

Syphilis Treatment Protocol

CLINICAL GUIDANCE FOR PRIMARY, SECONDARY, 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:

- 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 people
- Men who have sex with men
- Sexual partners of men who have sex with men
- People 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
 - Early in third trimester (28-32 weeks' gestation)
- 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.
- 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 described above.
 - Any woman delivering a stillborn at 20 weeks gestation or later should be tested for syphilis at the time of delivery.
 - 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:

Two types of serologic tests are required to diagnosis syphilis, nontreponemal and treponemal. Use of only one type is insufficient since when used alone, each type of tests has major limitations.

- Nontreponemal tests:
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 people, nontreponemal antibodies can persist for a long period of time, a response referred to as the “serofast reaction”
- Treponemal tests:
Fluorescent Treponemal Antibody Absorption (FTA-ABS), Treponemal Pallidum Particle

Agglutination Assay (TT-PA), Enzyme Immunoassay (EIA), chemiluminescence immunoassays (CIA), or Microbead Immunoassay (MIA)

- People with a reactive nontreponemal test should always receive a treponemal test to confirm the diagnosis of syphilis.
- People 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.
- Standard (traditional) screening algorithm: Initial screening with a nontreponemal test (VDRL, RPR, or USR), with further testing of positive samples by a treponemal test (TT-PA or FTA_ABS)
- Reverse sequence screening algorithm: Starts with a treponemal test (EIA or CIA) with further testing of positive samples by a nontreponemal test. If there are discordant results with EIA or CIA being positive and the nontreponemal test being negative, then a second type of treponemal test (TP-PA) must be performed.
- In people 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:

- Lumbar puncture should be performed for people with clinical signs or symptoms of ocular, otic, or neurosyphilis (e.g., cognitive dysfunction, motor or sensory deficits, auditory symptoms, cranial nerve palsies, symptoms or signs of meningitis or stroke, new visual changes, uveitis, iritis, neuroretinitis, or optic neuritis) people diagnosed with tertiary syphilis, neonates (<30 days old) being evaluated for congenital syphilis, and infants >30 days old or children diagnosed with latent syphilis.
- CSF testing is helpful in supporting the diagnosis of infection involving the brain or spinal cord, 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 people with early syphilis and are of unknown significance in the absence of neurologic signs.
- CSF-VDRL is highly specific but insensitive

- People 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 Sexually Transmitted Diseases Treatment Guidelines, 2015 (<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 people 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.
- Do 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 people 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 people 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 people 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 the Clinical Guidelines for Syphilis: guidance for syphilis during pregnancy and congenital syphilis, including infants and children (<https://www.health.state.mn.us/syphilis/hcp/clinicalguidepc.pdf>)
- HIV Infected People
People with HIV infection with latent syphilis should be treated as people 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>), pages 36-44.

Follow-up

- People with primary and secondary syphilis should have both clinical and serologic evaluation at 6 and 12 months after treatment.
- People with HIV infection should have both clinical and serological evaluation for treatment failure at 3, 6, 9, 12, and 24 months.
- People 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>), pages 37-44.

Management of Partners

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

SYPHILIS TREATMENT PROTOCOL

People 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.

People 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 people who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation's findings.

Additional information on syphilis epidemiology, diagnosis, screening, treatment, and patient education can be found at the National STD Curriculum (<https://www.std.uw.edu/>), a free continuing medical education resource.

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

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