

Sexually Transmitted Diseases Treatment Guidelines, 2015



or incision and drainage to prevent the formation of inguinal/femoral ulcerations.

Recommended Regimen

Doxycycline 100 mg orally twice a day for 21 days

Alternative Regimen

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

Although clinical data are lacking, azithromycin 1 g orally once weekly for 3 weeks is probably effective based on its chlamydial antimicrobial activity. Fluoroquinolone-based treatments also might be effective, but the optimal duration of treatment has not been evaluated.

Other Management Considerations

Patients should be followed clinically until signs and symptoms have resolved. Persons who receive an LGV diagnosis should be tested for other STDs, especially HIV, gonorrhea, and syphilis. Those who test positive for another infection should be referred for or provided with appropriate care and treatment.

Follow-up

Patients should be followed clinically until signs and symptoms resolve.

Management of Sex Partners

Persons who have had sexual contact with a patient who has LGV within the 60 days before onset of the patient's symptoms should be examined and tested for urethral, cervical, or rectal chlamydial infection depending on anatomic site of exposure. They should be presumptively treated with a chlamydia regimen (azithromycin 1 g 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. Doxycycline should be avoided in the second and third trimester of pregnancy because of risk for discoloration of teeth and bones, but is compatible with breastfeeding (317). Azithromycin might prove useful for treatment of LGV in pregnancy, but no published data are available regarding an effective dose and duration of treatment.

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*. The disease has been divided into stages based on clinical findings, helping to guide treatment and follow-up. Persons who have syphilis might seek treatment for signs or symptoms of primary syphilis infection (i.e., ulcers or chancre at the infection site), secondary syphilis (i.e., manifestations that include, but are not limited to, skin rash, mucocutaneous lesions, and lymphadenopathy), or tertiary syphilis (i.e., cardiac, gummatous lesions, tabes dorsalis, and general paresis). Latent infections (i.e., those lacking clinical manifestations) are detected by serologic testing. Latent syphilis acquired within the preceding year is referred to as early latent syphilis; all other cases of latent syphilis are late latent syphilis or syphilis of unknown duration. *T. pallidum* can infect the central nervous system and result in neurosyphilis, which can occur at any stage of syphilis. Early neurologic clinical manifestations (i.e., cranial nerve dysfunction, meningitis, stroke, acute altered mental status, and auditory or ophthalmic abnormalities) are usually present within the first few months or years of infection. Late neurologic manifestations (i.e., tabes dorsalis and general paresis) occur 10–30 years after infection.

Diagnostic Considerations

Darkfield examinations and tests to detect *T. pallidum* directly from lesion exudate or tissue are the definitive methods for diagnosing early syphilis (395). Although no *T. pallidum* detection tests are commercially available, some laboratories provide locally developed and validated PCR tests for the detection of *T. pallidum* DNA. A presumptive diagnosis of syphilis requires use of two tests: a nontreponemal test (i.e., Venereal Disease Research Laboratory [VDRL] or Rapid Plasma Reagin [RPR]) and a treponemal test (i.e., fluorescent treponemal antibody absorbed [FTA-ABS] tests, the *T. pallidum* passive particle agglutination [TP-PA] assay, various enzyme immunoassays [EIAs], chemiluminescence immunoassays, immunoblots, or rapid treponemal assays). Although many treponemal-based tests are commercially available, only a few are approved for use in the United States. Use of only one type of serologic test is insufficient for diagnosis and can result in false-negative results in persons tested during primary syphilis and false-positive results in persons without syphilis.

False-positive nontreponemal test results can be associated with various medical conditions and factors unrelated to syphilis, including other infections (e.g., HIV), autoimmune conditions, immunizations, pregnancy, injection-drug use, and older age (395,396). Therefore, persons with a reactive nontreponemal test should always receive a treponemal test to confirm the diagnosis of syphilis.

Nontreponemal test antibody titers might correlate with disease activity and are used to follow treatment response. Results should be reported quantitatively. A fourfold change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32), is considered necessary to demonstrate a clinically significant difference between two nontreponemal test results obtained using the same serologic test. Sequential serologic tests in individual patients should be performed using the same testing method (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 (397). Treponemal antibody titers do not predict treatment response and therefore should not be used for this purpose.

Some clinical laboratories are screening samples using treponemal tests, typically by EIA or chemiluminescence immunoassays (398,399). This reverse screening algorithm for syphilis testing can identify persons previously treated for syphilis, those with untreated or incompletely treated syphilis, and persons with false-positive results that can occur with a low likelihood of infection. Persons with a positive treponemal screening test should have a standard nontreponemal test with titer performed reflexively by the laboratory to guide patient management decisions. If the nontreponemal test is negative, the laboratory should perform a different treponemal test (preferably one based on different antigens than the original test) to confirm the results of the initial test. If a second treponemal test is positive, persons with a history of previous treatment will require no further management unless sexual history suggests likelihood of re-exposure. In this instance, a repeat nontreponemal test in 2–4 weeks is recommended to evaluate for early infection. Those without a history of treatment for syphilis should be offered treatment. Unless history or results of a physical examination suggest a recent

infection, previously untreated persons should be treated for late latent syphilis. If the second treponemal test is negative and the epidemiologic risk and clinical probability for syphilis are low, further evaluation or treatment is not indicated. Two studies demonstrate that high quantitative index values from treponemal EIA/CIA tests correlate with TPPA positivity; however, the range of optical density values varies among different treponemal immunoassays, and the clinical significance of these findings warrant further investigation (400,401).

For most persons with HIV infection, serologic tests are accurate and reliable for diagnosing syphilis and following a patient’s response to treatment. However, atypical nontreponemal serologic test results (i.e., unusually high, unusually low, or fluctuating titers) might occur regardless of HIV-infection status. When serologic tests do not correspond with clinical findings suggestive of early syphilis, presumptive treatment is recommended for persons with risk factors for syphilis, and use of other tests (e.g., biopsy and PCR) should be considered.

Further testing is warranted for persons with clinical signs of neurosyphilis (e.g., cranial nerve dysfunction, auditory or ophthalmic abnormalities, meningitis, stroke, acute or chronic altered mental status, and loss of vibration sense). Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis in all instances. The diagnosis of neurosyphilis depends on a combination of cerebrospinal fluid (CSF) tests (CSF cell count or protein and a reactive CSF-VDRL) in the presence of reactive serologic test results and neurologic signs and symptoms. CSF laboratory abnormalities are common in persons with early syphilis and are of unknown significance in the absence of neurologic signs or symptoms (402). CSF-VDRL is highly specific but insensitive. In a person with neurologic signs or symptoms, a reactive CSF-VDRL (in the absence of blood contamination) is considered diagnostic of neurosyphilis. When CSF-VDRL is negative despite the presence of clinical signs of neurosyphilis, reactive serologic test results, and abnormal CSF cell count and/or protein, neurosyphilis should be considered. In this instance, additional evaluation using FTA-ABS testing on CSF may be warranted. 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, especially among persons with nonspecific neurologic signs and symptoms (403).

Among persons with HIV infection, 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 (404).

Treatment

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

Selection of the appropriate penicillin preparation is important, because *T. pallidum* can reside in sequestered sites (e.g., the CNS and aqueous humor) that are poorly accessed by 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 (405).

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 recommendations for the treatment of syphilis are based not only on clinical trials and observational studies, but many decades of clinical experience.

Special Considerations

Pregnancy

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

Jarisch-Herxheimer Reaction

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, myalgia, fever, and other symptoms that can occur within the first 24 hours after the initiation of any therapy for syphilis. Patients should be informed about this possible adverse reaction and how to manage it if it occurs. The Jarisch-Herxheimer reaction

occurs most frequently among persons who have early syphilis, presumably because bacterial burdens are higher during these stages. Antipyretics can be used to manage symptoms, but they have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction might induce early labor or cause fetal distress in pregnant women, but this should not prevent or delay therapy (see Syphilis During Pregnancy).

Management of Sex Partners

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

- Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis within 90 days preceding the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative.
- Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis >90 days before the diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain. If serologic tests are negative, no treatment is needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and stage of syphilis.
- In some areas or populations with high rates of syphilis, health departments recommend notification and presumptive treatment of sex partners of persons with late latent syphilis who have high nontreponemal serologic test titers (i.e., >1:32), because high titers might be indicative of early syphilis. These partners should be managed as if the index case had early syphilis.
- Long-term sex partners of persons who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation's findings.
- The following sex partners of persons with syphilis are considered at risk for infection and should be confidentially notified of the exposure and need for evaluation: partners who have had sexual contact within 1) 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis, 2) 6 months plus duration of symptoms for those with secondary syphilis, and 3) 1 year for persons with early latent syphilis.

Primary and Secondary Syphilis

Treatment

Parenteral penicillin G has been used effectively 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 conducted to guide the selection of an optimal penicillin regimen. Substantially fewer data are available for nonpenicillin regimens.

Recommended Regimen for Adults*

Benzathine penicillin G 2.4 million units IM in a single dose

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

Available data demonstrate that use of additional doses of benzathine penicillin G, amoxicillin, or other antibiotics do not enhance efficacy when used to treat primary and secondary syphilis, regardless of HIV status (406,407).

Recommended Regimen for Infants and Children

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

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

Other Management Considerations

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

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

Invasion of CSF by *T. pallidum* accompanied by CSF laboratory abnormalities is common among adults who have primary or secondary syphilis (402). In the absence of

clinical neurologic findings, no evidence supports variation from the recommended treatment regimen for primary and secondary 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, routine CSF analysis is not recommended for persons who have primary or secondary syphilis.

Follow-Up

Clinical and serologic evaluation should be performed at 6 and 12 months after treatment; more frequent evaluation might be prudent if follow-up is uncertain or if repeat infection is a concern. Serologic response (i.e., titer) should be compared with the titer at the time of treatment. However, assessing serologic response to treatment can be difficult, and definitive criteria for cure or failure have not been well established. In addition, nontreponemal test titers might decline more slowly for persons previously treated for syphilis (408,409).

Persons who have signs or symptoms that persist or recur and those with at least a fourfold increase in nontreponemal test titer persisting for >2 weeks likely experienced treatment failure or were re-infected. These persons should be retreated and reevaluated for HIV infection. Because treatment failure usually cannot be reliably distinguished from reinfection with *T. pallidum*, a CSF analysis also should be performed; treatment should be guided by CSF findings.

Failure of nontreponemal test titers to decline fourfold within 6–12 months after therapy for primary or secondary syphilis might be indicative of treatment failure. However, clinical trial data have demonstrated that 15%–20% of persons with primary and secondary syphilis treated with the recommended therapy will not achieve the fourfold decline in nontreponemal titer used to define response at 1 year after treatment (406,409). Serologic response to treatment appears to be associated with several factors, including the person's stage of syphilis (earlier stages are more likely to decline fourfold and become negative) and initial nontreponemal antibody titers (lower titers are less likely to decline fourfold than higher titers) (409). Optimal management of persons who have less than a fourfold decline in titers after treatment of syphilis is unclear. At a minimum, these persons should receive additional clinical and serologic follow-up and be evaluated for HIV infection. If additional follow-up cannot be ensured, retreatment is recommended. Because treatment failure might be the result of unrecognized CNS infection, CSF examination can be considered in such situations.

For retreatment, weekly injections of benzathine penicillin G 2.4 million units IM for 3 weeks is recommended, unless

CSF examination indicates that neurosyphilis is present (see Neurosyphilis). Serologic titers might not decline despite a negative CSF examination and a repeated course of therapy (410). In these circumstances, although the need for additional therapy or repeated CSF examinations is unclear, it is not generally recommended.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Data to support use of alternatives to penicillin in the treatment of primary and secondary syphilis are limited. However, several therapies might be effective in nonpregnant, penicillin-allergic persons who have primary or secondary syphilis. Regimens of doxycycline 100 mg orally twice daily for 14 days (411,412) and tetracycline (500 mg four times daily for 14 days) have been used for many years. Compliance is likely to be better with doxycycline than tetracycline, because tetracycline can cause gastrointestinal side effects and requires more frequent dosing. Although limited clinical studies, along with biologic and pharmacologic evidence, suggest that ceftriaxone (1–2 g daily either IM or IV for 10–14 days) is effective for treating primary and secondary syphilis, the optimal dose and duration of ceftriaxone therapy have not been defined (413). Azithromycin as a single 2 g oral dose has been effective for treating primary and secondary syphilis in some populations (414–416). However, *T. pallidum* chromosomal mutations associated with azithromycin and other macrolide resistance and treatment failures have been documented in multiple geographical areas in the United States (417–419). Accordingly, azithromycin should not be used as first-line treatment for syphilis and should be used with caution only when treatment with penicillin or doxycycline is not feasible. Azithromycin should not be used in MSM, persons with HIV, or pregnant women. Careful clinical and serologic follow-up of persons receiving any alternative therapies is essential.

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

Pregnancy

Pregnant women with primary or secondary syphilis who are allergic to penicillin should be desensitized and treated with penicillin. For more information, see Management of Persons Who Have a History of Penicillin Allergy and Syphilis During Pregnancy.

HIV Infection

Persons with HIV infection who have primary or secondary syphilis should be treated as those without HIV infection. For more information on treatment and management, see Syphilis in Persons with HIV infection.

Latent Syphilis

Latent syphilis is defined as syphilis characterized by seroreactivity without other evidence of primary, secondary, or tertiary disease. Persons who have latent syphilis and who acquired syphilis during the preceding year are classified as having early latent syphilis, a subset of latent syphilis. Persons can receive a diagnosis of early latent syphilis if, during the year preceding the diagnosis, they had 1) a documented seroconversion or a sustained (>2 week) fourfold or greater increase in nontreponemal test titers; 2) unequivocal symptoms of primary or secondary syphilis; or 3) a sex partner documented to have primary, secondary, or early latent syphilis. In addition, for persons with reactive nontreponemal and treponemal tests whose only possible exposure occurred during the previous 12 months, early latent syphilis can be assumed. In the absence of these conditions, an asymptomatic person should be considered to have latent syphilis. Nontreponemal serologic titers usually are higher early in the course of syphilis infection. However, early latent syphilis cannot be reliably diagnosed solely on the basis of nontreponemal titers. All persons with latent syphilis should have careful examination of all accessible mucosal surfaces (i.e., the oral cavity, perianal area, perineum and vagina in women, and underneath the foreskin in uncircumcised men) to evaluate for mucosal lesions.

Treatment

Because latent syphilis is not transmitted sexually, the objective of treating persons in this stage of disease is to prevent complications and transmission from a pregnant woman to her fetus. Although clinical experience supports the effectiveness of penicillin in achieving this goal, limited evidence is available to guide choice of specific regimens or duration. Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early latent syphilis do not enhance efficacy, regardless of HIV infection (406,407).

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 persons with HIV infection and pregnant women are discussed elsewhere in this report (see Syphilis in Persons with HIV infection and Syphilis during Pregnancy).

Recommended Regimens for Infants and Children**Early Latent Syphilis****Benzathine penicillin G** 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose**Late Latent Syphilis****Benzathine penicillin G** 50,000 units/kg IM, up to the adult dose of 2.4 million units, administered as 3 doses at 1-week intervals (total 150,000 units/kg up to the adult total dose of 7.2 million units)

Infants and children aged ≥ 1 month diagnosed with latent syphilis should be managed by a pediatric infectious-disease specialist and receive a CSF examination. In addition, birth and maternal medical records should be reviewed to assess whether these infants and children have congenital or acquired syphilis. For those with congenital syphilis, treatment should be undertaken as described in the congenital syphilis section in this document. Those with acquired latent syphilis should be evaluated for sexual abuse (e.g., through consultation with child protection services) (see Sexual Assault or Abuse of Children). These regimens are for penicillin nonallergic children who have acquired syphilis and who have normal CSF examination results.

Other Management Considerations

All persons who have latent syphilis should be tested for HIV infection. Persons who receive a diagnosis of latent syphilis and have neurologic signs and symptoms (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis or stroke) should be evaluated for neurosyphilis (see Neurosyphilis).

If a person misses a dose of penicillin in a course of weekly therapy for latent syphilis, the appropriate course of action is unclear. Clinical experience suggests that an interval of 10–14 days between doses of benzathine penicillin for latent syphilis might be acceptable before restarting the sequence of injections (i.e., if dose 1 is given on day 0, dose 2 is administered between days 10 and 14). Pharmacologic considerations suggest that an interval of 7–9 days between doses, if feasible, might be more optimal (420–422). Missed doses are not acceptable for pregnant women receiving therapy for latent syphilis (423).

Pregnant women who miss any dose of therapy must repeat the full course of therapy.

Follow-Up

Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months. A CSF examination should be performed if 1) a sustained (>2 weeks) fourfold increase or greater in titer is observed, 2) an initially high titer ($\geq 1:32$) fails to decline at least fourfold within 12–24 months of therapy, or 3) signs or symptoms attributable to syphilis develop. In such circumstances, patients with CSF abnormalities should be treated for neurosyphilis. If the CSF examination is negative, retreatment for latent syphilis should be administered. Serologic titers might fail to decline despite a negative CSF examination and a repeated course of therapy, especially if the initial nontreponemal titer is low ($<1:8$); in these circumstances, the need for additional therapy or repeated CSF examinations is unclear but is generally not recommended. Serologic and clinical monitoring should be offered along with a reevaluation for HIV infection.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations**Penicillin Allergy**

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

Pregnancy

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin. For more information, see Management of Persons Who Have a History of Penicillin Allergy and Syphilis during Pregnancy.

HIV Infection

Persons with HIV infection with latent syphilis should be treated as persons who do not have HIV infection. For more information on treatment and management of latent syphilis, see Syphilis in Persons with HIV Infection.

Tertiary Syphilis

Tertiary syphilis refers to gummas and cardiovascular syphilis but not to neurosyphilis. Guidelines for all forms of neurosyphilis (e.g., early or late neurosyphilis) are discussed elsewhere in these recommendations (see Neurosyphilis). Persons who are not allergic to penicillin and have no evidence of neurosyphilis should be treated with the following regimen.

Recommended Regimen

Tertiary Syphilis with Normal CSF Examination
Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

Other Management Considerations

All persons who have tertiary syphilis should be tested for HIV infection and should receive a CSF examination before therapy is initiated. Persons with CSF abnormalities should be treated with a neurosyphilis regimen. Some providers treat all persons who have cardiovascular syphilis with a neurosyphilis regimen. These persons should be managed in consultation with an infectious-disease specialist. Limited information is available concerning clinical response and follow-up of persons who have tertiary syphilis.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Providers should ask patients about known allergies to penicillin. Any person allergic to penicillin should be treated in consultation with an infectious-disease specialist.

Pregnancy

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin. For more information,

see Management of Persons Who Have a History of Penicillin Allergy and Syphilis during Pregnancy.

HIV Infection

Persons with HIV infection who have tertiary syphilis should be treated as described for persons without HIV infection. For more information on the management of tertiary syphilis in persons with HIV infection, see Syphilis in Persons with HIV Infection.

Neurosyphilis

Treatment

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

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

Recommended Regimen

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

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

Alternative Regimen

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

Other Management Considerations

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

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

Follow-Up

If CSF pleocytosis was present initially, a CSF examination should be repeated every 6 months until the cell count is normal. Follow-up CSF examinations also can be used to evaluate changes in the CSF-VDRL or CSF protein after therapy; however, changes in these two parameters occur more slowly than cell counts, and persistent abnormalities might be less important (424,425). Leukocyte count is a sensitive measure of the effectiveness of therapy. If the cell count has not decreased after 6 months, or if the CSF cell count or protein is not normal after 2 years, retreatment should be considered. Limited data suggest that in immunocompetent persons and persons with HIV infection on highly active antiretroviral therapy, normalization of the serum RPR titer predicts normalization of CSF parameters following neurosyphilis treatment (425).

Management of Sex Partners

See Syphilis, 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 persons with neurosyphilis (426,427). Cross-sensitivity between ceftriaxone and penicillin can occur, but the risk for penicillin cross-reactivity between third-generation cephalosporins is negligible (428–431) (see Management of Persons Who Have a History of Penicillin Allergy). If concern exists regarding the safety of ceftriaxone for a patient with neurosyphilis, skin testing should be performed (if available) to confirm penicillin allergy and, if necessary, penicillin desensitization in consultation with a specialist is recommended. Other regimens have not been adequately evaluated for treatment of neurosyphilis.

Pregnancy

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin. For more information, see Syphilis during Pregnancy.

HIV Infection

Persons with HIV infection who have neurosyphilis should be treated as described for persons without HIV infection. For more information on neurosyphilis, see Syphilis in Persons with HIV infection.

Persons with HIV Infection

Diagnostic Considerations

Interpretation of treponemal and nontreponemal serologic tests for persons with HIV infection is the same as for the HIV-uninfected patient. Although rare, unusual serologic responses have been observed among persons with HIV infection who have syphilis; although most reports have involved post-treatment serologic titers that were higher than expected (high serofast) or fluctuated, false-negative serologic test results and delayed appearance of seroreactivity have also been reported (432).

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

Treatment

Persons with HIV infection who have early syphilis might be at increased risk for neurologic complications (433) and might have higher rates of serologic treatment failure with recommended regimens. The magnitude of these risks is not defined precisely, but is likely small. Although long-term (>1 year) comparative data are lacking, no treatment regimens for syphilis have been demonstrated to be more effective in preventing neurosyphilis in persons with HIV infection than the syphilis regimens recommended for persons without HIV infection (406). Careful follow-up after therapy is essential. The use of antiretroviral therapy as per current guidelines might improve clinical outcomes in persons with HIV infection and syphilis (425,434,435).

Primary and Secondary Syphilis among Persons with HIV Infection

Recommended Regimen

Benzathine penicillin G, 2.4 million units IM in a single dose

Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in primary and secondary syphilis do not result in enhanced efficacy (406,407).

Other Management Considerations

Most persons with HIV infection respond appropriately to the recommended benzathine penicillin treatment regimen for primary and secondary syphilis. CSF abnormalities (e.g., mononuclear pleocytosis and elevated protein levels) are common in persons with HIV infection, even in those without syphilis. The clinical and prognostic significance of such CSF laboratory abnormalities in persons with primary and secondary syphilis who lack neurologic symptoms is unknown. Certain studies have demonstrated that among persons with HIV infection and syphilis, CSF abnormalities are associated with a CD4 count of ≤ 350 cells/mL and/or an RPR titer of $\geq 1:32$ (404,436,437); however, CSF examination has not been associated with improved clinical outcomes in the absence of neurologic signs and symptoms. All persons with HIV infection and syphilis should have a careful neurologic exam (425,434,435).

Follow-Up

Persons with HIV infection and primary or secondary syphilis should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy; those who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or persons who have a sustained [>2 weeks] fourfold increase or greater in titer) should be managed in the same manner as HIV-negative patients (i.e., a CSF examination and retreatment guided by CSF findings). In addition, CSF examination and retreatment can be considered for persons whose nontreponemal test titers do not decrease fourfold within 12–24 months of therapy. If CSF examination is normal, treatment with benzathine penicillin G administered as 2.4 million units IM each at weekly intervals for 3 weeks is recommended. Serologic titers might not decline despite a negative CSF examination and a repeated course of therapy (410). In these circumstances, the need for additional therapy or repeated CSF examinations is unclear, but is not generally recommended. Serologic and clinical monitoring should be provided.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

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

Latent Syphilis among Persons with HIV Infection

Recommended Regimen for Early Latent Syphilis

Benzathine penicillin G, 2.4 million units IM in a single dose

Recommended Regimen for Late Latent Syphilis

Benzathine penicillin G, at weekly doses of 2.4 million units for 3 weeks

Other Management Considerations

All persons with HIV infection and syphilis should undergo a careful neurologic examination; those with neurologic symptoms or signs should undergo immediate CSF examination. In the absence of neurologic symptoms, CSF examination has not been associated with improved clinical outcomes and therefore is not recommended.

Follow-Up

Patients should be evaluated clinically and serologically at 6, 12, 18, and 24 months after therapy. If, at any time, clinical symptoms develop or a sustained (>2 weeks) fourfold or greater rise in nontreponemal titers occurs, a CSF examination should be performed and treatment administered accordingly. If the nontreponemal titer does not decline fourfold after 24 months, CSF examination can be considered and treatment administered accordingly, although initial low titers ($<1:8$) might not decline. Even after retreatment, serologic titers might fail to decline. In these circumstances, the need for repeated CSF examination or additional therapy is unclear but is generally not recommended. Serologic and clinical monitoring should be provided.

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

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

Neurosyphilis Among Persons with HIV Infection

All persons with HIV infection and syphilis should receive a careful neurologic examination. Persons with HIV infection and neurosyphilis should be treated according to the recommendations for HIV-negative persons with neurosyphilis (See Neurosyphilis).

Follow Up

Persons with HIV infection and neurosyphilis should be managed according to the recommendations for HIV-negative persons with neurosyphilis (see Neurosyphilis). Limited data suggest that changes in CSF parameters might occur more slowly in persons with HIV infection, especially those with more advanced immunosuppression (424,434).

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

Persons with HIV infection who are penicillin-allergic and have neurosyphilis should be managed according to the recommendations for penicillin-allergic, HIV-negative patients with neurosyphilis (See Neurosyphilis). Several small observational studies conducted in persons with HIV infection with neurosyphilis suggest that ceftriaxone 1–2 g IV daily for 10–14 days might be effective as an alternate agent (438–440). The possibility of cross-sensitivity between ceftriaxone and penicillin exists, but the risk of penicillin cross-reactivity between third-generation cephalosporins is negligible (428–431) (see Management of Persons Who Have a History of Penicillin Allergy). If concern exists regarding the safety of ceftriaxone for a person with HIV infection and neurosyphilis, skin testing should be performed (if available) to confirm penicillin allergy and, if necessary, penicillin desensitization

in consultation with a specialist is recommended. Other regimens have not been adequately evaluated for treatment of neurosyphilis.

Syphilis During Pregnancy

All women should be screened serologically for syphilis early in pregnancy (106). Most states mandate screening at the first prenatal visit for all women (441). In populations in which receipt of prenatal care is not optimal, RPR test screening and treatment (if the RPR test is reactive) should be performed at the time pregnancy is confirmed (442). Antepartum screening by nontreponemal antibody testing is typical, but treponemal antibody testing is being used in some settings. Pregnant women with reactive treponemal screening tests should have additional quantitative nontreponemal testing, because titers are essential for monitoring treatment response. For communities and populations in which the prevalence of syphilis is high and for women at high risk for infection, serologic testing should also be performed twice during the third trimester: once at 28–32 weeks' gestation and again at delivery. Any woman who has a fetal death after 20 weeks' gestation should be tested for syphilis. No mother or neonate should leave the hospital without maternal serologic status having been documented at least once during pregnancy, and if the mother is considered high risk, documented at delivery.

Diagnostic Considerations

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

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

infection can be confirmed. For women with a history of adequately treated syphilis who do not have ongoing risk, no further treatment is necessary. Women without a history of treatment should be staged and treated accordingly with a recommended penicillin regimen. If the second treponemal test is negative, the positive EIA/CIA is more likely to represent a false-positive test result in low-risk women with no history of treated syphilis (400). If the woman is at low risk for syphilis, lacks signs or symptoms of primary syphilis, has a partner with no clinical or serologic evidence of syphilis, and is likely to follow up, repeat serologic testing within 4 weeks can be considered to determine whether the EIA/CIA remains positive or if the RPR/VDRL or the TP-PA becomes positive. If both the RPR and TP-PA remain negative, no further treatment is necessary. If follow-up is not possible, women without a history of treated syphilis should be treated according to the stage of syphilis.

Treatment

Penicillin G is the only known effective antimicrobial for preventing maternal transmission to the fetus and treating fetal infection (443). Evidence is insufficient to determine optimal, recommended penicillin regimens (444).

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 is beneficial for pregnant women. For women who have primary, secondary, or early latent syphilis, a second dose of benzathine penicillin 2.4 million units IM can be administered 1 week after the initial dose (445–447).
- When syphilis is diagnosed during the second half of pregnancy, management should include a sonographic fetal evaluation for congenital syphilis. However, this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis (i.e., hepatomegaly, ascites, hydrops, fetal anemia, or a thickened placenta) indicate a greater risk for fetal treatment failure (448); cases accompanied by these signs 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 (449). 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. No data are available to suggest that corticosteroid treatment alters the risk for treatment-related complications in pregnancy.

- Missed doses are not acceptable for pregnant women receiving therapy for late latent syphilis (423). Pregnant women who miss any dose of therapy must repeat the full course of therapy.
- All women who have syphilis should be offered testing for HIV infection.

Follow-Up

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

Management of Sex Partners

See Syphilis, Management of Sex Partners.

Special Considerations

Penicillin Allergy

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

Tetracycline and doxycycline are contraindicated in the second and third trimester of pregnancy (317). Erythromycin and azithromycin should not be used, because neither reliably cures maternal infection or treats an infected fetus (444). Data are insufficient to recommend ceftriaxone for treatment of maternal infection and prevention of congenital syphilis.

HIV Infection

Placental inflammation from congenital infection might increase the risk for perinatal transmission of HIV. All women

with HIV infection should be evaluated for syphilis and receive a penicillin regimen appropriate for the stage of infection. Data are insufficient to recommend any alternative regimens for pregnant women with HIV infection (see Syphilis Among Persons with HIV infection).

Congenital Syphilis

Effective prevention and detection of congenital syphilis depends on the identification of syphilis in pregnant women and, therefore, on the routine serologic screening of pregnant women during the first prenatal visit. Additional testing at 28 weeks' gestation and again at delivery is warranted for women who are at increased risk or live in communities with increased prevalence of syphilis infection (442,450). Moreover, as part of the management of pregnant women who have syphilis, information concerning ongoing risk behaviors and 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, as diagnosis at this time does not prevent symptomatic congenital syphilis in some newborns. No mother or newborn infant should leave the hospital without maternal serologic status having been documented at least once during pregnancy, and preferably again at delivery if at risk.

Evaluation and Treatment of Neonates (Infants Aged <30 Days)

The diagnosis of congenital syphilis can be difficult, as maternal nontreponemal and treponemal IgG antibodies can be transferred through the placenta to the fetus, complicating the interpretation of reactive serologic tests for syphilis in neonates. Therefore, treatment decisions frequently must be made on the basis of 1) identification of syphilis in the mother; 2) adequacy of maternal treatment; 3) presence of clinical, laboratory, or radiographic evidence of syphilis in the neonate; and 4) comparison of maternal (at delivery) and neonatal nontreponemal serologic titers using the same test, preferably conducted by the same laboratory. Any neonate at risk for congenital syphilis should receive a full evaluation and testing for HIV infection.

All neonates born to mothers who have reactive nontreponemal and treponemal test results should be evaluated with a quantitative nontreponemal serologic test (RPR or VDRL) performed on the neonate's serum, because umbilical cord blood can become contaminated with maternal blood and yield a false-positive result, and Wharton's jelly within the umbilical cord can yield a false-negative result. Conducting a treponemal test (i.e., TP-PA, FTA-ABS, EIA, or CIA) on neonatal serum is not recommended because it is difficult to interpret. No commercially available immunoglobulin (IgM) test can be recommended.

All neonates born to women who have reactive serologic tests for syphilis should be examined thoroughly for evidence of congenital syphilis (e.g., nonimmune hydrops, jaundice, hepatosplenomegaly, rhinitis, skin rash, and pseudoparalysis of an extremity). Pathologic examination of the placenta or umbilical cord using specific staining (e.g., silver) or a *T. pallidum* PCR test using a CLIA-validated test should be considered; DFA-TP reagents are not available. Darkfield microscopic examination or PCR testing of suspicious lesions or body fluids (e.g., bullous rash and nasal discharge) also should be performed. In addition to these tests, for stillborn infants, skeletal survey demonstrating typical osseous lesions might aid in the diagnosis of congenital syphilis.

The following scenarios describe the congenital syphilis evaluation and treatment of neonates born to women who have reactive serologic tests for syphilis during pregnancy. Maternal history of infection with *T. pallidum* and treatment for syphilis must be considered when evaluating and treating the neonate for congenital syphilis in most scenarios, except when congenital syphilis is proven or highly probable (See Scenario 1).

Scenario 1: Proven or highly probable congenital syphilis

Any neonate with:

1. an abnormal physical examination that is consistent with congenital syphilis;
- OR
2. a serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer;[‡]
- OR
3. a positive darkfield test or PCR of lesions or body fluid(s).

Recommended Evaluation

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

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

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

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.

Scenario 2: Possible Congenital Syphilis

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

1. mother was not treated, inadequately treated, or has no documentation of having received treatment;
OR
2. mother was treated with erythromycin or a regimen other than those recommended in these guidelines (i.e., a nonpenicillin G regimen); ††
OR
3. mother received recommended treatment <4 weeks before delivery.

Recommended Evaluation

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

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.

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

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

Before using the single-dose benzathine penicillin G regimen, the complete evaluation (i.e., CSF examination, long-bone radiographs, and CBC with platelets) must be normal, and follow-up must be certain. If any part of the infant’s evaluation is abnormal or not performed, if the CSF analysis is uninterpretable because of contamination with blood, or if follow-up is uncertain, a 10-day course of penicillin G is required. If the neonate’s nontreponemal test is nonreactive and the provider determines that the mother’s risk of untreated syphilis is low, treatment of the neonate with a single IM dose of benzathine penicillin G 50,000 units/kg for possible incubating syphilis can be considered without an evaluation.

Neonates born to mothers with untreated early syphilis at the time of delivery are at increased risk for congenital syphilis, and the 10-day course of penicillin G may be considered even if the complete evaluation is normal and follow-up is certain.

Scenario 3: Congenital Syphilis less likely

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

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

Recommended Evaluation

No evaluation is recommended.

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 every 2–3 months for 6 months for infants whose mother’s nontreponemal titers decreased at least fourfold after appropriate therapy for early syphilis or remained stable for low-titer, latent syphilis (e.g., VDRL <1:2; RPR <1:4).

Scenario 4: Congenital Syphilis unlikely

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

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

Recommended Evaluation

No evaluation is recommended.

Recommended Regimen

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

Follow-Up

All neonates with reactive nontreponemal tests should receive careful follow-up examinations and serologic testing (i.e., a nontreponemal test) every 2–3 months until the test becomes nonreactive. In the neonate who was not treated because congenital syphilis was considered less likely or unlikely, nontreponemal antibody titers should decline by age 3 months and be nonreactive by age 6 months, indicating that the reactive test result was caused by passive transfer of maternal IgG antibody. At 6 months, if the nontreponemal test is nonreactive, no further evaluation or treatment is needed; if the nontreponemal test is still reactive, the infant is likely to be infected and should be treated. Treated neonates that exhibit persistent nontreponemal test titers by 6–12 months should be re-evaluated through CSF examination and managed in consultation with an expert. Retreatment with a 10-day course of a penicillin G regimen may be indicated. Neonates with a negative nontreponemal test at birth and whose mothers were seroreactive at delivery should be retested at 3 months to rule out serologically negative incubating congenital syphilis at the time of birth. Treponemal tests should not be used to evaluate treatment response because the results are qualitative and passive transfer of maternal IgG treponemal antibody might persist for at least 15 months.

Neonates whose initial CSF evaluations are abnormal should undergo a repeat lumbar puncture approximately every 6 months until the results are normal. A reactive CSF Venereal Disease Research Laboratory (VDRL) test or abnormal CSF

indices that persist and cannot be attributed to other ongoing illness requires retreatment for possible neurosyphilis and should be managed in consultation with an expert.

Special Considerations**Penicillin Allergy**

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

Penicillin Shortage

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

1. For neonates with clinical evidence of congenital syphilis (Scenario 1), check local sources for aqueous crystalline penicillin G (potassium or sodium). If IV penicillin G is limited, substitute some or all daily doses with procaine penicillin G (50,000 U/kg/dose IM a day in a single daily dose for 10 days).
 - If aqueous or procaine penicillin G is not available, ceftriaxone (in doses appropriate for birthweight) can be considered with careful clinical and serologic follow-up and in consultation with an expert, as evidence is insufficient to support the use of ceftriaxone for the treatment of congenital syphilis. Management might include a repeat CSF examination at age 6 months if the initial examination was abnormal. Ceftriaxone must be used with caution in infants with jaundice.
2. For neonates without any clinical evidence of congenital syphilis (Scenario 2 and Scenario 3), use
 - a. procaine penicillin G, 50,000 U/kg/dose IM a day in a single dose for 10 days
 - OR
 - b. benzathine penicillin G, 50,000 U/kg IM as a single dose.

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

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

HIV Infection

Evidence is insufficient to determine whether neonates who have congenital syphilis and HIV or whose mothers have HIV infection require different therapy or clinical management than is recommended for all neonates. All neonates with congenital syphilis and HIV infection should be managed similarly as neonates with congenital syphilis who do not have HIV infection.

Evaluation and Treatment of Infants and Children with Congenital Syphilis

Infants and children aged ≥ 1 month who are identified as having reactive serologic tests for syphilis should be examined thoroughly and have maternal serology and records reviewed to assess whether they have congenital or acquired syphilis (see Primary and Secondary Syphilis and Latent Syphilis, Sexual Assault or Abuse of Children). Any infant or child at risk for congenital 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, neuroimaging, 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 infant or child has no clinical manifestations of congenital syphilis and the evaluation (including the CSF examination) is normal, treatment with up to 3 weekly doses of benzathine penicillin G, 50,000 U/kg IM can be considered. A single dose of benzathine penicillin G 50,000 units/kg IM up to the adult dose of 2.4 million units in a single dose can be considered after the 10-day course of IV aqueous penicillin to provide more comparable duration of treatment in those who have no clinical manifestations and normal CSF. All of the above treatment regimens also would be adequate for children who might have other treponemal infections.

Follow-Up

Careful follow-up examinations and serologic testing (i.e., a nontreponemal test) of infants and children treated for congenital syphilis after the neonatal period (30 days of age) should be performed every 3 months until the test becomes nonreactive or the titer has decreased fourfold. The serologic response after therapy might be slower for infants and children than neonates. If these titers increase at any point for more than 2 weeks or do not decrease fourfold after 12–18 months, the infant or child should be evaluated (e.g., through CSF examination), treated with a 10-day course of parenteral penicillin G, and managed in consultation with an expert. Treponemal tests should not be used to evaluate treatment response, because the results are qualitative and persist after treatment; further, passive transfer of maternal IgG treponemal antibody might persist for at least 15 months after delivery.

Infants or children whose initial CSF evaluations are abnormal should undergo a repeat lumbar puncture approximately every 6 months until the results are normal. After 2 years of follow-up, a reactive CSF VDRL test or abnormal CSF indices that persists and cannot be attributed to other ongoing illness requires retreatment for possible neurosyphilis and should be managed in consultation with an expert.

Special Considerations

Penicillin Allergy

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

Penicillin Shortage

During periods when the availability of penicillin G is compromised, management options are similar to options for the neonate (see Evaluation and treatment of infants during the first month of life).

- For infants and children with clinical evidence of congenital syphilis, procaine penicillin G (50,000 U/kg/dose IM up to the adult dose of 2.4 million units a day in a single daily dose for 10 days) is recommended. A single dose of benzathine penicillin G 50,000 units/kg

IM up to the adult dose of 2.4 million units in a single dose can be considered after the 10-day course of procaine penicillin. If procaine or benzathine penicillin G is not available, ceftriaxone (in doses appropriate for age and weight) can be considered with careful clinical and serologic follow-up. Infants and children receiving ceftriaxone should be managed in consultation with an expert, as evidence is insufficient to support the use of ceftriaxone for the treatment of congenital syphilis in infants or children. For infants aged ≥ 30 days, use 75 mg/kg IV/IM of ceftriaxone a day in a single daily dose for 10–14 days (dose adjustment might be necessary based on current weight). For children, the dose should be 100 mg/kg of ceftriaxone a day in a single daily dose.

2. For infants and children without any clinical evidence of infection (see 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 or not performed, CSF examination is not interpretable, or follow-up is uncertain, procaine penicillin G is recommended.

HIV Infection

Evidence is insufficient to determine whether infants and children who have congenital syphilis and HIV or whose mothers have HIV infection require different therapy or clinical management than is recommended for all infants and children. All infants and children with congenital syphilis and HIV infection should be managed like infants and children without HIV infection.

Management of Persons Who Have a History of Penicillin Allergy

No proven alternatives to penicillin are available for treating neurosyphilis, congenital syphilis, or syphilis in pregnant women. Penicillin also is recommended, whenever possible, for persons with HIV infection. The prevalence of reported penicillin allergy in the United States is about 8%–10% (451–453) and might be higher in hospitalized persons (454). The prevalence of reported penicillin allergy in developing countries is unknown; however, limited data suggest that penicillin is one of the most frequently reported allergies in some developing countries (455,456). Of persons reporting penicillin allergy, 10%–15% have a positive skin

test suggestive of a penicillin allergy; these persons are at risk for an immunoglobulin E (IgE)-mediated allergic response to penicillin such as urticaria, angioedema, or anaphylaxis (i.e., upper airway obstruction, bronchospasm, or hypotension) (428–430,457,458). Re-administration of penicillin to patients with a history of IgE-mediated hypersensitivity reactions can cause severe, immediate reactions. Because anaphylactic reactions to penicillin can be fatal, every effort should be made to avoid administering penicillin to penicillin-allergic persons, unless they undergo induction of drug tolerance (also referred to as “desensitization”) to temporarily eliminate IgE-mediated hypersensitivity. However, many persons with a reported history of penicillin allergy likely have had other types of adverse drug reactions or have lost their sensitivity to penicillin over time and can safely be treated with penicillin.

Penicillin skin testing with the major and minor determinants of penicillin can reliably identify persons at high risk for IgE-mediated reactions to penicillin (458,459). Although the testing reagents are easily generated, only the major determinant (benzylpenicilloyl poly-L-lysine [Pre-Pen]) and penicillin G have been available commercially. These two tests identify an estimated 90%–99% of the allergic patients. However, because skin testing without the minor determinants would still fail to identify 1%–10% of allergic persons and because serious or fatal reactions can occur among these minor-determinant–positive persons, caution should be exercised when the full battery of skin-test reagents is not available (Box 2) (457–460). Manufacturers are working on a minor determinant mixture, but at the time of publication, no such product has been cleared by FDA for use in the United States. Penicillin skin testing has been used in a variety of settings to improve antibiotic use (453,461–463).

Some studies have reported cross-reactivity rates as high as 10% among persons with a history of penicillin allergy who take cephalosporins. However, more recent studies indicate a lower rate (<2.5%) of cross reactivity between these drugs (428–431,464). Risk is highest with first-generation cephalosporins and cephalosporins that have similar R-group side chains to specific penicillins (465,466). The risk for penicillin cross-reactivity between most second-generation (cefotaxime) and all third generation cephalosporins (cefixime and ceftriaxone) is negligible (428–431); cefotaxime, cefixime, and ceftriaxone do not have an R group side chain similar to penicillin G.

Recommendations

Persons with a history of severe non-IgE-mediated reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, and hemolytic anemia) are not candidates

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

- Benzylpenicilloyl poly-L-lysine (PrePen) (AllerQuest, Plainville Connecticut) (6×10^{-5} M)

Minor Determinant Precursors*

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

Positive Control

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

Negative Control

- Diluent (usually saline) or allergen diluent

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

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

for skin testing or challenge and should avoid penicillins indefinitely. If the full battery of skin-test reagents is available, including both major and minor determinants (see Penicillin Allergy Skin Testing), persons who report a history of penicillin reaction and who are skin-test negative can receive conventional penicillin therapy. Persons with positive skin test results should be desensitized before initiating treatment.

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

Penicillin Allergy Skin Testing

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

Procedures

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

Epicutaneous (Prick) Tests

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

Intradermal Test

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

Desensitization

Persons who have a positive skin test to one of the penicillin determinants can be desensitized (Table 1). This is a

straightforward, relatively safe procedure that can be performed orally or intravenously. Modified protocols might be considered based on an individual's symptoms, drug of choice, and route of administration (467–469). Although the two approaches have not been compared, oral desensitization is regarded as safer and easier to perform. Desensitization should occur in a hospital setting because serious IgE-mediated allergic reactions can occur; the procedure can usually be completed in approximately 4–12 hours, after which time the first dose of penicillin is administered. After desensitization, penicillin should be maintained continuously for the duration of the course of therapy. Once the course is completed, if penicillin is required in the future, the desensitization procedure should be repeated.

Diseases Characterized by Urethritis and Cervicitis

Urethritis

Urethritis, as characterized by urethral inflammation, can result from infectious and noninfectious conditions. Symptoms, if present, include dysuria; urethral pruritis; and mucoid, mucopurulent, or purulent discharge. Signs of urethral discharge on examination can also be present in persons without symptoms. Although *N. gonorrhoeae* and *C. trachomatis* are well established as clinically important infectious causes of urethritis, *Mycoplasma genitalium* has also been associated with urethritis and, less commonly, prostatitis (470–474). If point-of-care diagnostic tools (e.g., Gram, methylene blue [MB] or gentian violet [GV] stain microscopy, first void urine with microscopy, and leukocyte esterase) are not available, drug regimens effective against both gonorrhea and chlamydia should be administered. Further testing to determine the specific etiology is recommended to prevent complications, re-infection, and transmission because a specific diagnosis might improve treatment compliance, delivery of risk reduction interventions, and partner notification. Both chlamydia and gonorrhea are reportable to health departments. NAATs are preferred for the detection of *C. trachomatis* and *N. gonorrhoeae*, and urine is the preferred specimen in males (394). NAAT-based tests for the diagnosis of *T. vaginalis* in men have not been cleared by FDA; however, some laboratories have performed the CLIA-compliant validation studies (475) needed to provide such testing.

Etiology

Several organisms can cause infectious urethritis. The presence of Gram-negative intracellular diplococci (GNID)

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

Penicillin V suspension dose [†]	Amount [§] (units/mL)	mL	Units	Cumulative dose (units)
1	1,000	0.1	100	100
2	1,000	0.2	200	300
3	1,000	0.4	400	700
4	1,000	0.8	800	1,500
5	1,000	1.6	1,600	3,100
6	1,000	3.2	3,200	6,300
7	1,000	6.4	6,400	12,700
8	10,000	1.2	12,000	24,700
9	10,000	2.4	24,000	48,700
10	10,000	4.8	48,000	96,700
11	80,000	1.0	80,000	176,700
12	80,000	2.0	160,000	336,700
13	80,000	4.0	320,000	656,700
14	80,000	8.0	640,000	1,296,700

Source: Wendel GO, Jr, Stark BJ, Jamison RB, Melina RD, Sullivan TJ. Penicillin allergy and desensitization in serious infections during pregnancy. *N Engl J Med* 1985;312:1229–32.

* Observation period was 30 minutes before parenteral administration of penicillin.

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

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

or MB/GV purple intracellular diplococci on urethral smear is indicative of presumed gonorrhea infection, which is frequently accompanied by chlamydial infection. NGU, which is diagnosed when microscopy of urethral secretions indicates inflammation without GNID or MB/GV purple intracellular diplococci, is caused by *C. trachomatis* in 15%–40% of cases; however, prevalence varies by age group, with a lower burden of disease occurring among older men (476). Documentation of chlamydial infection as the etiology of NGU is essential because of the need for partner referral for evaluation and treatment to prevent complications of chlamydia, especially in female partners. Complications of *C. trachomatis*-associated NGU among males include epididymitis, prostatitis, and reactive arthritis.

M. genitalium, which can be sexually transmitted, is associated with symptoms of urethritis as well as urethral inflammation and accounts for 15%–25% of NGU cases in the United States (470–473). However, FDA-cleared diagnostic tests for *M. genitalium* are not available.

T. vaginalis can cause NGU in heterosexual men, but the prevalence varies substantially by region of the United States and within specific subpopulations. In some instances, NGU can be acquired by fellatio (i.e., oral penile contact), sometimes because of specific pathogens such as HSV, Epstein Barr Virus, and adenovirus (476); data supporting other *Mycoplasma* species and *Ureaplasma* as etiologic agents are inconsistent. Diagnostic