**Syphilis**

This is a PDF version of the following document:
Module 1: Pathogen-Based Diseases
Lesson 14: Syphilis

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**Background**

Syphilis is a systemic infection caused by *Treponema pallidum*, a spirochete bacterium that is transmitted primarily through sexual activity. In the absence of treatment, patients who acquire *T. pallidum* remain chronically infected and syphilis generally progresses in stages, characterized by episodes of active clinical manifestations interrupted by periods of latent infection. Chronic disease can result in significant morbidity, potentially affecting nearly every organ system, and rarely, can result in death. In addition, untreated syphilis in pregnant women can lead to fetal demise and devastating congenital infection for neonates born to a mother with *T. pallidum* infection.
Epidemiology in the United States

In the United States, the CDC reporting of syphilis incidence includes five categories:[1]

- All stages
- Primary and secondary
- Early latent
- Late and late latent
- Congenital

Reported cases of primary and secondary syphilis more accurately represent the incidence of syphilis than reported cases of latent infection, particularly late latent syphilis, which signifies infection acquired more than a year before syphilis is diagnosed. In the United States, the incidence of syphilis in the past 80 years has undergone major fluctuations (Figure 1).[1] During the past 10 years, the reported number of syphilis cases in the United States has dramatically increased, peaking with 129,813 reported cases (of all stages) in 2019 (Figure 2).[1] The sharp increase in syphilis cases since 2010 is primarily due to an increase in cases among men who have sex with men (MSM), including persons with HIV.[1] In 2019, a total of 38,992 cases of primary and secondary syphilis were reported in the United States, which corresponds to a rate of 11.9 cases per 100,000 population; the number of reported cases of primary and secondary syphilis in 2019 represent an 11.2% increase from 2018, a 63.3% increase from 2015, and the highest reported number of cases since 1991.[1]

Epidemiology Based on Specific Demographics

The following summarizes syphilis epidemiology in the United States based on specific demographics features per the 2019 CDC STD Surveillance report:[1]

- **Sex:** In 2019, the rate of reported primary and secondary syphilis cases among males (20.1 cases per 100,000 males) was approximately 5-fold higher than among females (3.9 cases per 100,000 females) and males accounted for 83% of these cases.[1] For both males and females, rates of reported primary and secondary syphilis have increased significantly in recent years (Figure 3).[1]
- **Sex Partner:** In 2019, men who have sex with men accounted for 47.1% of reported cases of primary and secondary syphilis, with a breakdown showing 41.6% of the total cases involved men who have sex with men only and 5.5% of the total were men who have sex with both men and women (Figure 4).[1]
- **Age:** The highest rates of reported primary and secondary cases of syphilis in 2019 occurred in persons 25 to 29 years of age, followed next by those 30 to 44 years of age (Figure 5).[1]
- **Sex and Age Group:** For females, the rates of reported primary and secondary cases of syphilis in 2019 were highest in persons aged 25 to 29 years of age and next highest in those 20 to 24 years of age; for males, the rates were highest in those 25 to 29 years of age, followed by those 30 to 34 years of age (Figure 6).[1]
- **Race/Ethnicity:** In 2019, the rate of primary and secondary syphilis among Black persons (31.0) and was next highest among Native Hawaiian/Pacific Islander individuals (Figure 7).[1]
- **Region and State:** In the United States, from 2012 to 2019, the rates of primary and secondary syphilis have shown an overall increase in each of the major regions, with the greatest increases occurring in the West (Figure 8).[1] In 2019, the West had the highest rate of reported primary and secondary syphilis, followed next by the South (Figure 9).[1] The five states with the highest rates of reported rates of primary and secondary syphilis in 2019 are (in descending order) Nevada, New Mexico, Mississippi, California, and Oklahoma; rates are extremely high in the District of Columbia (Figure 10).[1]
- **Congenital Syphilis:** The number of cases of congenital syphilis reported in the United States fluctuated during the years 2005-2012, but the number of cases have been consistently rising in recent years (Figure 11).[1] During the 6-year period from 2013-2019, the number of cases of
congenital syphilis in the United States increased by an alarming 417% (from 362 to 1,870 cases).\[1\] The recent increases in rate of congenital syphilis parallels the rise in primary and secondary syphilis among women.\[1\] Transmission to the fetus in pregnancy can occur during any stage of syphilis, but the risk is much higher with primary or secondary syphilis, especially if the mother acquires *T. pallidum* in the third trimester of pregnancy.\[1\]

- **HIV Coinfection**: In cases where HIV status is known, 44.2% of men who have sex with men diagnosed with primary and secondary syphilis have HIV coinfection, compared only 7.6% of the cases involving men who have sex only with women.\[1\] Among HIV-negative men who have sex with men, a diagnosis of primary or secondary syphilis is associated with a significant increased risk of subsequent HIV infection.\[2\] For women diagnosed with primary and secondary syphilis, 4.5% were identified having HIV (when the HIV status was known).\[1\]

### Prevalence

In the United States for 2018, the CDC estimates a syphilis prevalence of 156,000 in persons 14 to 49 years of age.\[3\] For these estimates, men accounted for approximately 70% of prevalent syphilis infections.\[3\] These CDC estimates that from 2008 to 2018 there was an 164% increase in prevalent syphilis infections.\[3\]

### Factors Associated with Syphilis Diagnosis

Persons with the highest rates of syphilis include men who have sex with men and individuals with HIV (men or women).\[1,4\] Additional factors associated with an increased rate of syphilis include a history of incarceration, history of commercial sex work, and, for males, age younger than 29 years.\[4\] Among men who have sex with men, use of methamphetamine has been associated with acquisition of STDs, including syphilis. In one report, investigators evaluated men who have sex with men who used methamphetamines and had early syphilis and found multiple risk factors associated with methamphetamine use, including multiple or anonymous partners, not using a condom, and meeting sex partners at bathhouses.\[5\]

### Cost

In the United States, the estimated lifetime cost for syphilis infections acquired in 2018 is $173.7 million.\[6\] These estimates correlate with approximately an estimated lifetime cost per syphilis infection of $1,190. The overall lifetime medical cost for syphilis represents about 1% of the 15.9 billion lifetime cost for all sexually transmitted infection, including HIV acquired in the United States in 2018 (approximately $13.7 billion of these total lifetime costs are attributed to costs for HIV).\[6\]
Microbiology and Pathogenesis

Organism and Classification

The etiologic agent in syphilis is *Treponema pallidum*—from the Greek terms trepo (“to turn”) and nema (“thread”) and the Latin term pallida (“pale”).[7] *Treponema pallidum* belongs to the spirochete class and is a corkscrew-shaped, motile microaerophilic bacterium that requires a live rabbit-model system for growth and cannot be viewed by normal light microscopy (Figure 12). This spirochete bacterium is thin (0.1 to 0.18 micrometers in diameter), and 6 to 20 micrometers in length (Figure 13).[8] *Treponema pallidum* has been erroneously described as gram-negative bacteria, but this organism lacks lipopolysaccharide (LPS), a hallmark of gram-negative organisms.

Transmission

The major routes of transmission for *T. pallidum* are sexual and vertical (in utero via hematogenous spread to a fetus). *Treponema pallidum* enters the body via skin and mucous membranes through macroscopic and microscopic abrasions during sexual contact. An infected individual is contagious to sex partners during the primary and secondary stages of infection—when lesions or rash are present. Although predominantly transmitted at genital sites, primary lesions have been described at diverse sites, including mouth, anorectal areas, and chest or neck from human bites. Transmission may also occur via placenta from mother to fetus during pregnancy. Transfusion-associated syphilis was well-recognized prior to the 1940s, but has been eliminated in the United States blood supply; this mode of transmission now occurs only in resource-limited countries.[9]
Clinical Manifestations

Syphilis has often been called “the great imitator” because so many of the signs and symptoms may be difficult to differentiate from those of other diseases.\cite{10,11,12,13} Before clinical signs or symptoms appear, \textit{T. pallidum} accesses the circulatory system, including the lymphatic system and regional lymph nodes. Invasion of the central nervous system can occur during any stage of syphilis. Early clinical manifestations (primary and secondary stages) predominantly involve the skin and mucosal surfaces, although secondary syphilis may be accompanied by systemic manifestations. Latent disease has no clinical signs or symptoms, but late manifestations (seen after years of infection) may affect virtually any organ system. Neurosyphilis and ocular syphilis can occur at any stage of infection. Obtaining a detailed history is critical for determining the duration of infection and assessing for the possibility of reinfection. When obtaining the patient’s history, the healthcare professional should assess whether the patient has had:

- A history of syphilis (if yes, obtain results of previous serologic tests for comparison)
- Known contact with someone with primary or secondary syphilis
- Signs or symptoms of syphilis in the past 12 months.

Primary Syphilis

Following the inoculation of \textit{T. pallidum} at the entry site, organisms proliferate, sensitize lymphocytes, and activate macrophages, causing the formation of a primary lesion or “chancre” at the site of inoculation.\cite{14} The initial manifestation of the chancre typically occurs about 3 weeks (range 10 to 90 days) after the acquisition of the infection.\cite{15} Chancre progresses from a papule to an ulcer, which is typically painless, indurated, well circumscribed, round to oval, with a clean base. The most common sites where chancres develop include the penis (Figure 14), labia, perianal region, or mouth (Figure 15). Regional firm, non-tender, lymphadenopathy often develops in proximity to primary syphilitic lesions (inguinal adenopathy with genital lesions and cervical adenopathy with oral lesions); in most patients, the lymphadenopathy is bilateral.\cite{16,17} Syphilitic chancres are highly infectious and heal spontaneously within 1 to 6 weeks; untreated patients may go on to develop other manifestations of syphilis. Less typical lesions often develop, with one study reporting only 42.7% had a “classic” single lesion. Atypical features may include painful lesions or multiple lesions; in some instances chancres can mimic herpes simplex infection or chancroid.\cite{18} Evaluation of patients with genital ulcers should include serologic testing for syphilis and a diagnostic evaluation for genital herpes. In addition, if available, suspected primary syphilis should be evaluated with darkfield microscopy or a polymerase chain reaction (PCR) test for \textit{T. pallidum}. In geographic regions where chancroid is endemic (Asia, Africa, and the Caribbean), testing for \textit{Haemophilus ducreyi} should also be performed.

Secondary Syphilis

Secondary lesions reflect hematogenous dissemination of \textit{T. pallidum} and generally appear 4 to 8 weeks after the onset of the primary chancre; patients with secondary syphilis may develop a wide array of cutaneous lesions.\cite{12} Signs and symptoms of secondary syphilis are often the first observed clinical manifestation of syphilis in those practicing receptive vaginal, oral, or anal intercourse because primary lesions may occur in the vagina, mouth, or anus and may not be recognized by the patient. In some patients, primary and secondary stages may overlap. Relapses of secondary symptoms may occur in up to 25% of untreated patients, usually within the first year of infection.

- **Rash**: A rash occurs in 75% to 100% of patients with secondary syphilis. The rash can be macular, papular, squamous, pustular (rarely), or a combination.\cite{19} Rash with secondary syphilis is usually nonpruritic, and characteristically involves the chest (Figure 16), back (Figure 17), palms (Figure 18), and soles (Figure 19). Any new onset of macular, papular, or squamous rash should be evaluated to rule out secondary syphilis.

- **Lymphadenopathy**: In 50% to 86% of cases, patients will develop lymphadenopathy. Epitrochlear lymphadenopathy should prompt consideration of secondary syphilis.
• **Systemic Symptoms**: Patients often present with malaise, fever, and other nonspecific constitutional symptoms.

• **Mucous Patches**: The development of mucous patches occurs in 6% to 30% of patients and manifest as flat patches located in the oral cavity (Figure 20), pharynx, larynx, or genital region.

• **Condylomata Lata**: Approximately 10 to 20% of persons with secondary syphilis will have condylomata lata lesions, which appear as moist, heaped-up, wart-like papules in warm intertriginous areas (most commonly gluteal folds, perineum, and perianal) (Figure 21); these lesions are highly contagious.

• **Alopecia**: About 5% of patients develop patchy alopecia, most often in the occipital or bitemporal scalp region, but some patients will have loss of the lateral region of the eyebrows.

• **Visceral Organ Involvement**: In some cases, syphilis may involve one or more visceral organs, including liver, kidney, lungs, gastrointestinal tract, and spleen.

• **Neurologic Symptoms**: Patients with secondary syphilis can develop neurosyphilis, characterized by either asymptomatic infection of the central nervous system, or acute syphilitic meningitis, a basilar meningitis that typically causes headache and stiff neck and may involve cranial nerves, which may result in hearing loss, facial weakness, or visual disturbances. Strokes may also occur. Patients may also develop ocular or otic syphilis without basilar meningitis.

**Latent Syphilis**

Latent syphilis is a stage of syphilis characterized by the persistence of *T. pallidum* organisms in the body without causing signs or symptoms. Periods of clinical latency may occur between the primary and secondary stages, between secondary relapses, and after the secondary stage. The diagnosis of latent syphilis is made when an individual has: (1) seroreactivity indicating infection with *T. pallidum*, (2) no past diagnosis of syphilis, and (3) no evidence of active primary, secondary, or tertiary syphilis.[20] Latent syphilis is classified into three subcategories based on duration of the infection: early latent, late latent, and latent of unknown duration.[21] It is often difficult to determine the duration of infection in a patient with latent syphilis. Individuals with latent syphilis should have HIV testing at the time of syphilis diagnosis (and at a 3-month follow-up if high risk for HIV acquisition), unless they are already known to have HIV. When evaluating an individual with latent syphilis, the health care provider should ask the patient whether they recall having symptoms of primary or secondary syphilis, and whether they had sex with someone with primary or secondary syphilis within the past year. A careful physical examination, with an emphasis on mucosal surfaces, and review of prior serology results are also useful tools for clarification of the duration of infection.

**Early Latent Syphilis (Infection of Less than 1 Year in Duration)**

Persons with latent syphilis are classified in the subcategory of early latent syphilis if they have no past diagnosis of syphilis, no clinical signs or symptoms of syphilis, and at least one of the following:[20]

- A documented seroconversion or a sustained (longer than 2 weeks) fourfold or greater increase in titer of a nontreponemal test during the prior 12 months
- Unequivocal symptoms of primary or secondary syphilis during the prior 12 months
- A history of sexual exposure to a partner within the prior 12 months who had documented primary, secondary, or early latent syphilis
- Sexual debut occurred in the prior 12 months and only possible sexual contact occurred in the prior 12 months

If an individual has a reactive nontreponemal and treponemal tests and the only possible exposure occurred during the previous 12 months, early latent syphilis can be assumed.

**Late Latent Syphilis (Infection Greater than 1 Year in Duration)**

Persons with latent syphilis are classified in the subcategory of late latent syphilis when there is no evidence that *T. pallidum* was acquired in the prior 12 months, they do not have clinical signs or symptoms consistent
with syphilis, and they meet criteria for at least one of the following:

- Reactive nontreponemal and treponemal tests and no past diagnosis of syphilis
- A past history of syphilis therapy and a current nontreponemal test titer demonstrating fourfold or greater increase from the last nontreponemal test titer

**Latent Syphilis of Unknown Duration**

In the situation when it is not possible to determine likely the duration of infection in a person with latent syphilis, they are categorized as having latent syphilis of unknown duration. From a practical standpoint, individuals with latent syphilis of unknown duration are effectively managed the same as persons with late latent syphilis.

**Tertiary Syphilis (other than neurosyphilis)**

Tertiary syphilis, also referred to as late syphilis, is rare because of widespread availability and use of antibiotics. Without treatment, however, approximately 30% of patients eventually progress to the tertiary stage of syphilis within 1 to 20 years of the original infection. Gummatous lesions can occur in skeletal, spinal, and mucosal areas, eyes, and viscera (lung, stomach, liver, genitals, breast, brain, and heart). The destructive lesions can clinically mimic carcinoma. The average onset is 10 to 15 years after infection. Cardiovascular syphilis is indicated by pathologic lesions of the aortic vasa vasorum. It clinically presents as ascending aortic aneurysm, aortic insufficiency, or coronary ostial stenosis. The average appearance is about 20 to 30 years after infection.

**Neurosyphilis**

Neurosyphilis occurs when *T. pallidum* invades the central nervous system and this may occur at any stage of syphilis. In addition, cerebrospinal fluid (CSF) abnormalities can occur in early syphilis and are of unknown significance in the absence of neurologic signs or symptoms; these inflammatory CSF changes are likely due to invasion of the central nervous system by *T. pallidum*, as up to 25% of CSF samples taken during early syphilis can reveal *T. pallidum* DNA via PCR.[22,23] Experts have postulated that several decades of widespread use of antibiotics active against *T. pallidum* underlies the notable shift in clinical presentation from paresis and tabes dorsalis to meningeal and meningovascular syndromes; this change has been particularly evident among persons with HIV infection.[24,25]

- **Early Neurosyphilis**: Early forms of neurosyphilis usually occur a few months to a few years after initial infection. Clinical manifestations include acute syphilitic meningitis, a basilar meningitis that typically involves cranial nerves III, VI, VII and VIII; or meningovascular syphilis, an endarteritis that presents as a stroke-like syndrome with seizures.
- **Late Neurosyphilis**: Late forms of neurosyphilis usually occur decades after infection, and they are rarely seen. Clinical manifestations include general paresis and tabes dorsalis but can present with a wide variety of neurologic symptoms. Serologic treponemal tests are usually reactive. Ocular involvement can occur in early or late neurosyphilis.

**Ocular Syphilis**

Since *T. pallidum* can potentially infect any part of the eye, the range of manifestations associated with ocular syphilis is broad and patients may present with an array of symptoms.[26,27,28,29] Ocular syphilis can develop at any stage of syphilis and patients can present with acute or chronic symptoms.[27] Ocular complications of syphilis have been reported in clusters in recent years.[29,30] Several recent studies have analyzed molecular strain type and found no clear evidence of a predominant strain trophic for the
eye.[30,31] Ocular syphilis can be seen in isolation with other neurologic symptoms—it can present with anterior, posterior, or pan-uveitis and can occur at any stage of syphilis.[27,28] Other described manifestations include lid involvement, episcleritis, vitritis, retinitis, papillitis, interstitial keratitis, acute retinal necrosis, and retinal detachment. Primary optic atrophy is unique to late syphilis (classically described with tabes dorsalis). The clinical presentations can have significant overlap with eye disease caused by tuberculosis, toxoplasmosis, histoplasmosis, and ocular Toxocara canis infections. Non-infectious causes such as rheumatoid arthritis and sarcoidosis must also be considered. Patients with syphilis and ocular complaints should undergo prompt ophthalmologic evaluation and have a lumbar puncture performed for cerebrospinal fluid evaluation.[20,29] Significant improvement of symptoms (including vision) may occur after treatment for syphilis, but this depends on the type of pathology and timing of initiating antimicrobial therapy; if scarring is present, it is unlikely to significantly change following treatment.

**Congenital Syphilis**

Congenital syphilis occurs when *T. pallidum* is transmitted from a pregnant woman with syphilis to her fetus. Untreated syphilis during pregnancy may lead to stillbirth, neonatal death, and infant disorders such as deafness, neurologic impairment, and bone deformities.[32,33] Transmission to the fetus in pregnancy can occur during any stage of syphilis, but the risk is much higher when a pregnant woman is in the primary or secondary stage of syphilis. Fetal infection can occur during any trimester of pregnancy and may range from mild to severe, with only severe cases manifesting clinically at birth. Congenital syphilis is traditionally classified as either early or late disease.[14] Early manifestations occur within the first two years of life, and late manifestations occur after two years of age. Early manifestations are the most common.

**Early Congenital Syphilis**

Early congenital syphilis is usually defined as manifestations of syphilis in infants and children younger than 2 years of age, with abnormalities that include the following:

- Hepatosplenomegaly is very common but is a non-specific finding.
- Bone involvement is the most common specific manifestation and is seen in 60% to 80% of infected infants.[34]
- Skin (bullous or exudative lesions) or mucous membranes lesions may be seen.
- Alopecia, generalized lymphadenopathy, meningitis, osteitis or osteochondritis can also occur.
- Hematologic abnormalities such as thrombocytopenia and anemia manifest in some cases.

**Late Congenital Syphilis**

Late congenital syphilis is generally defined as manifestations of syphilis in children older than 2 years of age, with disorders that include the following:

- Clinical manifestations typically result from scarring and chronic inflammatory changes from persistent infection and inflammation.
- Bone lesions including frontal bossing, shortened maxilla, high palatal arch are most common.[35]
- Interstitial keratitis is seen in about 40% of cases.
- Perforation of the hard palate may be observed (Figure 22).
- Hutchinson’s triad is the classic association of eighth cranial nerve deafness, interstitial keratitis, and Hutchinson teeth (Figure 23) and is described in 75% of patients.[35]
Laboratory Diagnosis

The laboratory diagnosis of syphilis is challenging and requires using a combination of clinical and laboratory criteria to differentiate active infection, prior infection, and absence of infection. Treponema pallidum cannot be cultivated on artificial medium, but the organism can be grown using special techniques that involve inoculation in rabbits. In clinical samples, spirochetes can occasionally be visualized in specimens taken from cutaneous lesions using dark-field microscopy techniques. In addition, silver staining and immunohistochemical staining of tissue samples can demonstrate characteristic spirochetes on clinical biopsy specimens. Use of dark-field microscopy or immunohistochemical staining on oral specimens is not recommended due to the extremely poor specificity caused by abundant non-syphilitic oral Treponema species. Serologic testing remains the primary tool for diagnosis in most patients with syphilis and these tests include “nontreponemal” and “treponemal” tests. Although PCR testing is sometimes used for research purposes, there is no FDA-approved PCR test for syphilis at present. Research use of PCR detection of T. pallidum DNA has expanded the clinical sites from which T. pallidum can be detected.

Direct Detection of Treponema pallidum

Dark-Field Microscopy

Dark-field microscopy of lesion exudate or tissue is the definitive method for diagnosing early syphilis. Treponema pallidum cannot be viewed by normal light microscopy. Dark-field microscopy can identify T. pallidum with its spiral shape, 10 to 14 coils, corkscrew motion, and a total length of 6 to 20 micrometers (Figure 24). Dark-field microscopy is rarely used in clinical practice because most facilities do not have dark-field microscopy and most clinicians do not know how to appropriately obtain specimens. Dark-field microscopy has the potential advantage of making a definitive and rapid diagnosis of primary or secondary syphilis. Several disadvantages exist with dark-field microscopy, including (1) requirement for specialized, expensive equipment, (2) need for clinician training on how to appropriately collect and prepare a specimen for dark-field microscopy, (3) need for experienced microscopist who can correctly identify T. pallidum with dark-field microscopy, (4) potential false-positive results in oral specimens (from nonpathogenic spirochetes in the oral cavity), (5) potential false-negative results if topical agents have been applied by the patient or the specimen is not collected appropriately, and (6) need to immediately view any collected specimen. Clinicians need to take special precautions to protect themselves from inoculation when collecting specimens for dark-field microscopy, since the lesions contain abundant viable organisms.

Direct Fluorescent Antibody Test

The direct fluorescent antibody test can detect T. pallidum antigens in tissue samples. The test uses antibodies specific to pathogenic treponemes and can generally identify T. pallidum in samples—such as oral or rectal lesions—that may have background non-pathogenic spirochetes.

Serologic Testing for Syphilis

In the absence of dark-field microscopy, a probable diagnosis of syphilis is possible with the use of two types of serologic tests: nontreponemal and treponemal. Use of only one type of serologic test is insufficient for diagnosis since each test used alone has major limitations, including false-positive results in persons without syphilis and the inability for treponemal tests to distinguish between recent and distant infection. Both types of tests have several advantages and disadvantages as well as differing test characteristics.

Nontreponemal Serologic Tests

The nontreponemal tests include Venereal Disease Research Laboratory (VDRL), Rapid Plasma Reagin (RPR), Toluidine Red Unheated Serum Test (TRUST), and Unheated Serum Reagin (USR). These tests measure IgM and IgG antibody and are not specific for T. pallidum. Nontreponemal test results are reported with a qualitative result and a quantitative titer, which usually correlates with disease activity. A fourfold
change in titer, equivalent to a change of two dilutions (e.g., from 1:16 to 1:4 or from 1:8 to 1:32) is considered necessary to demonstrate a clinically significant difference. Sequential serologic tests in individual patients should be performed using the same testing method, preferably by the same laboratory. The VDRL and RPR are equally valid assays, but quantitative results from the two tests cannot be compared directly because RPR titers are often slightly higher than VDRL titers. TRUST is similar to RPR whereas USR is similar to VDRL, though in the United States TRUST and USR are not often used. The nontreponemal tests have several drawbacks, including (1) they are labor intensive to perform, (2) results are typically not available for at least 7 days, (3) the tests have low sensitivity in certain stages, particularly early primary, late latent, and tertiary, and (4) false-positive reactions can occur. Nontreponemal tests usually become nonreactive with time after treatment. In some patients, however, nontreponemal antibodies can persist at a low titer (a titer less than 1:8 is generally considered “low”) for a long period of time, sometimes for the life of the patient. This response is referred to as the “serofast reaction.” In addition, in some patients, nontreponemal tests may, with time, become nonreactive in the absence of therapy.

Treponemal Serologic Tests

The treponemal serologic tests include *T. pallidum* particle agglutination (TP-PA), fluorescent treponemal antibody absorption (FTA-ABS), and various enzyme immunoassays (EIAs) and chemiluminescence immunoassays.[36] These tests measure antibody directed against *T. pallidum* antigens by particle agglutination, immunofluorescence, or enzyme immunoassay (Figure 25); some detect IgG only whereas others detect both IgM and IgG. These qualitative tests most often remain reactive for life, even after adequate treatment, but 15% to 25% of patients treated during the primary stage revert to being serologically nonreactive after two to three years.[38] Treponemal antibody titers correlate poorly with disease activity, and they should not be used to assess treatment response.

Patterns of Serologic Reactivity and Sensitivity of Tests

The common patterns for serologic reactivity with syphilis tests depend on the specific test used, the stage of syphilis, and whether the patient has received treatment.[39] The sensitivity of serologic testing also varies based on the test used and stage of syphilis (Table 1).[37,40] Serologic testing for syphilis has the highest yield during secondary syphilis. Serologic tests for syphilis may be negative during very early primary syphilis. Thus, when serologic tests do not correspond with clinical findings suggestive of primary syphilis, presumptive treatment is recommended if the patient has known risk factors for syphilis; in this setting, use of other tests, such as dark-field microscopy, biopsy, or PCR, should be considered.

Prior Serologic Testing for Syphilis

The healthcare professional should determine the date and results of the patient’s most recent serologic test for syphilis, even if the patient reports no history of the disease. Prior results, if available, are particularly helpful when evaluating a patient that has a low titer serologic test for syphilis, no signs or symptoms that suggest a clinical diagnosis of syphilis, and no known contact with an early case of syphilis. Local health departments can often provide information on whether the patient has been reported as having had syphilis in the past, including reported serologic test results and treatment history.

Serologic Testing Algorithms

Given that treponemal and nontreponemal tests each have significant advantages and disadvantages, these lab tests are used together as part of a screening algorithm in order to maximize sensitivity and specificity for the detection of syphilis infection. Clinicians should be aware of their institution’s chosen method in order to most efficiently use serologic tests to screen for, diagnose, and monitor syphilis disease.

Standard (Traditional) Screening Algorithm

Traditionally, the syphilis screening algorithm has consisted of initial screening with a nontreponemal test
(VDRL or RPR), with further testing on a positive initial test with a treponemal test (TP-PA or EIA) (Figure 26). [20] Patients with a negative screening test were relegated to periodic repeat screening whereas patients with positive results required a treponemal test to confirm a diagnosis of syphilis. The major limitations with using a nontreponemal test for initial screening include the personnel time required to perform a labor-intensive test, biologic false positives (i.e. pregnancy, medication use, and other conditions) and, as with all diagnostic tests for syphilis, the inability to detect early primary or latent infection.

**Reverse Sequence Screening Algorithm**

Another option for syphilis screening is to use *T. pallidum*-specific EIAs or chemiluminescence immunoassays as an initial screening test. In recent years, increasing numbers of clinical laboratories and blood banks have begun using treponemal EIA or chemiluminescence immunoassays (CIAs) as the initial screening laboratory test for syphilis. With this approach, a positive EIA or CIA test is followed by further testing with a nontreponemal test—often referred to as reverse screening (Figure 27). [41] In the reverse screening algorithm, negative treponemal results are relegated to follow-up screening as with the standard (traditional) algorithm. Positive treponemal results undergo a confirmatory nontreponemal test (i.e. RPR) to guide management. In the event of a positive EIA and a negative nontreponemal test, a second confirmatory treponemal test (TP-PA) is performed. If either of the confirmatory tests is positive and there is no history of prior, treated syphilis, the patient is diagnosed with syphilis. [41] This ‘reverse screening algorithm’ has several advantages and disadvantages distinguishing it from the standard (traditional) screening algorithm. Advantages of the reverse sequence algorithm include improved detection of early primary and treated infection, low cost, and reduced laboratory time and effort (much less pipetting and circumventing the manual dilutions of nontreponemal testing).

**Discordant Test Results Using Reverse Screening**

In the scenario where a patient has a positive treponemal screening test (EIA), a negative nontreponemal test, and a positive second treponemal test (TP-PA), there are several possible scenarios: prior treated syphilis, early syphilis, untreated latent syphilis, or false-positive test. If the patient has received prior treatment for syphilis and has no evidence by history or examination for recent infection with *T. pallidum*, then the patient does not require further evaluation or management. [20] Patients without prior treatment and no evidence for recent infection are considered to have latent syphilis and require further evaluation and treatment. If recent infection possibly occurred, then repeat nontreponemal testing should take place 2 to 3 weeks later; if this repeat testing is positive the patient likely has early syphilis and if the test is negative then further evaluation is usually not needed.

**Management of Positive Screening Results**

Current syphilis serologic screening algorithms include a nontreponemal titer (VDRL or RPR) to help clarify disease activity. Infections can thus be differentiated based on active disease, prior treatment, and time since prior screening. Symptomatic patients should be classified by stage of syphilis based on clinical findings, including determination of whether they have evidence of neurologic or ophthalmologic disease. Patients without a history of treatment for syphilis should be offered therapy based on clinical findings and the stage of disease. Asymptomatic, previously untreated persons who have not had syphilis testing in the prior year should be considered to have late latent syphilis. All patients who have syphilis should be tested for HIV infection, and those with primary or secondary syphilis who live in areas with a high prevalence of HIV should be retested for HIV after three months (if the first HIV test result was negative). Providers should consider screening patients with syphilis for other STDs, based on risk.

**Positive Titers in Patients Previously Treated for Syphilis**

Although patients with early syphilis usually have a fourfold or greater decline in nontreponemal titer within 12 months after treatment, some fail to achieve seroreversion at month 12. [42] Patients previously treated for syphilis who had a documented adequate reduction in nontreponemal titer after treatment may have a
persistent low-positive nontreponemal titer that does not significantly change; this is called a serofast state, and they do not require additional therapy. Patients with prior treatment and higher (but unchanged) nontreponemal titer are considered treatment failures unless there is clinical suspicion for reinfection.

**False-Positive Reactions**

With both nontreponemal and treponemal serologic tests for syphilis, false-positive reactions can occur. The most common caused of false-positive testings include older age, autoimmune disorders, cardiovascular disease, pregnancy, malaria, leprosy, other spirochete infections, and recent immunizations.

**False-Negative Reaction (“Prozone Effect”)**

Infrequently, patients may have a false-negative reaction with nontreponemal testing due to the “prozone effect”. The prozone effect occurs when very high serum antibodies supersaturate the antigens used in the nontreponemal assay, thereby interfering with the antigen-antibody lattice network needed to visualize a flocculation reaction. Overall, this occurs in less than 2% of cases of syphilis. This false-negative reaction is most likely to occur in patients with secondary syphilis and HIV infection. If clinical suspicion of secondary syphilis is high and the nontreponemal testing is negative, the clinician should alert the laboratory of a suspected prozone effect and the laboratory should reevaluate the clinical sample after diluting the serum, typically a 1/16 dilution.

**Diagnosis of Latent Syphilis**

Persons are diagnosed with latent syphilis when they have: (1) serologic evidence of *T. pallidum* infection, (2) no past diagnosis of syphilis, and (3) no active syphilis-related signs or symptoms. It is often difficult to determine the duration of infection in a patient with latent syphilis.

**Laboratory Evaluation for Neurosyphilis**

Neurologic involvement can occur during any stage of syphilis. Cerebrospinal fluid (CSF) abnormalities have been noted in 13% of patients with untreated primary syphilis and 25% to 40% of patients with untreated secondary syphilis. Although these CSF laboratory abnormalities are common in persons with early syphilis, no evidence exists to support variation from recommended treatment for syphilis at any stage in the absence of clinical neurologic findings, except for tertiary syphilis. In addition to work-up of clinically suspected neurosyphilis, there are a number of additional indications to perform CSF evaluation.

Several studies have shown that among persons with HIV and syphilis, CSF abnormalities (mononuclear pleocytosis and elevated protein) are associated with a CD4 count of 350 cells/mm$^3$ or less and/or a nontreponemal serologic test titer of greater than or equal to 1:32. Data are lacking regarding the benefits of a CSF examination in this setting. In general, persons with HIV infection tend to have more frequent CSF abnormalities in the absence of neurologic symptoms, and the presence of 20 or more white blood cells (WBC)/mm$^3$ might improve the specificity of probable neurosyphilis in this patient population. When using a nontreponemal test to evaluate for neurosyphilis, the CSF VDRL is preferred over the CSF RPR. For more detailed information on the diagnosis of neurosyphilis including interpretation of CSF findings, consult the 2015 STD Treatment Guidelines.

**Diagnosis of Syphilis in Patients with HIV Coinfection**

Syphilis and HIV infection frequently coexist. In general, the clinical course of syphilis in persons with HIV is similar to that in persons without HIV. Although not common, unusual serologic responses among persons with HIV infection can occur. If the clinical suspicion of syphilis is high and the serologic tests for syphilis are negative, then use of other tests (e.g., biopsy of the lesion or rash) should be considered. Conventional therapy is usually effective. After appropriate therapy, persons with HIV infection more frequently
demonstrate “high serofast” values of nontreponemal serologic tests (often defined as RPR greater than or equal to 1:8).[20]

**Diagnosis of Syphilis in Infants and Children**

The diagnosis of congenital syphilis is often difficult since maternal nontreponemal and treponemal IgG antibodies can be transferred through the placenta to the fetus. The decision to treat a neonate (aged fewer than 30 days) is based on: (1) identification of syphilis in the mother; (2) adequacy of maternal treatment; (3) clinical, laboratory, and radiographic evidence of disease in the neonate; and (4) comparison of maternal and neonatal nontreponemal serologic titer. Based on these factors, neonates are classified as: (1) proven or highly probable congenital syphilis, (2) possible congenital syphilis, (3) congenital syphilis less likely, or 4) congenital syphilis unlikely.

**Reporting and Referral to Health Departments**

Patients with primary, secondary or early latent syphilis, or syphilis of unknown duration with a high nontreponemal serologic test titer (greater than 1:32), should be referred to the local health department STD program for interview, partner elicitation, and partner follow-up. The follow-up of patients with early syphilis is a public health priority. Laws and regulations in all states require that persons diagnosed with syphilis be reported to public health authorities. Reporting can be provider-based or laboratory-based. Providers unsure of reporting requirements should seek advice from state or local health departments or STD programs. To locate a state health department, see the CDC resource tool [Public Health Resources: State or Territorial Health Departments](https://www.cdc.gov).
Screening for Infection

In the United States, the most influential recommendations for syphilis screening are from the 2015 STD Treatment Guidelines and the 2016 US Preventive Services Task Force (USPSTF) Recommendation Statement on Screening for Syphilis Infection in Nonpregnant Adults and Adolescents.[4,20] In addition, in 2009 the USPSTF issued screening recommendations for Syphilis Infection in Pregnancy.[50,51] The 2015 STD Treatment Guidelines and the 2016 USPSTF Recommendations both identify men who have sex with men and persons living with HIV as groups as high priority groups for syphilis screening.[4,52] Routine screening is recommended for several other specific populations, including persons who are pregnant, individuals taking HIV preexposure prophylaxis, and persons who have a sex partner diagnosed with syphilis. The following summarizes recommendations from the CDC and the USPSTF.[4,20]

Summary of Recommendations for Routine Screening for Syphilis

- **Women Who Have Sex with Men:** The CDC and USPSTF do not recommend routine syphilis screening for nonpregnant women.[4,20] The USPSTF recommends syphilis screening for nonpregnant women who are at increased risk for syphilis infection (see above “risk factors”). These recommendations are the same for women who have sex with men and women who have sex with women.
- **Women Who Have Sex with Women:** The CDC recommends that syphilis screening for sexually active women who have sex with women should be based on the same recommendations as for sexually active women who have sex with men.[53]
- **Men Who Have Sex Only with Women:** The CDC and the USPSTF do not recommend routine syphilis screening for men who have sex only with women. The USPSTF recommends syphilis screening men who are at increased risk of infection (see above “risk factors”).[53]
- **Men Who Have Sex with Men:** For sexually active men who have sex with men, the CDC and the USPSTF recommend syphilis screening at least annually. More frequent screening (every 3 to 6 months) is recommended for men who have sex with men who have ongoing risk for acquiring syphilis.[4,53]
- **Transgender Men and Transgender Women:** The CDC recommends the screening for syphilis in transgender men and transgender women should be based on age, current anatomy, and sexual practices.[53]
- **Persons with HIV:** The CDC and the USPSTF recommend syphilis screening should be performed at the initial HIV evaluation and at least annually thereafter in all sexually active persons with HIV.[4,20] More frequent screening (every 3 to 6 months) is indicated for persons with HIV who have ongoing risk for acquiring syphilis.
- **Pregnant Persons:** The CDC, USPSTF, and the American College of Obstetrics and Gynecology (ACOG) recommend syphilis screening at the first prenatal visit for all pregnant women.[4,50,51,53,54] The recommendation to screen pregnant persons for syphilis is mandated by most state laws.[54] Women who are at high risk for syphilis or live in areas of high syphilis morbidity should be screened again early in the third trimester (around 28 weeks gestation) and at delivery. Any woman who delivers a stillborn infant after 20 weeks of gestation should be tested for syphilis. Screening for syphilis should occur during each pregnancy.
- **Adolescents:** The CDC does not recommend routine screening of adolescents for syphilis, but young men who have sex with men and pregnant adolescent females should be screened for syphilis.[53]
- **Neonates:** Neonates should not be discharged from the hospital unless the syphilis serologic status of the mother has been determined at least one time during pregnancy (and again at delivery if there was ongoing risk for acquiring syphilis during pregnancy).[53]
- **Correctional Facilities:** The CDC recommends routine screening should be performed based the local area and institutional prevalence of early (primary, secondary, and early latent) infectious syphilis. Correctional facilities should stay apprised of syphilis prevalence as it changes over time.[20]
Treatment

General Considerations

Penicillin G, administered parenterally, is the preferred drug for treating all stages of syphilis. The preparation(s) of penicillin used (e.g. benzathine, aqueous procaine, or aqueous crystalline), the dosage, and the length of treatment depend on the stage and clinical manifestations of the disease. However, neither benzathine-procaine penicillin co-formulations nor oral penicillin preparations are considered appropriate for the treatment of syphilis.[20] Reports have identified the inappropriate use of combination benzathine-procaine penicillin (Bicillin C-R) instead of the standard benzathine penicillin G (Bicillin L-A) product.[55] Practitioners, pharmacists, and purchasing agents should be aware of the similar names of these two products and avoid use of the inappropriate combination therapy agent for treating syphilis. It is important to understand that benzathine penicillin G is slowly released from the intramuscular site due to extremely low solubility and is also hydrolyzed to penicillin G; the combination of slow absorption and hydrolysis results in prolonged low serum levels of penicillin. In addition, practitioners should be aware of ongoing shortages of parenteral penicillin in the United States. Updated information on penicillin shortages can be found on the FDA Drug Shortages site.

Primary and Secondary Syphilis

Parenteral penicillin G is effective in resolving clinical symptoms associated with primary and secondary syphilis and prevents late sequelae in those who receive appropriate treatment. The recommended regimen in the 2015 STD Treatment Guidelines for adults with primary and secondary syphilis is benzathine penicillin G given as 2.4 million units in a single intramuscular dose; for infants and children, the dose is 50,000 units/kg, with a maximum of 2.4 million units (Table 3).[20] The few available studies exploring optimal dosing regimens did not find any benefit from additional doses of penicillin or with combination therapy that included other antibiotics.[22,56]

Treatment of Primary or Secondary Syphilis in Penicillin-Allergic Patients

Treatment of primary and secondary syphilis for patients with documented allergy to penicillin is a topic with limited available data. Small studies and clinical experience suggest that regimens of doxycycline (100 mg orally twice daily for 14 days) or tetracycline (500 mg four times daily for 14 days) are acceptable alternatives for nonpregnant, penicillin-allergic persons who have primary or secondary syphilis.[57,58] Doxycycline is preferable to tetracycline because tetracycline can cause gastrointestinal side effects and requires more frequent dosing. In addition, intramuscular or intravenous ceftriaxone (1-2 grams daily for 10 to 14 days) is considered effective for treating primary and secondary syphilis, but the optimal dose and duration of ceftriaxone in this setting remains unknown.[59] Azithromycin as a single 2 gram oral dose has been effective for treating primary and secondary syphilis, but concerns for emerging macrolide resistance led the CDC to recommend avoiding azithromycin for first-line syphilis treatment and, if used, it should only be considered when treatment with penicillin or doxycycline is not feasible.[60] Further, azithromycin to treat syphilis should not be used in any circumstance to treat MSM, persons with HIV infection, or pregnant women. Any person receiving any of the alternative therapies for the treatment of syphilis should have careful clinical and serologic follow-up. Persons with a penicillin allergy for whom concern exists with adherence or follow-up should undergo penicillin desensitization and then receive treatment with benzathine penicillin G.

LATENT SYPHILIS

The treatment of patients with latent syphilis requires appropriate classification into early latent syphilis (acquired less than 1 year ago as detailed above) or late latent syphilis (acquired longer than 1 year ago), or undetermined duration. The goals of treating patients with latent syphilis are to prevent development of late manifestations of infection (tertiary/neurosyphilis), as well as to prevent transmission to the fetus by infected pregnant women. Early latent syphilis is treated with a single intramuscular dose of benzathine penicillin G
2.4 million units; late latent syphilis is treated with benzathine penicillin G 7.2 million units total split into three weekly intramuscular injections, each with 2.4 million units (Table 4).[20] There are limited data comparing the efficacy of specific regimens or duration, but available data do not suggest any added benefit of additional antibiotics. Alternative therapies for treatment of latent syphilis have not been well studied.

**Treatment of Late Latent Syphilis in Penicillin-Allergic Patients**

For penicillin-allergic, nonpregnant patients with early latent syphilis, the treatment approach should be the same as penicillin-allergic patients with primary or secondary syphilis. For penicillin-allergic patients with late latent syphilis, the only acceptable treatment alternatives are doxycycline (100 mg orally twice daily) or tetracycline (500 mg orally four times daily), each for 28 days.[20] Ceftriaxone may be a reasonable option in this setting, but the optimal number of doses or schedule has not been determined and use of ceftriaxone to treat latent syphilis should involve consultation with a syphilis expert. All patients treated with alternative regimens require close serologic and clinical follow-up, especially in persons with HIV infection. Patients for whom adherence and follow-up is a concern should be desensitized and treated with benzathine penicillin G if possible.

**NEUROSYPHILIS**

Involvement of the CNS can occur during any stage of syphilis, which makes it essential that any patient receiving treatment for primary, secondary, or latent infection be evaluated for clinical evidence of neurologic involvement. If signs or symptoms of neurologic involvement are noted, a CSF examination should be performed.[25] The recommended regimen for both neurosyphilis and ocular syphilis is aqueous crystalline penicillin G 18-24 million units per day, given as 3-4 million units intravenously every 4 hours (or as continuous infusion), for a total of 10 to 14 days (Table 5).[20] If adherence to therapy can be ensured, an acceptable alternative regimen is intramuscular procaine penicillin G 2.4 million units once daily with probenecid 500 mg orally four times a day. Both agents are given for 10 to 14 days. It is important to note that some experts believe the duration of neurosyphilis therapy is not sufficient for treatment of late latent syphilis. Therefore, intramuscular benzathine penicillin G 2.4 million units once per week for up to 3 weeks can be considered after completion of a neurosyphilis regimen in order to provide a comparable total duration of therapy. In addition, systemic corticosteroids have been used by some experts or specialists as adjunctive therapy for otologic syphilis, but data are insufficient to support the use of systemic corticosteroid therapy for otologic syphilis or any other form of syphilis.

**Treatment of Neurosyphilis in Penicillin-Allergic Patients**

Limited data suggest that intramuscular or intravenous ceftriaxone 2 grams daily for 10 to 14 days can be used as an alternative treatment for persons with neurosyphilis.[20, 61] Other regimens have not been adequately studied for use in patients with neurosyphilis.

**TERTIARY SYPHILIS**

The recommended regimen for tertiary syphilis (not neurosyphilis) is benzathine penicillin G 7.2 million units total split into three weekly intramuscular injections of 2.4 million units (Table 6).[20] All persons diagnosed with tertiary syphilis should undergo a CSF examination prior to starting therapy. This is done because of the high rates of clinically inapparent neurosyphilis in patients with tertiary syphilis. Patients with tertiary syphilis have potential for a wide variety of sequelae and should be managed in consultation with a syphilis expert. Patients diagnosed with tertiary syphilis who have a documented penicillin allergy also should be treated in consultation with a syphilis expert; for these patients, there is no alternative therapy suggested in the STD Guidelines.[20]

**TREATMENT OF SYPHILIS IN PERSONS WITH HIV**
Available data suggest that persons with HIV who have early syphilis may have an increased risk of developing neurologic complications.[62] The extent of this increased risk has not been clarified and current CDC guidelines do not recommend routinely performing CSF examination in persons with HIV infection diagnosed with syphilis, but all persons with HIV infection and syphilis should undergo careful neurologic examination and those with abnormal findings should promptly undergo lumbar puncture for CSF examination.[20] There is no evidence that more intensive syphilis treatment improves outcomes or prevents neurosyphilis in persons with HIV infection who have early syphilis.[22] The recommended regimens for the treatment of syphilis in persons with HIV infection are the same as for persons without HIV infection (Table 7).[20] Initiation of antiretroviral therapy for HIV concurrently with syphilis treatment has been shown to reduce serologic failure rates for syphilis.[63]

**MISSING DOSES**

The decision to restart a treatment regimen in the event of missed doses of benzathine penicillin G remains somewhat unclear. Although clinical experience suggests that an interval of 10 to 14 days between doses for late latent syphilis (or latent syphilis with unknown duration) might be acceptable, the pharmacokinetic profile of benzathine penicillin G suggests an interval of 7 to 9 days between doses would be optimal.[64] Clinicians have differing practices within these limitations, but intervals greater than 14 days should always be restarted and pregnant women should repeat the full course if any doses are missed.[20,65]

**Syphilis in Pregnancy**

All pregnant persons diagnosed with syphilis should receive treatment according to stage of infection and whether there is any evidence of neurologic disease. Erythromycin is no longer an acceptable alternative drug for penicillin-allergic patients. Persons who are skin-test-reactive to penicillin should be desensitized in the hospital and treated with penicillin.[20] Some experts recommend giving a second dose of intramuscular benzathine penicillin G 2.4 million units 1 week after the initial dose for pregnant women who have primary, secondary, or early latent infection. Treatment of the mother during the last month of pregnancy or with a drug other than penicillin is not considered adequate treatment for the fetus. Pregnant women should be informed that treatment for syphilis may precipitate early labor and that they should notify an obstetrician if problems develop.

**Infants and Children with Syphilis**

The regimen for proven or highly probable and possible congenital syphilis is either 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 intramuscular procaine penicillin G 50,000 units/kg/dose in a single daily dose for 10 days. Neonates classified as possible congenital syphilis have the additional option of receiving treatment with intramuscular benzathine penicillin G 50,000 units/kg in a single dose. The single dose regimen is only acceptable if all elements of the neonate’s lab work-up were performed and unequivocally normal. In addition, follow-up must be assured. Neonates with disease classified as “congenital syphilis less likely” should be given benzathine penicillin G 50,000 units/kg/dose intramuscularly in a single dose. Neonates for whom congenital syphilis is deemed unlikely do not require therapy but should be followed to ensure that their nontreponemal titer returns to nonreactive (as mother’s antibodies are lost). For additional details regarding the diagnosis and management of congenital syphilis, refer to the 2015 STD Treatment Guidelines for information on the management of congenital and acquired syphilis in infants and children or the American Academy of Pediatrics' Red Book.[20] Diagnosis and treatment of congenital syphilis is complex and challenging and should be done in consultation with a congenital syphilis expert. Notably, infants and children with a history of penicillin allergy or who develop signs of allergic reaction during treatment with penicillin present a unique challenge and should be managed with close follow-up and consultation with a syphilis expert.

**Jarisch-Herxheimer Reaction**
The Jarisch-Herxheimer reaction is a self-limited reaction associated with initiation of anti-treponemal therapy that most often occurs in persons treated for early syphilis, presumably because bacterial burdens are higher during these stages. The Jarisch-Herxheimer reaction is characterized by fever, malaise, nausea, vomiting, and less frequently, chills and exacerbation of a secondary syphilis rash.[66] This reaction almost always occurs within 24 hours after initiating antimicrobial therapy and usually resolves within 24 hours. For patients who develop a Jarisch-Herxheimer reaction, the clinician should clarify this reaction is not an allergic reaction to penicillin. It occurs more frequently after treatment with penicillin and treatment of early syphilis, especially at the secondary stage. Antipyretics can be used to manage symptoms associated with the Jarisch-Herxheimer reaction, but they do not prevent this reaction.

Follow-Up

The follow-up of patients with syphilis is extremely important to document response to therapy and to reevaluate for reinfection. The following are general recommendations for follow-up after treatment.

- Patients treated for primary or secondary syphilis should be reexamined clinically and serologically 6 months and 12 months following treatment.
- Patients with latent syphilis should be followed up clinically and serologically at 6, 12, and 24 months.
- Persons with HIV infection should be evaluated more frequently; for primary or secondary syphilis at 3, 6, 9, 12, and 24 months and for latent syphilis at 6, 12, 18, and 24 months.
- If CSF pleocytosis was present initially, a CSF examination should be repeated every 6 months until the CSF cell count is normal. If the cell count has not decreased after 6 months, or if the CSF cell count or protein is not normal after 2 years, retreatment should be considered.
- Follow-up titers should be compared to the maximum or baseline nontreponemal titer obtained prior to treatment.

Treatment Failure

A key reason for close follow-up of patients treated for syphilis is to monitor signs, symptoms, or serologic changes that indicate possible treatment failure. There are no well-established, definitive criteria for treatment failure. Treatment failure cannot usually be differentiated from reinfection and thus persons suspected to have treatment failure or reinfection should be retested for HIV and should have a CSF evaluation for neurosyphilis (regardless of symptoms or prior CSF findings). Indications of probable treatment failure or reinfection include the following:

- A patient has persistent or recurring signs or symptoms.
- Repeat testing shows sustained fourfold increase in nontreponemal titer. These patients should be retreated and reevaluated for HIV infection. Because treatment failure may be a result of unrecognized central nervous system (CNS) infection, CSF examination should be considered.
- Failure of nontreponemal titers to decline fourfold within twelve months after therapy for primary or secondary syphilis may be indicative of treatment failure. Additional clinical and serological follow-up is necessary since the optimal management is unclear. Examination of CSF can be considered in these instances.[64] If follow-up cannot be ensured, retreatment is recommended.

When patients are retreated for primary, secondary, or latent syphilis (assuming no evidence of neurosyphilis), the recommended regimen is weekly intramuscular injections of benzathine penicillin G 2.4 million units for 3 weeks. If neurosyphilis is diagnosed, aqueous crystalline penicillin G 18-24 million units per day is given as 3 to 4 million units IV every 4 hours (or as continuous infusion), for a total of 10 to 14 days.[20] Refer to the 2015 STD Treatment Guidelines[20] for more detailed information on assessment and management of probable treatment failure.

Partner Management and Public Health Measures
In general, the transmission of *T. pallidum* between sex partners only occurs when the person with syphilis has mucocutaneous lesions. In general, all persons who have sexual contact with a person diagnosed with primary, secondary, or early latent syphilis infection should undergo evaluation and testing for syphilis. Potential treatment for syphilis depends on the circumstances, as recommended in the 2015 STD Treatment Guidelines and outlined below.[20]

- 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 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 greater than 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 needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and stage of syphilis.
- In some areas or populations with high rates of syphilis, health departments recommend notification and presumptive treatment of sex partners of persons with late latent syphilis who have high nontreponemal serologic test titers (i.e., greater than 1:32), because high titers might be indicative of early syphilis. These partners should be managed as if the index case had early syphilis.
- Long-term sex partners of persons who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated based on these findings.
- Certain sex partners of persons with syphilis are considered at risk for infection and should be confidentially notified of the exposure and the need for evaluation. These include partners who have had sexual contact within 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis, 6 months plus duration of symptoms for those with secondary syphilis, and 1 year for persons with early latent syphilis.

**Expedited Partner Therapy**

There is insufficient data to support the use of expedited partner therapy in management of syphilis contacts. Accordingly, use of expedited partner therapy is not recommended for sexual contacts of persons diagnosed with syphilis. Transmission of *T. pallidum* is highly unlikely in persons when more than 1 year has elapsed since the time of infection.
Patient Counseling and Education

Patient counseling and education should cover the nature of the disease, transmission, treatment, follow-up, and risk reduction.

Nature of the Disease

Syphilis may be symptomatic or asymptomatic and a wide range of symptoms and manifestations can develop with syphilis. Patients with untreated syphilis can have progressive and severe complications, including neurologic and cardiovascular disorders. Untreated syphilis in pregnancy can cause severe disability of the fetus. Treatment of syphilis is not universally effective and all patients need follow-up evaluation following treatment.

Transmission Issues

Syphilis is transmitted by having sex with someone who has syphilis, or via vertical transmission from an infected pregnant mother to her fetus. Syphilis is most infectious during the primary and secondary stages (when lesions or rashes are present) and persons infected with *T. pallidum* for longer than 1 year are unlikely to transmit syphilis to others. All sexual contacts of persons with syphilis need to undergo evaluation and possibly receive treatment. Syphilis is associated with increased susceptibility to HIV acquisition.

Risk Reduction

The following risk reduction plan is recommended for clinicians to assist persons in reducing their risk of reacquiring *T. pallidum* infection:

- Assess the patient’s potential for behavior change.
- Discuss prevention strategies such as abstinence, mutual monogamy with an uninfected partner, use of condoms, and limiting the number of sex partners.
- Discuss latex condoms, which when used consistently and correctly, can reduce the risk of syphilis transmission.
- Develop individualized risk-reduction plans.
Summary Points

- Syphilis is a systemic infection caused by *Treponema pallidum*, and in the absence of treatment, patients remain chronically infected and progress through stages of disease, characterized by episodes of active clinical manifestations interrupted by periods of asymptomatic latent infection.
- Of primary and secondary syphilis cases diagnosed in men who have sex with men, approximately one-half of the men are coinfected with HIV.
- Neurosyphilis and ocular syphilis can occur at any stage of infection.
- Untreated syphilis in pregnancy can lead to devastating consequences, including stillbirth, neonatal death, and congenital syphilis.
- The laboratory diagnosis of syphilis is challenging and requires using a combination of clinical criteria and laboratory tests (both treponemal and nontreponemal tests) to differentiate active infection, prior infection, and absence of infection.
- Screening for syphilis is recommended in all pregnant women, men who have sex with men, persons with HIV infection, and other groups at high risk for acquisition of syphilis.
- Penicillin G, administered parenterally, is the preferred drug for treatment of all stages of syphilis and is effective in resolving clinical symptoms associated with primary and secondary syphilis as well as preventing late sequelae.
- The Jarisch-Herxheimer reaction is a self-limited reaction associated with initiation of anti-treponemal therapy and is characterized by fever, malaise, nausea, vomiting, and less frequently, chills and exacerbation of a secondary syphilis rash.
- Persons who have had sexual contact within 90 days preceding that contact's diagnosis of primary, secondary, or early latent syphilis should receive presumptive treatment for early syphilis; if serologic testing is not immediately available, presumptive treatment should be started even if the sexual contact occurred more than 90 days prior.
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Figures

Figure 1 Syphilis Cases, United States, 1941-2019

NOTE: Data collection for syphilis began in 1941; however, syphilis became nationally notifiable in 1944. This graphic shows the number of reported cases of syphilis for all stages, primary and secondary, and early non-primary non-secondary.

Figure 2 Syphilis Cases, All Stages of Infection, United States, 2000-2019

Figure 3 Primary and Secondary Syphilis—Rates by Sex, 2012-2019

Figure 4 Primary and Secondary Syphilis — Distribution of Cases by Sex and Sex of Sex Partners, United States, 2019

Figure 5 Primary and Secondary Syphilis—Rates by Age Group in United States, 2019

Figure 6 Primary and Secondary Syphilis—Rates by Age and Sex in United States, 2019


*Per 100,000 population*
Figure 7 Primary and Secondary Syphilis—Rates by Race/Ethnicity in United States, 2019

Figure 8 Primary and Secondary Syphilis—Rates by United States Region, 2012-2019

Figure 9 Primary and Secondary Syphilis—Rates by United States Region, 2019

Figure 10 Primary and Secondary Syphilis—Rates by State in United States and Surrounding Areas, 2019

Figure 11 Congenital Syphilis — Reported Cases by Year of Birth, United States, 2005-2019

Figure 12 *Treponema pallidum*-Electron Micrograph

This electron micrograph shows the 'corkscrew' shape of *Treponema pallidum* growing in cultures of cottontail rabbit epithelium cells.

Source: Centers for Disease Control and Prevention Public Health Image Library (CDC/Dr. David Cox).
Figure 13 *Treponema pallidum*-Photomicrograph

This photomicrograph shows an isolated *Treponema pallidum* spirochete bacterium, which is approximately 6 to 20 micrometers in length and 0.1 to 0.18 micrometers in width.

Source: Centers for Disease Control and Prevention Public Health Image Library (CDC/Susan Lindsley, 1972).
Figure 14 Primary Syphilis—Penile Chancre

This patient with primary syphilis had a large firm ulcerated lesion on the penis accompanied by right-sided inguinal adenopathy.

Photograph credit: Negusse Ocbamichael, PA; Public Health—Seattle & King County STD Clinic
**Figure 15 Primary Syphilis—Oral Chancre**

This woman with primary syphilis developed an oral chancre at the right corner of her mouth. Syphilitic chancres are typically round, firm, and painless.

Figure 16 Secondary Syphilis-Diffuse Rash on Chest

This patient with secondary syphilis developed a diffuse erythematous macular rash prominent on the chest, back, palms, and soles.

Photograph credit: Negusse Ocbamichael, PA; Public Health—Seattle & King County STD Clinic
**Figure 17 Secondary Syphilis-Diffuse Rash on Back**

This patient with secondary syphilis developed a diffuse erythematous macular rash prominent on the chest and back.

Photograph credit: David H. Spach, MD
Figure 18 Secondary Syphilis—Maculopapular Rash on Palms of Hands

Source: photograph from Negusse Ocbamichael, PA; Public Health—Seattle & King County STD Clinic
Figure 19 Secondary Syphilis—Maculopapular Rash on Feet

Photograph credit: Negusse Ocbamichael, PA; Public Health—Seattle & King County STD Clinic
**Figure 20 Secondary Syphilis—Oral Lesions**

This patient with secondary syphilis had multiple shallow ulcerations on the tongue (black arrows).

Photograph credit: Negusse Ocbamichael, PA; Public Health—Seattle & King County STD Clinic
Figure 21 Secondary Syphilis—Condylomata lata

This patient with secondary syphilis developed multiple vulvar and intertriginous condylomata lata lesions; these lesions typically appear as moist, gray, raised papules, often resembling warts (condyloma acuminata).

Photograph credit: Centers for Disease Control and Prevention Public Health Image Library (CDC/J.Pledger, 1976).
Figure 22 Congenital Syphilis–Palatal Perforation

This photograph shows an intraoral view of the hard palate of a patient with congenital syphilis. The patient’s hard palate perforation was caused by congenital syphilis, which also perforated the nasal cavity.

Figure 23 Congenital Syphilis—Hutchinson’s Teeth

This photograph demonstrates the dentition within the oral cavity of a young African-American female patient with a history of congenital syphilis. The patient has a triangular-shaped deformity of an upper central incisor (top arrow) and a lower lateral incisor (lower arrow). These deformities are known as Hutchinson incisors and are caused by congenital syphilitic infection.

**Figure 24 Treponema pallidum-Dark-Field Microscopy**

This photomicrograph shows the typical 'corkscrew' appearance of several *Treponema pallidum* spirochetes with the dark-field microscopy technique.

Source: Centers for Disease Control and Prevention Public Health Image Library (CDC/Renelle Woodall, 1969).
Figure 25 *Treponema pallidum* Indirect Fluorescent Antibody (FA) Serologic Test

The fluorescent treponemal antibody absorption (FTA-ABS) test uses indirect fluorescent antibody technique in serum samples. This image shows abundant *Treponema pallidum* spirochetes with the use of a sample treated with Fluorescent Treponemal Antibody (FTA) antigen. The specimen shown here is enhanced by ultraviolet (UV) illumination.

Source: Centers for Disease Control and Prevention Public Health Image Library (CDC/Russell, 1967).
Figure 26 Syphilis Serologic Screening—Traditional Sequence Algorithm

The traditional (standard) serologic screening sequence algorithm uses a quantitative nontreponemal test (RPR or VDRL) for screening followed by a treponemal test for confirmation of positive screening tests. Abbreviations: RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory; TP-PA = *Treponema pallidum* particle agglutination.
Figure 27 Syphilis Serologic Screening—Reverse Sequence Algorithm

The reverse serologic screening algorithm uses an initial treponemal test for screening, followed by a nontreponemal test confirmation. A specimen with reactive EIA/CIA results should be tested reflexively with a quantitative nontreponemal test (RPR or VDRL). Abbreviations: EIA = enzyme immunoassay; CIA = chemiluminescence immunoassays; RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory; TP-PA = Treponema pallidum particle agglutination.

Table 1.

**Sensitivity and Specificity of Common Serological Tests in Untreated Syphilis**

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary</th>
<th>Secondary</th>
<th>Latent</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDRL</td>
<td>78 (74-87)</td>
<td>100</td>
<td>95 (88-100)</td>
<td>71 (37-94)</td>
</tr>
<tr>
<td>RPR</td>
<td>86 (77-99)</td>
<td>100</td>
<td>98 (95-100)</td>
<td>73</td>
</tr>
<tr>
<td>FTA-ABS</td>
<td>84 (70-100)</td>
<td>100</td>
<td>100</td>
<td>96</td>
</tr>
<tr>
<td>TP-PA</td>
<td>88 (86-100)</td>
<td>100</td>
<td>100</td>
<td>NA</td>
</tr>
<tr>
<td>ELISA (IgG)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>NA</td>
</tr>
</tbody>
</table>

*FTA-ABS and TP-PA are generally considered equally sensitive in the primary stage of disease.*

**Abbreviations**

NA = not available
VDRL = Venereal Disease Research Laboratory
RPR = Rapid Plasma Reagin
FTA-ABS = Fluorescent Treponemal Antibody Absorbed
TP-PA = *Treponema pallidum*-Particle agglutination
ELISA = Enzyme Linked Immunoassay

Source:

### Table 2.

**Indications for Cerebrospinal Fluid Testing in Patients with Syphilis**

#### Indications for Cerebrospinal Fluid (CSF) Analysis at Initial Diagnosis of Syphilis

- Signs or symptoms suggesting neurologic disease (e.g. cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis or stroke)
- Signs or symptoms suggesting ophthalmic disease (e.g., new visual changes, uveitis, iritis, neuroretinitis, or optic neuritis)
- Diagnosis of tertiary syphilis (e.g. aortitis, gumma)
- Neonates (age younger than 30 days) with proven, highly probable, or possible congenital syphilis
- Infants and children 1 month or older diagnosed with latent syphilis

#### Indications for Cerebrospinal Fluid Analysis in Patients Following Treatment for Syphilis

- As follow-up for patients with CSF pleocytosis present at time of initial CSF examination, a CSF examination should be repeated every 6 months until the cell count is normal (CSF-VDRL or CSF protein may lag or fail to normalize)
- Suspected treatment failure with signs or symptoms that persist or recur (in patients that have not had reexposure)
- Suspected treatment failure with fourfold or greater increase in nontreponemal test titer that persists longer than 2 weeks
- An initially high titer (1:32 or higher) that fails to decline at least fourfold within 12 to 24 months following treatment
- Treated neonates with persistent nontreponemal titers by 6-12 months
- Neonates with abnormal initial CSF evaluations should undergo a repeat lumbar puncture approximately every 6 months until the results are normal

#### Consider Cerebrospinal Fluid Analysis

- Patients with neurologic symptoms that are non-classic, very mild, or not readily explained by other diagnoses
- Patients with less than a fourfold decline in titers after treatment of syphilis
Table 3. 2015 STD Treatment Guidelines: Primary and Secondary Syphilis
Treatment of Primary and Secondary Syphilis

<table>
<thead>
<tr>
<th>Recommended for Adults</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzathine penicillin G</strong></td>
<td></td>
</tr>
<tr>
<td>2.4 million units IM in a single dose</td>
<td></td>
</tr>
</tbody>
</table>

Note: Available data demonstrate that use of additional doses of benzathine penicillin G, amoxicillin, or other antibiotics do not enhance efficacy when used to treat primary and secondary syphilis, regardless of HIV status.

<table>
<thead>
<tr>
<th>Recommended for Infants and Children</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzathine penicillin G</strong></td>
<td></td>
</tr>
<tr>
<td>50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose</td>
<td></td>
</tr>
</tbody>
</table>

Note: Infants and children aged ≥1 month with primary or secondary syphilis should be managed by a pediatric infectious disease specialist and evaluated for sexual abuse (e.g., through consultation with child-protection services)

### Table 4. 2015 STD Treatment Guidelines: Latent Syphilis

#### Treatment of Latent Syphilis

**Recommended for Adults with Early Latent Syphilis**

**Benzathine penicillin G**

- **2.4 million units IM in a single dose**

*Note: Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in early latent syphilis do not enhance efficacy, regardless of HIV infection.*

**Recommended for Adults with Late Latent Syphilis or Latent Syphilis of Unknown Duration**

**Benzathine penicillin G**

- **7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals**

**Recommended for Infants and Children with Early Latent Syphilis**

**Benzathine penicillin G**

- **50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose**

*Note: Infants and children aged ≥1 month diagnosed with latent syphilis should be managed by a pediatric infectious disease specialist and receive a CSF examination. These regimens are for penicillin nonallergic children who have acquired syphilis and who have normal CSF examination results.*

**Recommended for Infants and Children with Late Latent Syphilis**

**Benzathine penicillin G**

- **50,000 units/kg IM, up to the adult dose of 2.4 million units, administered as 3 doses at 1-week intervals (total 150,000 units/kg up to the adult total dose of 7.2 million units)**

*Note: Infants and children aged ≥1 month diagnosed with latent syphilis should be managed by a pediatric infectious disease specialist and receive a CSF examination. These regimens are for penicillin nonallergic children who have acquired syphilis and who have normal CSF examination results.*

Table 5. 2015 STD Treatment Guidelines: Neurosyphilis

### Treatment of Neurosyphilis

#### Recommended for Treatment of Neurosyphilis and Ocular Syphilis

<table>
<thead>
<tr>
<th>Aqueous crystalline penicillin G</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-24 million units per day, administered as 3-4 million units IV every 4 hours or continuous infusion, for 10-14 days</td>
</tr>
</tbody>
</table>

Note: The durations of the recommended and alternative regimens for neurosyphilis are shorter than the duration of the regimen used for latent syphilis. Therefore, benzathine penicillin G, 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

#### Alternative for Treatment of Neurosyphilis and Ocular Syphilis

<table>
<thead>
<tr>
<th>Procaine penicillin G + Probenecid</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4 million units IM once daily for 10-14 days + 500 mg orally four times a day for 10-14 days</td>
</tr>
</tbody>
</table>

If compliance with therapy can be ensured, this alternative regimen might be considered.

Note: The durations of the recommended and alternative regimens for neurosyphilis are shorter than the duration of the regimen used for latent syphilis. Therefore, benzathine penicillin G 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

Table 6. 2015 STD Treatment Guidelines: Tertiary Syphilis
Treatment of Tertiary Syphilis

Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin.

<table>
<thead>
<tr>
<th>Recommended for Treatment of Tertiary Syphilis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzathine penicillin G</td>
</tr>
<tr>
<td>7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals</td>
</tr>
</tbody>
</table>

### Table 7. 2015 STD Treatment Guidelines: Syphilis in Persons with HIV Infection

**Treatment of Syphilis in Persons with HIV Infection**

**Recommended for Treatment of Primary and Secondary Syphilis in Persons with HIV Infection**

Benzathine penicillin G  
2.4 million units IM in a single dose

*Note:* Available data demonstrate that additional doses of benzathine penicillin G, amoxicillin, or other antibiotics in primary and secondary syphilis do not result in enhanced efficacy.

**Recommended for Treatment of Early Latent Syphilis in Persons with HIV Infection**

Benzathine penicillin G  
2.4 million units IM in a single dose

**Recommended for Treatment of Late Latent Syphilis in Persons with HIV Infection**

Benzathine penicillin G  
7.2 million units total, administered as 3 doses of 2.4 million units IM each at 1-week intervals

**Recommended for Treatment of Neurosyphilis and Ocular Syphilis in Persons with HIV Infection**

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

*Note:* The durations of the recommended and alternative regimens for neurosyphilis are shorter than the duration of the regimen used for latent syphilis. Therefore, benzathine penicillin, 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

**Alternative for Treatment of Neurosyphilis and Ocular Syphilis in Persons with HIV Infection**

Procaine penicillin G  
2.4 million units IM once daily x 10-14 days  
+  
Probenecid  
500 mg orally four times a day for 10-14 days

If compliance with therapy can be ensured, this alternative regimen might be considered.  
*Note:* The durations of the recommended and alternative regimens for neurosyphilis are shorter than the duration of the regimen used for latent syphilis. Therefore, benzathine penicillin G, 2.4 million units IM once per week for up to 3 weeks, can be considered after completion of these neurosyphilis treatment regimens to provide a comparable total duration of therapy.

Source: Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases