CDC Recommended Evaluation and Treatment for Congenital Syphilis

Evaluation and Treatment of Neonates

Diagnosis of congenital syphilis can be difficult because maternal nontreponemal and treponemal immunoglobulin G (IgG) antibodies can be transferred through the placenta to the fetus, complicating the interpretation of reactive serologic tests for syphilis among neonates (infants aged <30 days). Therefore, treatment decisions frequently must be made on the basis of identification of syphilis in the mother; adequacy of maternal treatment; presence of clinical, laboratory, or radiographic evidence of syphilis in the neonate; and comparison of maternal (at delivery) and neonatal nontreponemal serologic titers (e.g., RPR or VDRL) by 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.

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. The nontreponemal test performed on the neonate should be the same type of nontreponemal test performed on the mother.

Conducting a treponemal test (e.g., TP-PA, immunoassay-EIA, CIA, or microbead immunoassay) on neonatal serum is not recommended because it is difficult to interpret, as passively transferred maternal antibodies can persist for >15 months. Commercially available IgM tests are not recommended.

All neonates born to women who have reactive nontreponemal serologic tests for syphilis at delivery should be examined thoroughly for evidence of congenital syphilis (e.g., nonimmune hydrops, conjugated or direct hyperbilirubinemia[†] or cholestatic jaundice or cholestasis, hepatosplenomegaly, rhinitis, skin rash, or 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; direct fluorescence antibody (DFA-TP) reagents are unavailable (*565*). Darkfield microscopic examination or PCR testing of suspicious lesions or body fluids (e.g., bullous rash or 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 because these abnormalities are not detected on fetal ultrasound.

The following scenarios describe the recommended congenital syphilis evaluation and treatment of neonates born to women who had reactive nontreponemal and treponemal serologic tests for syphilis during pregnancy (e.g., RPR reactive, TP-PA reactive or EIA reactive, RPR reactive) and have a reactive nontreponemal test at delivery (e.g., RPR reactive). Maternal history of infection with *T. pallidum* and treatment for syphilis should be considered when evaluating and treating the neonate for congenital syphilis in most scenarios, except when congenital syphilis is proven or highly probable.

Scenario 1: Confirmed Proven or Highly Probable Congenital Syphilis

Any neonate with

- an abnormal physical examination that is consistent with congenital syphilis;
- a serum quantitative nontreponemal serologic titer that is fourfold[§] (or greater) higher than the mother's titer at delivery (e.g., maternal titer = 1:2, neonatal titer ≥1:8 or maternal titer = 1:8, neonatal titer ≥1:32)[¶]; or
- a positive darkfield test or PCR of placenta, cord, lesions, or body fluids or a positive silver stain of the placenta or cord.

Recommended Evaluation

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

- Other tests as clinically indicated (e.g., chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, and auditory brain stem response)

Recommended Regimens, Confirmed or Highly Probable Congenital Syphilis

Aqueous crystalline penicillin G 100,000–150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose by 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 body weight/dose IM in a single daily dose for 10 days

If >1 day of therapy is missed, the entire course should be restarted. Data are insufficient regarding 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 (*648–650*). Using agents other than penicillin requires close serologic follow-up for assessing therapy adequacy.

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 of the maternal titer at delivery (e.g., maternal titer = 1:8, neonatal titer ≤1:16) and one of the following:

- The mother was not treated, was inadequately treated, or has no documentation of having received treatment.
- The mother was treated with erythromycin or a regimen other than those recommended in these guidelines (i.e., a nonpenicillin G regimen).††
- The mother received the recommended regimen, but treatment was initiated <30 days before delivery.

Recommended Evaluation

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

This evaluation is not necessary if a 10-day course 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 long-bone radiographs) can be performed to further support a diagnosis of congenital syphilis.

Recommended Regimens, Possible Congenital Syphilis

Aqueous crystalline penicillin G 100,000–150,000 units/kg body weight/day, administered as 50,000 units/kg body weight/dose by 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 body weight/dose IM in a single daily dose for 10 days

OR

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

Before using the single-dose benzathine penicillin G regimen, the recommended evaluation (i.e., CSF examination, long-bone radiographs, and CBC with platelets) should be normal, and follow-up should be certain. If any part of the

neonate'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 for untreated syphilis is low, treatment of the neonate with a single IM dose of benzathine penicillin G 50,000 units/kg body weight 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 should be considered even if the neonate's nontreponemal test is nonreactive, 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 or less than fourfold of the maternal titer at delivery (e.g., maternal titer = 1:8, neonatal titer ≤1:16) and both of the following are true:

- The mother was treated during pregnancy, treatment was appropriate for the infection stage, and the treatment regimen was initiated ≥30 days before delivery.
- The mother has no evidence of reinfection or relapse.

Recommended Evaluation

No evaluation is recommended.

Recommended Regimen, Congenital Syphilis Less Likely

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

* Another approach involves not treating the newborn if follow-up is certain but providing close serologic follow-up every 2–3 months for 6 months for infants whose mothers' nontreponemal titers decreased at least fourfold after therapy for early syphilis or remained stable for low-titer, latent syphilis (e.g., VDRL <1:2 or 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 of the maternal titer at delivery[§] and both of the following are true:

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

Recommended Evaluation

No evaluation is recommended.

Recommended Regimen, Congenital Syphilis Unlikely

No treatment is required. However, any neonate 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 body weight as a single IM injection might be considered, particularly if follow-up is uncertain and the neonate has a reactive nontreponemal test.

The following situations describe management of neonates born to women screened during pregnancy by using the reverse sequence algorithm with reactive treponemal serologic tests and a nonreactive nontreponemal serologic test.

Reactive maternal treponemal serologies with a nonreactive nontreponemal serology (e.g., EIA reactive, RPR nonreactive, or TP-PA reactive) during pregnancy. Syphilis is highly unlikely for neonates born to mothers with a nonreactive nontreponemal test after adequate treatment for syphilis during pregnancy or documentation of adequate treatment before pregnancy (with no evidence of reinfection of relapse). If testing is performed again at delivery and 1) the maternal nontreponemal test remains nonreactive and 2) the neonate has a normal physical examination and nonreactive nontreponemal test (e.g., RPR nonreactive), the provider should consider managing similarly to Scenario 4 without a laboratory evaluation and with no treatment required. Benzathine penicillin G 50,000 units/kg body weight as a single IM injection might be considered if syphilis exposure is possible within 1 month of delivery and follow-up of the mother and infant is uncertain.

Isolated reactive maternal treponemal serology (e.g., EIA reactive, RPR nonreactive, or TP-PA nonreactive) during pregnancy. Syphilis is unlikely for neonates born to mothers screened with the reverse sequence algorithm with isolated reactive maternal treponemal serology. Among low-prevalence populations, these are likely false-positive results and might become nonreactive with repeat testing (*638*). If these neonates have a normal physical examination and the risk for syphilis is low in the mother, no evaluation and treatment are recommended for the neonate. If syphilis exposure is possible or unknown in the mother or the mother desires further evaluation to definitively rule out syphilis, repeat serology within 4 weeks is recommended to evaluate for early infection (see Syphilis During Pregnancy).

Isolated reactive maternal treponemal serology (e.g., rapid treponemal test) at delivery. For mothers with late or no prenatal care with a reactive rapid treponemal test at delivery, confirmatory laboratory-based testing should be performed; however, results should not delay evaluation and treatment of the neonate. These neonates should be evaluated and treated with a 10-day course of penicillin as recommended in Scenario 1, and consultation with a specialist is recommended.

Follow-Up

All neonates with reactive nontreponemal tests should receive thorough follow-up examinations and serologic testing (i.e., RPR or VDRL) every 2–3 months until the test becomes nonreactive.

For a neonate who was not treated because congenital syphilis was considered less likely or unlikely, nontreponemal antibody titers should decrease 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 age 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 infected and should be treated.

Treated neonates who exhibit persistent nontreponemal test titers by age 6–12 months should be reevaluated through CSF examination and managed in consultation with an expert. Retreatment with a 10-day course of a penicillin G regimen might be indicated.

Neonates with a negative nontreponemal test at birth and whose mothers were seroreactive at delivery should be retested at age 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 >15 months.

Neonates whose initial CSF evaluations are abnormal do not need repeat lumbar puncture unless they exhibit persistent nontreponemal serologic test titers at age 6–12 months. Persistent nontreponemal titers and CSF abnormalities should be managed in consultation with an expert.

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 (e.g., RPR reactive, TP-PA reactive or EIA reactive, RPR reactive) 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; Latent Syphilis; Sexual Assault or Abuse of Children). In the case of extremely early or incubating syphilis at the time of delivery, all maternal serologic tests might have been negative; thus, infection might be undetected until a diagnosis is made later in the infant or child. Any infant or child at risk for congenital syphilis should receive a full evaluation and testing for HIV infection.

International adoptee, immigrant, or refugee children from countries where treponemal infections (e.g., yaws or pinta) are endemic might have reactive nontreponemal and treponemal serologic tests, which cannot distinguish between syphilis and other subspecies of *T. pallidum* (*651*). These children might also have syphilis (*T. pallidum* subspecies *pallidum*) and should be evaluated for congenital syphilis.

Recommended Evaluation

The following evaluations should be performed:

- 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 for Congenital Syphilis Among Infants and Children

Aqueous crystalline penicillin G 200,000–300,000 units/kg body weight by IV, administered as 50,000 units/kg body weight 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 units/kg body weight IM can be considered. A single dose of benzathine penicillin G 50,000 units/kg body weight 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 G to provide more comparable duration for treatment in those who have no clinical manifestations and normal CSF. All of these treatment regimens should also be adequate for children who might have other treponemal infections.

Follow-Up

Thorough follow-up examinations and serologic testing (i.e., RPR or VDRL) of infants and children treated for congenital syphilis after the neonatal period (aged >30 days) 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 >2 weeks or do not decrease fourfold after 12–18 months, the infant or child should be evaluated (e.g., CSF examination), treated with a 10-day course of parenteral penicillin G, and managed in consultation with an expert. Treponemal tests (e.g., EIA, CIA, or TP-PA) should not be used to evaluate treatment response because the results are qualitative and persist after treatment, and passive transfer of maternal IgG treponemal antibody might persist for >15 months after delivery. Infants or children whose initial CSF evaluations are abnormal do not need repeat lumbar puncture unless their serologic titers do not decrease fourfold after 12–18 months. After 18 months of follow-up, abnormal CSF indices that persist and cannot be attributed to other ongoing illness indicate that retreatment is needed for possible neurosyphilis and should be managed in consultation with an expert.