

Syphilis Treatment Protocol

CLINICAL GUIDANCE FOR PRIMARY AND SECONDARY SYPHILIS
AND LATENT SYPHILIS

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Description

Syphilis is a systemic disease caused by the spirochete *Treponema pallidum*. It is transmitted through sexual contact, but can also be transmitted from mother to fetus during pregnancy. Syphilis is divided into three stages; primary, secondary and latent or tertiary syphilis. Stages are determined by clinical findings, which are used to provide guidance for treatment and follow-up. Syphilis affecting the central nervous system (CNS) can occur during any stage of syphilis.

Stages and Symptoms

Primary infection:

- Painless ulcers(s) or chancre(s) at the infection site
- Lesions are usually firm, round and painless
- Appear 10 to 90 days, with an average of 21 days, after exposure to syphilis
- Lesions may persist for 3-6 weeks then resolve

Secondary infection:

- Rash often on the palms of hands, bottom of feet, on the torso or other sites
- Mucus membrane lesions or sores in the mouth, vagina, or anus
- Flat wart-like growths, condylomata lata, in the perianal/genital area and other moist body sites
- Generalized lymphadenopathy, sore throat
- Alopecia
- Headaches
- Weight loss
- Muscle aches
- Fatigue

Onset of symptoms typically occurs six weeks to six months after onset of the lesion or chancre (can overlap with primary stage) and resolves in 2-10 weeks.

About 25 percent of people may have relapses of symptoms in the first year.

Tertiary syphilis:

Tertiary syphilis is defined as symptomatic late latent syphilis, gumma and cardiovascular syphilis, but not neurosyphilis.

- Damage to the heart, blood vessels, liver, bones and joints can develop
- Gummatous, soft noncancerous lesions, occur
- Uveitis or other ocular manifestations

Latent and late latent syphilis:

Latent syphilis is defined as seroreactivity without other evidence primary, secondary or tertiary disease. Early latent, latent and late latent syphilis overlap the primary, secondary and tertiary stages of syphilis based on length of time of infection and visible symptoms.

Latent syphilis acquired with the preceding year is classified as early latent syphilis. Criteria for early latent syphilis include a negative test in the past year, documented exposure to early syphilis in the past year and symptoms of syphilis that have resolved in the past year.

Latent syphilis acquired more than one year ago or of unknown duration is classified as late latent syphilis. The majority of people with late latent syphilis may be asymptomatic for many years.

Risk Factors

- Exposure to syphilis through oral, vaginal and anal sex
- Transmission from a pregnant woman to her fetus
- Lack consistent use of condoms with every sexual contact
- History of previous of STD diagnosis
- Multiple sex partners
- HIV infected persons
- Men who have sex with men
- Sexual partners of men who have sex with men
- Persons who exchange sex for drugs or money or having partners who do (male or female)
- Sexual assault victims

Routine screening is recommended:

- Annually for men who have sex with men
- Person with HIV infection and at least every 6 months for those at higher risk
- Annually for individuals with multiple sex partners, or a partner who has multiple sex partners
- All pregnant women at:
 - their first prenatal visit
 - 28-32 weeks
 - Delivery
- Any woman who has a fetal death after 20 weeks' gestation should be tested for syphilis
- Any person with primary or secondary syphilis should be tested for HIV

Diagnosing Syphilis

Darkfield examinations and tests to detect *T. pallidum* directly from lesion exudate or tissue are the definitive methods for diagnosing early syphilis. Presumptive diagnosis of syphilis requires use of two tests: a nontreponemal and a treponemal test. The nontreponemal is a quantitative measure and the treponemal is to confirm, both as part of diagnostic steps.

Serology:

- Nontreponemal screening:
Venereal Disease Research Laboratory Assay (VDRL), Rapid Plasma Reagin (RPR), or Unheated Serum Regain (USR)
 - Nontreponemal results should be reported quantitatively.
 - Nontreponemal antibody titers might correlate with disease activity and are used to follow treatment response.
 - A fourfold change in titer, equivalent to a change of two dilutions (e.g. 1:16 to 1:4 or 1:8 to 1:32), is necessary to demonstrate a clinically significant difference between two nontreponemal test results obtained using the same serologic test.
 - 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”
- Treponemal screening:
Fluorescent Treponemal Antibody Absorption (FTA-ABS), Treponemal Pallidum Particle Agglutination Assay (TT-PA)
 - Persons with a reactive nontreponemal test should always receive a treponemal test to confirm the diagnosis of syphilis.
 - Persons with reactive treponemal test tests will usually have a reactive test result for a lifetime.
 - Treponemal tests are done
 - To confirm nontreponemal reactive results and
 - At recent onset of suspicious new lesion
 - Treponemal assays do not predict response to treatment and should not be used for this purpose.
- Treponemal tests by, Enzyme Immunoassay (EIA), chemiluminescence immunoassays (CIA) or Microbead Immunoassay (MIA) are a reverse screening algorithm for syphilis.
 - This screening 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.
- In 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, 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 person with risk for syphilis, and use of other tests (e.g., biopsy and PCR) should be considered.

Cerebrospinal fluid (CSF) exam:

- Further testing is warranted for persons with clinical signs of neurosyphilis, infection of the nervous system including the brain and spinal cord. Laboratory testing is helpful in supporting the diagnosis of neurosyphilis, but no single test can be used for diagnosis.
- A combination of (CSF cell count or protein or a reactive CSF-VDRL) in the presence of reactive serologic test results and neurologic signs and symptoms should be used for diagnosis.
- CSF laboratory abnormalities are common in persons with early syphilis and are of unknown significance in the absence of neurologic signs.
- CSF-VDRL is highly specific but insensitive
- Persons who have HIV infection, CSF leukocyte count usually is elevated (>5 white blood [WBC]/mm³). Using a higher cutoff (>20 WBC/mm³) might improve the specificity of neurosyphilis diagnosis.
- For more details on testing and interpreting test results see the [CDC MMWR; Sexually Transmitted Diseases Treatment Guidelines, 2015 \(http://www.cdc.gov/std/tg2015/default.htm\)](http://www.cdc.gov/std/tg2015/default.htm), pages 34-35.

Treatment of Syphilis

- Penicillin G administered intramuscularly (IM) or intravenously (IV) is the preferred drug for treating 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 signs of the disease.
- Combinations of benzathine penicillin, procaine penicillin and oral penicillin preparations **are not** appropriate for the treatment of syphilis.
- Penicillin G administered IM or IV is the only therapy with documented efficacy for syphilis during pregnancy.
- Pregnant women in any stage of syphilis who report penicillin allergy should be desensitized and treated with penicillin.

Primary and secondary syphilis treatment:

- Administer benzathine penicillin G (Bicillin L-A) 2.4 million units Intramuscularly (IM) in a single dose
- For penicillin allergic persons administer regimens of:
 - doxycycline 100 mg orally twice daily for 14 days or
 - tetracycline 500 mg four times daily for 14 days.
- Compliance is likely to be better with doxycycline than tetracycline due to the gastrointestinal side effects and more frequent dosing of tetracycline.
- De not use Azithromycin as first-line treatment for syphilis, it should be used with caution **only** when recommended treatment options are not feasible. Treatment failures with azithromycin have been documented in multiple geographic areas in the United States.
- Other management considerations include testing all persons who have latent syphilis for HIV and evaluating anyone with neurological signs and symptoms for neurosyphilis.

Late latent (infection of more than one year) or latent syphilis of unknown duration:

- Administer benzathine penicillin G (Bicillin L-A) 7.2 million units total, administered as three doses of 2.4 million units IM each at one week intervals
- For penicillin allergic persons administer:
 - doxycycline 100mg orally twice daily for 28 days or
 - tetracycline 500mg orally four times daily for 28 days
- If compliance cannot be assured, the following regimen should be considered; Procaine penicillin G 2.4 million units IM once daily PLUS Probenecid 500mg orally four times a day, both for 10-14 days

Tertiary syphilis treatment:

- Tertiary Syphilis with Normal CSF Examination
 - Administer benzathine penicillin G (Bicillin L-A) 7.2 million units total, three doses of 2.4 million units IM each at one week intervals
- All persons who have tertiary syphilis should be tested for HIV and receive a CSF examination before treatment is initiated

Special populations:

- Pregnancy, Congenital Syphilis, Infants/Children
See "[Sample Clinical Guidelines for Pregnancy, Congenital Syphilis and Infants/Children](http://www.health.state.mn.us/divs/idepc/diseases/syphilis/hcp/clinicalguidepc.pdf) (<http://www.health.state.mn.us/divs/idepc/diseases/syphilis/hcp/clinicalguidepc.pdf>)"
- HIV Infected Persons
Persons with HIV infection with latent syphilis should be treated as persons who do not have HIV infection.

Neurosyphilis and ocular syphilis:

- Administer aqueous crystalline penicillin G 18-24 million units per day, 3-4 million units IV every four hours or continuous infusion, for 10-14 days.
- For more details on treatment of syphilis see the [CDC MMWR; Sexually Transmitted Diseases Treatment Guidelines, 2015](http://www.cdc.gov/std/tg2015/clinical.htm) (<http://www.cdc.gov/std/tg2015/clinical.htm>), pages 36-44.

Follow-up

- Persons with primary and secondary syphilis should have both clinical and serologic evaluation at 6 and 12 months after treatment.
- Persons with HIV infection should have both clinical and serological evaluation for treatment failure at 3, 6, 9, 12, and 24 months.
- Persons with latent syphilis should have quantitative nontreponemal serologic tests repeated at 6, 12, and 24 months. CSF examination should be performed if serology fails to indicate response to treatment.
- For more details on Follow up, see the [CDC MMWR; Sexually Transmitted Diseases Treatment Guidelines, 2015](http://www.cdc.gov/std/tg2015/clinical.htm) (<http://www.cdc.gov/std/tg2015/clinical.htm>), pages 37-44.

Management of Partners

All persons who have had sexual contact with persons with primary, secondary or latent syphilis should be examined clinically and serologically, and receive treatment based on:

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 the 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 necessary. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and stage of syphilis.

Under Minnesota state law, physicians, health care facilities, and medical laboratories are required to report all laboratory-confirmed cases of syphilis to the Minnesota Department of Health (MDH) [Minnesota Rules, part 4605.7030-7040]. MDH will make every attempt to contact the patient and to obtain partner information for follow-up.

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.

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