INTRODUCTION
The Centers for Disease Control and Prevention (CDC) has recently updated the guidelines for treatment of sexually transmitted diseases (STD's)(1). Over the next few months, current treatment guidelines for selected STD's will be included in the Disease Control Newsletter. This issue covers current treatment and management of patients with syphilis.

GENERAL PRINCIPLES
Background
Syphilis is a systemic disease caused by Treponema pallidum. Patients who have syphilis may seek treatment for signs or symptoms of primary infection (i.e., ulcer or chancre at the infection site), secondary infection (i.e., manifestations that include rash, mucocutaneous lesions, and adenopathy), or tertiary infection (i.e., cardiac, neurologic, ophthalmic, auditory, or gummatous lesions). Infections also may be detected by serologic testing during the latent stage. Latent syphilis acquired within the preceding year is referred to as early latent syphilis; all other cases of latent syphilis are either late latent syphilis or syphilis of unknown duration.

Diagnostic Considerations and Use of Serologic Tests
Darkfield examinations and direct fluorescent antibody tests of lesion exudate or tissue are the definitive methods for diagnosing early syphilis. A presumptive diagnosis is possible with the use of two types of serologic tests for syphilis: a) nontreponemal (e.g., Venereal Disease Research Laboratory [VDRL] and RPR) and b) treponemal (e.g., fluorescent treponemal antibody absorbed [FTA-ABS] and microhemagglutination assay for antibody to T. pallidum [MHA-TP]). The use of only one type of test is insufficient for diagnosis because false-positive nontreponemal test results occasionally occur secondary to various medical conditions. Nontreponemal test antibody titers usually correlate with disease activity, and results should be reported quantitatively. A fourfold change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32), usually is considered necessary to demonstrate a clinically significant difference between two nontreponemal test results that were obtained by using the same serologic test. It is expected that the nontreponemal test will eventually become nonreactive after treatment; however, in some patients, nontreponemal antibodies can persist at a low titer for a long period, sometimes for the remainder of their lives. This response is 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%–28% of patients treated during the primary stage might revert to being serologically nonreactive after 2–3 years. Treponemal test antibody titers correlate poorly with disease activity and should not be used to assess treatment response.

Sequential serologic tests should be performed by using the same testing method (e.g., VDRL or RPR), preferably by the same laboratory. The VDRL and RPR are equally valid, but quantitative results from the two tests cannot be compared directly because RPR titers often are slightly higher than VDRL titers.

No single test can be used to diagnose all cases of neurosyphilis. The diagnosis of neurosyphilis can be made based on various combinations of reactive serologic test results, abnormalities of cerebrospinal fluid (CSF) cell count or protein, or a reactive VDRL-CSF with or without clinical manifestations. The CSF leukocyte count usually is elevated (>5 WBCs/mm³) when neurosyphilis is present, and it also is a sensitive measure of the effectiveness of therapy.

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The VDRL-CSF is the standard serologic test for CSF; when reactive in the absence of substantial contamination of CSF with blood, it is considered diagnostic of neurosyphilis. However, the VDRL-CSF may be nonreactive when neurosyphilis is present. Some experts recommend performing an FTA-ABS test on CSF. The CSF FTA-ABS is less specific (i.e., yields more false-positive results) for neurosyphilis than the VDRL-CSF. However, the test is believed to be highly sensitive, and some experts believe that a negative CSF FTA-ABS test excludes neurosyphilis.

**Treatment**

Parenteral penicillin G is the preferred drug for treatment of all stages of syphilis. The preparation(s) used (i.e., benzathine, aqueous procaine, or aqueous crystalline), the dosage, and the length of treatment depend on the stage and clinical manifestations of disease.

Parenteral penicillin G is the only therapy with documented efficacy for neurosyphilis or for syphilis during pregnancy. Patients who report a penicillin allergy, including pregnant women with syphilis in any stage and patients with neurosyphilis, should be desensitized and treated with penicillin. Skin testing for penicillin allergy may be useful in some settings.

The Jarisch-Herxheimer reaction is an acute febrile reaction—often accompanied by headache, myalgia, and other symptoms—that might occur within the first 24 hours after any therapy for syphilis; patients should be advised of this possible adverse reaction. The Jarisch-Herxheimer reaction often occurs among patients who have early syphilis. Antipyretics may be recommended, but no proven methods prevent this reaction. The Jarisch-Herxheimer reaction may induce early labor or cause fetal distress among pregnant women. This concern should not prevent or delay therapy (see Syphilis During Pregnancy).

**Management of Sex Partners**

Sexual transmission of *T. pallidum* occurs only when mucocutaneous syphillic lesions are present; such manifestations are uncommon after the first year of infection. However, persons exposed sexually to a patient who has syphilis in any stage should be evaluated clinically and serologically according to the following recommendations:

- Persons who were exposed within the 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner might be infected even if seronegative; therefore, such persons should be treated presumptively.
- Persons who were exposed >90 days before the diagnosis of primary, secondary, or early latent syphilis in a sex partner should be treated presumptively if serologic test results are not available immediately and the opportunity for follow-up is uncertain.
- For purposes of partner notification and presumptive treatment of exposed sex partners, patients with syphilis of unknown duration who have nontreponemal serologic test titers (i.e., $\geq 1:32$) may be considered as having early syphilis. However, serologic titers should not be used to differentiate early from late latent syphilis for the purpose of determining treatment (see Treatment of Latent Syphilis).
- Long-term sex partners of patients who have late syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the findings of the evaluation.

The time periods before treatment used for identifying at-risk sex partners are a) 3 months plus duration of symptoms for primary syphilis, b) 6 months plus duration of symptoms for secondary syphilis, and c) 1 year for early latent syphilis.

**PRIMARY AND SECONDARY SYPHILIS**

**Treatment**

Parenteral penicillin G has been used effectively for four decades to achieve a local cure (i.e., healing of lesions and prevention of sexual transmission) and to prevent late sequelae.

**Recommended Regimen for Adults**

Patients who have primary or secondary syphilis should be treated with the following regimen: **Benzathine penicillin G** 2.4 million units IM in a single dose.

**Recommended Regimen for Children**

After the newborn period, children in whom syphilis is diagnosed should have a CSF examination to detect asymptomatic neurosyphilis, and birth and maternal medical records should be reviewed to assess whether the child has congenital or acquired syphilis (see Congenital Syphilis). Children with acquired primary or secondary syphilis should be evaluated (including consultation with child-protection services) and treated by using the following pediatric regimen: **Benzathine penicillin G** 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose.

**Other Management Considerations**

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

Patients who have syphilis and who also have symptoms or signs suggesting neurologic disease (e.g., meningitis) or ophthalmic disease (e.g., uveitis) should be evaluated fully for neurosyphilis and syphilitic eye disease; this evaluation should include CSF analysis and ocular slit-lamp examination. Such patients should be treated appropriately according to the results of this evaluation.

**Invasion of CSF by *T. pallidum* accompanied by CSF abnormalities is common among adults who have primary or secondary syphilis. However, neurosyphilis develops in only a few patients after treatment with the regimens described in this report. Therefore, unless clinical signs or symptoms of neurologic or ophthalmic involvement are present, lumbar puncture is not recommended for routine evaluation of patients who have primary or secondary syphilis.**

**Follow-Up**

Treatment failures can occur with any regimen. However, assessing response to treatment often is difficult, and no definitive criteria for cure or failure have been established. Serologic test titers may decline more slowly for patients continued...
who previously had syphilis. Patients should be reexamined clinically and serologically at both 6 months and 12 months; more frequent evaluation may be prudent if follow-up is uncertain.

Patients who have signs or symptoms that persist or recur or who have a sustained fourfold increase in nontreponemal test titer (i.e., in comparison with either the baseline titer or a subsequent result) probably failed treatment or were reinfected. These patients should be retreated after reevaluation for HIV infection. Unless reinfection with T. pallidum is certain, a lumbar puncture also should be performed.

Failure of nontreponemal test titers to decline fourfold within 6 months after therapy for primary or secondary syphilis identifies persons at risk for treatment failure. Such persons should be reevaluated for HIV infection. Optimal management of such patients is unclear. At a minimum, these patients should have additional clinical and serologic follow-up. HIV-infected patients should be evaluated more frequently (i.e., at 3-month intervals instead of 6-month intervals). If additional follow-up cannot be ensured, retreatment is recommended. Some experts recommend CSF examination in such situations.

When patients are retreated, most experts recommend retreatment with three weekly injections of benzathine penicillin G 2.4 million units IM, unless CSF examination indicates that neurosyphilis is present.

Penicillin Allergy
Nonpregnant penicillin-allergic patients who have primary or secondary syphilis should be treated with one of the following regimens. Close follow-up of such patients is essential.

Recommended Regimens

**Doxycycline** 100 mg orally twice a day for 2 weeks, OR **Tetracycline** 500 mg orally four times a day for 2 weeks.

There is less clinical experience with doxycycline than with tetracycline, but compliance is likely to be better with doxycycline. Therapy for a patient who cannot tolerate either doxycycline or tetracycline should depend on whether the patient's compliance with the therapy regimen and with follow-up examinations can be ensured. Pharmacologic and bacteriologic considerations suggest that ceftriaxone should be effective, but data concerning ceftriaxone are limited and clinical experience is insufficient to enable identification of late failures. The optimal dose and duration have not been established for ceftriaxone, but a suggested daily regimen of 1 g may be considered if treponemacidal levels in the blood can be maintained for 8–10 days. Single-dose ceftriaxone therapy is not effective for treating syphilis.

For nonpregnant patients whose compliance with therapy and follow-up can be ensured, an alternative regimen is erythromycin 500 mg orally four times a day for 2 weeks. However, erythromycin is less effective than the other recommended regimens.

Patients whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin. Skin testing for penicillin allergy may be useful in some circumstances in which the reagents and expertise to perform the test adequately are available.

**LATENT SYPHILIS**

Latent syphilis is defined as those periods after infection with T. pallidum when patients are seroreactive, but demonstrate no other evidence of disease. Patients who have latent syphilis and who acquired syphilis within the preceding year are classified as having early latent syphilis. Patients can be demonstrated as having early latent syphilis if, within the year preceding the evaluation, they had a) a documented seroconversion, b) unequivocal symptoms of primary or secondary syphilis, or c) a sex partner who had primary, secondary, or early latent syphilis. Almost all other patients have latent syphilis of unknown duration and should be managed as if they had late latent syphilis. Nontreponemal serologic titers usually are higher during early latent syphilis than late latent syphilis. However, early latent syphilis cannot be reliably distinguished from late latent syphilis solely on the basis of nontreponemal titers. Regardless of the level of the nontreponemal titers, patients in whom the illness does not meet the definition of early syphilis should be treated as if they have late latent infection. All sexually active women with reactive nontreponemal serologic tests should have a pelvic examination before syphilis staging is completed to evaluate for internal mucosal lesions. All patients who have latent syphilis should be tested for HIV infection.

**Treatment**

Treatment of latent syphilis is intended to prevent occurrence or progression of late complications. Although clinical experience supports the effectiveness of penicillin in achieving these goals, limited evidence is available for guidance in choosing specific regimens. There is minimal evidence to support the use of non-penicillin regimens.

**Recommended Regimens for Adults**

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

**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 three doses of 2.4 million units IM each at 1-week intervals.

**Recommended Regimens for Children**

After the newborn period, children in whom syphilis is diagnosed should have a CSF examination to exclude neurosyphilis, and birth and maternal medical records should be reviewed to assess whether the child has congenital or acquired syphilis (see Congenital Syphilis). Older children with acquired latent syphilis should be evaluated as described for adults and treated using the following pediatric regimens. These regimens are for nonallergic children who have acquired syphilis and whose results of the CSF examination were normal.

**Early Latent Syphilis:** Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose.

**Late Latent Syphilis or Late Syphilis of Unknown Duration:** Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units, administered as three doses at 1-week intervals (total 150,000 units/kg up to the adult total dose of 7.2 million units).

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Other Management Considerations
All patients who have latent syphilis should be evaluated clinically for evidence of tertiary disease (e.g., aortitis, neurosyphilis, gumma, and iritis). Patients who have syphilis and who demonstrate any of the following criteria should have a prompt CSF examination:

- Neurologic or ophthalmic signs or symptoms;
- Evidence of active tertiary syphilis (e.g., aortitis, gumma, and iritis);
- Treatment failure; and
- HIV infection with late latent syphilis or syphilis of unknown duration.

If dictated by circumstances and patient preferences, a CSF examination may be performed for patients who do not meet these criteria. If a CSF examination is performed and the results indicate abnormalities consistent with neurosyphilis, the patient should be treated for neurosyphilis (see Neurosyphilis).

Follow-Up
Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months. Limited data are available to guide evaluation of the treatment response for patients who have latent syphilis. Patients should be evaluated for neurosyphilis and retreated appropriately if (a) titers increase fourfold, (b) an initially high titer ($\geq 1:32$) fails to decline at least fourfold (i.e., two dilutions) within 12–24 months, or (c) signs or symptoms attributable to syphilis develop in the patient.

Penicillin Allergy
Nonpregnant patients who have latent syphilis and who are allergic to penicillin should be treated with one of the following regimens.

Recommended Regimens

- **Doxycycline** 100 mg orally twice a day, OR **Tetracycline** 500 mg orally four times a day.

Both drugs should be administered for 2 weeks if the duration of infection is known to have been <1 year; otherwise, they should be administered for 4 weeks.

TERTIARY SYphilIS
Tertiary syphilis refers to gumma and cardiovascular syphilis, but not to neurosyphilis.

Treatment
Nonallergic patients without evidence of neurosyphilis should be treated with the following regimen.

**Recommended Regimen**

- **Benzathine penicillin G** 7.2 million units total, administered as three doses of 2.4 million units IM at 1-week intervals.

Other Management Considerations
Patients who have symptomatic late syphilis should have a CSF examination before therapy is initiated. Some experts treat all patients who have cardiovascular syphilis with a neurosyphilis regimen. The complete management of patients who have cardiovascular or gummatous syphilis is beyond the scope of these guidelines. These patients should be managed in consultation with an expert.

Follow-Up
Information is lacking with regard to follow-up of patients who have late syphilis. The clinical response depends partially on the nature of the lesions.

Penicillin Allergy
Patients allergic to penicillin should be treated according to the recommended regimens for late latent syphilis.

NEUROSYphilIS
Treatment
Central nervous system disease can occur during any stage of syphilis. A patient who has clinical evidence of neurologic involvement with syphilis (e.g., ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis) should have a CSF examination.

Syphilitic uveitis or other ocular manifestations frequently are associated with neurosyphilis; patients with these symptoms should be treated according to the recommendations for neurosyphilis. A CSF examination should be performed for all such patients to identify those with abnormalities who should have follow-up CSF examinations to assess treatment response.

Patients who have neurosyphilis or syphilitic eye disease (e.g., uveitis, neuroretinitis, or optic neuritis) and who are not allergic to penicillin should be treated with the following regimen:

**Recommended Regimen**

- **Aqueous crystalline penicillin G** 18–24 million units a day, administered as 3–4 million units IV every 4 hours for 10–14 days.

If compliance with therapy can be ensured, patients may be treated with the following alternative regimen:

**Alternative Regimen**

- **Procaine penicillin** 2.4 million units IM a day, 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 that of the regimen used for late syphilis in the absence of neurosyphilis. Therefore, some experts administer benzathine penicillin, 2.4 million units IM, after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

Other Management Considerations
Other considerations in the management of patients who have neurosyphilis are as follows:

- All patients who have syphilis should be tested for HIV.
- Many experts recommend treating patients who have evidence of auditory disease caused by syphilis in the same manner as for neurosyphilis, regardless of the findings on CSF examination. Although systemic steroids are used frequently as adjunctive therapy for otologic syphilis, such drugs have not been proven 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 VDRL-CSF or CSF protein after therapy; however, changes in these two parameters are slower, and persistent abnormalities are of less importance. If the cell count has not decreased after 6 months, or if the CSF is not entirely normal after 2 years, retreatment should be considered.

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Penicillin Allergy
Data have not been collected systematically for evaluation of therapeutic alternatives to penicillin for treatment of neurosyphilis. Patients who report being allergic to penicillin should either be desensitized to penicillin or be managed in consultation with an expert. In some situations, skin testing to confirm penicillin allergy may be useful.

SYphilIS IN HIV-INFECTED PERSONS
Diagnostic Considerations
Unusual serologic responses have been observed among HIV-infected persons who have syphilis. Most reports involved serologic titers that were higher than expected, but false-negative serologic test results or delayed appearance of seroreactivity also have been reported. Nevertheless, both treponemal and nontreponemal serologic tests for syphilis can be interpreted in the usual manner for most patients who are coinfected with T. pallidum and HIV.

When clinical findings suggest that syphilis is present, but serologic tests are nonreactive or unclear, alternative tests (e.g., biopsy of a lesion, darkfield examination, or direct fluorescent antibody staining of lesion material) may be useful.

Neurosyphilis should be considered in the differential diagnosis of neurologic disease in HIV-infected persons.

Treatment
In comparison with HIV-negative patients, HIV-infected patients who have early syphilis may be at increased risk for neurologic complications and may have higher rates of treatment failure with currently recommended regimens. The magnitude of these risks, although not defined precisely, is probably minimal. No treatment regimens for syphilis are demonstrably more effective in preventing neurosyphilis in HIV-infected patients than the syphilis regimens recommended for HIV-negative patients. Careful follow-up after therapy is essential.

Primary and Secondary Syphilis in HIV-Infected Persons
Treatment
Treatment with benzathine penicillin G, 2.4 million units IM, as for HIV-negative patients, is recommended. Some experts recommend additional treatments (e.g., three weekly doses of benzathine penicillin G as suggested for late syphilis) or other supplemental antibiotics in addition to benzathine penicillin G 2.4 million units IM.

Other Management Considerations
CSF abnormalities often occur among both asymptomatic HIV-infected patients in the absence of syphilis and HIV-negative patients who have primary or secondary syphilis. Such abnormalities in HIV-infected patients who have primary or secondary syphilis are of unknown prognostic significance. Most HIV-infected patients respond appropriately to the currently recommended penicillin therapy; however, some experts recommend CSF examination before therapy and modification of treatment accordingly.

Follow-up
It is important that HIV-infected patients be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy. Although of unproven benefit, some experts recommend a CSF examination after therapy (i.e., at 6 months).

HIV-infected patients who meet the criteria for treatment failure should be managed the same as HIV-negative patients (i.e., a CSF examination and retreatment). CSF examination and retreatment also should be strongly considered for patients whose nontreponemal test titer does not decrease fourfold within 6–12 months. Most experts would retreat patients with 7.2 million units of benzathine penicillin G (administered as three weekly doses of 2.4 million units each) if CSF examinations are normal.

Penicillin Allergy
Penicillin-allergic patients who have primary or secondary syphilis and HIV infection should be managed according to the recommendations for penicillin-allergic HIV-negative patients.

Latent Syphilis in HIV-Infected Persons
Diagnostic Considerations
HIV-infected patients who have early latent syphilis should be managed and treated according to the recommendations for HIV-negative patients who have primary and secondary syphilis.
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.

Treatment
Penicillin is effective for preventing maternal transmission to the fetus and for treating fetal-established infection. Evidence is insufficient to determine whether the specific, recommended penicillin regimens are optimal.

Recommended Regimens
Treatment during pregnancy should be the penicillin regimen appropriate for the stage of syphilis.

Other Management Considerations
Some experts recommend additional therapy in some settings. A second dose of benzathine penicillin 2.4 million units IM may be administered 1 week after the initial dose for women who have primary, secondary, or early latent syphilis. Ultrasonographic signs of fetal syphilis (i.e., hepatomegaly and hydrops) indicate a greater risk for fetal treatment failure; such cases should be managed in consultation with obstetric specialists.

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. These women should be advised to seek obstetric attention after treatment if they notice any contractions or decrease in fetal movements. Still-birth is a rare complication of treatment, but concern for this complication should not delay necessary treatment. All patients who have syphilis should be offered testing for HIV infection.

Follow-Up
Coordinated prenatal care and treatment follow-up are important, and syphilis case management may help facilitate prenatal enrollment. Serologic titers should be repeated in the third trimester and at delivery. Serologic titers may be checked monthly in women at high risk for reinfection or in geographic areas in which the prevalence of syphilis is high. The clinical and antibody response should be appropriate for the stage of disease.

Most women will deliver before their serologic response to treatment can be assessed definitively.

Penicillin Allergy
There are no proven alternatives to penicillin for treatment of syphilis during pregnancy. Pregnant women who have a history of penicillin allergy should be desensitized and treated with penicillin; skin testing may be helpful.

Tetracycline and doxycycline usually are not used during pregnancy. Erythromycin should not be used, because it does not reliably cure an infected fetus. Data are insufficient to recommend azithromycin or ceftriaxone.

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 at the time of the first prenatal visit. Serologic testing and a sexual history also should be obtained at 28 weeks of gestation and at delivery in communities and populations in which the risk for congenital syphilis is high. Moreover, as part of the management of pregnant women who have syphilis, information concerning treatment of sex partners should be obtained in order to assess possible maternal reinfection. All pregnant women who have syphilis should be tested for HIV infection.

Routine screening of newborn sera or umbilical cord blood is not recommended because tests performed on infant serum can be nonreactive if the mother’s serologic test result is of low titer or if the mother was infected late in pregnancy.

Evaluation and Treatment of Infants During the First Month of Life
Diagnostic Considerations
The diagnosis of congenital syphilis is complicated by the transplacental transfer of maternal nontreponemal and treponemal IgG antibodies to the fetus. This transfer of antibodies makes the interpretation of reactive serologic tests for syphilis in infants difficult. Treatment decisions often must be made based on a) identification of syphilis in the mother; b) adequacy of maternal treatment; c) presence of clinical, laboratory, or radiographic evidence of syphilis in the infant; and d) comparison of the infant’s nontreponemal serologic test results with those of the mother.

Who Should Be Evaluated
All infants born to seroreactive mothers should be evaluated with a quantitative nontreponemal serologic test (RPR or VDRL) performed on infant serum (i.e., umbilical cord blood might be contaminated with maternal blood and might yield a false-positive result). A treponemal test (i.e., MHA-TP or FTA-ABS) of a newborn’s serum is not necessary.

Evaluation
All infants born to women who have reactive serologic tests for syphilis should be examined thoroughly for evidence of congenital syphilis (e.g., nonimmune hydrops, jaundice, hepatosplenomegaly, rhinitis, skin rash, and/or pseudoparalysis of an extremity). Pathologic examination of the placenta or umbilical cord using specific fluorescent antitreponemal antibody staining is suggested. Darkfield microscopic examination or direct fluorescent antibody staining of suspicious lesions or body fluids (e.g., nasal discharge) also should be performed. Further evaluation of the infant is dependent on a) whether any abnormalities are present on physical examination, b) maternal treatment history, c) stage of infection at the time of treatment, and d) comparison of maternal (at delivery) and infant nontreponemal titers utilizing the same test and preferably the same laboratory.

Treatment
Infants should be treated for presumed congenital syphilis if they were born to mothers who met any of the following criteria:

• Had untreated syphilis at delivery;
• Had serologic evidence of relapse or reinfection after treatment (i.e., a fourfold or greater increase in nontreponemal antibody titer);
• Was treated with erythromycin or other nonpenicillin regimen for syphilis during pregnancy;
• Was treated for syphilis ≤ 1 month before delivery;

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

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• Did not have a well-documented history of treatment for syphilis;
• Was treated for early syphilis during pregnancy with the appropriate penicillin regimen, but nontreponemal antibody titers did not decrease at least fourfold; or
• Was treated appropriately before pregnancy but had insufficient serologic follow-up to ensure an adequate treatment response and lack of current infection (i.e., an appropriate response includes a) at least a fourfold decrease in nontreponemal antibody titers for patients treated for early syphilis and b) stable or declining nontreponemal titers of ≤1:4 for other patients).

Regardless of a maternal history of infection with *T. pallidum* or treatment for syphilis, the evaluation should include the following tests if the infant has either a) an abnormal physical examination that is consistent with congenital syphilis, b) a serum quantitative nontreponemal serologic titer that is fourfold greater than the mother’s titer, or c) a positive darkfield or fluorescent antibody test of body fluid(s).

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

**Recommended Regimens**

**Aqueous crystalline penicillin G**

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

**Procaine penicillin G**

50,000 units/kg IM a day in a single dose for 10 days.

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

In all other situations, the maternal history of infection with *T. pallidum* and treatment for syphilis must be considered when evaluating and treating the infant. For infants who have a normal physical examination and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer, the evaluation depends on the maternal treatment history and stage of infection.

- The infant should receive the following treatment if a) the maternal treatment was not given, was undocumented, was a nonpenicillin regimen, or was administered ≤4 weeks before delivery; b) the adequacy of maternal treatment for early syphilis cannot be evaluated because the nontreponemal serologic titer has not decreased fourfold; or c) relapse or reinfection is suspected because of a fourfold increase in maternal nontreponemal serologic titer.
  a. Aqueous penicillin G or procaine penicillin G for 10 days. Some experts prefer this therapy if the mother has untreated early syphilis at delivery. A complete evaluation is unnecessary if 10 days of parenteral therapy is given. However such evaluation may be useful: a lumbar puncture may document CSF abnormalities that would prompt close follow-up. Other tests (e.g., CBC and platelet count and bone radiographs) may be performed to further support a diagnosis of congenital syphilis; or
  b. Benzathine penicillin G 50,000 units/kg (single dose IM) if the infant’s evaluation (i.e., CSF examination, long-bone radiographs, and CBC with platelets) is normal and follow-up is certain. If any part of the infant’s evaluation is abnormal or not done, or the CSF analysis is uninterpretable secondary to contamination with blood, then a 10-day course of penicillin is indicated.

- Evaluation is unnecessary if the maternal treatment a) was during pregnancy, appropriate for the stage of infection, and >4 weeks before delivery; b) was for early syphilis and the nontreponemal serologic titers decreased fourfold after appropriate therapy; or c) was for late latent infection, the nontreponemal titers remained stable and low, and there is no evidence of maternal reinfection or relapse. A single dose of benzathine penicillin G 50,000 units/kg IM should be administered. (Note: Some experts would not treat the infant but would provide close serologic follow-up.) Furthermore, in these situations, if the infant’s nontreponemal test is nonreactive, no treatment is necessary.

- Evaluation and treatment are unnecessary if the maternal treatment was before pregnancy, after which the mother was evaluated multiple times, and the nontreponemal serologic titer remained low and stable before and during pregnancy and at delivery (VDRL ≤1:2; RPR ≤1:4). Some experts would treat with benzathine penicillin G 50,000 units/kg as a single IM injection, particularly if follow-up is uncertain.

**Evaluation and Treatment of Older Infants and Children Who Have Congenital Syphilis**

Children who are identified as having reactive serologic tests for syphilis after the neonatal period (i.e., at >1 month of age) should have maternal serology and records reviewed to assess whether the child has congenital or acquired syphilis (for acquired syphilis, see Primary and Secondary Syphilis and Latent Syphilis). If the child possibly has congenital syphilis, the child should be evaluated fully (i.e., a CSF examination for cell count, protein, and VDRL [abnormal CSF evaluation includes a reactive VDRL test; >5 WBCs/mm³, and/or protein >40 mg/dL]; an eye examination; and other tests such as long-bone radiographs, CBC, platelet count, and auditory brainstem response as indicated clinically). Any child who possibly has congenital syphilis or who has neurologic involvement should be treated with 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.

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

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

Infants whose initial CSF evaluation is abnormal should undergo a repeat lumbar puncture approximately every 6 months until the results are normal. A reactive CSF VDRL test or abnormal CSF indices that cannot be attributed to other ongoing illness requires retreatment for possible neurosyphilis. Follow-up of children treated for congenital syphilis after the newborn period should be the same as that prescribed for congenital syphilis among neonates.

Special Considerations
Penicillin Allergy
Infants and children who require treatment for syphilis but who have a history of penicillin allergy or develop an allergic reaction presumed secondary to penicillin should be desensitized, if necessary, and treated with penicillin. Skin testing may be helpful in some patients and settings. Data are insufficient regarding the use of other antimicrobial agents; if a nonpenicillin agent is used, close serologic and CSF follow-up is indicated.

REFERENCES