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Sexually Transmitted Diseases Treatment Guidelines, 2015

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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]/mm^3). Using a higher cutoff (>20 WBC/ mm^3) might improve the specificity of neurosyphilis diagnosis (*404*).

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