

Clinical Guidelines for Syphilis

GUIDANCE FOR SYPHILIS DURING PREGNANCY AND CONGENITAL
SYPHILIS, INCLUDING INFANTS AND CHILDREN

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Syphilis during Pregnancy

Syphilis Screening Recommendations during Pregnancy

- Screen **ALL pregnant women** for syphilis at least twice, as follows:
 - First prenatal visit
 - Early in third trimester (28-32 weeks' gestation). Screening during this time period is important to allow enough time for treatment to occur prior to delivery, in order to prevent CS.
- Screening at delivery is also needed for **MANY pregnant women**, including:
 - Women who do not have a **documented** syphilis screening test result from earlier in the third trimester, regardless of the presence or absence of any known risk factors for syphilis.
 - Women with one or more of the following risk factors:
 - No or inconsistent prenatal care
 - A sexually transmitted disease (STD) diagnosed during the past year
 - Current illicit drug use
 - Incarceration in past year
 - Currently experiencing homelessness or unstable housing
 - Multiple sexual partners
 - A sexual partner who has any of the following risk factors: STD in past year, multiple sexual partners, current illicit drug use, recent incarceration, or homelessness.
 - Even in the absence of any of the above risk factors, clinicians always have discretion in deciding to screen for syphilis at time of delivery.
- **Do not discharge a mother or newborn infant to home after delivery without a documented or provider-verified maternal syphilis test result from the third trimester or delivery.** Verbal reports from mothers of syphilis screen performed is not sufficient.
- Additional syphilis testing is needed at the time of identification for pregnant women with signs of primary or secondary syphilis and for women with sexual partners recently diagnosed with an STD, in addition to the two to three screening time points.
- Test any woman delivering a stillborn at 20 weeks gestation or later, for syphilis at the time of delivery.

Additional pregnancy-related syphilis screening guidance

- Become familiar with MDH syphilis screening guidelines and protocols.
- Review how to recognize, diagnose, and treat all stages of syphilis including CS. Free online CME for syphilis and other STDs is available through the [National STD Curriculum \(https://www.std.uw.edu\)](https://www.std.uw.edu). Consider contacting your local infectious disease specialist if you suspect a case of CS, neurosyphilis or ocular syphilis.
- Obtain a complete sexual history that includes the discussion of risk factors such as drug use, multiple sex partners, infections with other STDs, and prior syphilis infection.

- Conduct an HIV test along with the initial syphilis screen at the first prenatal visit. HIV testing should be repeated if syphilis or another STD is diagnosed later in pregnancy.
- Make sure to test and treat sex partners of patients who test positive. Obtain partner information from patients and encourage them to work with the MDH Partner Services Program.
- Pregnant women with syphilis must always be treated with a penicillin regimen appropriate for their stage of infection. Pregnant women with a penicillin allergy must undergo a penicillin desensitization protocol. The 2015 CDC STD Treatment Guidelines (<https://www.cdc.gov/std/tg2015/syphilis-pregnancy.htm>) contain additional recommendations for pregnant women.
- Report cases (including syphilitic stillbirths) within 24 hours to MDH at 651-201-5414 or 1-877-676-5414.

Diagnostic Considerations

- In general, the risk for antepartum fetal infection or congenital syphilis at delivery is related to the mother's stage of syphilis during pregnancy, with the highest risk being with the primary and secondary stages.
- Quantitative maternal nontreponemal titer, especially if >1:8, might be a marker of early infection and bacteremia. Early syphilis is defined primary, secondary, or early latent syphilis. Early latent syphilis is asymptomatic infection acquired within the past 12 months. seroreactivity without clinical signs and symptoms acquired within the last year.
- Risk for fetal infection is still significant in pregnant women who have been treated for syphilis with stable, serofast low antibody titers and 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 tests should be reflexed to a quantitative nontreponemal test (RPR, VDRL or USR). 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 is confirmed.
- For women with a documented history of adequate treatment for syphilis, who do not have an ongoing risk, no further treatment is necessary.
- Women without a documented history of treatment should be staged and treated accordingly with a 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. If the woman is low risk for 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. If both the RPR and TP-PA remain negative, no further treatment is necessary.
- If follow-up is not possible, women without a documented history of treated syphilis should be treated according to the stage of syphilis.

Treatment

- Penicillin G is the only known effective treatment to prevent maternal transmission to the fetus and treating fetal infection.
- Pregnant women should be treated with the penicillin regimen appropriate for their stage of infection.
- Pregnant women who report penicillin allergy should be desensitized and treated with penicillin.
- **Missed doses are NOT acceptable** for pregnant women receiving therapy for late latent syphilis. Pregnant women who miss any dose of therapy must repeat the entire course of therapy.
- Never confuse Bicillin®C-R for Bicillin®L-A. Bicillin®C-R should not be used to syphilis.

Other Management Considerations

- Syphilis diagnosed during the second half of pregnancy should be treated as recommended. Management of therapy should also include a sonographic fetal evaluation for congenital syphilis.
 - Sonographic signs of fetal or placental syphilis include: hepatomegaly, ascites, hydrops, fetal anemia or a thickened placenta; these findings indicate greater risk of fetal treatment failure.
 - Cases accompanied by these signs 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 Jarish-Herxheimer reaction.
 - These women should be advised to seek immediate obstetrical attention after treatment if they notice any fever, contractions or decrease in fetal movements.
- All women who have syphilis should be offered testing for HIV infection.

Follow-Up

- Coordinated prenatal care and treatment are critical:
 - Repeat serology at 28 -32 weeks gestation and at delivery at a minimum
 - Repeat titers can be checked monthly for women at high risk for reinfections or in geographical areas where prevalence of syphilis is high
 - Ensure that clinical and antibody responses are appropriate for the patient's stage of disease.
- Most women will deliver their babies before their response to treatment can be assessed definitively and will require continued follow-up post- partum.
 - Their babies will require thorough assessment, possible treatment and close follow-up.

Congenital Syphilis

- Identification of syphilis in pregnant women is vital to effectively prevent and detect congenital syphilis.
- Routine serologic screening of pregnant women during their first prenatal visit and at 28-32 weeks for all women, and at delivery for women with risk factors described above.
- As part of prenatal care for a woman who has syphilis, information concerning ongoing risk behaviors and treatment of sex partners should be obtained to assess the risk of 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 be discharged to home after delivery without a documented or provider-verified maternal syphilis test result from the third trimester or delivery.

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

- Transfer of maternal nontreponemal and treponemal IgG antibodies through the placenta to the fetus, can makes diagnosis of congenital syphilis complicated.
- 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.
 - 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.
 - 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.
- All neonates born to women who have reactive serological tests for syphilis should be examined thoroughly for:
 - Evidence of congenital syphilis, e.g., nonimmune hydrops, jaundice, hepatosplenomegaly, rhinitis, skin rash and pseudoparalysis of and extremity.
 - Pathological 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.

- For stillborn infants, skeletal survey demonstrating presence of typical osseous lesions that might aid in the diagnosis of congenital syphilis.

Clinical Management by Level of Evidence of Congenital Syphilis

The following scenarios describe the congenital syphilis evaluation and treatment of neonates born to women who have had reactive serologic tests for syphilis during her 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.

1: Proven or Highly Probable Congenital Syphilis

Any neonate with:

- An abnormal physical examination that is consistent with congenital syphilis. OR
- A serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer.*

OR

- A positive darkfield test or PCR of lesions or body fluid(s).

* Absence of a fourfold or greater titer for neonate does not exclude congenital syphilis.

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).

Treatment:

- Aqueous crystalline penicillin G 100,000-150,000 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.
 - A full 10-day course of penicillin is preferred, even if ampicillin was initially provided for possible sepsis.

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

2: Possible Congenital Syphilis

Any neonate who:

- Has a normal physical examination.

AND

- A serum quantitative nontreponemal serologic titer equal to less than fourfold the maternal titer.

AND one of the following:

- Mother was not treated, inadequately treated, or has no documentation of having received treatment.

OR

- Mother was treated with erythromycin or a regimen other than those recommended in these guidelines (i.e., a nonpenicillin G regimen).*

OR

- Mother received recommended treatment <4 weeks before delivery.

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

Evaluation:

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

**See: [CDC Sexually Transmitted Diseases Treatment Guideline, 2015](http://www.cdc.gov/std/tg2015/default.htm)

(<http://www.cdc.gov/std/tg2015/default.htm>), pp. 46 -47 for details on interpreting these results.

A complete evaluation is not necessary if 10 days of parenteral therapy is administered, although such evaluation might be useful. For instance, a lumbar puncture might document CSF abnormalities that would prompt close follow-up.

Treatment:

- 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 dose for 10 days. OR
- Benzathine penicillin G 50,0000 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 CDC 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 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.

3: Less Likely 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 both of the following are true:

- Mother was treated during pregnancy, treatment was appropriate for the stage of infection, and treatment was administered >4 weeks before delivery.

AND

- Mother has no evidence of reinfection or relapse.

Evaluation:

- No evaluation is recommended.

Treatment:

- 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)

4: Unlikely 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 both of the following are true:

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

Evaluation:

- No evaluation is recommended.

Treatment:

- No treatment is required, but infants with reactive nontreponemal test should be followed serologically to ensure the nontreponemal test returns to negative.
- 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 for Neonates

- All neonates with reactive nontreponemal tests should receive careful follow-up examinations and serologic testing every 2-3 months until the test becomes nonreactive.
- In the child who was not treated because congenital syphilis was considered less likely or unlikely, nontreponemal antibody should decline by 3 months and be nonreactive by age 6 months, indicating that the reactive test was caused by passive transfer of maternal IgG antibody.
- At 6 months if the nontreponemal test is nonreactive, no further evaluation or follow-up is indicated. 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 infectious diseases specialist. Retreatment with a 10-day course of 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 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 infectious diseases specialist.

Special Considerations for Neonates

- Penicillin allergy or shortage: [CDC Sexually Transmitted Diseases Treatment Guideline, 2015](http://www.cdc.gov/std/tg2015/default.htm) (<http://www.cdc.gov/std/tg2015/default.htm>), pp. 47-48.
- HIV infection: Evidence is insufficient to determine whether neonate who have congenital syphilis and HIV or whose mother have HIV infection require different therapy or clinical management than is recommended for 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

- 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 [Syphilis Treatment Protocol \(www.health.state.mn.us/diseases/syphilis/hcp/protocol.pdf\)](http://www.health.state.mn.us/diseases/syphilis/hcp/protocol.pdf)
- Any infant or child at risk for congenital syphilis should receive a full evaluation and testing HIV infection.

Evaluation:

- CSF analysis for VDRL, cell count, and protein
- CDC, 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)

Treatment:

- 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 3 weekly doses of benzathine penicillin G, 50,000 units/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 for Infants and Children

- 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) should be performed every 3 months until the test becomes nonreactive or the titer has decreased fourfold.
- 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 an infectious disease specialist.
- 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; antibody may persist for at least 15 months after delivery.
- Infants for 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 persist and cannot be attributed to other ongoing illness requires retreatment for possible neurosyphilis and should be managed in consultation with an infectious disease specialist.

Special Considerations for Infants and Children

Please see the [CDC Sexually Transmitted Disease Treatment Guidelines, 2015](http://www.cdc.gov/std/tg2015/default.htm) (<http://www.cdc.gov/std/tg2015/default.htm>) for more information on the following:

- Penicillin allergy and penicillin shortage: pages 47-48.
- HIV infection: page 49.
- Sexual assault or abuse: page 104.

Minnesota Department of Health
STD, HIV, and TB Section
651-201-5414
www.health.state.mn.us/std

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