National
Family Planning
& Reproductive Health Association

CLINICAL PROTOCOL TEMPLATE

SYPHILIS SCREENING, DIAGNOSIS & TREATMENT

This template protocol is intended to assist family planning providers in developing local protocols for screening, diagnosis, and treatment of syphilis.

A clinical protocol is a site-specific policy for the provision of high-quality health care to patients. It clarifies the scope of care that can be provided by clinicians and care team members, consistent with state regulations. Clinical protocols from one organization should never be adopted intact by another organization without first revising them, since these protocols will not include an accurate description of the adopting organization's policies and procedures, nor will they account for other organizational considerations.

Refer to the National Family Planning & Reproductive Health Association's (NFPRHA's) resource, **Developing Clinical Protocols for Family Planning Services,** for more information on clinical protocols, including best practices for development.

CLINICAL PROTOCOL TEMPLATE

HOW TO USE A TEMPLATE PROTOCOL

Each NFPRHA sample template protocol is written with the understanding that several decision points must be addressed by an organization before the protocol is ready for use. When an organization decides to use a template protocol, the author should tailor the contents to their own organization and create a draft local protocol. It is recommended that, before organization-wide implementation, a draft of the new or updated local protocol be reviewed and tested by clinical staff to allow them to weigh in on accuracy, completeness, and usability.

REVIEW DECISION POINTS

Decision points are listed in **[blue]** throughout the template document. It is encouraged that those using the template protocol as a starting point will include the appropriate option that reflects their organization's current practices. If the organization has policies, procedures, or practices that are not listed as an option **[in blue]**, they should be inserted into (or retained) in the draft local protocol. When formatting the draft local protocol, the options in the template protocol that do not apply to the organization should not be included.

TEST WITH CLINICIANS

Once a draft local protocol is developed, following a template protocol as a guide, the draft document should be reviewed and edited by select clinicians who ultimately will provide care to patients under the guidance of the final version of the organization's local protocol. Not only will this serve as a "reality test" of whether the draft local protocol accurately reflects what currently is practiced within the organization, it will offer clinicians an opportunity to provide feedback regarding new policies and procedures that may have been included in the draft local protocol. In this way, it is much more likely that all clinicians will have a sense of "buy-in" to the new local protocol once implemented.

CLINICAL PROTOCOL TEMPLATE

INTEGRATING SYPHILIS TESTING, DIAGNOSIS & TREATMENT INTO FAMILY PLANNING SETTINGS

Since 2010, there has been a significant increase in the number of people of reproductive age diagnosed with primary and secondary syphilis, and a corresponding increase in reports of congenital syphilis in newborns. There are substantial inequities in syphilis rates by race and ethnicity, reflecting disparities in access to family planning and sexual health care and persistent and systemic racism in health care.

All providers can contribute to reducing the spread of syphilis in their service areas by completing the following activities:

- Check county-specific primary and secondary syphilis rates using the **US Centers for Disease Control and Prevention (CDC) AtlasPlus** map tool and determine whether your health center or system is located in a syphilis "hot spot" area.
    - If so, collaborate with health department and other public health agencies to address ways to improve screening, diagnosis, management, reporting, partner management, and (as indicated) referral of patients in need of expert consultation or care as listed in this protocol.
- Request from your contracted clinical lab(s) a two-year testing syphilis positivity rate, ideally broken down by 5-year age intervals. In addition to data from the CDC AtlasPlus map tool, this data may help guide policies regarding whether to perform routine or targeted syphilis screening by age group (e.g., routine screening among sexually active people aged 15-44 years).
- Provide in-service training to clinicians regarding:
    - **US Preventive Services Task Force (USPSTF) syphilis screening guidelines (PDF)**;
    - **CDC Sexually Transmitted Disease (STI) Treatment Guidelines, 2021**;
    - State and local public health policies regarding screening, diagnosis, and management of syphilis.
    - Updates to clinic/system protocols; and
    - Identification of specific clinician consultants to whom patients will be referred, as indicated.
- Offer immediate treatment for people diagnosed with syphilis.
    - If treatment cannot be offered onsite, have established referral pathways for expedited treatment and follow-up.

INTRODUCTION

[Name of health center or system] offers screening, diagnosis, [treatment of syphilis in females, males, and nonbinary individuals] and [treatment of sexual partners]. This protocol does not include guidance related to the diagnosis and management of tertiary syphilis or neurosyphilis; patients suspected of having either of these conditions should be referred to an expert in the management of these infections. [If your health center or system manages these patients, explain management here. If not, list where patients should be referred internally or in the community.] Screening and treatment of syphilis in pregnant people is addressed in the Appendix, as many family planning health centers do not provide care to pregnant patients. [If your health center or system offers antenatal care, you should integrate relevant information contained in the Appendix into your local protocol, as well as information about where to refer patients deemed to have high-risk pregnancies]

The term "people" refers to individuals assigned female at birth, individuals assigned male at birth, and individuals whose gender identity does not align with the sex, gender, and/or gender roles they were assigned at birth. When a national guideline is quoted directly, the original terms of woman/women, man/men, female, and male are used.

WHAT IS SYPHILIS?

Syphilis is a systemic disease caused by the spirochete *Treponema pallidum (T. pallidum)*. The disease is divided into five stages based on clinical findings, which guide treatment and follow-up, including incubating, primary, secondary, latent, and tertiary syphilis. People with asymptomatic syphilis include those with incubating syphilis (before the signs of primary syphilis are present) and latent syphilis. Latent infection acquired within the preceding year is referred to as early latent syphilis and all other cases are late latent syphilis or syphilis of unknown duration. Latent infections are detected by serologic screening.

Symptomatic presentations include primary syphilis [e.g., chancre(s) at the infection site], secondary syphilis (e.g., skin rash, mucocutaneous lesions, and lymphadenopathy), or tertiary syphilis (e.g., cardiac, hematologic, and skin manifestations). Neurosyphilis can occur at any stage of syphilis.

Screening for syphilis in high-risk populations is a crucial public health strategy for preventing the sexual transmission of syphilis and preventing congenital syphilis, which

occurs when syphilis is transmitted from a pregnant person to the fetus. Syphilis infection also increases the risk of acquiring or transmitting HIV infection.

SCREENING FOR SYPHILIS

The USPSTF has a **Grade A recommendation** for screening of asymptomatic, nonpregnant adults, and adolescents who are at increased risk for syphilis infection.[1]

Individuals at increased risk for syphilis include:

- MSM (men having sex with men), MSMW (i.e., a man who has sex with men and women), and transgender women: screen annually; more frequently if at increased risk.
- Males younger than 29 years of age
- Recent incarceration or a sex partner who was recently incarcerated
- Having transactional or survival sex in exchange for housing, money, or drugs
- Individuals who use illicit drugs, particularly methamphetamine
- Individuals who are experiencing homelessness or who have unstable housing
- Individuals with a history of military service
- Sex partners who are MSMW or who have other concurrent partners
- Individuals with a prior history of syphilis infection
- Diagnosis of another STI within the past 12 months, as this may signal that the person is having condomless sex.
- Persons living with HIV (all genders): screen annually; more frequently if at increased risk.
- Persons using HIV PrEP (all genders): screen every 3 months.
- Certain racial/ethnic groups (Black, Hispanic, Native American/Alaska Native, and Native Hawaiian/Pacific), primarily a reflection of social determinants of health.
- Regional variations (hot spots), which may change over time.
    - Living in a local health jurisdiction with high syphilis rates, including a local health jurisdiction with high-congenital syphilis rates
    - The CDC AtlasPlus map tool tracks syphilis prevalence by US county. It can be found at: **https://www.cdc.gov/nchhstp/atlas/syphilis/index.html.**
    - The CDC recommends offering syphilis screening to all sexually active people aged 15-44 years in counties with a rate of primary and secondary syphilis among women aged 15-44 years that is greater than 4.6 per 100,000 people.

In addition, providers have a unique role in offering syphilis screening to people who are intending to become pregnant. Offer syphilis screening as a component of pre-pregnancy care to patients who:

- Are seen for advice about achieving pregnancy or for basic infertility services;
- Request removal of an intrauterine device (IUD) or contraceptive implant in order to become pregnant;
- Request pregnancy testing (whether positive or negative); and/or
- Disclose during reproductive intentions counseling that they would like to become pregnant immediately or in the next 12 months, or those who are ambivalent or indifferent to becoming pregnant.

CONSULTATION/REFERRAL

[Your health center or system's indications for internal or external consultation with physician or a senior clinician should be listed here. Enter who this specialist is (e.g., obstetrician, infectious disease physician), how to refer a patient to them, and an acceptable time frame to complete the consultation and referral process.]

- Immediately refer pregnant patients who may or will continue their pregnancy to a prenatal care provider. The provider to whom the patient will be transferred must be contacted so that the patient's visit for evaluation and treatment can be expedited.
    - In some locations and circumstances, prompt transfer of care for pregnancy services, including the treatment of syphilis, is not possible. In this case, treat the pregnant client with benzathine penicillin and transmit this information to their presumed prenatal care provider. See **Appendix** for content that can be entered into your local protocol.
- Perform penicillin-allergy skin testing and desensitization, as necessary for some individuals with penicillin allergy, especially if pregnant. Benzathine penicillin is the only recommended treatment for syphilis in pregnancy.
- If there are signs or symptoms of neurologic, otologic or ophthalmic disease, refer to an infectious disease specialist or to the local emergency department for immediate evaluation.
- For lumbar puncture and cerebrospinal fluid (CSF) exam, as indicated in current **CDC STI Treatment Guidelines**.

- All primary and secondary syphilis cases should be referred to the local health department's Communicable Disease Specialist or Disease Intervention Specialist for further counseling and sex partner referral.

DIAGNOSING SYPHILIS

	Primary Syphilis	Secondary Syphilis

Subjective (Symptoms)	• Complaint of painless open sore at a site of sexual exposure (mouth, anus, genitals).
	• Localized, non-tender swollen lymph glands.
		• Constitutional: fever, fatigue, malaise.
		• Dermatologic:
		  ○ Rash on the body and/or extremities.
		  ○ Wart-like growths/lesions in the anogenital region.
		  ○ Hair falling out.
		  ○ White patches inside the mouth or on the tongue.
		• Hematologic/Lymphatic: swollen glands.
		• Neurologic: headache, stiff neck.

	Primary Syphilis	Secondary Syphilis
Objective (Physical Findings)	• Chancre at a site of sexual exposure. A typical chancre is a single painless ulcer with an indurated border and relatively smooth base. However, primary syphilis occasionally may present with multiple and/or painful chancres. • In females, chancres can occur on the outer genitals: vulva, perineum, or anus, as well as inside the vaginal or anal canal. • In males, chancres usually occur on the penis, underneath the foreskin in uncircumcised males, the scrotum, on the anus, or inside the anal canal. • In both females and males, chancres can appear within the mouth, on the tongue, or on the lip, and can also occur on the fingers. • Localized, firm non-tender lymphadenopathy (enlarged lymph nodes).	• Condyloma lata: large moist circular wart-like papules on anogenital skin. • Bilaterally symmetrical macular or papular, nonpruritic rash on body or extremities. May be present only on the palms and soles, or on the scrotum. • Patchy alopecia (hair loss) on scalp, eyebrows, or eyelashes. • Mucous patches in the mouth or on the cervix. • Generalized non-tender lymphadenopathy. • Fever, malaise.

DIAGNOSING SYPHILIS

	Point of Care Lab Tests	Clinical Lab Tests
Objective (Lab Testing) **NOTES:** Testing for other STIs, including HIV, should be recommended in persons infected with syphilis. When is person is found to have syphilis, the case must be reported to your local or state health department. **[Insert information in this section** about STI public health surveillance reporting procedures in your jurisdiction}	• Darkfield microscopy [The special microscopes used for darkfield evaluation are available only in some specialized STI clinics, public health departments, and a few emergency departments. Do not list this test unless it is available in your health center or system. If so, describe where it is located, how to use it, and who is authorized to perform this evaluation.] • Rapid serology test [Syphilis Health Check (SHC)] or [DPP® HIV-Syphilis Rapid Test] [The POC tests are performed on fingerstick whole blood and detects treponemal antibodies only. It cannot distinguish between old syphilis and recent infection; it should not be used in patients with a known history of syphilis. These tests are CLIA-waived and have a 10-15-minute turn-around time, depending on the test product. If positive, additional testing must be performed at a clinical laboratory to obtain treponemal (e.g., TP-PA, treponemal EIA) and nontreponemal test results (e.g., RPR). Testing can be performed with either the traditional or reverse sequence screening algorithm (see next column).	[There are two widely available algorithms used for serologic testing for syphilis. In this section, describe only the algorithm used by the lab(s) that your health center or system contracts with. If some contracted labs use one approach and others use a different algorithm, list both and differentiate here.] • The **traditional screening algorithm**: An initial nontreponemal test VDRL or RPR followed by a confirmatory treponemal antibody detection test [fluorescent treponemal antibody absorbed (FTA-ABS) test, or chemoluminescence immunoassays (CIA) or enzyme immunoassays (EIA); or T. pallidum particle agglutination (TP-PA) test]. ○ If the confirmatory test is reactive, the patient has a new (or old) syphilis infection. If non-reactive, syphilis is unlikely and the initial nontreponemal test may be a biologic false positive. • The **reverse sequence screening algorithm:** A treponemal test, [chemoluminescence immunoassays (CIA) or enzyme immunoassays (EIA)] is performed first, followed by a nontreponemal test. If the test results are discordant [e.g., enzyme immunoassay (EIA) -reactive, RPR-nonreactive], a second treponemal test (using a different treponemal antigen such as TP-PA) is performed. ○ If the second treponemal test is positive, a new or old syphilis infection is diagnosed. If negative, the initial test probably was a false positive. However, if the client is at high risk for syphilis, repeat a treponemal test in 2-4 weeks, followed by a non-treponemal test if the treponemal test is positive.

DIAGNOSING SYPHILIS

	Primary Syphilis (chancre or ulcer)	Secondary Syphilis	Latent Syphilis	Patients with HIV
Assessment **NOTE: Neurosyphilis can occur at any stage of syphilis and should be suspected in patients who report any neurologic symptoms**, including visual changes, vision loss**, hearing loss,** tinnitus (**ringing in the ears**), cognitive dysfunction, motor or sensory deficits, cranial nerve palsies, or symptoms or signs of meningitis or stroke	Any of: • A chancre or ulcer AND a reactive serology using the traditional algorithm (RPR/VDRL reactive and FTA-ABS/TPPA reactive) or reverse sequence algorithm [e.g., EIA/CIA-reactive, VDRL or RPR reactive]. • A four-fold or greater increase over the last known RPR or VDRL titer in a person with a history of syphilis. • A chancre or ulcer AND exposure to a known case of early syphilis in previous 10-90 days. • Identification of *T. pallidum* on darkfield microscopic exam of serum from a chancre.	• Signs of secondary syphilis and any of: • Identification of *T. pallidum* on darkfield microscopic exam of lesion material. • Typical signs (e.g., rash, mucous patches) AND a newly reactive RPR confirmed by a treponemal test. • A four-fold increase over the last known titer in a person with a previous history of syphilis. • Typical dermatologic signs AND exposure to a known case of early syphilis in the past six months.	**Early Latent Syphilis** No clinical symptoms or signs AND a reactive RPR and confirmatory tests AND has had, in the past year: ○ A nonreactive serologic test OR ○ A four-fold titer increase on serial RPR tests OR ○ Symptoms consistent with primary or secondary syphilis OR ○ Sexual exposure to a known case of primary, secondary, or early latent syphilis. **Late Latent Syphilis** No clinical symptoms or signs AND reactive RPR and confirmatory tests AND the criteria for having acquired the infection within the preceding 12 months (see early latent syphilis above) are not met. **Latent Syphilis of Unknown Duration** No clinical symptoms or signs AND reactive RPR and confirmatory tests AND the criteria for early latent syphilis (see above) are not met.	• While abnormal serologic findings (unusually high, unusually low, and fluctuating titers) have been observed in HIV-infected persons who also have syphilis, both treponemal and non-treponemal serologic tests can be interpreted in the usual manner for most co-infected patients. • Neurosyphilis should be considered in persons with HIV patients with neurologic symptoms.

NOTE: Differentiating new from old infection can be difficult. For cases when a person has a *prior* history of syphilis now tests positive:

- If previously untreated: stage and treat.
- If treated and the titer stable or decreasing, no further action.
- If treated and four-fold or greater increase of titer: assess for re-infection or treatment failure.

TREATMENT OF SYPHILIS

	Primary and Secondary Syphilis (including persons with HIV Infection)	Early Latent Syphilis	Late Latent Syphilis or Latent Syphilis of Unknown Duration	Persons with penicillin allergy or benzathine penicillin not available
Plan (Pharmacologic Treatment) **NOTE:** Parenteral penicillin G is the *only therapy* with documented efficacy during pregnancy. Pregnant patients should be referred or treated on-site (see **Appendix**)	• Benzathine penicillin G 2.4 million units IM in a single dose. **NOTE:** Bicillin LA comes in 2 mL (1.2 mU) and 4 mL (2.4 mU) syringes. The 2 mL dose requires *two* syringes per treatment. • **Alternatives** - Doxycycline 100 mg orally twice a day for 14 days - Tetracycline 500 mg orally 4 times a day for 14 days - Ceftriaxone 1 gm IV or IM daily for 10 days **NOTE:** Persons with a typical ulcer, newly reactive serology (i.e., VDRL or RPR, EIA/CIA, or rapid treponemal test), a newly reactive VDRL or RPR, and no history of previous syphilis may be treated for primary syphilis prior to receiving results of confirmatory testing.	• Benzathine penicillin G 2.4 million units IM in a single dose. • **Alternatives** - Doxycycline 100 orally twice a day for 14 days - Tetracycline 500 orally 4 times a day for 14 days - Ceftriaxone 1 gm IV or IM daily for 10 days	• Benzathine penicillin G 7.2 million units total administered as 3 doses of 2.4 million units IM each at 1-week intervals. • **Alternatives** - Doxycycline 100 mg orally twice a day for 28 days - Tetracycline 500 orally 4 times a day for 28 days	**Primary and Secondary Syphilis**: • Doxycycline 100 mg orally twice daily for 14 days **Latent Syphilis:** • Doxycycline 100 mg orally twice daily for 28 days **NOTE:** If compliance with therapy or follow-up cannot be ensured, desensitization and treatment with benzathine penicillin is recommended by CDC. Treatment should be performed in consultation with an infectious disease specialist. Careful clinical and serologic follow-up of persons receiving any alternative therapies is essential.

NOTE: There have been shortages of Benzathine penicillin G (Bicillin® L-A) in the US. Several organizations have published guidelines about responding to limited supplies by prioritizing who must receive Bicillin and advising that all others receive alternative regimens. Please check with your state health department's guidance on prioritization. If none, the California Department of Public Health (CDPH) STD Control Branch[3] recommends the following prioritization categories:

TREATMENT OF SYPHILIS

- *Pregnant* people with syphilis infection (or exposure) as well as infants exposed to syphilis in utero.
- Patients with contraindications to doxycycline (e.g., anaphylaxis, hemolytic anemia, Stevens Johnson syndrome) or those who are unwilling or unable to use an extended 14–28-day course of doxycycline or tetracycline.
- Conserve Bicillin® L-A by using alternative drugs for the treatment of infectious diseases (e.g., streptococcal pharyngitis) where oral medications or other effective antimicrobials are available.
- Contact your local health department if you are experiencing a Bicillin® L-A shortage and/or having trouble obtaining the medication.
- If you are experiencing difficulty in obtaining an adequate supply of benzathine penicillin, the US Food & Drug Administration (FDA) has temporarily approved an alternative source from Europe, powdered Benzathine Benzylpenicillin (Extencilline®). More information on the use of this medication, including ordering advice can be found at: https://www.cdc.gov/nchhstp/dear_colleague/2024/dcl-01122024-fda-bicillin.html.

PARTNER MANAGEMENT

	Patients with Primary Syphilis	Patients with Secondary Syphilis	Patients with Early Latent Syphilis
Plan **(Partner Notification)** The following sex partners of patients with early syphilis should be confidentially notified of their exposure and need for evaluation. [Note in your local protocol whether partner notification could be performed by your local health department, and, if so, how to refer cases]	• Partners within the past 3 months, plus duration of symptoms.	• Partners within the past 6 months, plus duration of symptoms.	• Partners within the last year.

	Contacts to Persons with Early Syphilis: Primary, Secondary, and Early Latent Syphilis	Partners Who Were Exposed >3 Months Before the Diagnosis	Contacts to Late Latent Syphilis or Latent Syphilis of Unknown Duration
Plan **(Management of Sex Partners)**	• Examine, test, and treat all partners exposed within 3 months of preceding the diagnosis, regardless of examination and serologic test results.	• Treat 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 needed. • If serologic tests are positive, treatment should be based on clinical and serologic evaluation and stage of syphilis.	• Evaluate steady (including marital) sex partners. No treatment is needed unless the partner is shown to be infected. • Children born to an infected female within the past few years should also be evaluated.

PATIENT EDUCATION, COUNSELING, AND FOLLOW-UP CHECKLISTS

Patient Education/Counseling

- ☐ People with syphilis should abstain from sex until seven days after benzathine penicillin treatment.
- ☐ Explain the significance of having syphilis and the importance of both partners completing treatment to prevent reinfection or infection of others.
- ☐ Clarify the fact that the patient's infection could have been introduced by any current or past sexual partner and may have been acquired years ago (in the case of late latent syphilis or syphilis of unknown duration).
- ☐ Explain the need for examination and treatment of sex partners and avoidance of sex with untreated partners.
- ☐ Clarify the need for, and schedule, follow-up blood tests to ensure that the infection is cured.
- ☐ Instruct patient to return for reevaluation if symptoms persist.
- ☐ Inform the patient of the possibility of a Jarisch-Herxheimer reaction and what to do if this reaction occurs. The Jarisch-Herxheimer reaction is an acute febrile reaction due to release of bacterial-endotoxin like products following death of *T. pallidum* organisms after treatment. It may be accompanied by headache, myalgia, fever, or tachycardia. Patients should be counseled that the Jarisch-Herxheimer reaction does not reflect an allergic reaction to penicillin or other antibiotics. Non-steroidal anti-inflammatory drugs (NSAIDs) may be used to manage symptoms but are not known to prevent this reaction. The Jarisch-Herxheimer reaction may induce early labor or cause fetal distress. If pregnant, advise patients to seek medical care immediately if notice a change in fetal movement or uterine contractions.
- ☐ Discuss the best way to prevent future episodes of syphilis is for people who are sexually active, to consistently and correctly use of condoms during all vaginal, genital, or oral sexual encounters.
- ☐ Assist patients in developing a personalized STI/HIV risk reduction plan.

PATIENT EDUCATION, COUNSELING, AND FOLLOW-UP CHECKLISTS

Follow-up: Primary and Secondary Syphilis

- Schedule a routine appointment for a clinical evaluation and repeat RPR or VDRL in six months, and then at 12 months. Consider more frequent evaluation (e.g., every three months) if follow-up is uncertain or repeat infection is a concern.
  - In persons with HIV, monitor RPR or VDRL titers at 3-month intervals for a year, and then at 24 months.

- Clinical and RPR titer response should be appropriate for the stage of disease. RPR titers may decline more slowly for patients who previously had syphilis.
  - If signs or symptoms persist or recur, or if a sustained fourfold increase in titer compared to the baseline or maximum titer occurs, the patient probably failed treatment or was re-infected. The patient should be re-treated and reevaluated for HIV infection and/or re-exposure.
  - Among patients with no recent sexual exposure or who have neurologic signs/symptoms, CSF analysis should be performed; treatment should be guided CSF findings. Among patients with recent sexual exposure, repeat treatment for early syphilis is recommended. If titers have not declined fourfold by 12 months, the patient should be reevaluated for HIV infection. If further clinical and serologic follow-up cannot be assured, re-treatment should be given.
  - In either instance above, re-treatment should consist of three weekly doses of benzathine penicillin 2.4 million units IM, unless the patient reports neurologic symptoms, including vision or hearing loss. Those patients should promptly be referred for evaluation to a specialist.

PATIENT EDUCATION, COUNSELING, AND FOLLOW-UP CHECKLISTS

Follow-up: Latent Syphilis

- Repeat RPR at six, 12, and 24 months.
  - If titers increase fourfold, if an initially high titer (at least 1:32) fails to decline at least fourfold within 24 months, or if the patient develops signs or symptoms attributable to syphilis, they should be retreated and reevaluated for HIV infection.
  - Among patients with recent sexual exposure and no signs or symptoms, repeat treatment for latent syphilis is recommended.
  - Among patients with no recent sexual exposure or who have developed neurologic signs/symptoms, CSF analysis should be performed; patients with CSF abnormalities should be treated for neurosyphilis.
  - If the RPR is nonreactive, rescreen at regular intervals according to risk status.

- If the patient has HIV, repeat RPR at six, 12, 18, and 24 months.
  - Patients with at least a four-fold increase in nontreponemal test titer persisting for more than two weeks likely experienced treatment failure or were re-infected.
  - Among patients with recent sexual exposure and no signs or symptoms, repeat treatment for latent syphilis is recommended.
  - Among patients with no recent sexual exposure or who have developed neurologic signs/symptoms, CSF analysis should be performed; patients with CSF abnormalities should be treated for neurosyphilis. If signs or symptoms of syphilis recur, if signs or symptoms of neurosyphilis develop, or if titers rise fourfold, refer patient for CSF exam and re-treat accordingly.

PREVENTION OF SYPHILIS

Given that horizontal transmission of syphilis occurs via contact with the blood, bodily fluids, or open chancre of an infected person, the same risk reduction advice given for other STIs applies to syphilis. In particular, patients should be advised to practice safer sex based on:

- Using external (penile) or internal (vaginal) condoms
- Using rubber dental dams for receptive oral sex
- Limiting the number of sexual partners
- Abstinence from oral, vaginal, and anal sex or participating in a long-term, mutually monogamous relationship with a partner known to be uninfected.
- Treatment of infected sexual partners (see page 9, above)
- For persons who are being treated for an STI (or whose partners are undergoing treatment), counseling that encourages abstinence from sexual intercourse until completion of the entire course of medication is vital for preventing reinfection.[2]

POST-EXPOSURE PROPHYLAXIS FOR SYPHILIS

STI post-exposure prophylaxis with doxycycline (Doxy-PEP) has been studied among MSM and transgender women. A randomized clinical trial performed the US used a single dose of doxycycline 200mg within 72 hours after condomless oral, anal, or insertive vaginal sex. Of the 501 participants who were people living with HIV, there were 74% and 77% reductions in incident chlamydia and syphilis, respectively, but only a 57% reduction in incident gonorrhea infections.[4] To address whether Doxy-PEP is effective in preventing these STIs in cisgender women, a randomized clinical trial in Kenya[5] with 449 cisgender women showed that Doxy-PEP was not protective. However, one follow-up study showed that many women in the treatment arm did not take the doxycycline as recommended, casting doubt on the validity of the findings in the original study. Of note, pharmacologic studies suggest that doxycycline levels in vaginal fluid should be sufficient to provide protection against these infections.[6]

Safety:[7] Taking doxycycline is safe and well tolerated, with no reported doxycycline associated Grade 2 or higher adverse events and no documented laboratory-related severe adverse events in the Doxy-PEP clinical trial. Long-term use of doxycycline has been prescribed safely for other medical indications (e.g., acne treatment, malaria prophylaxis).

Unknowns:[7] Data continue to be collected and reviewed for possible antimicrobial resistance among bacterial STIs, commensal *Neisseria*, and *Staphylococcus aureus*. The effects of Doxy-PEP on the gut microbiome among people with chronic illnesses, including diabetes, also are being studied.

PUBLISHED RECOMMENDATIONS

The CDC has not issued comprehensive guidelines on the topic of Doxy-PEP, but did publish proposed guidelines in October 2023, which state:[8]

1. Current efficacy data only applies to MSM and transgender women. Studies among other populations, including cisgender women, heterosexual cisgender men, transgender men, and other queer and nonbinary individuals, are ongoing.
2. Doxycycline 200 mg administered within 24-72 hours of condomless sex was the regimen evaluated in this study. Other antibiotics should not be considered for PEP.
3. In addition to informing MSM and transgender women patients about the potential STI prevention benefits of doxycycline as PEP, providers should also counsel about potential adverse side effects of doxycycline including phototoxicity, gastrointestinal symptoms, and, more rarely, esophageal ulceration.
4. Providers should continue to screen, test, and treat for bacterial STIs in accordance with the **CDC STI Treatment Guidelines** and the **CDC Pre-Exposure Prophylaxis for the Prevention of HIV (PDF)** clinical practice guideline, even among people who may be using doxycycline as PEP or pre-exposure prophylaxis (PrEP).

The California Department of Public Health (CDPH) is one example of a state agency that has broadened its Doxy-PEP guidelines to be more permissive than those of the CDC in response to the following factors: (1) studies of HIV PrEP show that is effective in a variety of individuals, including cisgender women and transgender men; (2) studies of doxycycline in vaginal secretions show levels that would be expected to be effective at inhibiting bacterial STIs; and (3) making DoxyPEP equally available to all who request it addresses a gender equity and health equity issue.

CDPH released the following recommendations on April 28, 2023:[7]

1. Recommend Doxy-PEP to MSM or transgender women who have had one or more bacterial STIs in the past 12 months.
2. Offer Doxy-PEP using shared decision-making to all non-pregnant individuals at increased risk for bacterial STIs and to those requesting Doxy-PEP, even if not previously diagnosed with an STI or have not disclosed their risk status.
3. Provide comprehensive preventive sexual health counseling and education to all sexually active individuals to include HIV/STI screening, Doxy-PEP, HIV PrEP, HIV PEP, vaccinations (e.g., Hepatitis A and B, HPV, Mpox), expedited partner therapy (EPT), and contraception when warranted.

PRESCRIBING DOXY-PEP

1. Prescribe 200 mg of doxycycline taken within 72 hours (ideally within 24 hours or as soon as possible) after condomless oral, anal, or vaginal sex. Doxycycline can be taken daily depending on sexual activity, but no more than 200 mg every 24 hours.
2. Screen for gonorrhea and chlamydia at all anatomic sites of exposure (urogenital, pharyngeal, and/or rectal), as well as test for syphilis and HIV (if not known as a person living with HIV) at initiation of Doxy-PEP and then every three months. If diagnosed with an STI, treat according to standard **CDC STI Treatment Guidelines**.
3. Counsel persons who can become pregnant that doxycycline should not be taken during pregnancy.[8] Rule-out pregnancy with a point-of-care pregnancy test as indicated by patient history.
4. Consider hematopoietic, renal, and hepatic laboratory monitoring, as clinically indicated, in addition to counseling patients on standard precautions and warnings while taking Doxy-PEP, as outlined in the drug package insert (e.g., sun sensitivity, pill esophagitis, rarely intracranial hypertension).

MONITORING WHILE TAKING DOXYCYCLINE

1. Per the doxycycline package insert, liver function tests (LFTs), renal function and a complete blood count (CBC) test should be checked periodically in patients taking doxycycline for a prolonged period. LFTs and CBCs were monitored in the Doxy-PEP study, and there were no laboratory-related severe adverse events.

Consider checking these laboratory parameters annually, particularly in individuals with a history of liver disease.

2. Persons taking Doxy-PEP should be screened every three months for gonorrhea and chlamydia at all anatomic sites of exposure, syphilis, and HIV (if not known to be living with HIV).
3. If a person is diagnosed with an STI while using Doxy-PEP, they should be treated according to standard CDC STI Treatment Guidelines (PDF).

CONSIDERATIONS REGARDING DOXY-PEP IN THE CONTEXT OF FAMILY PLANNING SERVICES

A health center or system should decide whether to adopt the current CDC draft recommendations, broadened guidelines, such as the CDPH guidelines, or other guidelines issued by its state health authority; or to delay provision of Doxy-PEP for STI prevention until the CDC issues final comprehensive recommendations.

Key considerations include:

1. **Offering Doxy-PEP to key affected groups:** Even in the absence of comprehensive CDC recommendations, family planning providers should consider offering Doxy-PEP prescriptions or supplies to the individuals listed as candidates in CDPH's first recommendation (i.e., MSM, transgender women).
2. **Making Doxy-PEP equally available to all who might benefit from it:** The CDPH guideline recommends offering Doxy-PEP using shared decision-making to all individuals at increased risk for bacterial STIs and to those requesting Doxy-PEP, even if not previously diagnosed with an STI or who have not disclosed their risk status; and inclusive of cisgender women, transgender men, and other queer and nonbinary individuals.
3. **Offering emergency contraception (EC) for pregnancy prevention:** A person who is a candidate for Doxy-PEP also may be a candidate for EC with oral EC pills or an IUD. Clinicians should provide patients with the opportunity of achieving post coital prevention of both STIs and pregnancy, as appropriate.

APPENDIX: TREATMENT OF SYPHILIS IN PREGNANCY

In 2021, 17% of women of childbearing age diagnosed with syphilis were pregnant. Congenital syphilis cases increased 1,500% between 2012 and 2021. These trends mirror a sharp increase in early syphilis among females, which increased more than 1,113% during the same period.

Under ideal circumstances, a pregnant person who is diagnosed with syphilis and planning to continue the pregnancy should be managed by their prenatal care provider. This allows the clinician to both treat the patient and perform the necessary follow-up titers to ensure that syphilis is cured. Continuity of care is fractured if a family planning provider begins treatment, and the prenatal care provider must do the follow-up care.

However, studies have shown that 40% of pregnant people with syphilis receive no prenatal care[9,10], and for that reason, if transfer for prenatal care is delayed or unavailable, family planning providers should treat pregnant people found to have syphilis to avoid loss to follow-up.

Given that the only treatment for syphilis in pregnancy is benzathine penicillin, if a pregnant person is penicillin-allergic, they must go through the penicillin desensitization process. This often is done by a perinatologist, sometimes with the consultation of an infectious disease physician or allergist.

If a pregnant person is committed to having an abortion, there is no longer a concern about vertical transmission to a fetus resulting in congenital syphilis. In this case, treatment can be provided using the same regimens as in non-pregnant people.

The **2021 CDC STI Treatment Guidelines section on treatment of syphilis in pregnancy** includes the following points:

- All patients who have syphilis should be offered testing for HIV at the time of diagnosis.
- Risk factors for syphilis during pregnancy include sex with multiple partners; sex in conjunction with drug use or transactional sex, late entry to prenatal care (i.e., first visit during the second trimester or later) or no prenatal care; methamphetamine or heroin use; incarceration of the pregnant person or their partner; and being unhoused or experiencing housing instability.
- Antepartum screening can be performed by using the traditional syphilis screening algorithm or by the reverse sequence algorithm.
- Pregnant people with positive treponemal screening tests (e.g., EIA, CIA, or immunoblot) should have additional quantitative nontreponemal testing because titers are essential for monitoring treatment response.
- Any person who has a fetal death after 20 weeks' gestation should be tested for syphilis.

- Benzathine penicillin G is the only known effective antimicrobial for treating fetal infection and preventing congenital syphilis. Pregnant people should be treated with the recommended penicillin regimen for their stage of infection.
- Certain evidence indicates that additional therapy is beneficial in pregnancy to prevent congenital syphilis. For those who have primary, secondary, or early latent syphilis, a second dose of benzathine penicillin G 2.4 million units IM can be administered one week after the initial dose [Determine if this is the preferred regimen used in your community or by the provider(s) to whom the patient will be referred].
- Missed doses more than nine days between doses are not acceptable for pregnant people receiving therapy for late latent syphilis. In pregnancy, the optimal interval between doses is seven days. If the patient does not return for the next dose on day seven, every effort should be made to make contact and link to immediate treatment within two days to avoid retreatment. Pregnant people who miss a dose of therapy should repeat the full course of therapy.

This document was prepared by the National Family Planning & Reproductive Health Association (NFPRHA), in consultation with its Clinical Fellow, Michael Policar, MD, MPH. It is intended for informational purposes and does not constitute legal or medical advice or NFPRHA's endorsement of a specific product.

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