar dilution and stored at the local laboratory and/or CDC in case further testing is needed. Testing and/or storage of specimens or isolates at CDC should be facilitated by the state or local health department according to local public health protocol. Instructions for shipping isolates to CDC can be found at www.cdc.gov/std/Gonorrhea/arg/specimen_shipping_instructions_1-29-08.pdf.

For persons with suspected treatment failure, the treating clinician should consult an infectious disease specialist, an STD/HIV Prevention Training Center clinical expert (<http://www.nnptc.org>), the local or state health department STD program, or CDC (telephone: 404-639-8659) for advice on obtaining cultures, antimicrobial susceptibility testing, and treatment. Suspected treatment failure should be reported to CDC through the local or state health department within 24 hours of diagnosis.

Persons with suspected treatment failure after treatment with alternative regimens should be treated with ceftriaxone 250 mg as a single intramuscular dose and azithromycin 2 gram orally as a single dose. Dual treatment with single doses of oral gemifloxacin 320 mg plus oral azithromycin 2 g or dual treatment with single doses of intramuscular gentamicin 240 mg plus oral azithromycin 2 g may be considered especially if isolates are identified with elevated cephalosporin MICs. A test-of-cure at relevant clinical sites should be obtained 7–14 days after retreatment; culture is the recommended test, preferably with simultaneous NAATs, and antimicrobial susceptibility testing of *N. gonorrhoeae* if isolated. Clinicians should ensure that the patient's sex partners from the preceding 60 days are evaluated promptly with culture and presumptively treated using the same regimen as was used for the patient.

Gonococcal Conjunctivitis

In the only published study of the treatment of gonococcal conjunctivitis among adults, all 12 study participants responded to a single 1-g IM injection of ceftriaxone⁵⁷¹. Because gonococcal conjunctivitis is uncommon, and data on treatment of gonococcal conjunctivitis in adults is limited, consultation with an infectious disease specialist should be considered.

| <i>Recommended Regimen</i> |
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| Ceftriaxone 1 g IM in a single dose |
| PLUS |
| Azithromycin 1 g orally in a single dose |

Consider lavage of the infected eye with saline solution once.

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

Disseminated gonococcal infection (DGI) frequently results in petechial or pustular acral skin lesions, asymmetrical polyarthralgia, tenosynovitis, or oligoarticular septic arthritis⁵⁷². The infection is complicated occasionally by perihepatitis and rarely by endocarditis or meningitis. Some strains of *N. gonorrhoeae* that cause DGI can cause minimal genital inflammation. If DGI is suspected, NAAT or culture specimens from urogenital and extragenital sites, as applicable, should be collected and processed in addition to culture specimens from disseminated sites of infections (e.g.; skin, synovial, blood and CNS). All *N. gonorrhoeae* isolates should be tested for antimicrobial susceptibility.

Hospitalization and consultation with an infectious disease specialist are recommended for initial therapy, especially for patients who might not comply with treatment, for those in whom diagnosis is uncertain, and for those who 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

| <i>Recommended Regimen</i> |
|--|
| Ceftriaxone 1 g IM or IV every 24 hours |
| PLUS |
| Azithromycin 1 g orally in a single dose |
| <i>Alternative Regimens</i> |

Cefotaxime 1 g IV every 8 hours
 or ceftizoxime 1 g IV every 8 hours
 PLUS
 Azithromycin 1 g orally in a single dose

Treatment of Gonococcal Meningitis and Endocarditis

Recommended Regimen
 Ceftriaxone 1–2 g IV every 12–24 hours
 PLUS
 Azithromycin 1 g orally in a single dose

No recent studies have been published on the treatment of DGI. The duration of treatment of DGI has not been systematically studied, and treatment of DGI should be undertaken in consultation with an infectious disease specialist. Treatment for DGI should be guided by the results of antimicrobial susceptibility testing. Pending antimicrobial susceptibility results, treatment with one of the recommended regimens should be based on the clinical presentation. When treating for the arthritis-dermatitis syndrome, the provider can switch to another oral agent guided by antimicrobial susceptibility testing 24–28 hours after substantial clinical improvement for a total course of at least seven days. Therapy for meningitis should be continued with recommended parenteral therapy for 10–14 days. Parenteral antimicrobial therapy for endocarditis should be continued for at least 4 weeks.

Management of Sex Partners

Owing to the unique properties of many strains of *N. gonorrhoeae* prone to cause DGI, gonococcal infection frequently is asymptomatic in sex partners of persons who have DGI. Providers should instruct patients to refer their sex partners in the past 60 days for evaluation, testing, and presumptive treatment (see Gonococcal Infection, Management of Sex Partners).

Gonococcal Infections Among Neonates

Prenatal screening and treatment of pregnant women is the best method for preventing GC 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. The prevalence of infection among infants depends on the prevalence of infection among pregnant women, whether pregnant women are screened and treated for gonorrhea, and whether newborns receive ophthalmia prophylaxis. The most severe manifestations of *N. gonorrhoeae* infection in

newborns are ophthalmia neonatorum and sepsis, which can include arthritis and meningitis. Less severe manifestations include rhinitis, vaginitis, urethritis, and infection at sites of fetal monitoring.

Ophthalmia Neonatorum Prophylaxis

To prevent gonococcal ophthalmia neonatorum, a prophylactic agent should be instilled into both eyes of all newborn infants this procedure is required by law in most states. Ocular prophylaxis is warranted because it can prevent sight-threatening gonococcal ophthalmia and because it is safe, easy to administer, and inexpensive. The recommended prophylactic regimen prevents gonococcal ophthalmia, however, its efficacy for prevention of chlamydial ophthalmia is less clear, and it does not eliminate nasopharyngeal colonization by *C. trachomatis*. The diagnosis and treatment of gonococcal and chlamydial infections in pregnant women is the best method for preventing neonatal gonococcal and chlamydial disease. Not all women, however, receive prenatal care, and therefore go untreated.

| Recommended Regimen |
|---|
| Erythromycin (0.5%) ophthalmic ointment in each eye in a single application |

This preparation should be instilled into both eyes of every neonate as soon as possible after delivery regardless of whether they are delivered vaginally or by cesarean section. Ideally, ointment should be applied 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 infants receive prophylaxis.

Erythromycin is the only antibiotic ointment recommended for use in neonates. Silver nitrate and tetracycline ophthalmic ointment are no longer manufactured in the United States, bacitracin is not effective and povidone iodine has not been studied adequately^{573,574}. Gentamicin ophthalmic ointment has been associated with severe ocular reactions in neonates and should not be used for ocular prophylaxis^{575,576}. If erythromycin ointment is not available, infants at risk for exposure to *N. gonorrhoeae* (especially those born to a mother with untreated gonococcal infection or who has received no prenatal care) can be administered ceftriaxone 25-50 mg/kg IV or IM, not to exceed 125 mg in a single dose⁵⁷⁷.

Ophthalmia Neonatorum Caused by *N. gonorrhoeae*

Although *N. gonorrhoeae* causes ophthalmia neonatorum relatively infrequently in the United States, identifying and treating this infection is especially important because ophthalmia neonatorum can result in perforation of the globe of the eye and blindness.

Diagnostic Considerations

Infants at increased risk for gonococcal ophthalmia are those whose mothers have had no prenatal care or whose mothers have a history of STDs or substance abuse. 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 susceptibility testing for *N. gonorrhoeae* are performed. Presumptive treatment for *N. gonorrhoeae* might be indicated for newborns who are at increased risk for gonococcal ophthalmia and who have increased WBCs (but not intracellular gram negative diplococci) in a Gram-stained smear of conjunctival exudate. Nongonococcal causes of neonatal ophthalmia include *Moraxella catarrhalis* and other *Neisseria* species, organisms that are indistinguishable from *N. gonorrhoeae* on Gram-stained smear but can be differentiated in the microbiology laboratory.

| Recommended Regimen |
|---|
| Ceftriaxone 25–50 mg/kg IV or IM in a single dose, not to exceed 125 mg |

One dose of ceftriaxone is adequate therapy for gonococcal conjunctivitis. Ceftriaxone should be administered cautiously to hyperbilirubinemic infants, especially those born prematurely. There are no data on the use of dual therapy for the treatment of gonococcal ophthalmia. Topical antibiotic therapy alone is inadequate and is unnecessary if systemic treatment is administered.

Other Management Considerations

Appropriate chlamydial testing should be done simultaneously from the inverted eyelid specimen (see Ophthalmia Neonatorum Caused by *C. trachomatis*). Infants who have gonococcal ophthalmia should be evaluated for signs of disseminated infection (e.g., sepsis, arthritis, meningitis).

Follow-Up

Infants who have gonococcal ophthalmia should be managed in consultation with an infectious diseases specialist.

Management of Mothers and Their Sex Partners

The mothers of infants who have ophthalmia neonatorum caused by gonococcal and their sex partners should be evaluated, tested and presumptively treated for gonorrhea (see Gonococcal Infections in Adolescents and Adults).

DGI and Gonococcal Scalp Abscesses in Neonates

DGI may 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. Detection of gonococcal infection in neonates who have sepsis, arthritis, meningitis, or scalp abscesses requires cultures of blood, CSF, and joint aspirate. Specimens obtained from the conjunctiva, vagina, oropharynx, and rectum are useful for identifying the primary site(s) of infection. Antimicrobial testing of all isolates should be

performed. Positive Gram-stained smears of exudate, CSF, or joint aspirate provide a presumptive basis for initiating treatment for *N. gonorrhoeae*.

| Recommended Regimens |
|--|
| Ceftriaxone 25–50 mg/kg/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 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 hyperbilirubinemic infants, especially those born prematurely. There are no data on the use of dual therapy for the treatment of DGI or gonococcal scalp abscesses.

Other Management Considerations

Appropriate chlamydial testing should be done simultaneously in neonates with gonococcal infection (see *C. trachomatis*).

Follow-Up

Infants who have DGI should be managed in consultation with an infectious diseases specialist.

Management of Mothers and Their Sex Partners

The mothers of infants who have DGI of scalp abscesses cause by gonococcal and their sex partners should be evaluated, tested and presumptively treated for gonorrhea (see Gonococcal Infections in 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 and treated presumptively for gonorrhea as recommended below. Both mother and infant should be tested for chlamydial infection. Mothers who have gonorrhea and their sex partners should be evaluated, tested, and presumptively treated for gonorrhea (see Gonococcal Infections).

| Recommended Regimen in the Absence of Signs of Gonococcal Infection |
|--|
| Ceftriaxone 25–50 mg/kg IV or IM, not to exceed 125 mg, in a single dose |

There are no data on the use of dual therapy for the treatment of neonates born to mothers who have gonococcal infection.

Gonococcal Infections Among Children

Sexual abuse is the most frequent cause of gonococcal infection in preadolescent 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 is likely less common in preadolescents than adults. Among sexually abused children, anorectal and pharyngeal infections with *N. gonorrhoeae* are common and frequently asymptomatic.

Diagnostic Considerations

NAATs can be used for vaginal and urine specimens from girls (see Sexual Assault or Abuse of Children), however there are insufficient data to recommend the use of NAATs for use in boys and extragenital sites (rectum and pharynx) in boys and girls. Culture remains the preferred method for diagnosis for boys and extragenital sites (rectum and pharynx) in boys and girls⁵²⁶. Gram stains are inadequate for evaluating prepubertal children for gonorrhea and should not be used to diagnose or exclude gonorrhea. If evidence of disseminated gonococcal infection, gonorrhea culture and antimicrobial susceptibility testing should be obtained from relevant clinical sites (see DGI).

| |
|---|
| Recommended Regimen for Children Who Weigh ≤ 45 kg and Who Have Uncomplicated Gonococcal Vulvovaginitis, Cervicitis, Urethritis, Pharyngitis, or Proctitis |
|---|

| |
|--|
| Ceftriaxone 125 mg IM in a single dose |
|--|

| |
|--|
| Recommended Regimen for Children Who Weigh >45 kg and Who Have Uncomplicated Gonococcal Vulvovaginitis, Cervicitis, Urethritis, Pharyngitis, or Proctitis |
|--|

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|---|
| Treat with one of the regimens recommended for adults (see Gonococcal Infections) |
|---|

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|---|
| Recommended Regimen for Children Who Weigh \leq45 kg and Who Have Bacteremia or Arthritis |
|---|

| |
|--|
| Ceftriaxone 50 mg/kg (maximum dose: 1 g) IM or IV in a single dose daily for 7 days |
|--|

| |
|---|
| Recommended Regimen for Children Who Weigh $>$45 kg and Who Have Bacteremia or Arthritis |
|---|

| |
|--|
| Ceftriaxone 1 g IM or IV every 24 hours for seven days |
|--|

There are no data on the use of dual therapy for the treatment of children with gonococcal infection.

Follow-Up

Follow-up cultures are unnecessary.

Other Management Considerations

Only parenteral cephalosporins (i.e., ceftriaxone) are recommended for use in children; cefotaxime is approved for gonococcal ophthalmia only. All children found to have gonococcal infections should be tested for *C. trachomatis*, syphilis, and HIV. (For a discussion of concerns regarding sexual assault, see Sexual Assault or Abuse of Children).

Diseases Characterized by Vaginal Discharge

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

Obtaining a medical history alone has been shown to be insufficient for accurate diagnosis of vaginitis and can lead to the inappropriate administration of medication. Therefore, a careful history, examination, and laboratory testing to determine the etiology of vaginal complaints are warranted. Information on sexual behaviors and practices, gender of sex partners, menses, vaginal hygiene practices (such as douching), and self-treatment with medications should be elicited. The three diseases most frequently associated with vaginal discharge are BV (replacement of the vaginal flora by an overgrowth of anaerobic bacteria including *Prevotella sp.*, *Mobiluncus sp.*, *G. vaginalis*, *Ureaplasma*, *Mycoplasma*, and numerous fastidious or

uncultivated anaerobes), *T. vaginalis*, and candidiasis. Cervicitis can also cause an abnormal discharge. Although vulvovaginal candidiasis (VVC) is usually not transmitted sexually, it is included in this section because it is frequently diagnosed in women who have vaginal complaints or who are being evaluated for STDs.

Various diagnostic methods are available to identify the etiology of an abnormal vaginal discharge. Clinical laboratory testing can identify the cause of vaginitis in most 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 might be determined by pH, a potassium hydroxide (KOH) test, and microscopic examination of fresh samples of the discharge. The pH of the vaginal secretions can be determined by narrow-range pH paper; an elevated pH (i.e., ≥ 4.5) is common with BV or trichomoniasis. Because pH testing is not highly specific, discharge should be further examined microscopically by first diluting one sample in one to two 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). Cover slips are then placed on the slides, and they are examined under a microscope at low and high power.

The saline-solution specimen might show motile trichomonads, or clue cells (i.e., epithelial cells with borders obscured by small bacteria), which are characteristic of BV. The KOH specimen typically is used to identify hyphae or blastospores seen with candidiasis. However, the 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)⁴⁶⁵. The presence of WBCs without evidence of trichomonads or yeast may also suggest cervicitis (see Cervicitis).

In settings where pH paper, KOH, and microscopy are not available, alternative commercially available point-of-care tests or clinical laboratory testing can be used to diagnose vaginitis. The presence of objective signs of vulvar inflammation in the absence of vaginal pathogens after laboratory testing suggests the possibility of mechanical, chemical, allergic, or other noninfectious causes of vulvovaginal symptoms. In patients with persistent symptoms and no clear etiology, referral to a specialist may be helpful.

Bacterial Vaginosis

BV is a polymicrobial clinical syndrome resulting from replacement of the normal hydrogen peroxide producing *Lactobacillus* sp. in the vagina with high concentrations of anaerobic bacteria (e.g., *Prevotella* sp. and *Mobiluncus* sp.), *G. vaginalis*, *Ureaplasma*, *Mycoplasma*, and numerous fastidious or uncultivated anaerobes. Some women experience transient vaginal microbial changes, whereas others experience them for longer intervals of time. Among women presenting for care, BV is the most prevalent cause of vaginal discharge or malodor; however, in a nationally representative survey, most women with BV were asymptomatic¹⁸⁶.

BV is associated with having multiple male or female partners, a new sex partner, douching, lack of condom use, and lack of vaginal lactobacilli; women who have never been sexually active are rarely affected⁵⁷⁸. 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 not known. Nonetheless, women with BV are at increased risk for the acquisition of some STDs (e.g., HIV, *N. gonorrhoeae*, *C. trachomatis*, and HSV- 2), complications after gynecologic surgery, complications of pregnancy, and recurrence of BV⁵⁷⁹⁻⁵⁸². BV also increases the risk of HIV transmission to male sex partners⁵⁸³. Although BV-associated bacteria can be found in the male genitalia, treatment of male sex partners has not been beneficial in preventing the recurrence of BV⁵⁸⁴.

Diagnostic Considerations

BV can be diagnosed by the use of clinical criteria (i.e., Amsel's Diagnostic Criteria) (319) or Gram stain. A Gram stain (considered the gold standard laboratory method for diagnosing BV) is used to determine the relative concentration of lactobacilli (i.e., long Gram-positive rods), Gram-negative and Gram-variable rods and cocci (i.e., *G. vaginalis*, *Prevotella*, *Porphyromonas*, and peptostreptococci), and curved Gram-negative rods (i.e., *Mobiluncus*) characteristic of BV. Clinical criteria require three of the following symptoms or signs:

- homogeneous, thin, white discharge that smoothly coats the vaginal walls;
- presence of clue cells on microscopic examination;
- pH of vaginal fluid >4.5; or
- a fishy odor of vaginal discharge before or after addition of 10% KOH (i.e., the whiff test).

Detection of three of these criteria has been correlated with results by Gram stain⁵⁸⁵. Other tests, including a DNA probe-based test for high concentrations of *G. vaginalis* (Affirm VP III, Becton Dickinson, Sparks, Maryland), and the OSOM BV Blue test (Sekisui Diagnostics), which detects vaginal fluid sialidase activity, have acceptable performance characteristics compared with Gram stain. Although a prolineaminopeptidase card test is available for the detection of elevated pH and trimethylamine, it has low sensitivity and specificity and therefore is not recommended. PCR has been used in research settings for the detection of a variety of organisms associated with BV, but evaluation of its clinical utility is still underway. Detection of one organism or group of organisms might be predictive of BV by PCR^{586,587}. Additional validation is needed before these tests can be recommended to diagnose BV. Culture of *G. vaginalis* is not recommended as a diagnostic tool because it is not specific. Cervical Pap tests have no clinical utility for the diagnosis of BV because of their low sensitivity and specificity.

Treatment

Treatment is recommended for women with symptoms. The established benefits of therapy in nonpregnant women are to relieve vaginal symptoms and signs of infection. Other potential benefits to treatment include reduction in the risk for acquiring *C. trachomatis* or *N. gonorrhoeae*, HIV, and other viral STDs^{588 581,582}.

| Recommended Regimens |
|---|
| Metronidazole 500 mg orally twice a day for 7 days* |
| OR |
| Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days |
| OR |
| Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for 7 days† |
| * Consuming alcohol should be avoided during treatment and for 24 hours thereafter to reduce the possibility of a disulfiram-like reaction. |
| † 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 use condoms, consistently and correctly during the treatment regimen. Douching might increase the risk for relapse, and no data support the use of douching for treatment or relief of symptoms.

| Alternative Regimens |
|---|
| Tinidazole 2 g orally once daily for 2 days |
| OR |
| Tinidazole 1 g orally once daily for 5 days |
| OR |
| Clindamycin 300 mg orally twice daily for 7 days |
| OR |
| Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days |

Alternative regimens include several tinidazole regimens⁵⁸⁹ or clindamycin (oral or intravaginal)⁵⁹⁰. An additional regimen includes metronidazole (750-mg extended release tablets once daily for 7 days), however data on the performance of this alternative regimen is limited.

Several studies have evaluated the clinical and microbiologic efficacy of using intravaginal lactobacillus formulations to treat BV and restore normal flora.^{591,592, Antonio, 2009 #1027,593,594 595}

Overall, no studies support the addition of any available lactobacillus formulations or probiotic as an adjunctive or replacement therapy in women with BV. Further research efforts to determine the role of these regimens in BV treatment and prevention are ongoing.

Other Management Considerations

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

Follow-Up

Follow-up visits are unnecessary if symptoms resolve. Because persistent or recurrence of BV is common, women should be advised to return for evaluation if symptoms recur. Detection of certain BV-associated organisms have been associated with antimicrobial resistance and might determine risk for subsequent treatment failure⁵⁹⁶⁻⁶⁰¹. Limited data are available regarding optimal management strategies for women with persistent or recurrent BV. Using a different recommended treatment regimen might be an option in women who have a recurrence; however, re-treatment with the same recommended regimen is an acceptable approach for treating persistent or recurrent BV after the first occurrence⁶⁰². For women with multiple recurrences after completion of a recommended regimen, metronidazole gel twice weekly for 4-6 months has been shown to reduce recurrences, although this benefit might not persist when suppressive therapy is discontinued⁶⁰³. Limited data suggest that an oral nitroimidazole followed by intravaginal boric acid and suppressive metronidazole gel twice weekly for 4-6 months for those women in remission might be an option in women with recurrent BV⁶⁰⁴. Monthly oral metronidazole administered with fluconazole has also been evaluated as suppressive therapy which reduced the incidence of BV and promoted colonization with normal vaginal flora.⁶⁰⁵

Management of Sex Partners

The results of 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(s). Therefore, routine treatment of sex partners is not recommended.

Special Considerations

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. Although alcohol use is not a strict contraindication, patients may prefer to avoid consuming alcohol until 24 hours after completion of metronidazole or 72 hours after completion of tinidazole, to reduce the possibility of a disulfiram-like reaction.

Pregnancy

Treatment is recommended for all pregnant women with symptoms. Several trials have been undertaken to determine the efficacy of BV treatment among pregnant women. One trial involving a limited number of participants revealed that treatment with oral metronidazole 500 mg twice daily was equally effective as metronidazole gel, with cure rates of 70% using Amsel criteria to define cure⁶⁰⁶, and another demonstrated a cure rate of 85% using Gram stain criteria after 4 weeks with oral clindamycin⁶⁰⁷. Multiple studies and meta-analyses have not demonstrated an association between metronidazole use during pregnancy and teratogenic or mutagenic effects in newborns^{608,609}. Because oral therapy has not been shown to be superior to topical therapy for treating symptomatic BV in effecting cure or in preventing adverse outcomes of pregnancy, symptomatic pregnant women can be treated with either of the oral or vaginal regimens recommended for non-pregnant women. While older studies indicated a possible link between use of vaginal clindamycin during pregnancy and adverse outcomes, newer data support that this approach is safe in pregnant women⁶¹⁰.

Although adverse pregnancy outcomes, including premature rupture of membranes, preterm labor, preterm birth, intra-amniotic infection, and postpartum endometritis have been associated with symptomatic BV in some observational studies, the only established benefit of therapy for BV in pregnant women is the reduction of symptoms and signs of vaginal infection. A meta-analysis has concluded that no antibiotic regimen prevented preterm birth (early or late) in women with BV, but in one study, oral BV therapy did reduce the risk of late miscarriage and, in two studies, adverse outcomes in the neonate⁶¹¹.

Treatment of asymptomatic BV among pregnant women who are at high risk for preterm delivery (i.e., those with a previous preterm birth) has been evaluated by several studies, which have yielded mixed results. Seven trials have evaluated treatment of pregnant women with asymptomatic BV at high risk for preterm delivery; one showed harm⁶¹², two showed no benefit^{613,614}, and four demonstrated benefit⁶¹⁵⁻⁶¹⁸.

Similarly, data are inconsistent regarding whether the treatment of asymptomatic pregnant women with BV who are at low risk for preterm delivery reduces adverse outcomes of pregnancy. One trial demonstrated a 40% reduction in spontaneous preterm birth among women using oral clindamycin during weeks 13–22 of gestation⁶¹⁸. Several additional trials have shown that intravaginal clindamycin given at an average gestation of later than 20 weeks did not reduce preterm birth^{614,619-621}. Therefore, evidence is insufficient to recommend routine screening for BV in asymptomatic pregnant women at high or low risk for preterm delivery to prevent preterm birth¹¹².

Metronidazole crosses the placenta and human data suggest that it is low risk in pregnancy³¹⁰. No evidence of teratogenicity or mutagenic effects has been found in multiple cross-sectional and cohort studies of pregnant women⁶²².

Metronidazole is secreted in breast milk. With maternal intravenous and oral therapy, breastfed infants receive metronidazole in doses that are less than those used to treat infections in infants, although the active metabolite adds to the total infant exposure. Plasma levels of the drug and metabolite are measurable, but less than maternal plasma levels (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>). Although there was no evidence of adverse effects in infants in several

reported case series, some clinicians advise deferring breastfeeding for 12–24 hours following maternal treatment with a 2 g dose of metronidazole⁶²³. Lower doses used to treat BV produce a lower concentration in breast milk and are considered compatible with breastfeeding^{624,625}. There is limited human data on the use of tinidazole in pregnancy, and animal data suggest it is moderate risk. Thus tinidazole should be avoided since the treatment for BV is a multidose regimen³¹⁰.

HIV Infection

BV appears to recur with higher frequency in women who have HIV infection⁶²⁶. Women with HIV who have BV should receive the same treatment regimen as those who do not have HIV infection.

Trichomoniasis

Trichomoniasis is caused by the protozoan parasite *Trichomonas vaginalis*, which is the most prevalent nonviral sexually transmitted infection, affecting an estimated 3.7 million people in the United States⁵²⁵. *T. vaginalis* infection, affects over 11% of women age 40 years and above⁶²⁷ and 13% of black women in the United States⁶²⁸. Particularly high prevalences have been detected among STD clinic patients⁶²⁹ (26% of symptomatic women tested) and incarcerated individuals (9–32% of incarcerated women,^{134,135,627,630,631} and 2–9% of incarcerated men screened)^{135,136,632,633}.

Some infected men have symptoms of urethritis, epididymitis, or prostatitis, and some infected women have vaginal discharge that may be diffuse, malodorous, or yellow-green with or without vulvar irritation. However, most (70–85%) infected persons have minimal or no symptoms, and untreated infections may last for months to years.^{85,628,634,635} Although partners may be unaware of their infection, it is readily passed between sex partners during penile-vaginal sex⁶³⁶. Among sexually active individuals, the best way to prevent trichomoniasis is by using condoms consistently and correctly during all penile-vaginal sexual encounters²² especially with casual or concurrent sexual partners or partners with concurrent partners. Partners of men who have been circumcised might have a somewhat reduced risk of *T. vaginalis* infections^{52,637}. Douching is not recommended, as it might increase the risk of vaginal infections including trich⁶³⁸.

T. vaginalis infection is associated with significantly increased risks of HIV acquisition (two to three-fold)⁶³⁹⁻⁶⁴². *T. vaginalis* infection is also associated with significantly increased risk of preterm birth and other adverse pregnancy outcomes, and pelvic inflammatory disease (PID) among women with HIV infection⁶⁴³⁻⁶⁴⁵.

For asymptomatic individuals, routine screening of women with HIV infection is recommended because of the adverse events associated with *T. vaginalis* infection. Screening may be considered for persons receiving care in high-prevalence settings including STD clinics and correctional facilities; also, in other settings, screening and treatment may be considered for asymptomatic individuals at high risk for infection (e.g., persons with new or multiple sex partners, or history of any STD). However, data are lacking on whether effective screening and treatment for trichomoniasis can also reduce associated adverse events and health disparities. It is also

unknown if screening and treatment in high prevalence settings or high risk individuals reduces community burden of infection or any adverse outcomes other than symptoms of trichomoniasis. Decisions about screening may be informed by local, regional, or national epidemiology of *T. vaginalis* infection.

Diagnostic Considerations

The use of highly sensitive and specific tests is encouraged for *T. vaginalis* detection in both women and men. Among women, nucleic acid amplification tests (NAATs) may detect a prevalence three to five times higher than wet mount microscopy, a method with poor sensitivity (51% to 65%).^{646,647} The APTIMA Trichomonas vaginalis assay (Hologic Gen-Probe, San Diego, CA) is FDA-cleared for detection of *T. vaginalis* from vaginal or endocervical specimens or urine from symptomatic or asymptomatic women. This assay detects RNA by transcription-mediated amplification with a clinical sensitivity of 95.3–100% and specificity of 95.2–100%^{648 649}. Among women, vaginal swab and urine have up to 100% concordance⁶⁴⁶. As analyte-specific reagents, this assay can be used with urine or urethral swabs from men if validated per CLIA specifications. The sale, distribution and use of analyte specific reagents are covered under 21 C.F.R. 809.30 pertaining to *in vitro* diagnostic products for human use. For *T. vaginalis* diagnosis in men, the sensitivity of self-collected penile-meatal swabs was higher than that of urine in one study (80% and 39%, respectively)⁶⁵⁰. The BD Probe Tec TV Q^x Amplified DNA Assay (Becton Dickinson, Franklin Lakes, NJ) is FDA-cleared for detection of trichomoniasis from endocervical, vaginal, or urine specimens in women. Although it may be feasible to perform these NAATs on the same specimen used for chlamydia/gonorrhea screening tests, the epidemiology of trichomoniasis is distinct and should not be overlooked in older adults.

Other FDA-cleared tests to detect *T. vaginalis* in vaginal secretions in women include the OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Framingham, MA), an antigen-detection test using immunochromatographic capillary flow dipstick technology that is CLIA-waived and may be performed at the point of care, and the Affirm VP III (Becton Dickinson, Sparks, MD), a nucleic acid probe-hybridization test that evaluates for *T. vaginalis*, *Gardnerella vaginalis*, and *Candida albicans*. The results of the OSOM Trichomonas Rapid Test are available in approximately 10 minutes, with sensitivity 82–95% and specificity 97–100%^{649,651}. Self-testing may be an option, as a study of 209 young women aged 14–22 years found that over 99% could correctly perform and interpret her own self-test using the OSOM assay, with a high correlation with clinician interpretation (96% agreement, $\kappa=0.87$)⁶⁵². The results of the Affirm VP III are available within 45 minutes, with sensitivity 63% and specificity of 99.9% compared with culture and TMA; sensitivity may be higher among women who are symptomatic^{653,654}. Neither the OSOM nor the Affirm VP III test is FDA-cleared for use with male specimens.

Culture was considered the gold standard method for diagnosing *T. vaginalis* infection before molecular detection methods became available. Culture has a sensitivity of 75–96% and a specificity of up to 100%⁴⁶⁵. In women, vaginal secretions are the preferred specimen type for culture, as urine culture is less sensitive^{465,655,656}. In men, culture specimens require a urethral swab, urine, and/or semen. Multiple specimens from men can be used to inoculate a single culture to improve yield.

The most common method for *T. vaginalis* diagnosis may be microscopic evaluation of wet preparations of genital secretions, due to convenience and relatively low cost. Unfortunately, the sensitivity of wet mount is 51%–65% in vaginal specimens^{465 649}. Clinicians using wet mounts should attempt to evaluate slides immediately since sensitivity declines as evaluation is delayed, decreasing by up to 20% within one hour after collection^{657 658}. Where highly-sensitive (e.g., NAAT testing on all specimens is not feasible, a testing algorithm may be an option for improving diagnostic sensitivity in persons with an initial negative result by wet mount⁴⁶⁵. Although *T. vaginalis* may be an incidental finding on a Pap test, neither conventional nor liquid-based Pap tests are considered diagnostic tests for trichomoniasis since false negatives and false positives can occur.

It is unclear whether the rectum can be a reservoir for *T. vaginalis* infection, or whether this occasional finding might reflect recent depositing/contamination in up to 5% of individuals reporting recent receptive anal sex^{659,660}. Furthermore, efficacy, benefit, and cost-effectiveness of rectal screening are unknown, so rectal testing for *T. vaginalis* is not recommended. Similarly, oral testing for *T. vaginalis* is not recommended due to a lack of evidence for oral infections. *T. vaginalis* infection is not a nationally notifiable condition in the United States^{119,661}.

Treatment

Treatment reduces symptoms and signs of *T. vaginalis* infection and may reduce transmission; associated adverse outcomes in women with HIV are also reduced.

Recommended Regimens

Metronidazole 2 g orally in a single dose

OR

Tinidazole 2 g orally in a single dose

Alternative Regimen

Metronidazole 500 mg orally twice a day for 7 days

It is advised to avoid consuming alcohol during treatment with nitroimidazoles. Abstinence from alcohol use should continue for 24 hours after completion of metronidazole or 72 hours after completion of tinidazole, to reduce the possibility of a disulfiram-like reaction.

The nitroimidazoles are the only class of antimicrobial medications known to be effective against *T. vaginalis* infections. Of these drugs, metronidazole and tinidazole are available in the United States and are cleared by the FDA for the oral or parenteral treatment of trichomoniasis. Tinidazole is generally more expensive, reaches higher levels in the serum and the genitourinary

tract, has a longer half-life than metronidazole (12.5 hours versus 7.3 hours), and has fewer gastrointestinal side effects⁶⁶²⁻⁶⁶⁴. In randomized clinical trials, the recommended metronidazole regimens have resulted in cure rates of approximately 84–98%⁶⁶⁵⁻⁶⁶⁷, and the recommended tinidazole regimen has resulted in cure rates of approximately 92–100%^{666,668-671}. Randomized controlled trials comparing single 2 g doses of metronidazole and tinidazole suggest that tinidazole is equivalent or superior to metronidazole in achieving parasitologic cure and resolution of symptoms⁶⁷².

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

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

Follow-up

Because of the high rate of reinfection among women diagnosed with trichomoniasis (17% in one study)⁸⁵, retesting for *T. vaginalis* is recommended for all sexually active women within 3 months following initial treatment. Data are insufficient to support retesting men. NAAT testing may be conducted as soon as 2 weeks after treatment^{673,674}.

Management of Sex Partners

Concurrent treatment of all sex partners is critical for symptomatic relief, microbiologic cure, and prevention of ongoing transmission and reinfections. Partners should be advised to abstain from unprotected sex until they have completed therapy and any symptoms have resolved. Patient-delivered partner therapy might have a role in partner management for trichomoniasis^{95,96,675} and may be used in states where permissible by law. While there are no definitive data to guide treatment for partners of individuals with persistent or recurrent trichomoniasis where nonadherence or reinfection are unlikely, it is suggested that partners should undergo evaluation and receive the same regimen as the patient (see persistent or recurrent trichomoniasis).

Persistent or Recurrent Trichomoniasis

Persistent or recurrent infection due to antimicrobial-resistant *T. vaginalis* or other causes should be distinguished from the possibility of reinfection from an untreated sex partner. While most recurrent *T. vaginalis* infections are thought to result from reinfection, some infections may be attributed to antimicrobial resistance. Metronidazole resistance may occur in 4%–10% of cases of vaginal trichomoniasis^{676,677}, and tinidazole resistance in 1%⁶⁷⁷. In general, *T. vaginalis* isolates have lower minimum lethal concentrations (MLCs) to tinidazole than metronidazole⁶⁷⁸. Emerging nitroimidazole-resistant trichomoniasis is concerning, since few alternatives to standard therapy exist. Singledose therapy should be avoided for treating recurrent trichomoniasis that is not likely due to reinfection. If treatment failure has occurred with

metronidazole 2 g single dose and reinfection is excluded, the patient (and their partner/s) can be treated with metronidazole 500 mg orally twice daily for 7 days. If this regimen fails, clinicians should consider treatment with metronidazole or tinidazole at 2 g orally for 7 days. If several one week regimens have failed in a person who is unlikely to have nonadherence or reinfection, testing of the organism for metronidazole and tinidazole susceptibility is recommended⁶⁷⁹ CDC (telephone: 404-718-4141; website: <http://www.cdc.gov/std>) has accumulated experience with testing and treatment of nitroimidazole-resistant *T. vaginalis* and can offer susceptibility testing and management assistance. Higher dose tinidazole at 2–3g for 14 days, often in combination with intravaginal tinidazole can be considered. Such cases should be managed in consultation with an expert.

Alternative regimens might be effective but have not been systematically evaluated. Clinical improvement has been reported with several alternative regimens including intravaginal paromomycin in combination with high-dose tinidazole⁶⁸⁰⁻⁶⁸²; intravaginal boric acid^{683,684} and nitazoxanide⁶⁸⁵. The following topically applied agents have shown minimal success (<50%) and are not recommended: intravaginal betadine (povidone-iodine), clotrimazole, acetic acid, furazolidone, gentian violet, nonoxonyl-9, or potassium permanganate⁶⁸⁶. No topical microbicide has shown an effect on trichomoniasis⁶⁸⁷.

Special Considerations

Allergy, Intolerance, and Adverse Reactions

Metronidazole and tinidazole are both nitroimidazoles. Patients with an IgE mediated-type allergy to a nitroimidazole can be managed by metronidazole desensitization according to a published regimen⁶⁸⁸ and in consultation with a specialist.

Pregnancy

Maternal *T. vaginalis* infection is associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm delivery, and delivery of a low birth weight infant^{644,689-691}. However, while metronidazole treatment produces parasitologic cure, several trials have shown no significant difference in perinatal morbidity following metronidazole treatment. One trial suggested the possibility of increased preterm delivery in women with *T. vaginalis* infection who received metronidazole treatment⁶⁹², yet study limitations prevented definitive conclusions regarding the risks of treatment. More recent, larger studies have shown no positive or negative association between metronidazole use during pregnancy and adverse outcomes of pregnancy^{622,693-696}. Treatment of *T. vaginalis* infection can relieve symptoms of vaginal discharge in pregnant women reduce sexual transmission to partners, and might prevent respiratory or genital infection of the newborn even though perinatal transmission of trichomoniasis is uncommon^{697,698}.

Symptomatic pregnant women, regardless of pregnancy stage, should be tested and considered for treatment, as well as counseled that partner treatment and condoms may help prevent ongoing sexual transmission. Screening at the first prenatal visit and prompt treatment, are recommended for women with HIV infection who are pregnant, since *T. vaginalis* infection is a risk factor for

vertical transmission of HIV⁶⁹⁹. Pregnant women with HIV treated for *T. vaginalis* infection should be retested at 3 months after treatment. The benefit of routine screening for *T. vaginalis* in pregnant women has not been established. Metronidazole crosses the placenta and human data suggest that it is low risk in pregnancy³¹⁰. No evidence of teratogenicity or mutagenic effects has been found in multiple cross-sectional and cohort studies of pregnant women^{694-696,700}. Women may be treated with 2 g metronidazole in a single dose at any stage of pregnancy.

Metronidazole is secreted in breast milk. With maternal therapy, breastfed infants receive metronidazole in doses that are lower than those used to treat infections in infants., although the active metabolite adds to the total infant exposure. Plasma levels of the drug and metabolite are measurable, but less than maternal plasma levels (<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>) . Although there was no evidence of adverse effects in infants in several reported case series, some clinicians advise deferring breastfeeding for 12–24 hours following maternal treatment with a 2 g dose of metronidazole⁶²³. Lower doses produce a lower concentration in breast milk and are considered compatible with breastfeeding over longer periods^{624,625}.

There is limited human data on the use of tinidazole in pregnancy, and animal data suggest it is moderate risk. Thus tinidazole should be avoided especially during the first trimester of pregnancy and breastfeeding should be deferred for 12-24 hours following a single 2 g dose of tinidazole.³¹⁰

HIV Infection

Among women with HIV infection, as many as 53% are also infected with *T. vaginalis*^{701,702}. *T. vaginalis* infection in these women is significantly associated with PID⁶⁴⁵ and treatment of trichomoniasis is associated with significant decreases in genital tract HIV viral load and viral shedding^{703,704}. For these reasons, 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 infection and *T. vaginalis* infection demonstrated that a single dose of metronidazole 2 g orally was less effective than 500 mg twice daily for 7 days⁷⁰⁵. Thus, women with HIV infection who are diagnosed with *T. vaginalis* infection should be treated with metronidazole 500 mg twice daily for 7 days (rather than a 2 g single dose of metronidazole) in order to improve cure rates. Factors that may interfere with standard single-dose treatment for trichomoniasis in these women include high rates of asymptomatic bacterial vaginosis co-infections, use of antiretroviral therapy, changes in vaginal ecology and impaired immunity^{642,706,707}.

In women with HIV infection who are diagnosed with *T. vaginalis* infection, retesting is recommended within 3 months following initial treatment; high-sensitivity testing is encouraged. There are insufficient data to recommend this approach in men.

Vulvovaginal Candidiasis

VVC usually is caused by *C. albicans* but occasionally is caused by other *Candida* sp. 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 2). Approximately 10%–20% of women will have complicated VVC, which require special diagnostic and therapeutic considerations.

Uncomplicated VVC

Diagnostic Considerations

A diagnosis of *Candida* vaginitis is suggested clinically by the presence of external dysuria and vulvar pruritus, pain, swelling, and redness. Signs include vulvar edema, fissures, excoriations, or thick curdy vaginal discharge. The diagnosis can be made in a woman who has signs and symptoms of vaginitis when either 1) a wet preparation (saline, 10% KOH) or Gram stain of vaginal discharge demonstrates budding yeasts, hyphae or pseudohyphae or 2) a culture or other test yields a positive result for a yeast species. *Candida* vaginitis is associated with a 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 receive treatment. For those with negative wet mounts, vaginal cultures for *Candida* should be considered for those with any sign or multiple symptoms. If *Candida* cultures cannot be done, empiric treatment can be considered for symptomatic women with any sign of VVC on examination when the wet mount is negative. 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* sp. and other yeasts in the vagina. PCR testing for yeast is not FDA-cleared; culture for yeast remains the gold standard for diagnosis. VVC can occur concomitantly with STDs. The majority of healthy women with uncomplicated VVC have no identifiable precipitating factors.

Treatment

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

| <i>Recommended Regimens</i> |
|---|
| <i>Intravaginal Agents:</i> |
| Butoconazole 2% cream (single dose bioadhesive product), 5 g intravaginally in a single application |
| OR |
| 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 in a single application for 1 day* |
| OR |
| Terconazole 0.4% Cream 5 G Intravaginally for 7 Days |
| OR |

Terconazole 0.8% cream 5 g intravaginally for 3 days

OR

Terconazole 80 mg vaginal suppository, one suppository for 3 days

OR

Tioconazole 6.5% ointment 5 g intravaginally in a single application*

Oral Agent:

Fluconazole 150 mg orally in single dose

* Over-the-counter (OTC) preparations.

The creams and suppositories in this regimen are oil-based and might weaken latex condoms and diaphragms. Refer to condom product labeling for further information.

Intravaginal preparations of clotrimazole, miconazole, and tioconazole are available over-the-counter (OTC). Even women who have previously been diagnosed with VVC by a clinician are not necessarily more likely to be able to diagnose themselves; therefore, any woman whose symptoms persist after using an OTC preparation, or who has a recurrence of symptoms within 2 months after treatment for VVC, should be clinically evaluated and tested. Unnecessary or inappropriate use of OTC preparations is common and can lead to a delay in the treatment of other vulvovaginitis etiologies, which can in turn result in adverse outcomes.

Box 3. Classification of vulvovaginal candidiasis (VVC)

Uncomplicated VVC

- Sporadic or infrequent vulvovaginal candidiasis
AND
- Mild-to-moderate vulvovaginal candidiasis
AND
- Likely to be *C. albicans*
AND
- Non-immunocompromised women

Complicated VVC

- Recurrent vulvovaginal candidiasis
OR
- Severe vulvovaginal candidiasis
OR
- Non-albicans candidiasis
OR
- Women with diabetes, immunocompromising conditions (e.g., HIV infection), debilitation, or immunosuppressive therapy (e.g., corticosteroids)

Follow-Up

Women should be instructed to return for follow-up visits only if symptoms persist or recur after treatment of onset of initial symptoms.

Management of Sex Partners

Uncomplicated VVC is not usually acquired through sexual intercourse; thus, there are no data to support the treatment of sex partners. A minority of male sex partners might have balanitis, which is 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

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 been associated rarely with abnormal elevations of liver enzymes. Clinically important interactions can occur when oral azoles agents are administered with other drugs.⁷⁰⁸

Complicated VVC

Diagnostic Considerations

Vaginal cultures should be obtained from women with VVC to confirm the clinical diagnosis and to identify unusual species, including nonalbicans species, particularly *Candida glabrata* (*C. glabrata* does not form pseudohyphae or hyphae and is not easily recognized on microscopy). Although *C. albicans* azole resistance is possibly becoming more common in vaginal isolates,^{709,710} susceptibility testing is usually not warranted for individual treatment guidance.

Recurrent Vulvovaginal Candidiasis (RVVC)

RVVC, usually defined as four or more episodes of symptomatic VVC in 1 year, affects a small percentage of women (<5%). The pathogenesis of RVVC is poorly understood, and the majority of women with RVVC have no apparent predisposing or underlying conditions. *C. glabrata* and other nonalbicans *Candidia* species are observed in 10%–20% of women with RVVC. Conventional antimycotic therapies are not as effective against these nonalbicans species as against *C. albicans*.

Treatment

Each individual episode of RVVC caused by *C. albicans* responds well to short duration oral or topical azole therapy. However, to maintain clinical and mycologic control, some specialists recommend 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 (day 1, 4, and 7) to attempt mycologic remission before initiating a maintenance antifungal regimen.

Oral fluconazole (i.e., 100-mg, 150-mg, or 200-mg dose) weekly for 6 months is the first line maintenance regimen. If this regimen is not feasible, topical treatments can also be considered. Suppressive maintenance therapies are effective in reducing RVVC. However, 30%–50% of women will have recurrent disease after maintenance therapy is discontinued. Symptomatic women who remain culture-positive despite maintenance therapy should be managed in consultation with a specialist.

Severe VVC

Severe vulvovaginitis (i.e., extensive vulvar erythema, edema, excoriation, and fissure formation) is associated with lower clinical response rates in 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 VVC

Since at least 50% of women with positive cultures for non-albicans *Candida* may be minimally or not symptomatic at all and since successful treatment is often difficult, clinicians should make every effort to exclude other causes of vaginal symptoms in women with non-

albicans yeast⁷¹¹. The optimal treatment of non-*albicans* VVC remains unknown. Options include longer duration of therapy (7–14 days) with a nonfluconazole azole regimen (oral or topical) as first-line therapy. If recurrence occurs, 600 mg of boric acid in a gelatin capsule is recommended, administered vaginally once daily for 2 weeks. This regimen has clinical and mycologic eradication rates of approximately 70%⁷¹². If symptoms recur, referral to a specialist is advised.

Compromised Host

Women with underlying immunodeficiency, those with uncontrolled diabetes, or other immunocompromising conditions (e.g., HIV), or those receiving immunosuppression therapy (e.g., corticosteroid treatment) do 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.

Management of Sex Partners

There are no data to support the treatment of sex partners of patient with complicated VVC.

Special Considerations

Pregnancy

VVC occurs frequently during pregnancy. Only topical azole therapies, applied for 7 days, are the recommended regimens for use among pregnant women.

HIV Infection

Vaginal *Candida* colonization rates among women with HIV infection are higher than among seronegative women with similar characteristics, and the colonization rates correlate with increasing severity of immunosuppression. Symptomatic VVC is also more frequent and similarly correlates with severity of immunodeficiency. In addition, among women with HIV infection, systemic azole exposure is associated with the isolation of nonalbicans *Candida* species from the vagina.

Based on available data, therapy for uncomplicated and complicated VVC in women with HIV infection should not differ from that for seronegative women. Although long-term prophylactic therapy with fluconazole at a dose of 200 mg weekly has been effective in reducing *C. albicans* colonization and symptomatic VVC⁷¹³, this regimen is not recommended for women with HIV infection in the absence of complicated VVC²³⁵. Although VVC is associated with increased HIV seroconversion in HIV-negative women and increased HIV cervicovaginal levels in women with HIV infection, the effect of treatment for VVC on HIV acquisition and transmission remains unknown.

Pelvic Inflammatory Disease (PID)

PID comprises a spectrum of inflammatory disorders of the upper female genital tract, including any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis⁷¹⁴. Sexually transmitted organisms, especially *N. gonorrhoeae* and *C. trachomatis*, are implicated in many cases. Modern studies suggest that the proportion of PID cases due to *N. gonorrhoeae* or *C. trachomatis* is declining, with less than half of women diagnosed with acute PID testing positive for either of these organisms^{715 716 261}. Microorganisms that comprise the vaginal flora (e.g., anaerobes, *G. vaginalis*, *Haemophilus influenzae*, enteric Gram-negative rods, and *Streptococcus agalactiae*) have been associated with PID⁷¹⁷. In addition, cytomegalovirus (CMV), *M. hominis*, *U. urealyticum*, and *M. genitalium* might be associated with some cases of PID^{255,256,258,718}. Newer data suggest that *M. genitalium* may play a role in the pathogenesis of PID^{476 261} and may be associated with milder symptoms²⁵⁸. However, one study did not demonstrate a significant increase in PID following detection of *M. genitalium* in the lower genital tract⁷¹⁹. All women who have acute PID should be tested for *N. gonorrhoeae* and *C. trachomatis* using NAATs and should be screened for HIV infection. The role of testing women with PID for *M. genitalium* has not been established.

Screening and treating sexually active women for chlamydia reduces their risk for PID^{462,688}. Although BV is associated with PID, whether the incidence of PID can be reduced by identifying and treating women with BV is unclear^{717, 720}.

Diagnostic Considerations

Acute PID is difficult to diagnose because of the wide variation in the symptoms and signs. Many women with PID have subtle or nonspecific symptoms or are asymptomatic. Delay in diagnosis and treatment probably contributes to inflammatory sequelae in the upper reproductive 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 easy to justify when symptoms are mild or vague. Moreover, laparoscopy will not detect endometritis and might not detect subtle inflammation of the fallopian tubes. Consequently, a diagnosis of PID usually is based on imprecise clinical findings^{721,722}.

Data indicate that a clinical diagnosis of symptomatic PID has a positive predictive value (PPV) for salpingitis of 65%–90% compared with laparoscopy. The PPV of a clinical diagnosis of acute PID depends on the epidemiologic characteristics of the population, with higher PPVs among sexually active young women (particularly adolescents), women attending STD clinics, and those who live in communities where the rates of gonorrhea or chlamydia are high. Regardless of PPV, however, in all clinical settings, 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 but also reduces the number of women with PID who are identified.

Many episodes of PID go unrecognized. Although some cases are asymptomatic, others are not diagnosed because the patient or the health-care provider fails to 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 may be at-risk for infertility.⁷²³ 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 diagnosis of PID⁷¹⁴. The optimal treatment regimen and long-term outcome of early treatment of women with subclinical PID are unknown.

The following recommendations for diagnosing PID are intended to help health-care providers recognize when PID should be suspected and when they need to obtain additional information to increase diagnostic certainty. Diagnosis and management of other common causes of lower abdominal pain (e.g., ectopic pregnancy, acute appendicitis, and functional pain) are unlikely to be impaired by initiating antimicrobial therapy for PID.

Presumptive treatment for PID should be initiated in sexually active young women and other women at risk for STDs if they are experiencing pelvic or lower abdominal pain, if no cause for the illness other than PID can be identified, and if one or more of the following minimum clinical criteria are present on pelvic examination:

- cervical motion tenderness

or

- uterine tenderness

or

- adnexal tenderness.

The requirement that all three minimum criteria be present before the initiation of empiric treatment could result in insufficient sensitivity for the diagnosis of PID. Upon deciding whether to initiate empiric treatment, clinicians should also consider the risk profile for STDs.

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 exudates, 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 diagnosis of PID:

- oral temperature $>101^{\circ}\text{F}$ ($>38.3^{\circ}\text{C}$);
- abnormal cervical mucopurulent discharge or cervical friability;
- presence of abundant numbers of WBC on saline microscopy of vaginal fluid;

- elevated erythrocyte sedimentation rate;
- elevated C-reactive protein; and
- laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*.

Most 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, the diagnosis of PID is unlikely, and alternative causes of pain should be considered. A wet prep of vaginal fluid offers the ability to detect the presence of concomitant infections (e.g., BV and trichomoniasis).

The most specific criteria for diagnosing PID include:

- endometrial biopsy with histopathologic evidence of endometritis;
- transvaginal sonography or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler studies suggesting pelvic infection (e.g., tubal hyperemia); or
- laparoscopic findings consistent with PID.

A diagnostic evaluation that includes some of these more extensive procedures might be warranted in some cases. Endometrial biopsy is warranted in women undergoing laparoscopy who do not have visual evidence of salpingitis, because endometritis is the only sign of PID for some women.

Treatment

PID treatment regimens must provide empiric, broad spectrum coverage of likely pathogens. Several oral and parenteral antimicrobial regimens have been effective in achieving clinical and microbiologic cure in randomized clinical trials with short-term follow-up^{718, 724, 725}. However, only a limited number of investigations have assessed and compared these regimens with regard to elimination of infection in the endometrium and fallopian tubes or determined the incidence of long-term complications (e.g., tubal infertility and ectopic pregnancy) after antimicrobial regimens^{715, 726, 727}.

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-reproductive-tract infection. The need to eradicate anaerobes from women who have PID has not been determined definitively. Anaerobic bacteria have been isolated from the upper-reproductive 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 present in many women who have PID^{717, 720}. 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, the use of 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 appropriate antibiotics. When selecting a treatment regimen, health-care providers should consider availability, cost, and acceptance.⁷²⁵ Women should be instructed to abstain from sexual intercourse until therapy is completed and until they and their sex partners no longer have symptoms.

In 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 the judgment of the provider and whether the woman meets any of the following suggested criteria:

- surgical emergencies (e.g., appendicitis) cannot be excluded;
- tubo-ovarian abscess.
- pregnancy;
- severe illness, nausea and vomiting, or high fever;
- unable to follow or tolerate an outpatient oral regimen; or
- no clinical response to oral antimicrobial therapy;

No evidence is available to suggest 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

Several randomized trials have demonstrated the efficacy of parenteral regimens^{720,724,725}. Clinical experience should guide decisions regarding transition to oral therapy, which usually can be initiated within 24–48 hours of clinical improvement. In women with tubo-ovarian abscesses, at least 24 hours of inpatient observation is recommended.

| |
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| <i>Recommended Parenteral Regimens</i> |
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|---------------------------------|
| 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**

OR

Clindamycin 900 mg IV every 8 hours

PLUS

Gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing (3–5 mg/kg) can be substituted*.

*Although use of a single daily dose of gentamicin has not been evaluated for the treatment of PID, it is efficacious in analogous situations.

**Because of the pain associated with intravenous infusion, doxycycline should be administered orally when possible. Oral and IV administration of doxycycline provide similar bioavailability.

Clinical experience should guide decisions regarding transition from parenteral to oral therapy, which usually can be initiated 24-48 hours after clinical improvement. When using the Cefotetan or Cefoxitin regimens, oral therapy with doxycycline can be used to complete the 14

day course; for the Clindamycin/gentamicin regimen, oral therapy with clindamycin (450 mg orally four times daily) or doxycycline (100 mg twice daily) can be used. However, when tubo-ovarian abscess is present, clindamycin (450 mg orally four times daily) or metronidazole (500 mg twice daily) should be used with doxycycline to provide more effective anaerobic coverage than doxycycline alone.

Limited data are available to support the use of other parenteral second- or third-generation cephalosporins (e.g., ceftizoxime, cefotaxime, and ceftriaxone), so are not recommended. In addition, these cephalosporins are less active than cefotetan or ceftiofex against anaerobic bacteria.

Alternative Parenteral Regimens

Ampicillin/sulbactam plus doxycycline has been investigated in at least one clinical trial and has broad-spectrum coverage⁷²⁸. Ampicillin/sulbactam plus doxycycline is effective against *C. trachomatis*, *N. gonorrhoeae*, and anaerobes in women with tubo-ovarian abscess. Another trial demonstrated high short-term clinical cure rates with azithromycin, either as monotherapy for 1 week (500 mg IV for 1 or 2 doses followed by 250 mg orally for 5–6 days) or combined with a 12-day course of metronidazole⁷²⁹. Limited data are available to support the use of other parenteral regimens.

Alternative Parenteral Regimens

Ampicillin/Sulbactam 3 g IV every 6 hours

PLUS

Doxycycline 100 mg orally or IV every 12 hours

Intramuscular/Oral Treatment

Intramuscular/oral therapy can be considered for women with mild-to-moderately severe acute PID, because the clinical outcomes among women treated with these regimens are similar to those treated with intravenous therapy⁷¹⁵. Women who do not respond to IM/oral therapy within 72 hours should be reevaluated to confirm the diagnosis and should be administered intravenous therapy.

Recommended Regimen

Ceftriaxone 250 mg IM in a single dose

PLUS

Doxycycline 100 mg orally twice a day for 14 days

WITH* or WITHOUT

Metronidazole 500 mg orally twice a 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 twice a day for 14 days

WITH or WITHOUT

Metronidazole 500 mg orally twice a day for 14 days

OR

Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)

PLUS

Doxycycline 100 mg orally twice a day for 14 days

WITH* or WITHOUT

Metronidazole 500 mg orally twice a day for 14 days

* Because of the limitations in coverage of anaerobes by the recommended third generation cephalosporins and until it is known that extended anaerobic coverage is not important for treatment of acute PID, the addition of metronidazole to treatment regimens with third generation cephalosporins should be considered ⁷²⁴

These regimens provide coverage against frequent etiologic agents of PID although 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 in women with PID. Ceftriaxone has better coverage against *N. gonorrhoeae*. The addition of metronidazole will also effectively treat BV, which is frequently associated with PID. No data have been published regarding the use of oral cephalosporins for the treatment of PID.

Alternative IM/Oral Regimens

Although information regarding other IM/oral regimens is limited, a few regimens have undergone at least one clinical trial and have demonstrated broad spectrum coverage. Azithromycin has demonstrated short-term clinical effectiveness in one randomized trial when used as monotherapy (500 mg IV for 1-2 doses, followed by 250 orally daily for 12-14 days) or in combination with metronidazole⁷²⁹, and in another study, it was effective when used 1 g orally once a week for 2 weeks in combination with ceftriaxone 250 mg IM single dose⁷³⁰. When considering these alternative regimens, the addition of metronidazole should be considered to provide anaerobic coverage.

As a result of the emergence of quinolone-resistant *Neisseria gonorrhoeae*, regimens that include a quinolone agent are no longer recommended for the treatment of PID. If allergy precludes the use of cephalosporin therapy or if the community prevalence and individual risk for gonorrhea are low, and follow-up is likely, use of fluoroquinolones (levofloxacin 500 mg orally once daily, ofloxacin 400 mg twice daily for 14 days, or moxifloxacin 400 mg orally once daily or) with metronidazole (500 mg orally twice daily for 14 days) can be considered.^{731 732 733} Diagnostic tests for gonorrhea must be obtained before instituting therapy and managed as follows if the test is positive.

- If the 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* (QRNG) or if antimicrobial susceptibility cannot be assessed (e.g., if only NAAT testing is available), retreatment with ceftriaxone 250 mg IM in combination with azithromycin 1 gram is recommended for gonorrhea, in addition to doxycycline and metronidazole for 14 days. If cephalosporin treatment is not feasible, the addition of azithromycin 2 g orally as a single dose to a quinolone based PID regimen is recommended.

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) within 3 days after initiation of therapy.

If no clinical improvement has occurred within 72 hours after outpatient IM/oral therapy, hospitalization, assessment of the antimicrobial regimen, and additional diagnostics (including

the consideration of diagnostic laparoscopy for alternative diagnoses) are recommended. All women who have been diagnosed with chlamydial or gonococcal PID should be retested 3 months after treatment, regardless of whether their sex partners were treated¹⁰⁸. If retesting at 3 months is not likely because of unpredictable follow-up behavior, then retesting should occur whenever they next present for medical care in the 1-12 months following treatment. All women diagnosed with acute PID should be offered HIV testing.

Management of Sex Partners

Male sex partners of women with PID should be examined, tested, and presumptively treated for chlamydia and gonorrhea, regardless of the etiology of PID or pathogens isolated from the woman, if they had sexual contact during the 60 days preceding the women's onset of symptoms. If a woman's last sexual intercourse was >60 days before onset of symptoms or diagnosis, the most recent sex partner should be treated. Male partners of women who have PID caused by *C. trachomatis* and/or *N. gonorrhoeae* frequently are asymptomatic. Arrangements should be made to link male partners to care. If linkage is delayed or unlikely, then expedited partner treatment and enhanced referral (see Partner Services) are alternative approaches to treating male partners of women who have chlamydia or gonococcal infections^{91,92}. Partners should be instructed to abstain from sexual intercourse until they have been adequately treated (i.e.; until therapy is completed and symptoms have resolved, if originally present).

Special Considerations

Allergy, Intolerance, and Adverse Reactions

The cross reactivity between penicillins and cephalosporins is <2.5% in persons with a history of penicillin allergy^{418-421,454}. The risk of penicillin cross-reactivity between most second-generation (cefotaxime) and all third generation cephalosporins (ceftriaxone) is negligible⁴¹⁸⁻⁴²¹.

Pregnancy

Because of the high risk for maternal morbidity and preterm delivery, pregnant women who have suspected PID should be hospitalized and treated with intravenous antibiotics.

HIV Infection

Differences in the clinical manifestations of PID between women with HIV infection and women without HIV infection have not been well delineated. In early observational studies, women with HIV infection with PID were more likely to require surgical intervention. More comprehensive observational and controlled studies now have demonstrated that women with HIV infection with PID have similar symptoms when compared with uninfected controls^{257,734,735}, except they are more likely to have a tubo-ovarian abscess; women with HIV infection responded equally well to standard antibiotic regimens as women without HIV infection. The microbiologic findings for women with HIV infection and women without HIV infection were similar, except women with HIV infection had higher rates of concomitant *M. hominis*, and streptococcal infections. These data are insufficient to determine if women with HIV infection

with PID requires more aggressive management (e.g., hospitalization or intravenous antimicrobial regimens).

Intrauterine Contraceptive 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^{736,737}. If an IUD user is diagnosed with PID, the IUD does not need to be removed⁵⁹. However, the woman should be treated accordingly to these practice recommendations and should have close clinical follow-up. If there is no clinical improvement within 48-72 hours, providers should consider removing the IUD. A systematic review of evidence found that treatment outcomes did not generally differ between women with PID who retained the IUD and those who had the IUD removed⁷³⁸. These studies primarily included women using copper or other non-hormonal IUDs; no evidence has been identified regarding treatment outcomes in women using levonorgestrel-releasing IUDs.

Epididymitis

Acute epididymitis is a clinical syndrome consisting of pain, swelling, and inflammation of the epididymis that lasts <6 weeks⁷³⁹. Sometimes the testis is also involved in the process — a condition referred to as epididymo-orchitis. A high index of suspicion for spermatic cord (testicular) torsion must be maintained in those that present with a sudden onset of symptoms associated with epididymitis, as this condition is a surgical emergency.

Among sexually active men <35 years, acute epididymitis is most frequently caused by *C. trachomatis* or *N. gonorrhoeae*. Acute epididymitis caused by sexually transmitted enteric organisms (e.g., *Escherichia coli*) also occurs among men who are the insertive partner during anal intercourse. Sexually transmitted acute epididymitis usually is accompanied by urethritis, which frequently is asymptomatic. Other non-sexually transmitted infectious causes of acute epididymitis are uncommon (e.g.; Fournier's gangrene etc), and should be managed in consultation with a urologist.

In older men >35 who do not report insertive anal intercourse, sexually transmitted acute epididymitis is less common. In this group, the epididymis usually becomes infected in the setting of bacteriuria secondary to bladder outlet obstruction (e.g., benign prostatic hyperplasia)⁷⁴⁰. In this older population, non-sexually transmitted acute epididymitis is also associated with prostate biopsy, urinary tract instrumentation or surgery, systemic disease, and/or immunosuppression.

Chronic epididymitis is characterized by a ≥6 week history of symptoms of discomfort and/or pain in the scrotum, testicle, or epididymis. Chronic infectious epididymitis is most frequently seen in conditions associated with a granulomatous reaction; *Mycobacterium tuberculosis* (TB) is the most common granulomatous disease affecting the epididymis and should be suspected, especially in men with a known history of or recent exposure to TB. The differential diagnosis of chronic non-infectious epididymitis, sometimes termed “orchalgia/epididymalgia” is broad (e.g., trauma, cancer, autoimmune, and idiopathic conditions) and these men should be referred to a

urologist for clinical management^{739,741}.

Diagnostic Considerations

Men who have acute epididymitis typically have unilateral testicular pain and tenderness, hydrocele and palpable swelling of the epididymis. Although the inflammation and swelling usually begin in the tail of the epididymis, they can spread to involve 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, but it occurs more frequently among adolescents and in men without evidence of inflammation or infection. When the onset of pain is sudden, unilateral, and severe, the test results do not support a diagnosis of urethritis or urinary-tract infection, or diagnosis of acute epididymitis is questionable, immediate referral to a urologist for evaluation of testicular torsion is important because testicular viability might be compromised.

Bilateral symptoms should raise suspicion of other causes of testicular pain. Radionuclide scanning of the scrotum is the most accurate method to diagnose epididymitis, but it is not routinely available. Ultrasound should be primarily used for ruling out torsion of the spermatic cord in cases of acute, unilateral, painful scrotum swelling. Differentiation between spermatic cord torsion and epididymitis must be made on the basis of clinical evaluation, when torsion is not ruled out by ultrasound, because partial spermatic cord torsion can mimic epididymitis on scrotal ultrasound. While ultrasound can demonstrate epididymal hyperemia and swelling associated with epididymitis, it provides minimal utility for men with a clinical presentation consistent with epididymitis; because a negative ultrasound does not alter clinical management. Ultrasound, therefore, should be reserved for men with scrotal pain who cannot be diagnosed accurately 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 point of care tests:

- Gram, methylene blue or gentian violet (MB or GV) stain of urethral secretions demonstrating ≥ 2 WBC per oil immersion field⁴⁶⁸. These stains are preferred point of care diagnostic tests for evaluating urethritis because they are highly sensitive and specific for documenting both urethral inflammation and the 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's or MB/GV stain, respectively.
- Positive leukocyte esterase test on first-void urine
- Microscopic examination of first-void urine sediment demonstrating ≥ 10 WBC per high spun power field.

All suspected cases of acute epididymitis should be tested for *C. trachomatis* and *N. gonorrhoeae*, in the absence of a positive gram, MB or GV stain smear, using nucleic acid amplification tests (NAATs). Urine is the preferred specimen for NAAT testing in men. Urine cultures for sexually transmitted chlamydia and gonococcal epididymitis have low diagnostic

yield; a negative urine culture does not exclude the presence of these sexually transmitted infections. Urine bacterial culture may have a higher yield in men with sexually transmitted enteric infections or in older men where genitourinary bacteruria is the cause of the acute epididymitis. All men with acute epididymitis should be tested for other STDs including HIV.

Treatment

Presumptive therapy is indicated at the time of the visit before all laboratory test results are available to prevent complications and onward transmission of sexually transmitted infections. The goals of treatment of acute epididymitis are 1) microbiologic cure of infection, 2) improvement of signs and symptoms, 3) prevention of transmission of chlamydia and gonorrhea to others, and 4) a decrease in potential chlamydia/gonorrhea complications (e.g., infertility or chronic pain). As an adjunct to therapy, bed rest, scrotal elevation, and non-steroidal anti-inflammatory drugs are recommended until fever and local inflammation have subsided. Because presumptive therapy is often initiated before laboratory tests are available, men at risk for sexually transmitted chlamydia and gonorrhea should receive ceftriaxone plus doxycycline for the initial therapy of epididymitis. For men who are at risk for both sexually transmitted chlamydia, gonorrhea, and enteric organisms (e.g., men who report insertive anal intercourse), ceftriaxone and levofloxacin or ofloxacin are recommended. Therapy including levofloxacin or ofloxacin should be considered if the infection is most likely caused by enteric organisms 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. Complete resolution of discomfort may take a few weeks after the antibiotic regimen is completed.

Recommended Regimens

For acute epididymitis most likely caused by sexually transmitted CT and GC

Ceftriaxone 250 mg IM in a single dose

PLUS

Doxycycline 100 mg orally twice a day for 10 days

For acute epididymitis most likely caused by sexually-transmitted Chlamydia and Gonorrhea and enteric organisms (men who practice insertive anal sex)

Ceftriaxone 250 mg IM in a single dose

PLUS

Levofloxacin 500 mg orally once a day for 10 days

OR

Ofloxacin 300 mg orally twice a day for 10 days

For acute epididymitis most likely caused by enteric organisms

Levofloxacin 500 mg orally once daily for 10 days

OR

Ofloxacin 300 mg orally twice a day for 10 days

Although most men with acute epididymitis can be treated on an out-patient basis, referral to a specialist and hospitalization should be considered when severe pain or fever suggests other diagnoses (e.g., torsion, testicular infarction, abscess, necrotizing fasciitis, etc) or when men are unable or unlikely to comply with an antimicrobial regimen. Because high fever is uncommon and indicates a complicated infection, these patients should be admitted for further evaluation.

Men who have acute epididymitis that is 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 completed treatment (i.e., until therapy is completed and symptoms have resolved).

Follow-Up

Men should be instructed to return to their health-care providers if their symptoms fail to improve within 48 hours of the initiation of treatment. Signs and symptoms of epididymitis that do not subside within 3 days require re-evaluation of the diagnosis and therapy. Swelling and tenderness that persist after completion of antimicrobial therapy should be evaluated for alternative diagnoses including tumor, abscess, infarction, testicular cancer, tuberculosis, and fungal epididymitis.

Management of Sex Partners

Men who have acute sexually transmitted epididymitis that is confirmed or suspected to be caused by *N. gonorrhoeae* or *C. trachomatis* should be instructed to refer sex partners for evaluation, testing, and presumptive treatment for CT and GC (see chlamydia and gonorrhea sections), if the contact was within the 60 days preceding onset of symptoms. If the last sexual intercourse was >60 days before onset of symptoms or diagnosis, the most recent sex partner should be treated. Arrangements should be made to link female partners to care. If linkage is delayed or unlikely, then expedited partner treatment and enhanced referral (see Partner Services) are alternative approaches to treating female partners of men who have chlamydia or gonococcal infections^{91,92}

Partners should be instructed to abstain from sexual intercourse until they and their sex partners have been adequately treated (i.e., until therapy is completed and patient and partners no longer have symptoms).

Special Considerations

Allergy, Intolerance, and Adverse Reactions

The cross reactivity between penicillins and cephalosporins is <2.5% in persons with a history of penicillin allergy^{418-421,454}. The risk of penicillin cross-reactivity between most second-generation (cefotaxime) and all third generation cephalosporins (ceftriaxone) is negligible⁴¹⁸⁻⁴²¹. The treatment of men with epididymitis and IgE allergic reactions to cephalosporins are rare. Alternative regimens have not been studied and providers should consult infectious disease specialists.

HIV Infection

Men with HIV infection who have uncomplicated acute epididymitis should receive the same treatment regimen as those who are HIV negative. Other etiologic agents have been implicated in acute epididymitis in men with HIV infection including CMV, salmonella, toxoplasmosis,

Ureaplasma urealyticum, *Corynebacterium* sp., *Mycoplasma* sp., and *Mima polymorpha*. Fungi and mycobacteria are also more likely to cause acute epididymitis in men with HIV infection than in immunocompetent men. These data are insufficient to recommend different treatment in men with HIV and acute epididymitis.

Human Papillomavirus (HPV) Infection

More than 100 types of HPV exist, at least 40 of which can infect the genital area. Most HPV infections are asymptomatic or unrecognized. Oncogenic, or high-risk HPV infection (e.g., HPV types 16 and 18), causes most cervical cancers and many penile, vulvar, vaginal, and anal cancers, as well as oropharyngeal cancers⁷⁴². Nononcogenic, or low-risk HPV types (e.g., HPV types 6 and 11), are the cause of genital warts and recurrent respiratory papillomatosis. Asymptomatic genital HPV infection is common and usually self-limited. It is estimated that most sexually active persons become infected at least once in their lifetime^{525,743}. Persistent oncogenic HPV infection is the strongest risk factor for development of HPV-associated precancers and cancers.

There is a substantial burden of cancers and anogenital warts due to HPV. In 2009 there were an estimated 34,788 new HPV-associated cancers in men and women in the United States^{744,745}, and an estimated 355,000 new cases of anogenital warts⁷⁴⁶.

Prevention

HPV vaccines

Two HPV vaccines are licensed in the United States: a bivalent vaccine (Cervarix[®]) that prevents infection with HPV types 16 and 18 and a quadrivalent vaccine (Gardasil[®]) that prevents infection with HPV types 6, 11, 16, and 18. Both vaccines offer protection against the HPV types that cause 70% of cervical cancers (i.e., types 16 and 18), and the quadrivalent HPV vaccine also protects against the types that cause 90% of genital warts (i.e., types 6 and 11). Either vaccine is recommended routinely for girls aged 11–12 years and can be administered beginning at 9 years of age^{17,19}; girls and women aged 13–26 years who have not started or completed the vaccine series should receive the vaccine. The quadrivalent HPV vaccine is recommended routinely for boys aged 11–12 years and can be administered beginning at 9 years of age; boys and men aged 13–21 years who have not started or completed the vaccine series should receive the vaccine¹⁵⁹. For immunocompromised males (including persons with HIV infection) and men who have sex with men, vaccination is recommended through age 26 years of age¹⁵⁹ for men not previously vaccinated. In the United States, the vaccines are not licensed or recommended for use in men or women aged >26 years.

Both HPV vaccines are administered as a 3-dose series of IM injections over a 6-month period, with the second doses given 1–2 months after the first and the third dose 6 months after the first dose. If the vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be given as soon as possible, and second and third doses should be separated by an interval of at least 12 weeks and 24 weeks after the first dose. Either vaccine may be administered regardless of prior history

of anogenital warts, abnormal Pap/HPV test or history of anogenital precancer. Women who have received HPV vaccine should continue routine cervical cancer screening if they are aged 21 years or older because 30% of cervical cancers are caused by HPV types other than 16 or 18.

HPV vaccine is available for eligible male and female children and adolescents aged <19 years through the Vaccines for Children (VFC) program (information available by calling CDC INFO [800-232-4636]). Patient assistance programs are available for uninsured or underinsured male and females aged 19-26 years from the vaccine manufacturers.

Over 62 million doses of HPV vaccine have been distributed in the U.S. as of March, 2014; prelicensure and postlicensure safety evaluations have found the vaccine to be well tolerated⁷⁴⁷ (<http://www.cdc.gov/vaccinesafety/Vaccines/HPV/index.html>). Impact monitoring studies in the U.S. have demonstrated reductions of genital warts and HPV vaccine types^{748,749}.

Providers in STD clinics should routinely recommend the HPV vaccine to eligible attendees who have not started or completed the vaccine series. Settings that provide STD services should either provide the vaccine at the clinic or refer to a provider or facility that provides the vaccine. Clinical providers are key to vaccination uptake, and providers should be knowledgeable about HPV and HPV vaccine (<http://www.cdc.gov/vaccines/who/teens/for-hcp/hpv-resources.html>).

Other HPV prevention approaches include consistent and correct condom use, and limiting the number of sex partners. These interventions may not fully protect against HPV but they can lower the chances of HPV acquisition and transmission.

Diagnostic Considerations

HPV Tests

HPV tests are available to detect oncogenic types of HPV infection and are used in the context of cervical cancer screening and for management or follow-up of abnormal cervical cytology or histology (see cervical cancer screening section)

Treatment

Treatment is directed to the macroscopic (e.g., genital warts) or pathologic precancerous lesions caused by HPV. Precancerous lesions are detected by cervical cancer screening (see cervical cancer screening) and management of HPV-related precancer should be managed based on existing guidance.

Treatment of anogenital and oral warts should be performed in an appropriately ventilated room using Standard Precautions (<http://www.cdc.gov/hicpac/pdf/isolation/Isolation2007.pdf>) and local exhaust ventilation⁷⁵⁰ (e.g., smoke evacuator) (<http://www.cdc.gov/niosh/docs/hazardcontrol/hc11.html>).

Counseling

Key messages for persons with HPV infection

General

- HPV is a very common virus that can infect the genital areas of men and women. It can also infect other areas including the mouth and throat. Most sexually active people get HPV at some time in their lives, although most never know it.
- Most persons who acquire HPV do not develop health problems from it. In most cases, the body's natural defenses control HPV before it can cause any health problems. When the body does not control HPV infection, genital warts can develop. HPV can also cause cervical cancer and other cancers, including cancers of the anus, penis, vulva, vagina, and head and neck.
- The types of HPV that cause genital warts are different from the types that can cause cancer.
- HPV is often transmitted from one sex partner to another. It is transmitted on through genital contact, mainly during vaginal and anal sex. HPV may also be transmitted during oral sex. In rare cases, a pregnant woman can transmit HPV to an infant during delivery.
- Having HPV does not make it harder for a woman to get or stay pregnant. However, some of the cancers that HPV can cause, as well as the treatments needed to prevent or treat them, may lower a woman's ability to get pregnant or have a healthy delivery.
- Partners who have been together tend to share HPV. There is no way to know if which partner transmitted HPV. Having HPV does not mean that a person or his/her partner is having sex outside the relationship.
- There are treatments for the conditions caused by HPV, but not for the virus itself.
- There is no HPV test to check "HPV status." There are HPV tests that can help detect HPV in women, and can be used to determine who is at increased risk of cervical cancer. These tests are not designed to test for other HPV-related problems. Nor are they useful in women under 25 years old or men (regardless of age).

Prevention of HPV

- There are two HPV vaccines that can prevent important diseases and cancers caused by HPV. HPV vaccines are recommended routinely for 11-12 year old boys and girls. Two vaccines (Cervarix[®] and Gardasil[®]) protect against most cases of cervical cancer, and one vaccine (Gardasil[®]) also protects against most genital warts. Either vaccine is recommended for girls/women, and one vaccine (Gardasil) is recommended for boys/men. These vaccines are given as 3 injections over 6 months.
(<http://www.cdc.gov/vaccines/vpd-vac/hpv/>).
- Condoms used consistently and correctly may lower the chances of acquiring and transmitting HPV and developing HPV-related diseases, such as genital warts and cervical cancer. However, HPV can infect areas that are not covered by a condom; so condoms may not fully protect against HPV.
- Limiting the number of sex partners can prevent HPV. However it is important to note, even people with only one lifetime sex partner can get HPV.

Genital Warts

Anogenital Warts

Ninety percent of anogenital warts are caused by nononcogenic HPV 6 or 11. HPV types 6 or 11 are commonly found before or at the same time that anogenital warts are detected⁷⁵¹. HPV types 16, 18, 31, 33, and 35 are also occasionally found in anogenital warts (usually as co-infections with HPV 6 or 11) and can be associated with foci of high-grade squamous intraepithelial lesions (HSIL), particularly in 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, but 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 and scrotum). Intra-anal warts are observed predominantly in persons who have had receptive anal intercourse, but can also occur in men and women who do not have a history of anal sexual contact.

Diagnostic Considerations

Diagnosis of anogenital warts is usually made by visual inspection. The diagnosis of anogenital warts can be confirmed by biopsy, which is indicated if lesions are atypical such as pigmented, indurated, fixed to underlying tissue, bleeding, or ulcerated. Biopsy might also be indicated if: 1) the diagnosis is uncertain; or 2) the lesions do not respond to standard therapy; or 3) the disease worsens during therapy. Biopsy should be considered in these circumstances especially if the patient is immunocompromised (including HIV infection).

The use of HPV DNA testing for anogenital wart diagnosis is not recommended, because test results do not confirm the diagnosis and do not assist with genital warts management.

The application of 3%–5% acetic acid, which might cause affected areas to turn white, has been used by some providers to detect HPV-infected genital mucosa. However, acetic acid application is not a specific test for HPV infection and treatment of these findings without macroscopic or pathologic precancerous lesions is of unknown benefit. Therefore, the routine use of this procedure for screening to detect mucosal changes attributed to HPV infection is not recommended.

Treatment

Most genital warts are asymptomatic; however, symptoms when they occur include itching, pain, and bleeding. The appearance of warts can also result in significant psychosocial distress. The aim of treatment is removal of the wart and amelioration of symptoms, if present. In most patients, treatment results in resolution of the wart(s). If left untreated, anogenital warts

can resolve on their own, remain unchanged, or increase in size or number. Because warts may spontaneously resolve within a year, an acceptable alternative for some persons is to forego treatment and wait for spontaneous resolution. Available therapies for anogenital warts may reduce, but probably do not eradicate, HPV infectivity. Whether the reduction in HPV viral DNA resulting from treatment reduces future transmission remains unclear.

Recommended Regimens

Treatment of anogenital warts should be guided by the preference of the patient, available resources, and the experience of the health-care provider. No definitive evidence suggests that any of the recommended treatments are superior to any other, and no single treatment is ideal for all patients or all warts. The use of locally developed and monitored treatment algorithms has been associated with improved clinical outcomes and should be encouraged. Because all available treatments have shortcomings, some clinics employ 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 of complications associated with combination therapy.

Factors that influence selection of treatment include wart size, number, anatomic site, and morphology; patient preference, cost of treatment, convenience, adverse effects, and provider experience. Factors that might affect response to therapy include immunosuppression and compliance with therapy. The treatment modality should be changed if there is no substantial improvement after a complete course of treatment or if side effects are severe. Most anogenital warts respond within 3 months of therapy. The response to treatment and any side effects should be evaluated throughout the course of therapy.

Complications occur rarely when treatment is administered properly. Persistent hypopigmentation or hyperpigmentation can occur with ablative modalities (e.g.; cryotherapy, electrocautery) and have been described with immune modulating therapies (e.g.; imiquimod cream). 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.

Treatment regimens are classified as either patient-applied or provider-administered modalities. Patient-applied modalities are preferred by some persons because they can be administered in the privacy of their home. To ensure that patient-applied modalities are effective, instructions should be provided in the clinic and all anogenital warts should be accessible and identified. Follow-up visits after several weeks of therapy enable providers to answer any questions about the use of the medication and address any side effects they have experienced; follow-up visits also facilitate the assessment of the response to treatment.

Recommended Regimens for External Anogenital Warts (i.e., penis, groin, scrotum, vulva, perineum, external anus, and 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 either by tangential scissor excision, tangential shave excision, curettage, laser or electrosurgery.

OR

Trichloroacetic acid (TCA) or Bichloroacetic acid (BCA) 80%–90% solution

* Might weaken condoms and vaginal diaphragms

† Many persons with external anal warts also have intra-anal warts, so persons with external anal warts might benefit from an inspection of the anal canal by digital examination, standard anoscopy, or high-resolution anoscopy.

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, three times a week for up to 16 weeks⁷⁵². Similarly, imiquimod 3.75% cream should be applied once at bedtime, but is applied every night⁷⁵³. 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/erosions, and vesicles may occur with the use of imiquimod, and hypopigmentation has also been described⁷⁵⁴. In a small number of case reports, treatment with imiquimod cream might have been associated with worsened inflammatory or autoimmune skin diseases such as psoriasis, vitiligo, and lichenoid dermatoses

⁷⁵⁵⁻⁷⁵⁷. There are limited human data on the use of imiquimod in pregnancy, but animal data suggest that it is low risk. ³¹⁰

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 visible anogenital warts twice a 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 cm², and the total volume of podofilox should be limited to 0.5 mL per day. If possible, the health-care provider should apply the initial treatment to demonstrate the proper application technique and identify which warts should be treated. Mild to moderate pain or local irritation might develop after treatment. Podofilox is contraindicated in pregnancy. ³¹⁰

Sinecatechins is a patient-applied green-tea extract with an active product (catechins). Sinecatechins 15% ointment should be applied three times daily (0.5 cm strand of ointment to each wart) 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 longer than 16 weeks⁷⁵⁸⁻⁷⁶⁰. The medication should not be washed off after use. Sexual (i.e., genital, anal, or oral) contact should be avoided while the ointment is on the skin. The most common side effects of sinecatechins are erythema, pruritus/burning, pain, ulceration, edema, induration, and vesicular rash. The medication is not recommended for persons with HIV infection, other immunocompromised conditions, or with 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-applied therapy that destroys warts by thermal-induced cytolysis. Health-care providers must be trained on the proper use of this therapy because over- and 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 usually eliminating warts at a single visit, however recurrence can occur. Surgical removal requires substantial clinical training, additional equipment, and sometimes a longer office visit. After local anesthesia is applied, visible anogenital warts can be physically destroyed by electrocautery, in which case no additional hemostasis is required. Care must 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 carbon dioxide (CO₂) 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 very minor bleeding, a chemical styptic (e.g., an aluminum chloride solution). Suturing is neither required nor indicated in most cases. In patients with large or extensive warts, surgical therapy, including CO₂ laser may be most beneficial. Surgical therapy, including CO₂ laser might also be useful for intraurethral warts, particularly for those persons who have not responded to other treatments.

Trichloroacetic acid (TCA) and bichloroacetic acid (BCA) are provider-applied 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 powdered with talc, covered with sodium bicarbonate (i.e., baking soda), or washed with liquid soap preparations to neutralize the acid or remove unreacted acid. TCA/BCA treatment can be repeated weekly if necessary.

Alternative Regimens

Alternative regimens have less data on efficacy and might be associated with more side effects, including intralesional interferon, photodynamic therapy, topical cidofovir, and podophyllin resin. Podophyllin resin is no longer a recommended regimen because of the array of safe and effective regimens available, and because there have been reports of severe systemic toxicity when podophyllin resin was applied to large areas of friable tissue and was not washed off within 4 hours⁷⁶¹⁻⁷⁶³. Podophyllin resin 10%–25% in compound tincture of benzoin can be considered for provider-administered treatment if strict adherence to the recommendations for application. Podophyllin should be applied to each wart and then allowed to air-dry before the treated area comes into contact with clothing. Over-application 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: 1) application should be limited to <0.5 mL of podophyllin or an area of <10 cm² of warts per session 2) the area to which treatment is administered should not contain any open lesions, wounds, or friable tissue, and 3) the preparation should be thoroughly washed off 1–4 hours after application. Podophyllin resin preparations differ in the concentration of active components and contaminants. The shelf-life and stability of podophyllin preparations are unknown.

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

TCA or BCA 80%–90% applied to warts.

OR

Surgical removal

Recommended Regimens for Cervical Warts

Cryotherapy with liquid nitrogen

OR

TCA or BCA 80%–90% applied to warts

OR

Surgical removal

Management of cervical warts should include consultation with a specialist.

For women who have exophytic cervical warts, a biopsy evaluation to exclude high-grade SIL must be performed before treatment is initiated.

Recommended Regimens for Intra-anal Warts

Cryotherapy with liquid nitrogen

OR

TCA or BCA 80%–90% applied to warts

OR

Surgical removal

Management of intra-anal warts should include consultation with a specialist.

Counseling

Key messages for persons with anogenital warts

- If left untreated, genital warts may go away, stay the same, or increase in size or number. Genital warts do not turn into cancer. 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.
- Genital warts can develop months or years after getting HPV. Genital warts can be passed on to another person even when there are no visible signs of warts.
- There is no sure way to know when HPV was acquired. Sex partners who have been together tend to share HPV, even though both partners may not show signs of HPV.
- Although genital warts are common and benign, there is considerable psychosocial impact of this diagnosis.
- There are treatments for the conditions caused by HPV, such as genital warts. However, treating genital warts does not treat the virus itself. For this reason, it is common for genital warts to come back after treatment, especially in the first 3 months.
- Inform current sexual partner(s) that genital warts may be transmitted to a partner(s). Partner(s) may benefit from getting tested for other sexually transmitted diseases (STDs). A current partner may already have HPV, even though s/he may not have visible signs of warts.
- Sexual activity should be avoided with new partners until the warts are gone or removed. HPV may remain and can still be passed on to partners, even after the warts are gone.
- Condoms may lower the chances of transmitting genital warts if used with every sex act, however HPV can infect areas that are not covered by a condom and may not fully protect against HPV.
- There is a vaccine available for males and females that prevents genital warts (Gardasil®) but it will not treat existing HPV or genital warts. This vaccine can prevent most cases of genital warts in persons who have not yet been exposed to wart-causing types of HPV.
- It is not clear if there is any health benefit to informing (future) partners about a past diagnosis of genital warts. This is because it is not known how long the virus remains after warts are gone.

Management of Sex Partners

Patients should inform current partner(s) about having genital warts because the warts may be passed on to partners. Patients and partner(s) may benefit from getting tested for other sexually transmitted diseases (STDs). Patients with genital warts should avoid sexual activity with new partners until the warts are gone or removed. However, HPV may remain and can still be passed on to partners, even after the warts are gone. There are no recommendations to inform future sex partners about a diagnosis of genital warts. It is not clear if there is any health benefit to informing future sex partners because it is not known how long HPV remains after visible warts are gone.

Special Considerations

Pregnancy

Sinecatechins, podophyllin, and podofilox (podophyllotoxin) should not be used during pregnancy. Imiquimod seems to be low risk, but until more data are available, it should also be avoided. 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 in infants and children, although the route of transmission (i.e., transplacental, perinatal, or postnatal) is not completely understood. Whether cesarean section prevents respiratory papillomatosis in infants and children also is unclear⁷⁶⁴; 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 concerning the low risk for warts on the larynx (recurrent respiratory papillomatosis) in their infants or children.

HIV infection and other causes of immunosuppression

Persons with HIV infection or are otherwise immunosuppressed are more likely to develop anogenital warts than persons who do not have HIV infection⁷⁶⁵; moreover, lesions are often more recalcitrant to treatment. No data suggest that treatment modalities for external anogenital warts should be different for persons with HIV infection. Although there is a theoretical risk that local immunomodulation with imiquimod could cause changes to systemic iatrogenic immunosuppression and graft failure in organ transplant patients, there have been no reports of this occurring. However, persons who are immunosuppressed because of HIV or other reasons might have larger or more numerous warts, might not respond as well as immunocompetent persons to therapy for anogenital warts, and might have more frequent recurrences after treatment⁷⁶⁵⁻⁷⁶⁸. 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 cases⁷⁶⁹⁻⁷⁷¹

High grade Squamous Intraepithelial Lesions (HSIL)

If a biopsy of an anogenital lesion or atypical wart reveals HSIL or cancer of the anogenital tract, the patient should be referred to a specialist for treatment because careful follow-up is essential for patient management.

HPV-Associated Cancers

Persistent infection with oncogenic HPV types has a causal role in nearly all cervical cancers and in many vulvar, vaginal, penile, anal and oropharyngeal cancers⁷⁷². The only HPV-associated cancer for which routine screening is recommended is cervical cancer.

Cervical Cancer

Screening Recommendations

The recommendations for cervical cancer screening in the United States are based on systematic evidence reviews and are largely consistent across the major medical organizations including the American Cancer Society, American College of Obstetricians and Gynecologists and the US Preventive Services Task Force¹²⁴⁻¹²⁶. (<http://www.cdc.gov/cancer/cervical/index.htm>).

Routine cervical cancer screening is screening for asymptomatic average-risk women. Routine cervical screening to prevent invasive cervical cancer should be performed starting at age 21, through age 65 using either conventional or liquid-based cytologic tests (i.e., Pap tests), and can include several FDA-approved HR (oncogenic or high risk)-HPV tests as part of screening for women 30 years of age and older. For cytopathologic and HR HPV testing, clinics should use CLIA-certified laboratories using acceptable terminology (Bethesda 2001 or LAST terminology)^{773 774}. Pap testing is recommended every 3 years between ages 21-29 years; and then either a Pap test every 3 years between ages 30-65 years or a Pap test plus HPV test (co-test) every 5 years between ages 30-65 years is recommended. Co-testing can be done by either collecting one swab for the Pap test and another for the HPV test or by using the remaining liquid cytology material for the HPV test. Because of the high negative predictive value of two tests that are negative, women who test negative for both HPV and Pap test should not be screened again for 5 years. Cervical screening programs should screen women who have received HPV vaccination in the same manner as unvaccinated women. Women should be asked about their most recent Pap test, Pap test results, evaluation and treatment (e.g. LEEP, colposcopy) to assist with management considerations; every effort should be made to obtain copies of recent results.

When available, a copy of the Pap test and (HPV test result if applicable) should be provided along with general recommendations on when the next visit should be for women who have normal results. Women with abnormal screening or diagnostic tests should be referred to providers who are experienced in managing these cases (see Follow-Up). Women should be given specific reassurance and counseling of what abnormal cervical cancer screening tests means for follow as well as any implications it has for the partner.

Provision of cervical cancer screening services in STD clinics may be an opportunity to reach

underserved women at risk for cervical cancer. If these settings not are able to provide cervical cancer screening and appropriately ensure that women who have receive an abnormal test receive adequate follow-up or referral then, they should refer eligible women to a provider or facility that provides cervical cancer screening.

The following additional considerations are associated with performing Pap tests:

- All women should receive cervical cancer screening, regardless of sexual orientation (i.e., women who identify as lesbian, bisexual or heterosexual).
- Ideally the woman should be advised to have a Pap test 10-20 days after first day of menses. However, if a woman is menstruating, a Pap test may or may not be postponed, depending on the menses flow and type of cytology used (liquid-based cytology can differentiate cells from blood and mucus; conventional Pap test may not).
- If specific infections other than HPV are identified, the patient might need to have a repeat Pap test after appropriate treatment for those infections. However, in most instances (even in the presence of some severe infections), Pap tests will be reported as satisfactory for evaluation, and reliable final reports can be produced without the need to repeat the Pap test after treatment is received.
- The presence of a mucopurulent discharge should not postpone Pap testing. The test can be performed after removal of the discharge with a saline-soaked cotton swab.
- In the absence of other indications, women who have external genital warts do not need Pap tests more frequently than women who do not have warts.
- The sequence of Pap testing in relation to collection of other endocervical specimens does not influence Pap test results or their interpretation⁷⁷⁵. In general vaginal specimens are preferred for chlamydia and gonorrhea screening in women but in the setting of a pelvic exam, endocervical specimens for STD testing can be collected first.
- Women who have had a total hysterectomy do not require a routine Pap test unless the hysterectomy was performed because of cervical cancer or its precursor lesions.

In women whose cervix remains intact after a hysterectomy, regularly scheduled Pap tests should be performed as indicated⁷⁷⁶⁻⁷⁷⁸.

- Health-care providers who receive basic training on Pap test collection and clinics that use simple quality assurance measures are more likely to obtain satisfactory test results as determined by the laboratory.
- The use of instruments that are designed to sample to the cervical transformation zone (e.g., cytobrushes) improves the accuracy of Pap tests.⁷⁷⁹
- Liquid-based cytology is an acceptable alternative to conventional Pap tests, as it has similar

test-performance characteristics.

HPV Tests

Clinical tests for oncogenic types of HPV can be used for cervical cancer screening, for triage of abnormal cervical cytology results, and follow-up after treatment of cervical precancers. These tests are only approved for use with cervical specimens, not oral or anal specimens. They should also not be used, for men, for women aged <25 years, or as a general test for STDs.

Current FDA-cleared HPV tests detect viral nucleic acid (DNA) or messenger RNA (mRNA). Several FDA-cleared tests for HPV testing are available for use in the United States but the use of the low risk type (non-oncogenic) tests are not recommended¹¹¹. The Hybrid Capture 2 High-Risk HPV DNA test (Qiagen, Gaithersburg, Maryland) and the Cervista HPV High-Risk DNA test (Hologic, Bedford, Massachusetts) detect presence of 13–14 high-risk HPV types, whereas the Cervista HPV 16/18 DNA test detects type-specific infection with HPV types 16 and 18. The Digene HC2 HPV DNA test (Qiagen, Gaithersburg, Maryland) detects 13 high-risk or five low-risk HPV types. The Cobas 4500 (Roche, Pleasanton California) test detects 14 high-risk HPV DNA types and can detect individual types HPV 16 and 18, while the APTIMA HPV (Gen Probe, San Diego CA) test detects 14 high-risk HPV types of HPV mRNA. Aptima HPV 16/18/45 test is also FDA-cleared to triage its pooled Aptima HR HPV test further—although there are no algorithms for HPV 16/18/45 testing in any of the guidelines. It is important to confirm that the HPV assays are FDA-cleared, and that the test is being used for the appropriate indications¹¹¹.

The most common use of HPV tests to detect oncogenic types of HPV infection in the United States has been as a triage test for atypical squamous cells of undetermined significance (ASC-US) Pap tests. Newer management recommendations prefer that HPV tests not be used for women under <25 years for management of ASC-US Pap tests, however they can still be used as part of ASC-US triage in women ≥ 25 years¹¹¹. HPV testing for oncogenic types are now being incorporated into cervical cancer screening recommendations with Pap tests (i.e.; co-testing) to reduce follow-up visits. One recommended screening strategy is HPV testing with a Pap test every five years for women aged 30–65 years. HPV testing for 16 and 18 is also used to triage discordant co-tests (e.g.; negative Pap test and positive HPV test). Oncogenic (high-risk) HPV tests may be considered in the future for primary cervical cancer screening, but there are no current recommendations.

HPV testing (including oncogenic HPV and HPV 16/18 tests) is not recommended for the following situations:

- Deciding whether to vaccinate against HPV;
- Conducting STD screening in women or men at risk for STDs; persons with genital warts or their partners;
- Testing oral or anal specimens;
- Testing women aged <30 as part of routine cervical cancer screening; and
- Screening for cervical cancer as a stand-alone test (i.e., without a concurrent Pap test).

Follow-Up

If the results of the Pap test are abnormal, follow-up care should be provided according to the complex but thorough *ASCCP 2012 Consensus Guidelines for Management of Abnormal Cervical Cytology*¹¹¹ (management and follow-up care available at <http://www.asccp.org>). If resources in clinics do not allow for follow-up of women with abnormal results, protocols for linkage to follow-up care and management should be in place. Some highlights of these guidelines include:

- Women aged 21-24 years are managed more conservatively in general due to potential harms of overtreatment, and low risk of cancer. For example, if a women aged 21-24 years has ASC-US or LSIL, the preferred option is to repeat cytology in 12 months
- For women with ASC-US cytology, either repeat cytology in 12 months for all ages or reflex HPV testing for women ≥ 25 years is recommended.
- For women with ASC-US and HPV negative, a repeat HPV and Pap test in 3 years is recommended.
- For women who have normal cytology but lack endocervical cells, a repeat Pap is not required. For women who have unsatisfactory cytology, regardless of negative HPV result, a repeat cytology is required in 2-4 months.
- HPV 16/18 testing is one follow-up option for women who have discordant results (normal Pap test/positive HPV test). If positive, women should go immediately to colposcopy. If negative, repeating the HPV co- test in a year is recommended.

The establishment of colposcopy and biopsy services in STD clinics in which referrals are difficult and follow-up is unlikely, should be considered if resources are available. Available resources and eligibility criteria for programs that should be considered including federally qualified health centers, the National Breast and Cervical Cancer Early Detection Program (<http://www.cdc.gov/cancer/nbccedp/>), Title X (<http://www.hhs.gov/opa/title-x-family-planning/>), and others that offer screening and linkage to treatment. The ASCCP now has an app available for purchase and download for management of abnormal cytological and histological results. The app takes into consideration just the current results but clinicians need to take into consideration past abnormal Pap or cervical procedures

<http://www.asccp.org/Bookstore/ASCCP-Algorithms-Mobile-App> .

Management of Sex Partners

Sex partners should receive counseling messages that partners do not need to be tested for HPV as it is unclear the timing or source of HPV. Additional messages include:

- HPV is very common. Most women will get HPV at some point in their lives.
- There is no way of knowing how long HPV has been present or who transmitted the virus.
- Having HPV is not a sign of infidelity or promiscuity.
- Most women who have HPV do not develop abnormal cells or cancer.
- Women who have HPV in their cells for a long time are at greater risk for developing abnormal cells or cancer.

Counseling

Women, especially younger and/or more vulnerable women, may believe the Pap test screens for conditions other than cervical cancer, or may be confused by abnormal results^{780, 781, 782}. Health-care providers, a trusted source of information about HPV and abnormal Pap test results, are key in educating women about high-risk HPV and moderating the psychosocial impact of abnormal results^{538, 783, 784, 720}. Women should be counseled on the risks, uncertainties, and the benefits of screening^{126, 785}. Education, counseling, and follow-up reminders by phone, text or email may increase screening and adherence to follow-up⁷⁸⁶. Multiple forms of communication, such as in-person counseling as well as printed or online information, may be more effective than one form alone⁷⁸⁷. Print materials and online resources are available at: http://www.cdc.gov/cancer/cervical/basic_info/screening.htm; <http://www.cdc.gov/std/hpv/common/>; http://www.ashastd.org/hpv/hpv_publications.cfm.

Abnormal Pap test and/or HPV test results can cause short-term anxiety, stress, fear, and confusion, decreasing women's ability to absorb and retain information, and possibly acting as a barrier to follow-up care^{781, 788-790}. A positive HPV test might exacerbate these feelings and elicit partner concerns, worry about disclosure, and feelings of guilt, anger, and stigmatization^{783, 789}. Providers should frame high-risk HPV positivity in a neutral, non-stigmatizing context and emphasize its common, asymptomatic, and transient nature. Also, providers should emphasize that HPV is often shared between partners and having HPV does not imply infidelity, nor should it necessarily raise concerns about a partner's health⁷⁸³.

Key messages for women regarding Cervical Cancer Screening

- Cervical cancer can be prevented with regular screening tests, like the Pap test and the HPV DNA test (HPV test). All women should start getting regular Pap tests at age 21 years.
- The Pap test finds abnormal cells on a woman's cervix. For this test, cells from your cervix can be looked at with a microscope. An HPV test detects HPV on a woman's cervix. The HPV test can be used at the same time as the Pap test, called the HPV co-test, for women 30 years of age and older. The HPV test may also be used after an inconclusive Pap test, called a reflex HPV test, for women 21 years of age and older.
- Cancer screening tests look for early signs of cancer. The Pap and HPV test both screen for early signs of cervical cancer. Cervical cancer often does not cause symptoms until it is advanced. So it is important to get screened even when you feel healthy.
- HPV is a common infection and often clears. A positive HPV test does not mean that a person has cancer.
- HPV is often shared between partners and can lie dormant for many years; having HPV does not imply infidelity, nor should it necessarily raise concerns about a partner's health.

http://www.cdc.gov/cancer/hpv/basic_info/screening/

Special Considerations

Pregnancy

Pregnant women should be screened at the same intervals as nonpregnant women; however, recommendations for management of abnormal screening tests differ in this population and women should be referred to a specialist⁷⁹¹⁻⁷⁹³. A swab, Ayre's spatula, or cytobrush can be used in pregnant women⁷⁹⁴⁻⁷⁹⁶.

HIV Infection

Several studies have documented an increased risk of cervical precancers and cancers in women with HIV infection⁷⁹⁷⁻⁷⁹⁸. HIV-infected women should be screened within one year of sexual activity or initial HIV test using conventional or liquid-based cytology (Pap test) and then again 6 months later. Screening and management recommendations for women with HIV infection are provided by the Opportunistic Infection Guidelines²³⁵.

Adolescents

Prevalence of oncogenic HPV types are high among adolescents aged <21 years of age⁷⁹⁹ and HPV and squamous intraepithelial lesions caused by HPV in adolescent girls tend to regress. For these reasons, cervical cancer screening or HPV testing is not recommended in adolescents. The guidelines for HIV-infected adolescents differ²³⁵. Because of the reported high rate of progression of abnormal cytology in adolescents with HIV infection and young women who were infected through sexual intercourse, providers should consider screening all adolescent and young women with HIV within 1 year of onset of sexual activity, regardless of age or mode of HIV infection (e.g., perinatally acquired, sexually acquired)²³⁵.

Anal Cancer

Data are insufficient to recommend routine anal cancer screening with anal cytology in persons with HIV infection or MSM without HIV infection, as well as in the general population. 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.

An annual digital anorectal examination may be useful to detect masses on palpation that could be anal cancer in persons with HIV infection and possibly HIV-negative MSM²³⁵; annual digital anorectal examination is not recommended for the general population. Some clinical centers perform anal cytology to screen for anal cancer among high-risk populations (e.g. persons with HIV infection, MSM), followed by high-resolution anoscopy (HRA) for those with abnormal cytologic results (e.g. ASC-US or worse).

High-risk HPV tests are not clinically useful for anal cancer screening among MSM due to a very high prevalence of anal HPV infection^{800,801}.

Vaccine Preventable STDs

Hepatitis A

Hepatitis A, caused by infection with HAV, has an incubation period of approximately 28 days (range: 15–50 days). HAV replicates in the liver and is shed in high concentrations in feces from 2 to 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 (CLD). However, up to 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 >70% of adults having symptoms compatible with acute viral hepatitis and most children having either asymptomatic or unrecognized infection. Antibody produced in response to HAV infection persists for life and confers protection against reinfection.

HAV infection is primarily transmitted by the fecal-oral route, by either person-to-person contact or through consumption of contaminated food or water. Although viremia occurs early in infection and can persist for several weeks after onset of symptoms, bloodborne transmission of HAV is uncommon. Transmission by saliva has not been demonstrated.

In the United States, among 2010 reported hepatitis A cases with risk information, a risk was identified in only 25%⁸⁰². Among adults with identified risk factors, most cases occurred among international travelers, individuals exposed to a common source food or water source outbreak, and contacts (e.g., sexual, household or employee of or child attending a nursery, daycare, or preschool), nonhousehold contacts (e.g., those encountered directly through play and daycare), MSM, and IDUs⁸⁰². Transmission of HAV during sexual activity probably results from fecal-oral contact. Efforts to promote good personal hygiene have not been successful in interrupting outbreaks of hepatitis A. Vaccination is the most effective means of preventing HAV transmission among persons at risk for infection (e.g., MSM, drug users, and persons with CLD).

Diagnosis

The diagnosis of hepatitis A cannot be made on clinical grounds alone; serologic testing also is required. The 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 hepatitis A 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 critical 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 hepatitis A.

Prevention

Two products are available for the prevention of HAV infection: hepatitis A vaccine (Table 2) and immune globulin (IG) for IM post exposure prophylaxis. Hepatitis A vaccines are prepared from formalin-inactivated, cell-culture–derived HAV. Two monovalent vaccines (HAVRIX, GlaxoSmithKline; VAQTA, Merck & Co., Inc), are cleared by FDA for persons aged ≥ 12 months, and these vaccines are available for eligible children and adolescents aged <19 years through the VFC program (800-232-4636).

Administered IM in a 2-dose series at 0 and 6–18 months, these vaccines induce protective antibody levels in virtually all adults; by 1 month after the first dose, 94%–100% of adults have protective antibody levels and 100% of adults after a second dose². Kinetic models of antibody decline indicate that protective levels of antibody persist for at least 20 years. A study in Alaska Native individuals has shown that seropositivity for hepatitis A persists for at least 10 years after completing two-dose vaccination at age 12 to 21 months⁸⁰³. Sustained protection and the need for booster dosing will continue to be assessed by persistence of anti-HAV^{804,805}. A combined hepatitis A and hepatitis B vaccine has been developed and licensed for use as a 3-dose series in adults aged ≥ 18 years (Table 3). When administered IM on a 0-, 1-, and 6-month schedule, the vaccine has equivalent immunogenicity to that of the monovalent vaccines.

IG is a sterile solution of concentrated immunoglobulins prepared from pooled human plasma processed by cold ethanol fractionation. In the United States, IG is produced only from plasma that has tested negative for hepatitis B surface antigen, 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 within 2 weeks after exposure to HAV, IG is $>85\%$ effective in preventing HAV infections.

Pre-exposure Vaccination

Persons in the following groups who seek STD services should be offered hepatitis A vaccine: 1) all MSM; 2) drug users (injection and noninjection illicit drugs); and 3) persons with CLD, including persons with chronic HBV and HCV infection who have evidence of CLD.

Prevaccination Serologic Testing for Susceptibility

Approximately one third of the U.S. population has serologic evidence of previous HAV infection, which increases with age⁸⁰⁶. The potential cost-savings of prevaccination testing should be weighed against the cost and the likelihood that testing will interfere with initiating vaccination. Thus, testing should not be a barrier to vaccination in at risk groups. In these cases the first vaccine dose should be administered immediately after collection of the blood sample for serologic testing. Vaccination of a person who is already immune is not harmful.

Persons who have a documented history of ≥ 2 -dose hepatitis A vaccination in the past do not need further vaccination or serologic testing.

TABLE 2. Recommended regimens: dose and schedule for hepatitis A vaccines

| Vaccine | Age (yrs) | Dose | Volume (mL) | Two-dose schedule (months)* |
|---------|-----------|---------------|-------------|-----------------------------|
| HAVRIX† | 1-18 | 720 (EL.U.) | 0.5 | 0 (6–12) |
| | >18 | 1,440 (EL.U.) | 1.0 | 0 (6–12) |
| VAQTA§ | 1-18 | 25 (U) | 0.5 | 0 (6–18) |
| | >18 | 50 (U) | 1.0 | 0 (6–18) |

Source: CDC. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006;55(No. RR-7).

Abbreviations: EL.U = Enzyme-linked immunosorbent assay (ELISA) units; U = units.

* 0 months represents timing of the initial dose; subsequent numbers represent months after the initial dose.

† Hepatitis A vaccine, inactivated, GlaxoSmithKline Biologicals; this vaccine is also licensed for a 3-dose series in children aged 2–18 years, with 360 EL.U, 0.5 mL doses at 0, 1, and 6–12 months.

§ Hepatitis A vaccine, inactivated, Merck & Co., Inc.

Postvaccination Serologic Testing

Postvaccination serologic testing is not indicated because most persons respond to the vaccine. In addition, the commercially available serologic test is not sensitive enough to detect the low, but protective, levels of antibody produced by vaccination.

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 IG (0.02 mL/kg) as soon as possible. Information about the relative efficacy of vaccine compared with IG postexposure is limited, and no data are available for persons aged >40 years or those with underlying medical conditions. Therefore, decisions to use vaccine or IG should take into account patient characteristics associated with more severe manifestations of hepatitis A, including older age, and CLD.

The magnitude of the risk for HAV transmission from the exposure should be considered in decisions to use IG or vaccine. IG should be used for children aged <12 months, immunocompromised persons, persons who have had diagnosed CLD, and persons for whom vaccine is contraindicated. For persons aged >40 years, IG is preferred because of the absence of information regarding vaccine performance and the more severe manifestations of hepatitis A in this age group; vaccine can be used if IG cannot be obtained. For healthy persons aged 12 months to 40 years, single-antigen hepatitis A vaccine at the age-appropriate dose is preferred over IG because of vaccine advantages, including long-term protection and ease of administration.

If IG is administered to persons for whom hepatitis A vaccine also is recommended, a dose of vaccine should be provided simultaneously with IG and the second vaccine dose should be administered according to the licensed schedule to complete the series. The efficacy of IG or vaccine when administered >2 weeks after exposure has not been established⁸⁰⁷.

Special Considerations

Limited data indicate that hepatitis A vaccination of persons with CLD and of persons with advanced HIV infection results in lower efficacy and antibody concentrations²³⁵. In persons with HIV infection, antibody response might be directly related to CD4+ levels.

Hepatitis B

Hepatitis B is caused by infection with the hepatitis B virus (HBV). The incubation period from the time of exposure to onset of symptoms is 6 weeks to 6 months. The highest concentrations of HBV are found in blood, with lower concentrations found in other body fluids including wound exudates, semen, vaginal secretions, and saliva^{808,809}. HBV is more infectious and relatively more stable in the environment than other bloodborne pathogens like HCV and HIV.

HBV infection can be self-limited or chronic. In adults, only approximately half of newly acquired HBV infections are symptomatic, and approximately 1% of reported cases result in acute liver failure and death. 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. Among persons with chronic HBV infection, the risk for premature death from cirrhosis or hepatocellular carcinoma (HCC) is 15%–25%.

HBV is efficiently transmitted by percutaneous or mucous membrane exposure to HBV-infected blood or body fluids that contain blood. The primary risk factors associated with infection among adolescents and adults are unprotected sex with an infected partner, multiple partners, MSM, history of other STDs, and injection-drug use. In addition, several studies have demonstrated other modes of HBV transmission, including through premarital and in healthcare settings, as a less common source of transmission^{216,810-812}.

Table 3. Recommended doses of currently licensed formulations of adolescent and adult hepatitis B vaccines

| Group | Single-antigen vaccine | | | | Combination vaccine | |
|---|------------------------|-------------|------------------------|-------------|------------------------|-------------|
| | Recombivax HB | Engerix-B | Engerix-B | Engerix-B | Twinrix* | Twinrix* |
| | Dose (μg) [†] | Volume (mL) | Dose (μg) [†] | Volume (mL) | Dose (μg) [†] | Volume (mL) |
| Adolescents aged 11–19 years§ | 5 | 0.5 | 10 | 0.5 | NA | NA |
| Adolescents aged 11–15 years¶ | 10 | 1.0 | NA | NA | NA | NA |
| Adults (aged ≥20 years) | 10 | 1.0 | 20 | 1.0 | 20 | 1.0 |
| Hemodialysis and other immunocompromised persons aged < 20 years§ | 5 | 0.5 | 10 | 0.5 | NA | NA |
| Hemodialysis and other immunocompromised persons aged ≥20 years | 40** | 1.0 | 40†† | 2.0 | NA | NA |

Sources: CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part 1: immunization of infants, children, and adolescents. MMWR 2005;54(No. RR-16). CDC. A comprehensive

immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR 2006;55(No. RR-16).

* Combined hepatitis A and hepatitis B vaccine. 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, in micrograms.

§ Pediatric formulation administered on a 3-dose schedule; higher doses might be more immunogenic, but no specific recommendations have been made.

¶ Adult formulation administered on a 2-dose schedule.

** Dialysis formulation administered on a 3-dose schedule at 0, 1, and 6 months.

†† Two 1.0-mL doses of the adult formulation administered at one site on a 4-dose schedule at 0, 1, 2, and 6 months.

CDC's national strategy to eliminate transmission of HBV infection includes 1) prevention of perinatal infection through routine screening of all pregnant women for HBsAg and immunoprophylaxis of infants born to HBsAg-positive mothers or mothers whose HBsAg status is unknown, 2) routine infant vaccination, 3) vaccination of previously unvaccinated children and adolescents through age 18 years, and 4) vaccination of previously unvaccinated adults at increased risk for infection^{3,4}. High vaccination coverage rates, with subsequent declines in acute hepatitis B incidence, have been achieved among infants and adolescents^{4,802,813}. In contrast, vaccination coverage among most high-risk adult groups (e.g., multiple sex partners, MSM, and IDUs) has remained low and most new infections occur in these high-risk groups^{3,161,814-816}. Aging of persons vaccinated when they were children and adolescents likely led to improved vaccination coverage in adults younger than 30 years⁸¹⁴, and corresponding lower rates of acute HBV infection in this group. STD clinics and other settings that provide STD services to high-risk adults are ideal sites in which to provide hepatitis B vaccination to adults at risk for HBV infection. All unvaccinated adults seeking STD services should be assumed to be at risk for hepatitis B and should be offered hepatitis B vaccination.

Diagnosis

Diagnosis of acute or chronic HBV infection requires serologic testing (Table 4). Because HBsAg is present in both acute and chronic infection, the 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 total anti-HBc, with a negative test for IgM anti-HBc, indicates chronic HBV infection. The presence of anti-HBc alone might indicate a false-positive result or acute, resolved, or chronic infection.

Treatment

No specific therapy is available for persons with acute hepatitis B; treatment is supportive. Persons with chronic HBV infection should be referred for evaluation to a physician experienced in the management of this infection. Therapeutic agents cleared by FDA for treatment of chronic hepatitis B can achieve sustained suppression of HBV replication and remission of liver disease⁸¹⁷.

Prevention

Two products have been approved for hepatitis B prevention: hepatitis B immune globulin (HBIG) for post exposure prophylaxis and hepatitis B vaccine^{3,4}. HBIG provides temporary (i.e., 3–6 months) protection from HBV infection and is typically used as PEP either as an adjunct to hepatitis B vaccination in previously unvaccinated persons or alone in 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.

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 two available monovalent hepatitis B vaccines for use in the United States are Recombivax HB (Merck and Co., Inc., Whitehouse Station, New Jersey) and Engerix-B (GlaxoSmithKline Biologicals, Pittsburgh, Pennsylvania). A combination vaccine (hepatitis A and hepatitis B) for use in adults, Twinrix (GlaxoSmithKline Biologicals, Pittsburgh, Pennsylvania), also is available. The recommended HBV dose and schedule varies by product and age of recipient (Table 3).

TABLE 4. Interpretation of serologic test results* for HBV infection

| Serologic marker | | | | Interpretation |
|------------------|-----------------|--------------------|-------|---|
| HBsAg† | Total anti-HBc§ | Anti-IgM¶ anti-HBc | HBs** | |
| - | - | - | - | Never infected |
| +†† | - | - | - | Early acute infection; transient (up to 18 days) after vaccination |
| + | + | + | - | Acute infection |
| - | + | + | - | Acute resolving infection |
| - | + | - | + | Recovered from past infection and immune |
| + | + | - | - | Chronic infection |
| - | + | - | - | False positive (i.e., susceptible); past infection; “low-level” chronic infection§§; passive transfer to infant born to HBsAg-positive mother |
| - | - | - | + | Immune if concentration is >10 mIU/mL,¶¶ passive transfer after HBIG administration |

* Symbol for negative test result, “-”; symbol for positive test result, “+”.

† Hepatitis B surface antigen.

§ Antibody to hepatitis B core antigen.

¶ Immunoglobulin M.

** Antibody to HBsAg.

+++ To ensure that an HBsAg-positive test result is not a false positive, samples with repeatedly reactive HBsAg results should be tested with an FDA-cleared (and, if appropriate, neutralizing confirmatory) test.

§§ 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 and organ transplantation).

¶¶ Milli-International Units per milliliter.

When selecting a hepatitis B vaccination schedule, the health-care provider should consider the need to achieve completion of the vaccine series. Approved adolescent and adult schedules for both monovalent hepatitis B vaccine (i.e., Engerix-B and Recombivax HB) include the following: 0, 1, and 6 months; 0, 1, and 4 months; and 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 μ g) is licensed for adolescents aged 11–15 years. When scheduled to receive the second dose, adolescents aged >15 years should be switched to a 3-dose series, with doses two and three consisting of the pediatric formulation (5 μ g) administered on an appropriate schedule. Twinrix can be administered to persons aged ≥ 18 years at risk for both HAV and HBV infections at 0, 1, and 6 months.

Hepatitis B vaccine should be administered IM in the deltoid muscle and can be administered simultaneously with other vaccines. For adolescents and adults, the needle length should be 1–2 inches, depending on the recipient's weight (1 inch for females weighing <70 kg, 1.5 inches for males weighing <120 kg, and 2 inches for males and females weighing >120 kg and >100 kg, respectively). A 22- to 25-gauge needle is recommended. 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 (800-232-4636).

In adolescents and healthy adults aged <40 years, approximately 30%–55% acquire a protective antibody response (anti-HBs ≥ 10 mIU/mL) after the first vaccine dose, 75% after the second, and >90% after the third. Vaccine-induced immune memory has been demonstrated to persist for at least 20 years^{813,818,819}. Periodic testing to determine antibody levels after routine vaccination in immunocompetent persons is not necessary, and booster doses of vaccine are not currently recommended.

Hepatitis B vaccination is generally well-tolerated by most 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 vaccinee will experience this type of reaction. No deaths have been reported in these patients^{3,4,815}. Vaccine is contraindicated in persons with a history of anaphylaxis after a previous dose of hepatitis B vaccine and in persons with a known anaphylactic reaction to any vaccine component. No evidence for a causal association has been demonstrated for other adverse events after administration of hepatitis B vaccine.

Pre-exposure Vaccination

Hepatitis B vaccination is recommended for all unvaccinated adolescents, all unvaccinated adults at risk for HBV infection, especially MSM and adults with more than one sexual partner, and all adults seeking protection from HBV infection. For adults, acknowledgement 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 STDs in other

settings. Other settings where all unvaccinated adults should be assumed to be at risk for hepatitis B and should receive hepatitis B vaccination include correctional facilities, facilities providing drug abuse treatment and prevention services, federally qualified health centers, and settings serving MSM including HIV care and prevention settings. If Hepatitis B vaccine is unavailable then persons should be referred to a setting where vaccine is available. Hepatitis B vaccine should be offered unless they have 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 showing evidence of past infection). In all settings, vaccination should be initiated before serologic results are available and even when completion of the vaccine series cannot be ensured.

Prevaccination Serologic Testing

Prevaccination serologic testing for susceptibility just prior to the initial vaccine dose might be considered to reduce the cost of completing the vaccination series in adult populations that have an expected high prevalence (20%–30%) of HBV infection (e.g., IDUs and MSM, especially those in older age groups). In addition, prevaccination testing for susceptibility is recommended for unvaccinated household, sexual, and needle-sharing contacts of HBsAg-positive persons¹⁶¹. Serologic testing should not be a barrier to vaccination, especially in populations that are difficult to access. 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 does not increase the risk for adverse events. If follow-up vaccination can be assured, vaccination can be deferred until serologic results are available.

Anti-HBc is the test of choice for prevaccination testing. Persons who are anti-HBc–positive should be tested for HBsAg. If persons are determined to be HBsAg negative, no further action is required. If a person is HBsAg positive, a referral to a specialist in the management of hepatitis B should be performed that includes prevention counseling, evaluation for antiviral treatment, and and serologic evaluation and vaccination of all household members, sex partners, and needle-sharing partners (see Management of HBsAg-Positive Persons).

Postvaccination Serologic Testing for Response

Serologic testing for immunity is not necessary 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 (e.g., health-care workers or public safety workers at high risk for continued percutaneous or mucosal exposure to blood or body fluids). In addition, postvaccination testing is recommended for 1) persons with HIV infection and other immunocompromised persons to determine the need for revaccination and 2) sex and needle-sharing partners of HBsAg-positive persons to determine the need for revaccination and for other methods to protect themselves from HBV infection.

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 provided with anti-HBs

testing 1–2 months after the third dose. Persons who do not respond to revaccination should be tested for HBsAg. If HBsAg positive, the person should receive appropriate management (see Management of HBsAg-Positive Persons); if HBsAg negative, the person should be considered susceptible to HBV infection and counseled concerning precautions to prevent HBV infection and the need for HBIG PEP for any known exposure (see Postexposure Prophylaxis).

Postexposure Prophylaxis

Both passive-active PEP (the administration of HBIG and hepatitis B vaccine at separate sites) and active PEP (the administration of hepatitis B vaccination alone) have been demonstrated to be highly effective in preventing transmission after exposure to HBV⁴. HBIG alone also has been demonstrated to be effective in preventing HBV transmission, but with the availability of hepatitis B vaccine, HBIG typically is used as an adjunct to vaccination.

Exposure to HBsAg-Positive Source

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 an HBsAg-positive source (Table 5). Hepatitis B vaccine should be administered simultaneously with HBIG at a separate injection site, and the vaccine series should be completed by using the age-appropriate vaccine dose and schedule (Table 3). Exposed persons who are in the process of being vaccinated but who have not completed the vaccine series should receive the appropriate dose of HBIG (i.e., 0.06 mL/kg) and should complete the vaccine series. Exposed persons who are known to have responded to vaccination are considered protected; therefore, they need no additional doses of vaccine or HBIG. 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. These persons can be managed according to guidelines for management of persons with occupational exposure to blood or body fluids that contain HBV⁸²⁰.

Exposure to Source with Unknown HBsAg Status

Unvaccinated persons who have a discrete, identifiable exposure to blood or body fluids containing blood from a source with unknown HBsAg status should receive the hepatitis B vaccine series, with the first dose initiated as soon as possible after exposure (preferably within 24 hours) and the series completed by using the age-appropriate dose and schedule. Exposed persons who are not fully vaccinated should complete the vaccine series. Exposed persons with written documentation of a complete hepatitis B vaccine series require no further treatment.

Table 5. Guidelines for postexposure immunoprophylaxis of unvaccinated persons who have an identifiable exposure to blood or body fluids that contain blood

| Cause | Action |
|---|---|
| Exposure to an HBsAg*-positive source | Percutaneous (e.g., bite or needlestick) or mucosal exposure to HBsAg-positive blood or body fluids that contain blood Administer hepatitis B vaccine & HBIG† Sexual or needle-sharing contact of an HBsAg-positive person Administer hepatitis B vaccine & HBIG† Victim of sexual assault/abuse by a perpetrator who is HBsAg positive Administer hepatitis B vaccine & HBIG† Victim of sexual assault/abuse by a perpetrator with unknown HBsAg status Administer hepatitis B vaccine† |
| Exposure to a source with unknown HBsAg status | Percutaneous (e.g., bite or needlestick) or mucosal exposure to blood or body fluids that contain blood from a source with unknown HBsAg status Administer hepatitis B vaccine† |

* Hepatitis B surface antigen.

† Immunoprophylaxis should be administered as soon as possible, preferably ≤ 24 hours. Studies are limited on the maximum interval after exposure during which postexposure prophylaxis is effective, but the interval is unlikely to exceed 7 days for percutaneous exposures and 14 days for sexual exposures. The complete, 3-dose hepatitis B vaccine series should be administered.

Special Considerations

Pregnancy

All pregnant women should be tested for HBsAg at the first prenatal visit and again if seeking STD services and at delivery if at high risk for HBV infection, regardless of whether they have been previously tested or vaccinated (see Special Populations Pregnant Women). All unvaccinated, HBsAg-negative pregnant women should receive hepatitis B vaccination including those seeking STD services. All HBsAg-positive pregnant women should be reported to state and local perinatal hepatitis B prevention programs and referred to a specialist. Management of HBsAg-positive pregnant women and their infants is available at <http://www.cdc.gov/mmwr/PDF/rr/rr5416.pdf>.

HIV Infection

HIV infection can impair the response to hepatitis B vaccination. Persons with HIV infection should be tested for anti-HBs 1–2 months after the third vaccine dose (see Postvaccination Serologic Testing for Response). Modified dosing regimens, including a doubling of the standard antigen dose and administration of additional doses, might increase the response rate ²³⁵.

Management of HBsAg-Positive Persons

Recommendations for management of all HBsAg-positive persons include the following:

- All persons with HBsAg-positive laboratory results should be reported to the state or local health department.
- To verify the presence of chronic HBV infection, HBsAg-positive persons 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 physician experienced in the management of hepatitis B.
- Household, sexual, and needle-sharing contacts of chronically infected persons should be identified. Unvaccinated sex partners and household and needle-sharing contacts should be tested for susceptibility to HBV infection (see Prevacination Antibody Screening) and should receive the first dose of hepatitis B vaccine immediately after collection of the blood sample for serologic testing. Susceptible persons should complete the vaccine series by using an age-appropriate vaccine dose and schedule.
- Sex partners of HBsAg-positive persons should be counseled to use latex condoms⁸²¹ 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, HBsAg-positive persons should be advised about the risk for transmission to household, sexual, and needle-sharing contacts and the need for such contacts to receive hepatitis B vaccination. HBsAg-positive persons 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 injection equipment) that could become contaminated with blood. In addition, refrain from prechewing food provided to susceptible persons.
- To protect the liver from further harm, HBsAg-positive persons 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 OTC and herbal medicines, without checking with their health-care provider; and
- obtain vaccination against hepatitis A.

When seeking medical or dental care, HBsAg-positive persons should be advised to inform their health-care providers of their HBsAg status so that they can be appropriately evaluated and managed. The following counseling messages should be considered for HBsAg-positive persons:

- 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, child care, or other settings because they are infected with HBV.
- Involvement with a support group might help patients cope with chronic HBV infection.

Additional recommendations for management of HBsAg-positive persons who have HIV infection are available²³⁵.

Proctitis, Proctocolitis, and Enteritis

Sexually transmitted gastrointestinal syndromes include proctitis, proctocolitis, and enteritis. Evaluation for these syndromes should include appropriate diagnostic procedures (e.g., anoscopy or sigmoidoscopy, stool examination, and culture).

Proctitis is inflammation of the rectum (i.e., the distal 10–12 cm) that can be associated with anorectal pain, tenesmus, or rectal discharge. *N. gonorrhoeae*, *C. trachomatis* (including LGV serovars), *T. pallidum*, and HSV are the most common sexually transmitted pathogens involved. In persons with HIV infection, herpes proctitis can be especially severe. Proctitis occurs predominantly among persons who participate in receptive anal intercourse.

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. Pathogenic organisms include *Campylobacter* sp., *Shigella* sp., *Entamoeba histolytica*, and LGV serovars of *C. trachomatis*. CMV or other opportunistic agents can be involved in immunosuppressed HIV-infected patients. Proctocolitis can be acquired through receptive anal intercourse or by oral-anal contact, depending on the pathogen.

Enteritis usually results in diarrhea and abdominal cramping without signs of proctitis or proctocolitis; it occurs among persons whose sexual practices include oral-anal contact. In otherwise healthy persons, *Giardia lamblia* is most frequently implicated. 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. Among persons with HIV infection, enteritis can be caused by a variety of pathogens, that may not be

sexually transmitted, including CMV, *Mycobacterium avium–intracellulare*, *Salmonella* sp., *Campylobacter* sp., *Shigella* sp., *Cryptosporidium*, *Microsporidium*, and *Isospora*. Multiple stool examinations might be necessary to detect *Giardia*, and special stool preparations are required to diagnose cryptosporidiosis and microsporidiosis. In addition, enteritis can be directly caused by HIV infection.

Diagnostic Considerations for Acute Proctitis

Persons who present 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 HSV (PCR or culture), *N. gonorrhoeae* (NAAT or culture), *C. trachomatis* (NAAT), and *T. pallidum* (Darkfield if available and serologic testing) (see pathogen specific sections). If the *C. trachomatis* test is positive on a rectal swab, then a molecular test for LGV should be done, if available, to confirm an LGV diagnosis (see LGV section).

When laboratory diagnostic capabilities are available, treatment decisions should be tailored to the specific diagnosis. However, treatment decisions should be made based on the clinical presentation before specific test results are available. Diagnostic and treatment recommendations for colitis, enteritis, and enteric infections are not discussed in these guidelines.

Treatment for Proctitis

Acute proctitis of recent onset among persons who have recently practiced receptive anal intercourse is usually sexually acquired^{822,823}. If an anorectal exudate is detected on examination, if polymorphonuclear leukocytes are detected on a Gram-stained smear of anorectal exudate or secretions, or if anoscopy or gram stain is unavailable and the clinical presentation is consistent with sexually acquired acute proctitis, presumptive therapy should be prescribed while awaiting additional laboratory tests.

Recommended Regimen

Ceftriaxone 250 mg IM

PLUS

Doxycycline 100 mg orally twice a day for 7 days

MSM with proctitis and a positive rectal Chlamydia NAAT and MSM with HIV infection and proctitis, and : bloody discharge, perianal ulcers or mucosal ulcers should be offered presumptive treatment for LGV with doxycycline 100 mg twice daily orally for a total of 3 weeks^{824,825}. (see

LGV)

All persons with acute proctitis should be tested for HIV, if their HIV status is unknown or negative.

Follow-Up

Follow-up should be based on specific etiology and severity of clinical symptoms. For gonorrhea or chlamydia proctitis, retesting for the respective pathogen should be performed 3 months after treatment. Reinfection might be difficult to distinguish from treatment failure.

Management of Sex Partners

Partners who have had sexual contact with persons treated for GC, CT including LGV within the 60 days before the onset of the persons symptoms should be evaluated, test and presumptively treated for the respective pathogen (see GC, CT). Partners of persons with sexually transmitted enteric infections should be evaluated for any diseases diagnosed in the index patient.

Allergy, Intolerance, and Adverse Reactions

Allergic reactions with third-generation cephalosporins, such as ceftriaxone, are uncommon in persons with a history of penicillin allergy^{418,420,454}. In those persons with a history of an IgE mediated penicillin allergy (anaphylaxis, Stevens Johnson syndrome, or toxic epidermal necrolysis), the use of ceftriaxone is contraindicated^{418,421}.

HIV Infection

In persons with HIV infection and acute proctitis who have bloody discharge, painful perianal ulcers or mucosal ulcers presumptive treatment 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 usually transmitted by sexual contact⁸²⁶.

| |
|---|
| <i>Recommended Regimens</i> |
| Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes |
| OR |
| Pyrethrins with piperonyl butoxide applied to the affected area and washed off after 10 minutes |
| <i>Alternative Regimens</i> |
| Malathion 0.5% lotion applied for 8–12 hours and washed off |
| OR |
| Ivermectin 250 ug/kg repeated in 2 weeks |

Reported resistance to pediculicides has been increasing and is widespread^{827,828}. Malathion may be used when treatment failure is believed to have occurred because of resistance. The odor and long duration of application for malathion make it a less attractive alternative than the recommended pediculicides. Ivermectin has limited ovicidal activity⁸²⁹. Ivermectin may not prevent recurrences from eggs at the time of treatment and therefore treatment should be repeated in 14 days^{774,830,831}. Ivermectin should be taken with food because bioavailability is increased and thus the penetration of the drug into the epidermis increases. Adjustment of ivermectin is not required in persons with renal impairment but the safety of multiple doses in persons with severe liver disease is not known.

Lindane is recommended as an alternative therapy because of toxicity⁸³². It should only be used if there is an inability to tolerate other therapies or if other therapies have failed. Lindane toxicity, as indicated by seizure and aplastic anemia, has not been reported when treatment was limited to the recommended 4-minute period. Lindane should not be used immediately after a bath or shower, and it should not be used by persons who have extensive dermatitis, women who are pregnant or lactating or children aged <2 years.

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, such as petroleum jelly to the eyelid margins twice a day for 10 days. Bedding and clothing should be decontaminated (i.e., machine-washed and dried using the heat cycle, or dry cleaned) or removed from body contact for at least 72 hours. Fumigation of living areas is not necessary.

Persons with pediculosis pubis should be evaluated for other STDs including HIV.

Follow-Up

Evaluation should be performed after 1 week if symptoms persist. Re-treatment might be necessary if lice are found or if eggs are observed at the hair-skin junction. If there is no clinical response 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 with sex partner(s) should be avoided until patients and partners have been treated, bedding and clothing decontaminated and reevaluated to rule out persistent disease.

Special Considerations

Pregnancy

Existing human data suggest that pregnant and lactating women should be treated with either permethrin or pyrethrins with piperonyl butoxide. Since no teratogenicity or toxicity attributable to ivermectin has been observed in human pregnancy experience, ivermectin is classified as “human data suggest low risk” in pregnancy.³¹⁰ In humans, no published reports have linked lindane with mutagenic, toxic or congenital defects, and a surveillance of > 1400 exposed infants yielded no associations with birth defects.³¹⁰ Animal studies of lindane failed to find either teratogenic or reproductive impairment. Thus, it is recommended that lindane should be limited to no more than two treatments during pregnancy, and is classified as “limited human data, low risk” in pregnancy.³¹⁰ Both ivermectin and lindane are listed as “limited human data probably compatible” with breastfeeding.³¹⁰

HIV Infection

Persons who have pediculosis pubis and also HIV infection should receive the same treatment regimen as those who are HIV negative.

Scabies

The predominant symptom of scabies is pruritus. Sensitization to *Sarcoptes scabiei* occurs before pruritus begins. The first time a person is infested with *S. scabiei*, sensitization takes up to several weeks to develop. However, pruritus might occur within 24 hours after a subsequent reinfestation. Scabies in adults frequently is sexually acquired, although scabies in children usually is not.^{833,834}

Recommended Regimens

Permethrin 5% cream applied to all areas of the body from the neck down and washed off after 8–14 hours

| |
|---|
| OR |
| Ivermectin 200ug/kg orally, repeated in 2 weeks |
| <i>Alternative Regimens</i> |
| 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 |

Lindane is recommended as an alternative therapy because of toxicity⁸³². It should only be used if the patient cannot tolerate the recommended therapies or if these therapies have failed⁸³⁵⁻⁸³⁷. Lindane should not be used immediately after a bath or shower, and it should not be used by persons who have extensive dermatitis, or children aged <2 years. Lindane resistance has been reported in some areas of the world, including parts of the United States. 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.

Permethrin is effective and safe and less expensive than ivermectin⁸³⁸. One study demonstrated increased mortality among elderly, debilitated persons who received ivermectin, but this observation has not been confirmed in subsequent reports⁸³⁹. Ivermectin has limited ovicidal activity and may 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. Ivermectin should be taken with food because bioavailability is increased and thus the penetration of the drug into the epidermis increases. Adjustment of ivermectin is not required in patients with renal impairment but the safety of multiple doses in patients with severe liver disease is not known.

Other Management Considerations

Bedding and clothing should be decontaminated (i.e., either machine-washed, machine-dried using the hot cycle, or dry cleaned) or removed from body contact for at least 72 hours. Fumigation of living areas is unnecessary.

Crusted Scabies

Crusted scabies (i.e., Norwegian scabies) is an aggressive infestation that usually occurs in 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, mentally retarded or physically incapacitated persons, and hematologic malignancies. Crusted scabies is associated with greater transmissibility than scabies⁸⁴⁰. No controlled therapeutic studies for crusted scabies have been conducted, and the appropriate treatment remains unclear. Substantial treatment failure might occur with a single topical scabicide or with oral ivermectin treatment. Combination treatment is recommended with a topical scabicide, either 5% topical benzyl benzoate or 5% topical permethrin cream (full body application to be repeated daily for 7 days then 2x weekly until discharge or cure), and repeated treatment with oral ivermectin 200 ug/kg on days 1,2,8,9 and 15. Additional ivermectin treatment on days 22 and 29 may be required for severe cases⁸⁴¹. Lindane should be avoided

because of the risks for neurotoxicity with heavy applications or denuded skin. Fingernails should be closely trimmed to reduce injury from excessive scratching.

Follow-Up

The rash and pruritus of scabies might persist for up to 2 weeks after treatment. Symptoms or signs that persist for >2 weeks can be attributed to several factors. Treatment failure might be caused by resistance to medication or by faulty application of topical scabicides. Persons with crusted scabies might have poor penetration into thick scaly skin and harbor mites in these difficult-to-penetrate layers. Particular attention must be given to the fingernails of these patients. Reinfection from family members or fomites might occur in the absence of appropriate contact treatment and decontamination of bedding and clothing. Even when treatment is successful and reinfection is avoided, symptoms can persist or worsen as a result of allergic dermatitis. Finally, other household mites can cause symptoms to persist as a result of cross reactivity between antigens. Re-treatment 1–2 weeks after the initial treatment regimen can be considered for those persons who are still symptomatic or when live mites are observed. Re-treatment with a different alternative regimen is recommended in those persons who do not respond to the recommended treatment.

Management of Sex Partners and Household Contacts

Both sexual and close personal or household contacts within the preceding month should be examined and treated.

Management of Outbreaks in Communities, Nursing Homes, and Other Institutional Settings

Scabies epidemics frequently occur in nursing homes, hospitals, residential facilities, and other communities⁸⁴². Control of an epidemic can only be achieved by treatment of the entire population at risk. Ivermectin can be considered in this setting, especially if treatment with topical scabicides fails. Epidemics should be managed in consultation with a specialist.

Special Considerations

Infants, Young Children, and Pregnant or Lactating Women

Infants and young children should not be treated with lindane. The safety of ivermectin in children who weigh <15 kg has not been determined. They can be treated with permethrin.

Lindane and ivermectin are probably low risk in pregnant women and compatible with breastfeeding (See Lice); however due to the limited data, permethrin is the preferred treatment for pregnant or lactating patients.³¹⁰

HIV Infection

Persons with HIV infection who have uncomplicated scabies should receive the same

treatment regimens as those who are HIV negative. Persons with HIV infection and others who are immunosuppressed are at increased risk for crusted scabies. Ivermectin has been reported to be useful in small, noncontrolled studies. Such persons should be managed in consultation with a specialist.

Sexual Assault and STDs

Adults and Adolescents

The recommendations in this report are primarily limited to the identification, prophylaxis, and treatment of STDs and conditions among adult and adolescent female sexual assault survivors. However, some of the following guidelines may still apply to male sexual assault survivors. The documentation of findings, collection of nonmicrobiologic specimens for forensic purposes, and the management of potential pregnancy or physical and psychological trauma are beyond the scope of this report.

Examinations of survivors of sexual assault should be conducted by an experienced clinician in a way that minimizes further trauma to the survivor. The decision to obtain genital or other specimens for STD 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 monitor for adverse reactions to any therapeutic or prophylactic regimens prescribed at initial examination. Laws in all 50 states strictly limit the evidentiary use of a survivor's previous sexual history, including evidence of previously acquired STDs, 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, STD diagnoses might later be accessed, and the survivor and clinician might opt to defer testing for this reason. While collection of specimens at initial examination for laboratory STD diagnosis gives the survivor and clinician the option to defer empiric prophylactic antimicrobial treatment, compliance with follow up visits is traditionally poor^{843,844}. Among sexually active adults, the identification of an STD might represent an infection acquired prior to the assault, and therefore might be more important for the psychological and medical management of the patient than for legal purposes.

Trichomoniasis, BV, gonorrhea, and chlamydial infection are the most frequently diagnosed infections among women who have been sexually assaulted. Such conditions are relatively prevalent, and the presence after an assault does not necessarily imply acquisition during the assault. However, a postassault examination presents an important opportunity to identify or prevent STDs. Chlamydial and gonococcal infections in women are of particular concern because of the possibility of ascending infection. In addition, HBV infection can be prevented by postexposure vaccinations. Due to the risk of HPV infection among female survivors and high vaccine efficacy^{845 846}, HPV vaccinations are also recommended through the age of 26 years. Reproductive-aged female survivors should be evaluated for pregnancy.

Evaluating Adults and Adolescents for Sexually Transmitted Diseases

Initial Examination

Decisions to perform these tests should be made on an individual basis. An initial examination might include the following procedures:

- NAATs for *C. trachomatis* and *N. gonorrhoeae* at the sites of penetration or attempted penetration³⁸⁵. These tests are preferred for the diagnostic evaluation of adolescent or adult sexual assault survivors.
- NAATs or point-of-care testing (i.e. DNA probes) for *T.vaginalis*. Point-of-care testing and/or wet mount with measurement of vaginal pH and KOH application for the whiff test should be done for evidence of BV and candidiasis, especially if vaginal discharge, malodor, or itching is evident.
- A serum sample for immediate evaluation for HIV infection, hepatitis B, and syphilis.

Follow-Up Examinations

After the initial postassault examination, follow-up examinations provide an opportunity to 1) detect new infections acquired during or after the assault; 2) complete hepatitis B and human papilloma virus vaccinations, if indicated; 3) complete counseling and treatment for other STDs; and 4) monitor side effects and adherence to postexposure prophylactic medication, if prescribed.

If initial testing was done, follow-up examination should be conducted within 1 week to ensure that results of positive tests can be discussed promptly with the survivor, that treatment is provided if not given at the initial visit, and that any follow-up for the infection(s) can be arranged. If initial tests are negative and treatment was not provided, examination for STDs can be repeated within 1–2 weeks of the assault because infectious agents acquired through assault might not have produced sufficient concentrations of organisms to result in positive test results at the initial examination. If treatment was initially provided (with or without testing), testing should be conducted after treatment only if the survivor reports having symptoms. A follow-up examination at 1-2 months should also be considered to reevaluate for development of anogenital warts, especially among sexual assault survivors diagnosed with other STDs. Serologic tests for HIV and syphilis can be repeated at 6 weeks, 3 months, and 6 months using methods to identify acute HIV infection and at one and three months for syphilis after the assault if initial test results were negative and infection in the assailant could not be ruled out (see Sexual Assault and STDs, Risk for Acquiring HIV Infection).

Prophylaxis

Compliance with follow-up visits is poor among survivors of sexual assault^{843,844}. As a result, the following routine prophylactic therapy after a sexual assault is recommended:

- An empiric antimicrobial regimen for chlamydia, gonorrhea, and trichomonas.

- Emergency contraception. This measure should be considered when the assault could result in pregnancy in the survivor.
- Postexposure hepatitis B vaccination, without HBIG, if the hepatitis status of the assailant is unknown. 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 (see hepatitis B).
- Human papilloma virus (HPV) vaccination for female survivors aged 9 through 26 years and male survivors aged 9 through 21 years or through 26 years if MSM contact with no previous HPV vaccinations or an incomplete series is recommended. The vaccine should be administered to sexual assault survivors at the time of the initial examination and follow-up dose at 1–2 months and 6 months after the first dose.
- HIV PEP is individualized according to risk (see Risk for Acquiring HIV Infection and Postexposure HIV Risk Assessment for PEP)

| |
|------------------------------------|
| <i>Recommended Regimens</i> |
|------------------------------------|

Ceftriaxone 250 mg IM in a single dose

PLUS

Azithromycin 1 g orally in a single dose

PLUS

Metronidazole 2 g orally in a single dose OR
Tinidazole 2 g orally in a single dose

If alcohol has been recently ingested or emergency contraception is provided, metronidazole or tinidazole can be taken by the sexual assault survivor at home rather than as directly observed therapy to minimize potential side effects and drug interactions. For those requiring alternative treatments, refer to the specific sections in this report relevant to the specific agent. The efficacy of these regimens in preventing infections after sexual assault has not been evaluated. Clinicians should counsel persons regarding the possible benefits and toxicities associated with these treatment regimens; gastrointestinal side effects can occur with this combination.

Other Management Considerations

At the initial examination and, if indicated, at follow-up examinations, patients should be

counseled regarding 1) symptoms of STDs and the need for immediate examination if symptoms occur and 2) abstinence from sexual intercourse until STD prophylactic treatment is completed.

Risk for Acquiring HIV Infection

HIV seroconversion has occurred in persons whose only known risk factor was sexual assault or sexual abuse, but the frequency of this occurrence is probably low. In consensual sex, the per-act risk for HIV transmission from vaginal intercourse is 0.1%–0.2% and for receptive rectal intercourse, 0.5%–3%⁸⁴⁷. 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 STD or genital lesions in the assailant or survivor also might increase the risk for HIV.

Postexposure prophylaxis 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 blood⁸⁴⁸. On the basis of these results and the results of animal studies, post-exposure prophylaxis (PEP) has been recommended for health-care workers who have occupational exposures to HIV⁸⁴⁹. These findings have been extrapolated to nonoccupational injection or sexual HIV exposures, including sexual assault (nPEP). The possibility of HIV exposure from the assault should be assessed at the time of the post assault examination. The possible benefit of PEP in preventing HIV infection should also be discussed with the assault survivor if the assault poses a risk for HIV exposure. If HIV exposure has occurred, initiation of PEP as soon as possible after the exposure increases the likelihood of prophylactic benefit.

Several factors impact the medical recommendation for PEP and affect the assault survivor's acceptance of that recommendation, including 1) the likelihood of the assailant having HIV; 2) any exposure characteristics that might increase the risk for HIV transmission; 3) the time elapsed after the event; and 4) the potential benefits and risks associated with the PEP³⁰⁴. Determination of the assailant's HIV status at the time of the assault examination is usually not possible. Therefore, the health-care provider should assess any available information concerning the 1) characteristics and HIV risk behaviors of the assailant(s) (e.g., a man who has sex with other men and persons who use injection drugs or illicit drugs), 2) local epidemiology of HIV/AIDS, and 3) exposure characteristics of the assault. When an assailant's HIV status is unknown, factors that should be considered in determining whether an increased risk for HIV transmission exists include 1) whether vaginal or anal penetration occurred; 2) whether ejaculation occurred on mucous membranes; 3) whether multiple assailants were involved; 4) whether mucosal lesions are present in the assailant or survivor; and 5) 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: 1) the necessity of early initiation of PEP to optimize potential benefits (i.e., as soon as possible after and up to 72 hours after the assault; 2) the importance of close follow-up; 3) the benefit of adherence to recommended dosing; and 4) potential adverse effects of antiretrovirals. Providers should emphasize that severe adverse effects are rare from PEP⁸⁵⁰⁻⁸⁵². Clinical management of the

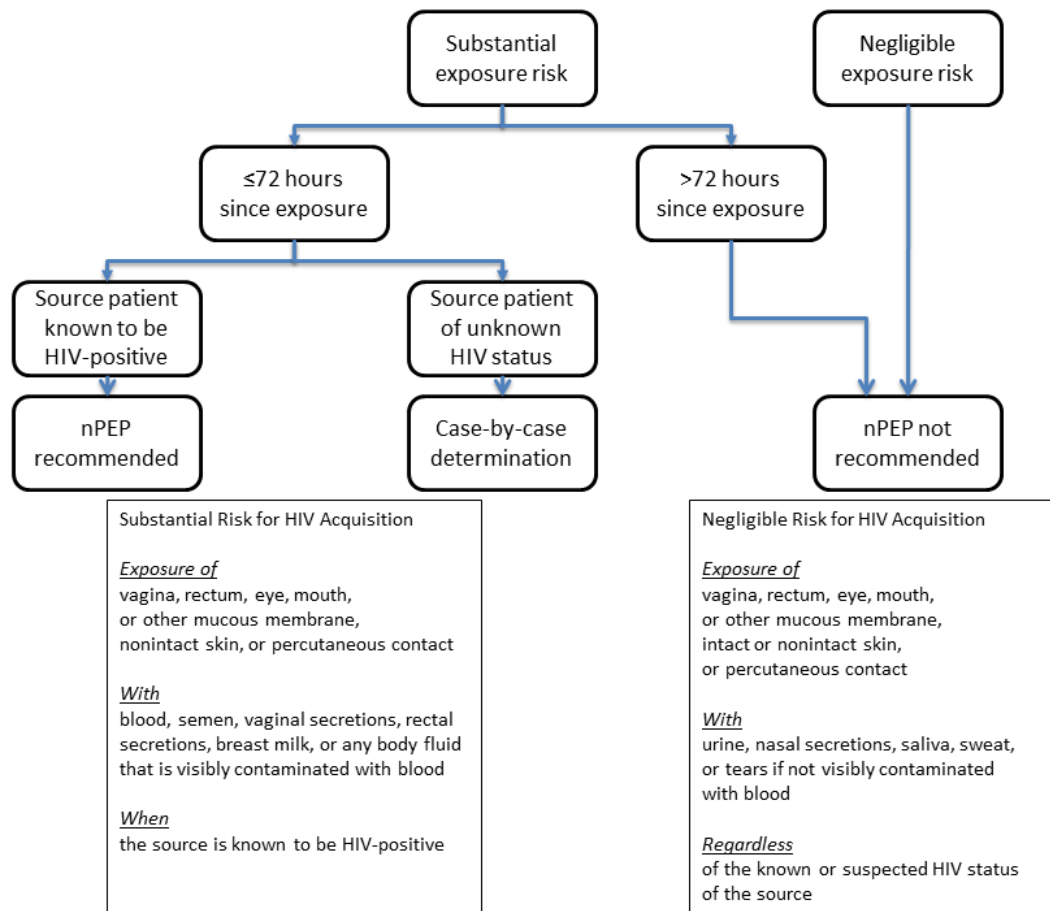
survivor should be implemented according to the HIV PEP guidelines³⁰⁴. Specialist consultation on PEP regimens is recommended if HIV exposure during the assault was possible and if PEP is being considered. The sooner PEP is initiated after the exposure, the higher the likelihood that it will prevent HIV transmission if HIV exposure occurred; however, distress after an assault also might prevent the survivor from accurately weighing exposure risks and benefits of PEP and from making an informed decision to start such therapy. If use of PEP is judged to be warranted, the survivor can be offered a 3–5-day supply of PEP, and a follow-up visit scheduled several days later to allow for additional counseling and provision of the remaining 23 days of medication if PEP is elected.

Recommendations for Postexposure HIV Risk Assessment of Adolescent and Adult Survivors Within 72 Hours of Sexual Assault**

- Assess risk for HIV infection in the assailant, and test that person for HIV whenever possible.
- Use the algorithm below to evaluate the survivor for the need for HIV PEP³⁰⁴.
- Consult with a specialist in HIV treatment, if PEP is being considered.
- If the survivor appears to be at risk for HIV acquisition from the assault, discuss antiretroviral postexposure prophylaxis, including benefits and risks.
- If the survivor chooses to start antiretroviral PEP³⁰⁴, provide enough medication to last until the next return visit; reevaluate the survivor 3–7 days after initial assessment and assess tolerance of medications.
- If PEP is started, perform CBC and serum chemistry at baseline
- Perform an HIV antibody test at original assessment; repeat at 6 weeks, 3 months, and 6 months.

** Assistance with PEP-related decisions can be obtained by calling the National Clinician's Post Exposure Prophylaxis Hotline (PEP Line) 888-448-4911.

Figure 1. Algorithm for evaluation and treatment of possible nonoccupational HIV exposures (nPEP)



Sexual Assault or Abuse of Children

Recommendations in this report are limited to the identification and treatment of STDs in pre-pubertal children. Management of the psychosocial or legal aspects of the sexual assault or abuse of children is beyond the scope of these recommendations.

The identification of sexually transmissible agents in children beyond the neonatal period strongly suggests sexual abuse⁸⁵³. The significance of the identification of a sexually transmitted agent in such children as evidence of possible child sexual abuse varies by pathogen. Postnatally acquired gonorrhea; syphilis; chlamydia infection; and nontransfusion, nonperinatally acquired HIV are indicative of sexual abuse. Sexual abuse should be suspected when *Trichomonas vaginalis*, genital herpes, or anogenital warts are diagnosed. The investigation of sexual abuse among children who have an infection that could 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 and the recommended action regarding reporting of suspected child sexual abuse varies by the specific organism; however, identification of most of these pathogens reaches a threshold for reporting to the agency in the community mandated to receive reports of suspected child abuse or neglect. In cases in which an STD has been diagnosed in a child, efforts should be made to evaluate the possibility of sexual abuse,

including conducting diagnostic testing for other commonly occurring STDs^{854,855 853}.

The general rule that sexually transmissible infections beyond the neonatal period are evidence of sexual abuse has exceptions. For example, genital infection with *T. vaginalis*⁸⁵⁶ or rectal or genital infection with *C. trachomatis* among young children might be the result of perinatally acquired infection and has, in some cases of chlamydia infection, persisted for as long as 2–3 years,^{857 858} though perinatal CT infection is now very uncommon because of prenatal screening and treatment of pregnant women. Genital warts have been diagnosed in children who have been sexually abused,⁸⁴⁵ but also in children who have no other evidence of sexual abuse^{859,860}. BV has been diagnosed in children who have been abused, but its presence alone does not prove sexual abuse. In addition, most HBV infections in children result from household exposure to persons who have chronic HBV infection.

Table 6: Implications of commonly encountered sexually transmitted (ST) or sexually associated (SA) infections for diagnosis and reporting of sexual abuse among infants and pre-pubertal children

| ST/SA confirmed | Evidence for sexual abuse | Suggested action |
|--|--------------------------------------|---------------------|
| Gonorrhea* | Diagnostic | Report† |
| Syphilis* | Diagnostic | Report† |
| Human immunodeficiency virus§ | Diagnostic | Report† |
| <i>Chlamydia trachomatis</i> * | Diagnostic | Report† |
| <i>Trichomonas vaginalis</i> * | Highly suspicious | Report† |
| Genital herpes | Highly suspicious (HSV-2 especially) | Report†¶ |
| <i>Condylomata acuminata</i> (anogenital warts)* | Suspicious | Consider report†¶** |
| Bacterial vaginosis | Inconclusive | Medical follow-up |

* If not likely to be perinatally acquired and rare nonsexual, vertical transmission is excluded.

† Reports should be made to the agency in the community mandated to receive reports of suspected child abuse or neglect.

§ If not likely to be acquired perinatally or through transfusion.

¶ Unless there is a clear history of autoinoculation.

** Report if there is additional evidence to suspect abuse, including history, physical examination or other infections identified.

Reporting

All U.S. states and territories have laws that require the reporting of child abuse. Although the exact requirements differ by state, if a health-care provider has reasonable cause to suspect child abuse, a report must be made. Health-care providers should contact their state or local child-protection service agency regarding child-abuse reporting requirements in their states.

Evaluating Children for Sexually Transmitted Diseases

Examinations of children for sexual assault or abuse should be conducted in a manner designed to minimize pain and trauma to the child. Collection of vaginal specimens in prepubertal children can be very 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 conduct an STD evaluation must be made on an individual basis. Because STDs are not common in prepubertal children evaluated for abuse, testing all sites for all organisms is not routinely recommended. Factors that should lead the physician to consider screening for STD include:⁸⁵³

1. Child has experienced penetration or has evidence of recent or healed penetrative injury to the genitals, anus, or oropharynx.
2. Child has been abused by a stranger.
3. Child has been abused by a perpetrator known to be infected with an STD or at high risk of STDs (intravenous drug abusers, men who have sex with men, or people with multiple sexual partners).
4. Child has a sibling or other relative in the household with an STD.
5. Child lives in an area with a high rate of STD in the community.
6. Child has signs or symptoms of STDs.
7. Children diagnosed with one STD should be screened for all STDs.

If a child has symptoms, signs, or evidence of an infection that might be sexually transmitted, the child should be tested for other common STDs before the initiation of any treatment that could interfere with the diagnosis of those other STDs. 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 diagnosis of an STD justifies deferring presumptive treatment until specimens for highly specific tests are obtained by providers with experience in the evaluation of sexually abused and assaulted children.

The scheduling of an examination should depend on the history of assault or abuse. If the initial exposure was recent, the infectious agents acquired through the exposure might not have produced sufficient concentrations of organisms to result in positive test results or examination

findings⁸⁶¹. Alternatively, positive test results following a recent exposure may represent the assailant's secretions (but would nonetheless be an indication for treatment of the child). A follow-up visit approximately 2-4 weeks after the most recent sexual exposure can include a repeat physical examination and collection of additional specimens. To allow sufficient time for antibodies or examination findings to develop, another follow-up visit approximately 12 weeks after the most recent sexual exposure might be necessary to collect sera and/or repeat the examination. A single examination 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.

The following recommendations for scheduling examinations serve as a general guide. The exact timing and nature of follow-up examinations should be determined on an individual basis and should be performed to minimize the possibility for psychological trauma and social stigma. Compliance with follow-up appointments might be improved when law enforcement personnel or child protective services are involved.

Initial and 2-Week Follow-Up Examinations

During the initial examination and 2-week follow-up examination (if indicated), the following should be performed.

- Visual inspection of the genital, perianal, and oral areas for genital discharge, odor, bleeding, irritation, warts, and ulcerative lesions. The clinical manifestations of some STDs are different in children than in adults. For example, typical vesicular lesions might not be present in the presence of HSV infection. Because this infection can be indicative of sexual abuse, specimens should be obtained from all vesicular or ulcerative genital or perianal lesions compatible with genital herpes and then sent for viral culture.
- Specimen collection for *N. gonorrhoeae* culture from the pharynx and anus in boys and girls, the vagina in girls, and the urethra in 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. Because of the legal implications of a diagnosis of *N. gonorrhoeae* infection in a child, if culture for the isolation of *N. gonorrhoeae* is done, only standard culture procedures should be performed. Gram stains are inadequate to evaluate prepubertal children for gonorrhea and should not be used to diagnose or exclude gonorrhea. 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 principles (e.g., biochemical, enzyme substrate, or serologic). Isolates should be preserved to enable additional or repeated testing. Data on use of NAATs for detection of *N. gonorrhoeae* in children are limited, and performance is test dependent^{385,855} {CDC and Association of Public Health Laboratories, #2065}. Consultation with an expert is necessary before using NAATs 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*, and *Moraxella catarrhalis*), and to ensure appropriate interpretation of positive results. NAATs can be

used as an alternative to culture with vaginal specimens or urine from girls, whereas culture remains the preferred method for urethral specimens or urine from boys and for extragenital specimens (pharynx and rectum) from all children. All positive specimens should be retained for additional testing for as long as necessary.

- Cultures for *C. trachomatis* from specimens collected from the anus in both boys and girls and from the vagina in girls. The likelihood of recovering *C. trachomatis* from the urethra of prepubertal boys is too low to justify the trauma involved in obtaining an intraurethral specimen. However, a meatal specimen should be obtained if urethral discharge is present. Pharyngeal specimens for *C. trachomatis* are not recommended for children of either sex because the yield is low, perinatally acquired infection might persist beyond infancy, and culture systems in some laboratories do not distinguish between *C. trachomatis* and *C. pneumoniae*. Only standard culture systems for the isolation of *C. trachomatis* should be used. The isolation of *C. trachomatis* should be confirmed by microscopic identification of inclusions by staining with fluorescein-conjugated monoclonal antibody specific for *C. trachomatis*; EIAs are not acceptable confirmatory methods. Isolates should be preserved. Nonculture tests for chlamydia (e.g., nonamplified probes, EIAs, and DFA) are not sufficiently specific for use in circumstances involving possible child abuse or assault. NAATs can be used for detection of *C. trachomatis* in vaginal specimens or urine from girls. All specimens should be retained for additional testing. No data are available regarding the use of NAATs in boys or for extragenital specimens (e.g., those obtained from the rectum) in boys and girls. Culture remains the preferred method for extragenital sites.
- Culture for *T. vaginalis* infection and wet mount of a vaginal swab specimen for *T. vaginalis* infection and BV. Testing for *T. vaginalis* should not be limited to those with vaginal discharge if other indications for testing exist, as there is some evidence to indicate that asymptomatic sexually abused children may be infected with TV and may benefit from treatment.^{862, 863} Data on use of NAATs for detection of *T. vaginalis* in children are too limited to recommend use, but no evidence suggests that performance of NAATs for detection of *T. vaginalis* in children would be different than performance of these assays in adults.
- Collection of serum samples to be evaluated immediately, preserved for subsequent analysis, and used as a baseline for comparison with follow-up serologic tests. Sera should be tested immediately for antibodies to sexually transmitted agents. Agents for which suitable tests are available include *T. pallidum*, HIV, and HBV. Decisions regarding the agents for which to perform serologic tests should be made on a case-by-case basis.

HIV infection has been reported in children where sexual abuse was the the only known risk factor.. Children might be at higher risk for HIV acquisition than adolescent and adult sexual assault or sexual abuse survivors, because the sexual abuse of children is frequently associated with multiple episodes of assault and mucosal trauma may be more likely. Serologic testing for HIV infection should be considered for sexually abused children. The decision to test for HIV infection should involve the family if possible, and be made on a case-by-case basis, depending on the likelihood of infection among assailant(s)⁸⁶⁴. Although data are insufficient concerning the efficacy of PEP among both children and adults, treatment is well tolerated by infants and

children (with and without HIV infection), and children have a minimal risk for serious adverse reactions because of the short period recommended for prophylaxis^{304,865}. In considering whether to offer antiretroviral PEP, health-care providers should consider whether the child can be treated soon after the sexual exposure (i.e., within 72 hours), the likelihood that the assailant is infected with HIV, and the likelihood of high compliance with the prophylactic regimen. The potential benefit of treating a sexually abused child should be weighed against the risk for adverse reactions. If antiretroviral PEP is being considered, a provider specializing in evaluating or treating HIV-infected children should be consulted.

Recommendations for HIV-Related Postexposure Assessment of Children within 72 Hours of Sexual Assault

- Review HIV/AIDS local epidemiology and assess risk for HIV infection in the assailant.
- Evaluate circumstances of assault that might affect risk for HIV transmission.
- Consult with a specialist in treating children with HIV infection to select age-appropriate dosing and regimen if PEP considered.
- If the child appears to be at risk for HIV transmission from the assault, discuss PEP with the caregiver(s), including its toxicity and unknown efficacy.
- If caregivers choose for the child to receive antiretroviral PEP provide enough medication to last until the return visit at 3–7 days after the initial assessment, at which time the child should be reevaluated and tolerance of medication assessed.^{304,305,866}
- Perform HIV antibody test at original assessment, 6 weeks and 3 months.

Follow-Up Examination After Assault

In circumstances in which transmission of syphilis, HPV, HIV, or hepatitis B is a concern but baseline tests and examinations are negative, an examination approximately 6 weeks and 3 months after the last suspected sexual exposure is recommended to allow time for examination findings or antibodies to infectious agents to develop. In addition, results of HBsAg testing must be interpreted carefully, because HBV can be transmitted nonsexually. Decisions regarding which tests should be performed must be made on an individual basis.

Presumptive Treatment

The risk of a child acquiring an STD 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 1) the incidence of most STDs in children is low after abuse/assault, 2) prepubertal girls appear to be at lower risk for ascending infection than adolescent or adult women, and 3) regular follow-up of children usually can be ensured. However, some children or their parent(s) or guardian(s) might be concerned about the possibility of infection with an STD, even if the risk is perceived to be low by the health-care provider. Such concerns might be an

appropriate indication for presumptive treatment in some settings and might be considered after all specimens for diagnostic tests relevant to the investigation have been collected.

Because child sexual assault survivors are a high risk group for future unsafe sexual practices that have been linked to increased risk of HPV acquisition,^{845,867} and are more likely to engage in these behaviors at an earlier age, HPV vaccination for female and male sexual assault survivors aged 9 years of age and through age 26 years for females, and through age 21 years for males is recommended in accordance with Advisory Committee on Immunization Practices guidelines. While HPV vaccine will not protect against progression of infection already acquired or promote clearance of the infection, the vaccine would protect against vaccine types not yet acquired. ACIP recommends vaccination of children who are victims of sexual abuse or assault at age 9 years or older who have not initiated or completed immunization. Second and third doses of vaccine should be administered at 1–2 months after the first dose, and 6 months after the first dose (minimum interval between first and second dose of vaccine is 4 weeks and between the second and third dose is 12 weeks).

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Terms and Abbreviations Used in This Report

AIDS Acquired immunodeficiency syndrome

ALT Alanine aminotransferase

anti-HBc Antibody to hepatitis B core antigen

anti-HCV Hepatitis C antibodies

ASC-US Atypical squamous cells of undetermined significance

BCA Bichloroacetic acid

BV Bacterial vaginosis

CBC Complete blood count

CI Confidence interval

CIN Cervical intraepithelial neoplasia

CLD Chronic liver disease

CLIA Clinical Laboratory Improvement Amendments

CNS Central nervous system

CSF Cerebrospinal fluid

DFA Direct fluorescent antibody

DGI Disseminated gonococcal infection

| | |
|---------|--|
| dL | Deciliter |
| DNA | Deoxyribonucleic acid |
| EC | Emergency contraception |
| EIA | Enzyme immunoassay |
| ELISA | Enzyme-linked immunosorbent assay |
| EPT | Expedited partner therapy |
| FDA | Food and Drug Administration |
| FTA-ABS | Fluorescent treponemal antibody absorbed |
| gG | Glycoprotein G |
| GNID | Gram-negative intracellular diplococci |
| HAART | Highly active antiretroviral therapy |

| | |
|-------|------------------------------|
| HAV | Hepatitis A virus |
| HBIG | Hepatitis B immune globulin |
| HbsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HCC | hepatocellular carcinoma |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| IFA | Immunofluorescence assay |
| IgE | Immunoglobulin E |
| Ig | Immune globulin |
| IgG | Immunoglobulin G |
| IgM | Immunoglobulin M |

| | |
|------|------------------------------------|
| IM | Intramuscularly |
| IUD | Intrauterine device |
| IV | Intravenous or intravenously |
| KOH | Potassium hydroxide |
| LGV | Lymphogranuloma venereum |
| MAC | <i>Mycobacterium avium</i> complex |
| MIC | Minimum inhibitory concentration |
| MSM | Men who have sex with men |
| N-9 | Nonoxynol-9 |
| NAAT | Nucleic acid amplification test |
| NGU | Nongonococcal urethritis |

| | |
|--------|--|
| Pap | Papanicolaou |
| PCR | Polymerase chain reaction |
| PEP | Postexposure prophylaxis |
| PID | Pelvic inflammatory disease |
| PO | By mouth |
| PPV | Positive predictive value |
| QRNG | Quinolone-resistant <i>Neisseria gonorrhoeae</i> |
| RNA | Ribonucleic acid |
| RPR | Rapid plasma reagin |
| RT-PCR | Reverse transcriptase polymerase chain reaction |
| RVVC | Recurrent vulvovaginal candidiasis |
| SIL | Squamous intraepithelial lesion |

| | |
|-------|--|
| STD | Sexually transmitted disease |
| TCA | Trichloroacetic acid |
| TE | Toxoplasmic encephalitis |
| TP-PA | <i>Treponema pallidum</i> particle agglutination |
| VDRL | Venereal Disease Research Laboratory |
| VVC | Vulvovaginal candidiasis |
| WB | Western blot |
| WBC | White blood count |
| WSW | Women who have sex with women |

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