CLINICAL GUIDANCE AND RECOMMENDATIONS FOR SYPHILIS TREATMENT

BACKGROUND

Syphilis is a chronic sexually transmitted disease caused by the bacterium Treponema pallidum. It is transmitted from person to person through abrasions in the skin and mucous membranes during sexual contact with a syphilitic chancre, but can also be transmitted in utero from mother to fetus during pregnancy. Syphilis is divided into four stages: primary, secondary, latent, and 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. Many people infected with syphilis may not develop any symptoms, yet remain at risk for late complications if they are not treated.

STAGES AND SYMPTOMS

PRIMARY SYPHILIS:

- Painless ulcer(s) or chancre(s) at the infection site
- Lesion(s) are usually firm, round, and painless
- Appear 10-90 days, average of 21 days, after exposure to syphilis
- Lesion(s) may persist for 1-6 weeks then resolve (with or without treatment)

SECONDARY SYPHILIS:

- Rash often on the palms of hands, bottom of feet, on the torso or other sites, usually non-itchy
- Mucus membrane patches in the mouth, vagina, or anus
- Flat wart-like growths, condylomata lata, in the perianal/genital areas and other moist body sites
- Generalized lymphadenopathy, sore throat
- Alopecia (patchy hair loss)
- Constitutional symptoms (headaches, fatigue, fever, chills, muscle aches, weight loss)

Onset of secondary symptoms usually occurs 6 weeks to 6 months after onset of lesion or chancre (can overlap with primary stage) and resolves in 2-10 weeks. About 25% may have relapses of secondary symptoms usually within the first year of infection. Serologic tests for syphilis antibodies are usually highest in titer during this stage.

LATENT AND LATE LATENT SYPHILIS:

- Characterized by positive serologic test for syphilis without other evidence of primary, secondary, or tertiary disease (no clinical manifestations)
- Latent syphilis acquired within the past 12 months is considered early latent syphilis. Criteria for early latent syphilis include: a negative test or fourfold or greater increase in nontreponemal test titer in the past year, documented exposure to primary, secondary, or early syphilis in the past year, or symptoms of primary or secondary syphilis that have resolved in the past year
- Latent syphilis acquired more than 1 year ago or of unknown duration is classified as late latent syphilis. Majority of people with late latent syphilis may be asymptomatic for many years.

TERTIARY SYPHILIS:

- Defined as symptomatic late latent syphilis, gummatous, or cardiovascular syphilis
- Onset 2 – 40 years after infection
- Damage to the heart, blood vessels, liver, bones, and joints can occur
- Gummatous, soft noncancerous lesions, may occur in soft tissue and viscera

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 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
- Homelessness
- History of incarceration
- History of or current IV drug use

ROUTINE SYPHILIS SCREENING RECOMMENDED FOR:

- At least annually for sexually active men who have sex with men (MSM); and every 3-6 months if at increased risk
- Persons with HIV at initial evaluation and at least annually thereafter; 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, at 28-32 weeks gestation, and at delivery if high risk
- Any woman who has a fetal death after 20 weeks gestation should be tested for syphilis

TREATMENT OF SYPHILIS

- Penicillin G (generic name) IM or IV is the preferred drug for treating all stages of syphilis. The preparation used, 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.

PRIMARY, SECONDARY, AND EARLY LATENT SYPHILIS TREATMENT FOR ADULTS

- Administer benzathine penicillin G (Bicillin L-A) 2.4 million units IM in a single dose
- For persons who are allergic to penicillin, 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 GI 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 with penicillin or doxycycline is not feasible. Treatment failures with azithromycin have been documented
- Clinical and serologic evaluation (i.e., RPR w/ reflex to titer) should be performed at 6 and 12 months after treatment to assess treatment response. For HIV infected persons, clinical and serologic follow-up are recommended at 3, 6, 9, 12, and 24 months.
- Test all persons who have primary and secondary syphilis for HIV
- Evaluate anyone with neurological signs and symptoms for neurosyphilis
- Persons with HIV infection who have primary or secondary syphilis should be treated as those without HIV infection

LATE LATENT SYPHILIS OR LATENT SYPHILIS OF UNKNOWN DURATION TREATMENT FOR ADULTS

- 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 persons who are allergic to penicillin, administer regimens of:
    - Doxycycline 100 mg orally twice daily for 28 days or
    - Tetracycline 500 mg orally four times daily for 28 days
- Interval of 10-14 days between doses may be acceptable before restarting sequence of injections in non-pregnant persons with latent syphilis; however, pharmacologic considerations suggest an interval of 7-9 days between doses might be more optimal
- Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months. Persons with HIV and latent syphilis should have clinical and serologic evaluations at 6, 12, 18, and 24 months after treatment.
- Test all persons who have latent syphilis for HIV
- Evaluate anyone with neurological signs and symptoms for neurosyphilis

TERTIARY SYPHILIS TREATMENT FOR ADULTS

- All persons with tertiary syphilis should be tested for HIV and receive a CSF examination before treatment is initiate
- Tertiary syphilis with normal CSF examination:
    - 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

NEUROSYPHILIS AND OCULAR SYPHILIS TREATMENT FOR ADULTS

- Administer aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units IV every 4 hours or continuous infusion, for 10-14 days
- If compliance with therapy can be assured, the following alternative regimen might be considered: Procaine penicillin G 2.4 million units IM once daily PLUS Probenecid 500 mg orally four times a day, both for 10-14 days
- If CSF pleocytosis was present initially, CSF exam should be repeated every 6 months until cell count is normal
- Persons with HIV infection and neurosyphilis should be managed the same as HIV-negative persons with neurosyphilis
- All persons with neurosyphilis should be tested for HIV

TREATMENT OF SYPHILIS DURING PREGNANCY

- Penicillin G IM or IV is the **only** treatment with documented efficacy for syphilis during pregnancy. Treat with penicillin according to stage of infection.
- Pregnant women in any stage of syphilis who report penicillin allergy should be desensitized and treated with penicillin.
- Some evidence suggests a second dose of benzathine penicillin G 2.4 million units IM one week after the initial dose for pregnant women with primary, secondary, or early latent syphilis is beneficial and can be administered.
- Pregnant women with late latent or latent unknown syphilis must adhere to the recommended treatment schedule of exactly 7 days between injections. Missed doses are not acceptable. Pregnant women who miss any dose of therapy should repeat the full course of treatment.
- Pregnant women treated during second half of pregnancy are at risk for premature labor and/or fetal distress if treatment precipitates the Jarisch-Herxheimer reaction. Counsel to seek OB attention after treatment for any signs or symptoms of fever, contractions, or decrease in fetal movement

PRESUMPTIVE TREATMENT RECOMMENDED FOR:

- Defined as a one-time treatment given for a presumed infection in a person, or a group of people, at high risk of infection

- 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, even if 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 preceding the diagnosis if serologic test results are not immediately available and opportunity for follow-up is uncertain

- **When the opportunity for follow up is uncertain, persons in high risk populations (see risk factors above) who exhibit clinical findings suggestive of primary or secondary syphilis, even if syphilis test results are negative or not immediately available. This local recommendation is based on Butte County epidemiologic syphilis data and trends from 2015-present.**

REFERENCES:

- Screening Recommendations and Considerations Referenced in Treatment Guidelines and Original Sources: https://www.cdc.gov/std/tg2015/screening-recommendations.htm
- Centers for Disease Control and Prevention MMWR: Sexually Transmitted Diseases Treatment Guidelines, 2015 / June 5, 2015 / Vol. 64 / No. 3: https://www.cdc.gov/std/tg2015/tg-2015-print.pdf
- Periodic Presumptive Treatment for Sexually Transmitted Infections: Experiences from the Field and Recommendations for Research: http://apps.who.int/iris/bitstream/10665/43950/1/9789241597050_eng.pdf
- The Use of Epidemiologic Mass Treatment and Syndrome Management for Sexually Transmitted Disease Control: http://journals.lww.com/stdjournal/Fulltext/1999/04001/The_Use_of_Epidemiologic_Mass_Treatment_and.4.aspx