Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

REVIEWED
By Chris Tighe at 2:44 pm, Sep 02, 2016

Diseases Characterized by Genital, Anal, or Perianal Ulcers

This web page is archived for historical purposes and is no longer being updated. Newer content is available at www.cdc.gov/std/treatment

Sexually Transmitted Diseases Treatment Guidelines, 2010

On this Page

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. HSV, syphilis, and chancroid have been associated with an increased risk for HIV transmission, and genital, anal, or perianal lesions might be associated with 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 for HSV or PCR testing for HSV; and 3) serologic testing for type-specific HSV antibody.

No FDA-cleared PCR test to diagnose either herpes or syphilis is available in the United States; however, such testing can be performed by clinical laboratories that have developed their own 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).

Health-care providers frequently must treat patients before test results are available, because early treatment decreases the possibility of ongoing transmission and because successful treatment of genital herpes depends on prompt initiation of therapy. The clinician should empirically treat for the diagnosis considered most likely on the basis of clinical presentation and epidemiologic circumstances (including travel history); even after complete diagnostic evaluation, at least 25% of patients who have genital ulcers have no laboratory-confirmed diagnosis.

Chancroid

The prevalence of chancroid has declined in the United States (93). 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 infection (144).

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% (145). 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 chancroid (146). 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 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; 3) the clinical presentation, appearance of genital ulcers and, if present, regional lymphadenopathy are typical for chancroid; and 4) a 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.

Recommended Regimens
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
* Ciprofloxacin is contraindicated for pregnant and lactating women.

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 coinfected 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

Ciprofloxacin is contraindicated during pregnancy and lactation. No adverse effects of chancroid on pregnancy outcome have been reported.

HIV Infection

HIV-infected patients 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. HIV-infected patients 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 ceftriaxone and azithromycin regimens in HIV-infected patients, 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 have been identified as causing 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 herpes (147). However, an increasing proportion of anogenital herpetic infections in some populations has been attributed to HSV-1 infection.

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 genital tract. 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 ulcers.

Diagnosis of HSV Infection

The clinical diagnosis of genital herpes is both nonsensitive and nonspecific. The classical painful multiple vesicular or ulcerative lesions are absent in many infected persons. HSV-1 is causing an increasing proportion of first episodes of anogenital herpes in some populations (e.g., young women and MSM) and might now account for most of these infections (148,149). Recurrences and subclinical shedding are much less frequent for genital HSV-1 infection than for genital HSV-2 infection (150,151). 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 laboratory testing (152). Both 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. PCR assays for HSV DNA are more sensitive and are increasingly used in many settings (153,154). PCR is the test of choice for detecting HSV in spinal fluid for diagnosis of HSV infection of the central nervous system (CNS). Viral culture isolates should be typed to determine which type of HSV is causing the infection. Failure to detect HSV by culture or PCR 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 nontype-specific 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). Such assays first became commercially available in 1999, but older assays that do not accurately distinguish HSV-1 from HSV-2 antibody (despite claims to the contrary) remain on the market (155); providers should specifically request serologic type-specific glycoprotein G (gG)-based assays when serology is performed for their patients (156-158).

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. The specificities of these assays are ≥96%. False-positive results can occur, especially in patients with a low likelihood of HSV infection. Repeat or confirmatory testing might be indicated in some settings, especially if recent acquisition of genital herpes is suspected. IgM testing for HSV is not useful, because the IgM tests are not type-specific and might be positive during recurrent episodes of herpes (159).

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. Most persons with HSV-1 antibody have oral HSV infection acquired during childhood, which might be asymptomatic. However, acquisition of genital HSV-1 appears to be increasing, and genital HSV-1 also can be asymptomatic (147-149). 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 cultures; 2) a clinical diagnosis of genital herpes without laboratory confirmation; or 3) a partner with 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 herpes episodes 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 famciclovir (160-168). 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
Famciclovir 250 mg orally three times a day for 7–10 days
OR
Valacyclovir 1 g orally twice 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 (169,170).

Suppressive Therapy for Recurrent Genital Herpes

Suppressive therapy reduces the frequency of genital herpes recurrences by 70%–80% in patients who have frequent recurrences (166-169); 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 (171,172). Quality of life is improved in many patients with frequent recurrences who receive suppressive therapy rather than episodic treatment.

The frequency of recurrent genital herpes outbreaks diminishes over time in many patients, and the patient's 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 with the patient.

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 infection (170). 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.

Recommended Regimens*
Acyclovir 400 mg orally twice a day OR **Famiciclovir** 250 mg orally twice a day OR **Valacyclovir** 500 mg orally once a day* OR **Valacyclovir** 1 g orally once a day * Valacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (i.e., ≥10 episodes per year).

Acyclovir, famciclovir, and valacyclovir appear equally effective for episodic treatment of genital herpes, but famciclovir appears somewhat less effective for suppression of viral shedding (163-167,147,173). 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

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

OR

Valacyclovir 500 mg orally twice a day for 3 days

OR

Valacyclovir 1 g orally once a day for 5 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. 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 (174,175). 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.ashastd.org (http://www.ashastd.org)) and printed materials, are available to assist patients, their partners, and clinicians who become involved in counseling.

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 (176), 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 frequently is 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, might reduce the risk for genital herpes transmission (21-23).
- 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. Patients should be informed that suppressive antiviral therapy does not reduce the increased risk for HIV acquisition associated with HSV-2 infection (177,178).

Management of Sex Partners

The sex partners of patients 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 lesions. 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 acyclovir, valacyclovir, and famciclovir are rare. Desensitization to acyclovir has been described (179).

HIV Infection

Immunocompromised patients can have prolonged or severe episodes of genital, perianal, or oral herpes. Lesions caused by HSV are common among HIV-infected patients and might be severe, painful, and atypical. HSV shedding is increased in HIV-infected persons. Whereas antiretroviral therapy reduces the severity and frequency of symptomatic genital herpes, frequent subclinical shedding still occurs (180). Clinical manifestations of genital herpes might worsen during immune reconstitution after initiation of antiretroviral therapy.

Suppressive or episodic therapy with oral antiviral agents is effective in decreasing the clinical manifestations of HSV among HIV-positive persons (181-183). The extent to which suppressive antiviral therapy will decrease HSV transmission from this population is unknown. HSV type-specific serologies can be offered to HIV-positive persons during their initial evaluation if infection status is unknown, and suppressive antiviral therapy can be considered in those who have HSV-2 infection.

Recommended Regimens for Daily Suppressive Therapy in Persons with HIV
Acyclovir 400–800 mg orally twice to three times a day OR **Famciclovir** 500 mg orally twice a day

OR

Valacyclovir 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 **Famciclovir** 500 mg orally twice a day for 5–10 days OR **Valacyclovir** 1 g 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.

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 testing (184). Such persons should be managed in consultation with an HIV specialist, and alternate therapy should be administered. All acyclovir-resistant strains are resistant to valacyclovir, and the majority are resistant to famciclovir. Foscarnet, 40 mg/kg IV every 8 hours until clinical resolution is attained, is frequently effective for treatment of acyclovir-resistant genital herpes. Intravenous cidofovir 5 mg/kg once weekly might also be effective. Imiquimod is a topical alternative, as is topical cidofovir gel 1%, which is not commercially available and must be compounded at a pharmacy. 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 with outbreaks (185).

Genital Herpes in Pregnancy

Most mothers of infants who acquire neonatal herpes lack histories of clinically evident genital herpes (186). 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 histories of recurrent herpes at term or who acquire genital HSV during the first half of pregnancy (187). However, because recurrent genital herpes is much more common than initial HSV infection during pregnancy, the proportion of neonatal HSV infections acquired from mothers with recurrent herpes is substantial. Prevention of neonatal herpes depends both on preventing acquisition of genital HSV infection during late pregnancy and avoiding exposure of the infant to herpetic lesions during delivery. Because the risk for herpes is high in infants of women who acquire genital HSV during late pregnancy, these women should be managed in consultation with an infectious disease specialist.

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. Some specialists believe that type-specific serologic tests are useful to identify pregnant women at risk for HSV infection and to guide counseling regarding the risk for acquiring genital herpes during pregnancy and that such testing should 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 section does not completely eliminate the risk for HSV transmission to the infant, women with recurrent genital herpetic lesions at the onset of labor should deliver by cesarean section to prevent neonatal HSV infection.

The safety of systemic acyclovir, valacyclovir, and famciclovir therapy in pregnant women has not been definitively established. Available data do not indicate an increased risk for major birth defects compared with the general population in women treated with acyclovir during the first trimester (188) — findings that provide assurance to women who have had prenatal exposure to acyclovir. However, data regarding prenatal exposure to valacyclovir and famciclovir are too limited to provide useful information on pregnancy outcomes. 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. Acyclovir treatment late in pregnancy reduces the frequency of cesarean sections among women who have recurrent genital herpes by diminishing the frequency of recurrences at term (189-191); the effect of antiviral therapy late in pregnancy on the incidence of neonatal herpes is not known. No data support the use of antiviral therapy among HSV seropositive women without a history of genital herpes.

Neonatal Herpes

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. Surveillance cultures of mucosal surfaces to detect HSV infection might be considered before the development of clinical signs of neonatal herpes. 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 21 days for disseminated and CNS disease or for 14 days for disease limited to the skin and mucous membranes.

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 Africa (192,193). Clinically, the disease is commonly characterized as painless, slowly progressive ulcerative lesions on the genitals or perineum without regional lymphadenopathy; subcutaneous granulomas (pseudoboboes) might also occur. The lesions are highly vascular (i.e., beefy red appearance) and bleed easily on contact. The clinical presentation also can include hypertrophic, necrotic, or sclerotic variants. 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 published (192). 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	
Doxycycline	100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed

Alternative Regimens	

Azithromycin 1 g orally once per week 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 an aminoglycoside (e.g., gentamicin 1 mg/kg IV every 8 hours) to these regimens can be considered if improvement is not evident within the first few days of therapy.

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

Special Considerations

Pregnancy

Pregnancy is a relative contraindication to the use of sulfonamides. Pregnant and lactating women should be treated with the erythromycin regimen, and consideration should be given to the addition of a parenteral aminoglycoside (e.g., gentamicin). Azithromycin might prove useful for treating granuloma inguinale during pregnancy, but published data are lacking. Doxycycline and ciprofloxacin are contraindicated in pregnant women.

HIV Infection

Persons with both granuloma inguinale and HIV infection should receive the same regimens as those who are HIV negative; however, the addition of a parenteral aminoglycoside (e.g., gentamicin) can also be considered.

Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is caused by C. trachomatis serovars L1, L2, or L3 (194). 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, including mucoid and/or hemorrhagic rectal discharge, anal pain, constipation, fever, and/or tenesmus (195,196). LGV is an invasive, systemic infection, and if it is not treated early, LGV proctocolitis can lead to chronic, colorectal fistulas and strictures. Genital and colorectal LGV lesions can also develop secondary bacterial infection or can be coinfected 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. C. trachomatis testing also should be conducted, if available.

Genital and lymph node specimens (i.e., lesion swab or bubo aspirate) can be tested for C. trachomatis by culture, direct immunofluorescence, or nucleic acid detection. NAATs for C. trachomatis are not FDA-cleared for testing rectal specimens, although some laboratories have performed the CLIA validation studies that are needed to provide results 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.

Chlamydia serology (complement fixation titers >1:64) can support the diagnosis of LGV in the appropriate clinical context. Comparative data between types of serologic tests are lacking, and the diagnostic utility of serologic methods other than complement fixation and some microimmunofluorescence 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 LGV diagnostic testing, patients with a clinical syndrome consistent with LGV, including proctocolitis or genital ulcer disease with lymphadenopathy, should be treated for LGV as described in this report.

Treatment

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

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 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 is contraindicated in pregnant women.

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 a series of overlapping stages, which are used to help guide treatment and follow-up. Persons who have syphilis might seek treatment for signs or symptoms of primary infection (i.e., ulcer or chancre at the infection site), secondary infection (i.e., manifestations that include, but are not limited to, skin rash, mucocutaneous lesions, and lymphadenopathy), neurologic infection (i.e., cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities, which might occur through the natural history of untreated infection), or tertiary infection (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 either late latent syphilis or

latent syphilis of unknown duration. Treatment for both late latent syphilis and tertiary syphilis might 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 in lesion exudate or tissue are the definitive methods for diagnosing early syphilis (197). Although no T. pallidum detection tests are commercially available, some laboratories provide locally developed PCR tests for the detection of T. pallidum. 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 EIAs, and chemiluminescence immunoassays). The use of only one type of serologic test is insufficient for diagnosis, because each type of test has limitations, including the possibility of false-positive test results in persons without syphilis. False-positive nontreponemal test results can be associated with various medical conditions unrelated to syphilis, including autoimmune conditions, older age, and injection-drug use (198,199); therefore, persons with a reactive nontreponemal test should receive a treponemal test to confirm the diagnosis of syphilis.

Nontreponemal test antibody titers may correlate with disease activity, and results should be reported quantitatively. A fourfold change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32), is considered necessary 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 years (200). Treponemal test antibody titers should not be used to assess treatment response.

Some clinical laboratories and blood banks have begun to screen samples using treponemal tests, typically by EIA or chemiluminescence immunoassays (201,202). This strategy will identify both persons with previous treatment for syphilis and persons with untreated or incompletely treated syphilis. The positive predictive value for syphilis associated with a treponemal screening test result might be lower among populations with a low prevalence of syphilis.

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. 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, further evaluation or treatment is not indicated.

For most HIV-infected persons, serologic tests are accurate and reliable for the diagnosis of syphilis and for following a patient's response to treatment. However, atypical syphilis serologic test results (i.e., unusually high, unusually low, or fluctuating titers) can occur in HIV-infected persons. When serologic tests do not correspond with clinical findings suggestive of early syphilis, use of other tests (e.g., biopsy and darkfield microscopy) should be considered.

Clinical signs of neurosyphilis (i.e., cranial nerve dysfunction, meningitis, stroke, acute or chronic altered mental status, loss of vibration sense, and auditory or ophthalmic abnormalities) warrant further investigation and treatment for neurosyphilis. Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis in all instances. Cerebrospinal fluid (CSF) laboratory abnormalities are common in persons with early syphilis. The VDRL in cerebrospinal fluid (CSF-VDRL), which is highly specific but

insensitive, is the standard serologic test for CSF. When reactive in the absence of substantial contamination of CSF with blood, it is considered diagnostic of neurosyphilis; however in early syphilis, it can be of unknown prognostic significance (203). Most other tests are both insensitive and nonspecific and must be interpreted in relation to other test results and the clinical assessment. Therefore, the laboratory diagnosis of neurosyphilis usually depends on various combinations of reactive serologic test results, CSF cell count or protein, and a reactive CSF-VDRL with or without clinical manifestations. 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 diagnosis (204). The CSF-VDRL might be nonreactive even when neurosyphilis is present; therefore, 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; neurosyphilis is highly unlikely with a negative CSF FTA-ABS test (205).

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 syphilis (206).

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 Patients 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 usually occur within the first 24 hours after the initiation of any therapy for syphilis. Patients should be informed about this possible adverse reaction. The Jarisch-Herxheimer reaction occurs most frequently among patients 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. Although such manifestations are uncommon after the first year of infection, persons exposed sexually to a patient who has syphilis in any stage 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.
- 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.
- For purposes of partner notification and presumptive treatment of exposed sex partners, patients with syphilis of unknown duration who have high nontreponemal serologic test titers (i.e., >1:32) can be assumed to have early syphilis. For the purpose of determining a treatment regimen, however, serologic titers should not be used

to differentiate early from late latent syphilis (see Latent Syphilis, Treatment).

- Long-term sex partners of patients 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 patients should be considered at risk and provided treatment if they have had sexual contact with the patient within 3 months plus the duration of symptoms for patients diagnosed with primary syphilis, 6 months plus duration of symptoms for those with secondary syphilis, and 1 year for patients 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 comparative trials have been adequately conducted to guide the selection of an optimal penicillin regimen (i.e., the dose, duration, and preparation). 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 HIV-infected persons and pregnant women are discussed later in this report (see Syphilis among HIV–Infected Persons and Syphilis in Pregnancy).

Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early syphilis (primary, secondary, and early latent) do not enhance efficacy, regardless of HIV status.

Recommended Regimen for Infants and Children

Infants and children aged ≥1 month diagnosed with syphilis should have a CSF examination to detect asymptomatic neurosyphilis, and birth and maternal medical records should be reviewed to assess whether such children have congenital or acquired syphilis (see Congenital Syphilis). Children with acquired primary or secondary syphilis should be evaluated (e.g., through consultation with child-protection services) (see Sexual Assault or Abuse of Children) and treated by using the following pediatric regimen.

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

Other Management Considerations

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

Patients who have syphilis and symptoms or signs suggesting neurologic disease (e.g., meningitis 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 syphilis (203). Therefore, in the absence of clinical neurologic findings, no evidence exists to support variation from the recommended treatment regimen for early syphilis. Symptomatic neurosyphilis develops in only a limited number of 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

Treatment failure can occur with any regimen. However, assessing response to treatment frequently is difficult, and definitive criteria for cure or failure have not been established. In addition, nontreponemal test titers might decline more slowly for persons who previously have had syphilis (207). 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.

Patients who have signs or symptoms that persist or recur or who have a sustained fourfold increase in nontreponemal test titer (i.e., compared with the maximum or baseline titer at the time of treatment) probably failed treatment or were reinfected. These patients 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.

Although 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, clinical trial data have demonstrated that >15% of patients with early syphilis treated with the recommended therapy will not achieve the two dilution decline in nontreponemal titer used to define response at 1 year after treatment (208). Persons whose titers do not decline should be reevaluated for HIV infection. Optimal management of such patients is unclear. At a minimum, these patients 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). In rare instances, serologic titers do not decline despite a negative CSF examination and a repeated course of therapy. In these circumstances, the need for additional therapy or repeated CSF examinations is unclear, but is not generally recommended.

Management of Sex Partners

See General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Data to support the use of alternatives to penicillin in the treatment of early syphilis are limited. However, several therapies might be effective in nonpregnant, penicillin-allergic patients who have primary or secondary syphilis. Doxycycline 100 mg orally twice daily for 14 days (209,210) 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. Although limited clinical studies, along with biologic and pharmacologic evidence, suggest that ceftriaxone (1 g daily either IM or IV for 10–14 days) is effective for treating early syphilis, the optimal dose and duration of ceftriaxone therapy have not been defined (211). Azithromycin as a single 2-g oral dose is effective for treating early syphilis (212-214). However, T. pallidum chromosomal mutations associated with azithromycin resistance and treatment failures have been documented in several geographical areas in the United States (215-217). As such, the use of azithromycin should be used with caution only when treatment with penicillin or doxycycline is not feasible. Azithromycin should not be used in MSM or pregnant women. Close 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 Patients Who Have a History of Penicillin Allergy).

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see Management of Patients Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

See Syphilis Among HIV-Infected Persons.

Latent Syphilis

Latent syphilis is defined as syphilis characterized by seroreactivity without other evidence of disease. Patients who have latent syphilis and who acquired syphilis during the preceding year are classified as having early latent syphilis. Patients' conditions can be diagnosed as early latent syphilis if, during the year preceding the evaluation, they had 1) a documented seroconversion or 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 whose only possible exposure occurred during the previous 12 months, reactive nontreponemal and treponemal tests are indicative of early latent syphilis. In the absence of these conditions, an asymptomatic person should be considered to have late latent syphilis or syphilis of unknown duration. 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 patients 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. All patients who have syphilis should be tested for HIV infection.

Treatment

Because latent syphilis is not transmitted sexually, the objective of treating patients with this stage of disease is to prevent complications. Although clinical experience supports the effectiveness of penicillin in achieving this goal, limited evidence is available to guide choice of specific regimens.

The following regimens are recommended for penicillin nonallergic patients who have normal CSF examinations (if performed).

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

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

Available data demonstrate no enhanced efficacy of additional doses of penicillin G, amoxicillin, or other antibiotics in early syphilis, regardless of HIV status.

Infants and children aged ≥1 month who have been diagnosed with syphilis should have a CSF examination to exclude neurosyphilis. In addition, birth and maternal medical records should be reviewed to assess whether children have congenital or acquired syphilis (see Congenital Syphilis). Older children with acquired latent syphilis should be evaluated as described for adults and treated using the following pediatric regimens (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.

Recommended Regimens for 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 or Latent Syphilis of Unknown Duration

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)

Other Management Considerations

Patients diagnosed with latent syphilis who demonstrate any of the following criteria should have a prompt CSF examination:

- Neurologic (e.g., auditory disease, cranial nerve dysfunction, acute or chronic meningitis, stroke, acute or chronic altered mental status, and loss of vibration sense) or ophthalmic signs or symptoms (e.g., iritis and uveitis);
- evidence of active tertiary syphilis (e.g., aortitis and gumma); or
- serologic treatment failure.

If a patient misses a dose of penicillin in a course of weekly therapy for late syphilis, the appropriate course of action is unclear. Pharmacologic considerations suggest that an interval of 10–14 days between doses of benzathine penicillin for late syphilis or latent syphilis of unknown duration might be acceptable before restarting the sequence of injections. Missed doses are not acceptable for pregnant patients receiving therapy for late latent syphilis. 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) titers increase fourfold, 2) an initially high titer (≥1:32) fails to decline at least fourfold (i.e., two dilutions) within 12–24 months of therapy, or 3) signs or symptoms attributable to syphilis develop. In such circumstances, even if the CSF examination is negative, retreatment for latent syphilis should be initiated. 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.

Management of Sex Partners

See General Principles, 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 therapies 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 or latent syphilis of unknown duration are doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times daily), both for 28 days. These therapies should be used only in conjunction with close serologic and clinical follow-up. Based on biologic plausibility and pharmacologic properties, ceftriaxone might be effective for treating late latent syphilis or syphilis of unknown duration. However, the optimal dose and duration of ceftriaxone therapy have not been defined, and treatment decisions should be discussed in consultation with a specialist. Some patients who are allergic to penicillin also might be allergic to ceftriaxone; in these circumstances, use of an alternative agent might be required. The efficacy of these alternative regimens in HIV-infected persons has not been well studied.

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see Management

of Patients Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

See Syphilis Among HIV-Infected Persons.

Tertiary Syphilis

Tertiary syphilis refers to gumma and cardiovascular syphilis but not to all neurosyphilis. Patients who are not allergic to penicillin and have no evidence of neurosyphilis should be treated with the following regimen.

Recommended Regimen
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

Patients who have symptomatic late syphilis should be given a CSF examination before therapy is initiated. Some providers treat all patients who have cardiovascular syphilis with a neurosyphilis regimen. These patients should be managed in consultation with an infectious disease specialist.

Follow-Up

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

Management of Sex Partners

See General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy

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

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see Management of Patients Who Have a History of Penicillin Allergy and Syphilis During Pregnancy).

HIV Infection

See Syphilis Among HIV-Infected Persons.

Neurosyphilis

Treatment

CNS involvement can occur during any stage of syphilis. However, 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 early syphilis for patients found to have such abnormalities. 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), a CSF examination should be performed.

Syphilitic uveitis or other ocular manifestations frequently are associated with neurosyphilis and should be managed according to the treatment recommendations for neurosyphilis. Patients who have neurosyphilis or syphilitic eye disease (e.g., uveitis, neuroretinitis, and optic neuritis) should be treated with the recommended regimen for neurosyphilis; those with eye disease should be managed in collaboration with an ophthalmologist. A CSF examination should be performed for all patients with syphilitic eye disease to identify those with abnormalities; patients found to have abnormal CSF test results should be provided follow-up CSF examinations to assess treatment response.

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

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

Alternative Regimen
Procaine penicillin 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 syphilis in the absence of neurosyphilis. 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 patients who have neurosyphilis are as follows:

- All persons who have syphilis 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 (219,220). 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 HIV-infected persons on highly active antiretroviral therapy, normalization of the serum RPR titer predicts normalization of CSF parameters (220).

Management of Sex Partners

See General Principles, Management of Sex Partners.

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 patients with neurosyphilis (221-222). However, the possibility of cross-reactivity between ceftriaxone and penicillin exists. Other regimens have not been adequately evaluated for treatment of neurosyphilis. Therefore, 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.

Pregnancy

Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin (see Syphilis During Pregnancy).

HIV Infection

See Syphilis Among HIV-Infected Persons.

Syphilis Among HIV-Infected Persons

Diagnostic Considerations

Although they are uncommon, unusual serologic responses have been observed among HIV-infected persons who have syphilis. Most reports have involved serologic titers that were higher than expected, but false-negative serologic test results and delayed appearance of seroreactivity also have been reported (223). Regardless, both treponemal and nontreponemal serologic tests for syphilis can be interpreted in the usual manner for most patients who are coinfected with T. pallidum and HIV.

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 disease in HIV-infected persons.

Treatment

Compared with HIV-negative patients, HIV-positive patients who have early syphilis might be at increased risk for neurologic complications (224) 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. No treatment regimens for syphilis have been demonstrated to be more effective in preventing neurosyphilis in HIV-infected patients than the syphilis regimens recommended for HIV-negative patients (208). Careful follow-up after therapy is essential.

Primary and Secondary Syphilis Among HIV-Infected Persons

Treatment

Treatment of primary and secondary syphilis among HIV-infected persons is benzathine penicillin G, 2.4 million units IM in a single dose.

Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early syphilis do not result in enhanced efficacy, regardless of HIV status (208).

Other Management Considerations

Most HIV-infected persons respond appropriately to standard benzathine penicillin for primary and secondary syphilis. CSF abnormalities (e.g., mononuclear pleocytosis and elevated protein levels) are common in HIV-infected persons, even in those without neurologic symptoms, although the clinical and prognostic significance of such CSF abnormalities with primary and secondary syphilis is unknown. Several studies have demonstrated that among persons infected with both HIV and syphilis, clinical and CSF abnormalities consistent with neurosyphilis are associated with a CD4 count of ≤350 cells/mL and/or an RPR titer of ≥1:32 (204,225,226); however, unless neurologic symptoms are present, CSF examination in this setting has not been associated with improved clinical outcomes.

The use of antiretroviral therapy as per current guidelines might improve clinical outcomes in HIV-infected persons with syphilis (220,227-228).

Follow-Up

HIV-infected persons should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy.

HIV-infected persons who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or persons who have a sustained fourfold increase in nontreponemal test titer) should be managed in the same manner as HIV-negative patients (i.e., a CSF examination and retreatment). CSF examination and retreatment also should be strongly considered for persons whose nontreponemal test titers do not decrease fourfold within 6–12 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.

Management of Sex Partners

See General Principles, Management of Sex Partners.

Special Considerations

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

Latent Syphilis Among HIV-Infected Persons

Treatment

HIV-infected persons with latent syphilis should be treated according to the stage-specific recommendations for HIV-negative persons.

- Treatment of early latent syphilis among HIV-infected persons is benzathine penicillin G, 2.4 million units IM in a single dose.
- Treatment of late latent syphilis or syphilis of unknown duration among HIV-infected persons is benzathine penicillin G, at weekly doses of 2.4 million units for 3 weeks.

Other Management Considerations

All HIV-infected persons with syphilis and neurologic symptoms should undergo immediate CSF examination. Some studies have demonstrated that clinical and CSF abnormalities consistent with neurosyphilis are most likely in HIV-infected persons who have been diagnosed with syphilis and have a CD4 count of ≤350 cells/ml and/or an RPR titer of ≥1:32 (204,225,226); however unless neurologic symptoms are present, CSF examination in this setting has not been associated with improved clinical outcomes.

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, a repeat CSF examination should be performed and treatment administered accordingly. If during 12–24 months the nontreponemal titer does not decline fourfold, CSF examination should be strongly considered and treatment administered accordingly.

Management of Sex Partners

See General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy. The efficacy of alternative nonpenicillin regimens in HIV-infected persons has not been well studied. Patients with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin (see Management of Patients Who Have a History of Penicillin Allergy). These therapies should be used only in conjunction with close serologic and clinical follow-up. Limited clinical studies, along with biologic and pharmacologic evidence, suggest that ceftriaxone might be effective (229,230). However, the optimal dose and duration of ceftriaxone therapy have not been defined.

Neurosyphilis Among HIV-Infected Persons

Treatment

HIV-infected patients with neurosyphilis should be treated according to the recommendations for HIV-negative patients with neurosyphilis (see Neurosyphilis).

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 gauge response after therapy. Limited data suggest that changes in CSF parameters might occur more slowly in HIV-infected patients, especially those with more advanced immunosuppression (219,227). If the cell count has not decreased after 6 months or if the CSF is not normal after 2 years, retreatment should be considered.

Management of Sex Partners

See General Principles, Management of Sex Partners.

Special Considerations

Penicillin Allergy. HIV-infected, penicillin-allergic patients who have neurosyphilis should be managed according to the recommendations for penicillin-allergic, HIV-negative patients with neurosyphilis. Several small observational studies conducted in HIV-infected patients with neurosyphilis suggest that ceftriaxone 1–2 g IV daily for 10-14 days might be effective as an alternate agent (218,229,230).

Syphilis During Pregnancy

All women should be screened serologically for syphilis early in pregnancy. Most states mandate screening at the first prenatal visit for all women (231); 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 confirmatory testing with nontreponemal tests with titers. 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 confirmed (232). For communities and populations in which the prevalence of syphilis is high and for patients at high risk, serologic testing should be performed twice during the third trimester (ideally at 28–32 weeks' gestation) and at delivery. Any woman who delivers a stillborn infant after 20 weeks' gestation should be tested for syphilis. No infant 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. Serofast low antibody titers might not require treatment; however, persistent higher titer antibody tests might indicate reinfection, and treatment might be required.

Treatment

Penicillin is effective for preventing maternal transmission to the fetus and for treating fetal infection (233). Evidence is insufficient to determine optimal, recommended penicillin regimens (234).

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) (235). 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 failure (231); 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 reaction (236). 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. All patients who have syphilis should be offered testing for HIV infection.

Follow-Up

Coordinated prenatal care and treatment are vital. Serologic titers should be repeated at 28–32 weeks' gestation and at delivery as recommended for the disease stage. 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. 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.

Management of Sex Partners

See General Principles, Management of Sex Partners.

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. Oral step-wise penicillin dose challenge or skin testing might be helpful in identifying women at risk for acute allergic reactions (see Management of Patients Who Have a History of Penicillin Allergy).

Tetracycline and doxycycline usually are not used during pregnancy. Erythromycin and azithromycin should not be used, because neither reliably cures maternal infection or treats an infected fetus (234). 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 HIV-infected women should be evaluated for syphilis and receive treatment as recommended. Data are insufficient to recommend a specific regimen for HIV-infected pregnant women (see Syphilis Among HIV-Infected Patients).

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. In communities and populations in which the risk for congenital syphilis is high, serologic testing and a sexual history also should be obtained at 28 weeks' gestation and at delivery. Moreover, as part of the management of pregnant women who have syphilis, information concerning 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. Serologic testing of the mother's serum is preferred rather than testing of the infant's serum because the serologic tests performed on infant 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). Screening can be performed using either a nontreponemal or treponemal test. If either screening test is positive, testing must be performed immediately using the other complimentary test (i.e., nontreponemal test followed by treponemal test or vice-versa). No infant or mother 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 should also occur at delivery.

Evaluation and Treatment of Infants During the First Month of Life

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 infants. 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 infant; and 4) comparison of maternal (at delivery) and infant nontreponemal serologic titers using the same test conducted preferably by the same laboratory.

All infants 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 infant serum, because umbilical cord blood can become contaminated with maternal blood and yield a false-positive result. Conducting a treponemal test (i.e., TP-PA, FTA-ABS, EIA, or chemiluminescence assay) on a newborn's serum is not necessary. No

commercially available immunoglobulin (IgM) test can be recommended.

All infants 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 fluorescent antitreponemal antibody staining is suggested. Darkfield microscopic examination of suspicious lesions or body fluids (e.g., nasal discharge) also should be performed.

The following scenarios describe the evaluation and treatment of infants for congenital syphilis.

Scenario 1

Infants with proven or highly probable disease and

1. an abnormal physical examination that is consistent with congenital syphilis;
2. a serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer;¶ or
3. a positive darkfield test of 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, cranial ultrasound, 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 sepsis. The use of agents other than penicillin requires close serologic follow-up to assess adequacy of therapy. In all other situations, the maternal history of infection with T. pallidum and treatment for syphilis must be considered when evaluating and treating the infant.

Scenario 2

Infants who have a normal physical examination and a serum quantitive nontreponemal serologic titer the same or less than fourfold the maternal titer and the

1. mother was not treated, inadequately treated, or has no documentation of having received treatment;
2. mother was treated with erythromycin or another nonpenicillin regimen;†† or
3. mother received treatment <4 weeks before delivery.

Recommended Evaluation

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

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. If a single dose of benzathine penicillin G is used, then the infant must be fully evaluated (i.e., by CSF examination, long-bone radiographs, and CBC with platelets), the full evaluation 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 rendered uninterpretable because of contamination with blood, then a 10-day course of penicillin is required.§§

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

If the mother has untreated early syphilis at delivery, 10 days of parenteral therapy can be considered.

Scenario 3

Infants who have a normal physical examination and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer and the

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 required.

Recommended Regimen
Benzathine penicillin G 50,000 units/kg/dose IM in a single dose* * Another approach involves not treating the infant, but rather providing close serologic follow-up in those whose mother's nontreponemal titers decreased fourfold after appropriate therapy for early syphilis or remained stable or low for late syphilis.

Scenario 4

Infants who have a normal physical examination and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer and the

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 required.

Recommended Regimen
No treatment is required; however, **benzathine penicillin G** 50,000 units/kg as a single IM injection might be considered, particularly if follow-up is uncertain.

Evaluation and Treatment of Older Infants and Children

Older 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 child at risk for congenital syphilis 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, and auditory brain stem response)

Recommended Regimen
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

If the 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. A single dose of benzathine penicillin G, 50,000 units/kg IM after the 10-day course of IV aqueous penicillin can be considered. This treatment also would be adequate for children who might have other treponemal infections.

Follow-Up

All seroreactive infants (or infants whose mothers were seroreactive at delivery) should receive careful follow-up examinations and serologic testing (i.e., a nontreponemal test) every 2–3 months until the test becomes nonreactive or the titer has decreased fourfold. Nontreponemal antibody titers should decline by age 3 months and should be nonreactive by age 6 months if the infant is not infected (i.e., if the reactive test result was caused by passive transfer of maternal IgG antibody) or was infected but adequately treated. The serologic response after therapy might be slower for infants treated after the neonatal period. If these titers are stable or increase after age 6–12 months, the child should be evaluated (e.g., given a CSF examination) and treated with a 10-day course of parenteral penicillin G.

Treponemal tests should not be used to evaluate treatment response, because the results for an infected child can remain positive despite effective therapy. Passively transferred maternal treponemal antibodies can be present in an infant until age 15 months; therefore, a reactive treponemal test after age 18 months is diagnostic of congenital syphilis. If the nontreponemal test is nonreactive at this time, no further evaluation or treatment is necessary. If the nontreponemal test is reactive at age 18 months, the infant should be fully (re)evaluated and treated for congenital syphilis.

Infants 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.

Follow-up of children treated for congenital syphilis after the newborn period should be conducted as recommended for neonates.

Special Considerations

Penicillin Allergy

Infants and children who require treatment for syphilis but who have a history of penicillin allergy or develop an allergic reaction presumed secondary to penicillin should be desensitized, if necessary, and then treated with penicillin (see Management of Patients With a History of Penicillin Allergy). Data are insufficient regarding the use of other antimicrobial agents (e.g., ceftriaxone); if a nonpenicillin agent is used, close serologic and CSF follow-up are indicated.

Penicillin Shortage

During periods when the availability of penicillin is compromised, the following is recommended (see /std/treatment/drugnotices/penicilling.htm).

1. For infants 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 age and weight) can be considered with careful clinical and serologic follow-up. Ceftriaxone must be used with caution in infants with jaundice. For infants aged ≥30 days, use 75 mg/kg IV/IM a day in a single daily dose for 10–14 days; however, dose adjustment might be necessary based on current weight. For older infants, the dose should be 100 mg/kg a day in a single daily dose. Evidence is insufficient to support the use of ceftriaxone for the treatment of congenital syphilis. Therefore, ceftriaxone should be used in consultation with a specialist in the treatment of infants with congenital syphilis. Management may include a repeat CSF examination at age 6 months if the initial examination was abnormal.
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.
3. For premature infants who have no other clinical evidence of infection (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 (see Penicillin Shortage, Number 1). Ceftriaxone dosing must be adjusted according to age and birth weight.

HIV Infection

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

¶ The absence of a fourfold or greater titer for an infant 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; some specialists, however, recommend that lower values (i.e., 5 WBCs/mm3 and protein of 40 mg/dL) be considered the upper limits of normal. Other causes of elevated values should be considered when an infant is being evaluated for congenital syphilis.

†† A woman treated with a regimen other than those recommended in these guidelines for treatment should be considered untreated.

§§ If the infant's nontreponemal test is nonreactive and the provider determines that the mother's risk for untreated syphilis is low, treatment of the infant (single IM dose of benzathine penicillin G 50,000 units/kg for possible incubating syphilis) without an evaluation can be considered.

Next

Page last reviewed: January 28, 2011 (archived document)
Content source: Division of STD Prevention (/std/dstdp), National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (/nchhstp), Centers for Disease Control and Prevention (/)