# Table of Contents

## Summary  
3

## Basics  
4

- **Definition**  
4
- **Epidemiology**  
4
- **Etiology**  
4
- **Pathophysiology**  
5
- **Classification**  
5

## Prevention  
7

- **Primary prevention**  
7
- **Screening**  
7
- **Secondary prevention**  
8

## Diagnosis  
10

- **Case history**  
10
- **Step-by-step diagnostic approach**  
10
- **Risk factors**  
17
- **History & examination factors**  
18
- **Diagnostic tests**  
23
- **Differential diagnosis**  
28

## Treatment  
30

- **Step-by-step treatment approach**  
30
- **Treatment details overview**  
32
- **Treatment options**  
34
- **Emerging**  
44

## Follow up  
45

- **Recommendations**  
45
- **Complications**  
46
- **Prognosis**  
47

## Guidelines  
48

- **Diagnostic guidelines**  
48
- **Treatment guidelines**  
49

## Online resources  
50

## References  
51

## Images  
59

## Disclaimer  
73
Syphilis is a common sexually transmitted infection. An estimated 6 million new infections occurred worldwide in 2016.

Caused by the spirochetal bacterium Treponema pallidum, subspecies pallidum.

Clinical presentation is often asymptomatic, but can manifest in a number of ways.

A painless ulcer (chancre) in the anogenital region is a hallmark of primary infection.

Diagnosis is usually straightforward after clinical exam and serologic tests. Treatment is with penicillin.

Untreated syphilis facilitates HIV transmission and causes considerable morbidity, such as cardiovascular and neurologic disease, as well as a congenital syndrome in the newborn.

Syphilis in pregnancy is a major cause of miscarriage, stillbirth, and perinatal morbidity and mortality in some parts of the world.
Definition

Syphilis is a sexually transmitted infection caused by the spirochetal bacterium *Treponema pallidum*, subspecies *pallidum*. It is found only in human hosts. Acquired infection is transmitted through direct person-to-person sexual contact with an individual with early (primary or secondary) syphilis. Most sexual transmission of syphilis probably occurs from direct contact with syphilitic lesions on the genitals or mucous membranes. Transmission from mother to fetus during pregnancy causes congenital infection. Syphilis has often been described as the great imitator because many of the symptoms and signs are difficult to distinguish from other diseases.[1]

Epidemiology

Syphilis is a common STI. There were an estimated 6 million new cases of syphilis worldwide in 2016.[8]

In 2017, the incidence rate of primary and secondary syphilis was 9.5 cases in 100,000 population (30,644 new cases).[9] This represents a 10.5% increase from 2016 (8.6 cases in 100,000 population), and a 72.2% increase from 2013 (5.5 cases in 100,000 population). Over half (57.9%) of all reported cases of primary and secondary syphilis occurred in men who have sex with men (MSM). The incidence rate of primary and secondary syphilis was 16.9 cases in 100,000 men in 2017, and 2.3 cases in 100,000 women.[9] In men, the incidence rate was highest in the age group 25-29 years, followed by age groups 20-24 years and 30-34 years (incidence was similar in these two age groups). In women, the highest rate was in the age group 20-24 years, followed by age group 25-29 years.

In 2017, the incidence rate of primary and secondary syphilis was highest in black people (24.2 cases in 100,000 population).[9] The incidence rate in black people was 4.5 times higher than in white people (5.4 cases in 100,000 population). From 2013-2017, rates have increased among all race/ethnicity groups. Between 2016-2017, the greatest increase was observed among American Indians/Alaska Natives (38.8%), and those identified as multiracial (31.7%), followed by Asians (15.7%), white people (10.2%), Native Hawaiians/other Pacific Islanders (9.4%), Hispanics (9.3%), and black people (5.7%).[9]

The incidence of congenital syphilis in 2017 was 23.3 cases in 100,000 live births (628 cases); a 43.8% increase from 2016 (16.2 cases in 100,000 live births) and a 153.3% increase from 2013 (9.2 cases in 100,000 live births).[9]

Etiology

Syphilis is caused by *Treponema pallidum* subspecies *pallidum*, a motile spirochete bacterium. Humans are the only natural host. In-vitro culture is not possible. Entry of *T pallidum* probably occurs via areas of minor abrasion (at genital and mucous membrane sites) that result from trauma during sexual intercourse.[10]

Orogenital sex is an important route of transmission and, therefore, transmission can occur despite the use of condoms.[11][12] The risk of acquiring syphilis after sex with someone with primary or secondary syphilis is between 30% and 60%.[13][14] Other modes of transmission are blood transfusion and transplacental transmission from mother to fetus.
Pathophysiology

Primary syphilis is characterized by ulceration (usually a solitary painless ulcer [chancre]) and local lymphadenopathy. The primary syphilis ulcer contains the *Treponema pallidum* bacterium and is characterized by mononuclear leukocytic infiltration. It heals spontaneously.

Secondary syphilis is caused by hematogenous spread of *T. pallidum*. This leads to a widespread vasculitis. The mucocutaneous lesions of secondary syphilis also contain treponemes. The reasons for the resolution of secondary syphilis are unclear, but are likely to be related to a combination of macrophage-driven uptake of opsonized spirochetes and cell-mediated immunity.

Perivascular infiltrates composed principally of lymphocytes, histiocytes (macrophages), and plasma cells, accompanied by varying degrees of endothelial cell swelling and proliferation, are the histologic hallmarks of primary and secondary syphilis lesions. Likewise, *T. pallidum* spirochetes are abundant in early syphilis lesions and are often observed in and around blood vessels and migrating from the dermis into the epidermis.

It is estimated that 15% to 40% of patients with untreated syphilis progress to tertiary syphilis (late symptomatic disease),[6] which includes neurosyphilis, gummatous syphilis, and cardiovascular syphilis. The theory that cell-mediated immunity is important in controlling syphilis infection is supported by the observation that progression to neurosyphilis may be more common in patients coinfected with HIV.

Neurosyphilis may occur at any stage of infection with syphilis, and is characterized by a chronic, insidious inflammation of the meninges. It may occur in up to 10% of patients with untreated syphilis.[15] Neurosyphilis is caused by central nervous system invasion by the *T. pallidum* bacterium. Early neurosyphilis syndromes are usually the result of meningovascular involvement; late neurosyphilis may occur due to meningovascular involvement or direct infection of the brain and spinal cord parenchyma. Parenchymal infection of the spinal cord by *T. pallidum* results in tabes dorsalis. This condition is predominantly due to dorsal column loss. General paresis occurs with parenchymal involvement of the brain with neuronal loss.

Cardiovascular syphilis is characterized by aortic involvement as the *T. pallidum* bacterium causes occlusion of the aortic vasa vasorum resulting in necrosis of the tunica media. Long-term inflammation and scarring weakens the aortic wall, leading to aortic aneurysm formation, as well as aortic incompetence and angina due to narrowing of the coronary ostia.

The hallmark of gummatous syphilis is the appearance of lesions on the skin, liver, bones, and testes. These lesions consist of granulomatous rubbery tissue with a necrotic center, and they may gradually replace normal tissue. *T. pallidum* is rarely found within these lesions.

Classification

Classification according to transmission

Acquired syphilis:

- Transmission through direct person-to-person sexual contact with an individual with early (primary or secondary) syphilis.

Congenital syphilis:
• Transmission of syphilis from the mother to the fetus during pregnancy
• May result in miscarriage, stillbirth, or neonatal death[2]
• Subdivided into:
  • Early (clinical manifestations occur from birth to 2 years of age)
  • Late (clinical manifestations occur >2 years of age).

**Acquired syphilis, classified according to stage of infection**[3]

**Primary syphilis:**

• Initial inoculation of *Treponema pallidum* causes local infection
• A single macule develops, which changes into a papule and then ulcerates, forming a chancre 9-90 days after exposure (usually 14-21 days after exposure).

**Secondary syphilis:**

• Clinical features develop 4-8 weeks after primary syphilis infection
• Characterized by spirochetemia and widespread dissemination of *T pallidum* to the skin and other tissues.

**Early latent syphilis:**

• Asymptomatic infection diagnosed on the basis of positive serology alone, acquired <1 year previously (according to Centers for Disease Control and Prevention [CDC] criteria) or <2 years previously (according to World Health Organization [WHO] criteria)[4] [5]
• Relapse to secondary syphilis may occur during the early latent stage.

**Late latent syphilis:**

• Asymptomatic infection acquired >1 year previously (according to CDC criteria) or >2 years previously (according to WHO criteria)[4] [5]
• The patient is not known to have been seronegative within the past year (according to CDC criteria) or past 2 years (according to WHO criteria).[4] [5]

**Tertiary syphilis:**

• It is estimated that 15% to 40% of patients with untreated syphilis progress to tertiary syphilis (late symptomatic disease)[6]
• Characterized by chronic end-organ complications, often many years after initial infection
• Includes cardiovascular syphilis, neurosyphilis, and gummatous syphilis.
Primary prevention

Protected sexual intercourse using condoms reduces the transmission of acquired syphilis.[21] However, orogenital sex is an important route of transmission and can occur despite the use of condoms.[11][12] There is no significant evidence to suggest that male circumcision reduces the incidence of syphilis.[22] National screening programs are in place prior to blood donation and as part of prenatal care during pregnancy. Prenatal screening aims to identify and treat asymptomatic women, thus preventing transplacental transmission.[20]

One open-label randomized trial found that post-exposure prophylaxis with a single dose of doxycycline in high-risk men who have sex with men reduced the risk of syphilis compared with no post-exposure prophylaxis at 10-month follow-up (hazard ratio: 0.27; 95% CI: 0.07 to 0.98; p = 0.047).[23]

Screening

Screening for syphilis is important for the following reasons:

- Syphilis infection is often asymptomatic but highly transmissible
- If untreated it causes in-utero mortality and considerable morbidity many years after initial infection
- Treatment of syphilis in the early stage of infection is curative and aims to halt disease progression and eliminate further transmission of infection
- Syphilis is an important facilitator of HIV transmission.

Screening is undertaken in:

- Asymptomatic patients who are at risk of the infection[73]
- Pregnant women [USPSTF: syphilis infection in pregnant women - screening]
- Blood donors.[74]

Screening tests

Many laboratories employ a "reverse sequence screening algorithm" whereby a treponemal serology test is used as the initial screening test (usually the treponemal enzyme immunoassay). A treponemal test will identify patients with an infection, but it cannot distinguish between an active infection (i.e., currently untreated or incompletely treated) and a past (treated) infection.[5] [36] [73]

False-negative results may occur in incubating and early primary syphilis. False-positive results may occur with other nonsexually transmitted treponemal infection (e.g., yaws, pinta, bejel).[38]

If the treponemal test is positive, a nontreponemal test, such as the Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) test, should be performed to confirm the diagnosis and provide evidence of active disease or reinfection. These tests enable a quantitative value of disease activity (titer) to guide treatment. If the nontreponemal test is subsequently negative, then a different treponemal test should be performed to confirm the results of the initial test.[5]

An alternative approach to screening is the use of a nontreponemal test (VDRL or RPR) as the initial test. Positive tests need to be confirmed by using a treponemal test because false-positive results can occur due to other medical conditions (e.g., pregnancy, autoimmune disorders, other infections).

In resource-poor countries and in nonclinical settings, rapid point-of-care tests (which are recommended by the World Health Organization [WHO]) may have an important role in the control of syphilis and the prevention of adverse outcomes associated with syphilis in pregnancy.[75] [76]
Screening in STI clinic

All patients with an STI should have syphilis screening, as should patients at higher risk of STIs, irrespective of where they are seen. [USPSTF: Syphilis infection in nonpregnant adults and adolescents: screening] This includes men who have sex with men (MSM), HIV-infected patients, people with multiple sexual partners, commercial sex workers, and people exchanging sex for drugs.[77] [73] [78] [CDC: sexually transmitted disease surveillance, 2017]

Prenatal screening

Screening of all pregnant women for syphilis infection is recommended by the US Preventive Services Task Force, the Centers for Disease Control and Prevention, the WHO, and the UK National Screening Committee.[4] [5] [79] [73] [80] [USPSTF: syphilis infection in pregnant women - screening] [NSC: the UK NSC recommendation on syphilis screening in pregnancy]

Syphilis serology should be performed on all pregnant women at the first prenatal visit, or as early as possible in pregnancy.[5] [USPSTF: syphilis infection in pregnant women - screening] Serology should be repeated again early in the third trimester and at delivery if serology has been positive, or if there is high maternal risk of syphilis acquisition.[5] The syphilis serologic status of the mother should be determined prior to discharge of the infant from the hospital.[5] Prenatal screening is cost-effective, even in areas of low prevalence.[81] Any woman who gives birth to a stillborn infant should be tested for syphilis, and all pregnant women who have syphilis should be tested for HIV.[5]

Prenatal screening detects syphilis infection in asymptomatic pregnant women, enabling treatment to prevent infection in newborns (congenital syphilis), and other associated risks such as miscarriage, stillbirth, or neonatal death.[66] Evidence strongly supports prenatal syphilis screening and early treatment as a measure for preventing congenital syphilis.[82] [83] [80] [84] [85] [86] [USPSTF: syphilis infection in pregnant women - screening]

Clinics that provide on-site rapid syphilis testing, and immediate treatment for positive cases and their partners, may reduce the rate of congenital syphilis in regions where lack of awareness of syphilis infection, and problematic access to prenatal syphilis screening services, are potential issues.[87]

Screening low-risk asymptomatic population

Screening is not recommended if the patient is asymptomatic and not at increased risk of syphilis infection. Given the low incidence of syphilis infection in the general population and the consequent low yield of screening, the potential harms (e.g., of false-positives) of screening in a low-incidence population may outweigh the benefits.[73]

Screening for HIV and other STIs

All patients with syphilis should be screened for chlamydia, gonorrhea, and blood-borne viruses such as hepatitis B and C. All patients with syphilis should be tested for HIV.[5] Syphilis is an important facilitator of HIV transmission. Coinfection is disproportionately high among MSM, particularly those on antiretroviral therapy.[16] [27] A high level of suspicion for the testing and treatment of syphilis in patients with HIV is advisable. In geographic areas in which the prevalence of HIV is high, patients who have primary syphilis should be retested for HIV after 3 months even if the first HIV test result is negative.[5] In patients with HIV, serologic responses to infection may be atypical, with high, low, or fluctuating titers.

Secondary prevention

All patients with syphilis should be screened for chlamydia, gonorrhea, and blood-borne viruses, such as hepatitis B and C. All patients with syphilis should be tested for HIV.[5] Syphilis is an important facilitator of HIV transmission. All patients with syphilis should be offered hepatitis B vaccination. Sexual contacts of patients with confirmed syphilis should be screened and offered presumptive treatment if follow-up may be problematic.[5] Antibiotics are the only treatment available for syphilis infection.

Strengthening STI services may have an important role in controlling STIs.[105]

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Preventive treatment when there has been sexual contact with an infected person:[5]

- People exposed within 90 days preceding diagnosis of primary, secondary, or early latent syphilis in a sexual partner should be treated presumptively, on the basis that they may be infected even if seronegative. It is estimated that 30% to 60% of sexual partners of people with early syphilis will develop the infection.[13][14]
- People exposed more than 90 days before diagnosis of primary, secondary, or early latent syphilis in a sexual partner should be treated presumptively if syphilis serology is not available immediately and if follow-up may be problematic.
- Treatment of long-term sexual partners of patients with latent syphilis is dependent on clinical evaluation and serology results.

At-risk time intervals:[5]

- For primary syphilis: exposure 3 months before treatment, plus duration of symptoms.
- For secondary syphilis: 6 months plus duration of symptoms.
- For early latent syphilis: 1 year.

The identification and treatment of syphilis should be used as an opportunity to promote safe-sex awareness, encourage condom use, and highlight health impacts associated with high risk behavior, such as illicit drug use. Conditional cash incentives to encourage safe sexual practices have demonstrated potential in rural Tanzania.[106]

In the US, syphilis is a nationally notifiable disease, as per the Centers for Disease Control and Prevention. Providers should contact their local state health department for details.

In cases of sexual assault, UK guidelines recommend that prophylaxis should be considered if the perpetrator is known to have infectious syphilis.[49]
Case history

Case history #1

A 27-year-old man notes a painless penile ulcer. He has recently started a new relationship. He is otherwise asymptomatic, as is his partner. On exam, the ulcer is indurated and the inguinal lymph nodes are rubbery and moderately enlarged.

Case history #2

A 30-year-old man presents with difficulty hearing conversations while in a crowded room. Following referral for audiometry, bilateral high-frequency hearing loss is diagnosed. On further questioning he reports a past history of an anal fissure about 10 weeks previously that healed spontaneously. He also describes a mild transient skin rash 2 weeks before his auditory symptoms appeared. He says that he has been feeling unusually tired.

Other presentations

The chancre (syphilitic ulcer) of primary syphilis is usually a solitary, painless, clean ulcer with an indurated base. Less commonly, there may be multiple or painful ulcers. This presentation may represent coinfection with chancroid or genital herpes. Uncommon presentations of secondary syphilis include specific organ involvement, such as hepatitis, iritis, choroidoretinitis, glomerulonephritis, nephrotic syndrome, neurosyphilis involving cranial nerves (particularly the eighth cranial nerve), and meningitis.[7] Gummata are an extremely rare manifestation of tertiary (late) syphilis. Gummatus syphilis (also known as benign tertiary syphilis) usually affects skin and bone but can also affect visceral organs, causing organomegaly or infiltrative or destructive lesions, as well as perforation or collapse of affected structures.

Step-by-step diagnostic approach

Patients with signs and symptoms of syphilis should undergo diagnostic testing. In patients with asymptomatic infection, diagnosis relies on routine screening.

History

Eliciting a history of sexual activity and risk factors is important when considering the diagnosis of syphilis. People at high risk of infection include those who have had sexual contact with an infected person, men who have sex with men (MSM), people infected with HIV or other STIs, people with multiple sexual partners, commercial sex workers, and people using illicit drugs. Pregnant women with syphilis are at risk of transmitting the infection transplacentally to the fetus.

It is important to establish whether a patient has a history of syphilis (and past treatment), as this can help with the interpretation of diagnostic test results and help confirm the stage of infection.
Signs and symptoms of primary syphilis

A solitary painless genital ulcer (chancre) in the anogenital or cervix area strongly suggests a diagnosis of primary syphilis.[24] It may not always be noticed by the patient and examining physician, and it heals spontaneously. There may also be discrete, painless, rubbery regional lymphadenopathy. Mouth ulceration may occur in primary infection. When this occurs, the ulcer is confined to the mouth.

Atypically, ulceration may be multiple and painful. Coinfection with genital herpes or chancroid may be a cause of painful ulceration. Coinfection with HIV may result in multiple ulcers. Approximately 30% of HIV antibody-negative and 70% of HIV antibody-positive patients with primary syphilis have multiple genital ulcers.

Signs and symptoms of secondary syphilis

Patients may develop clinical features of secondary syphilis 4 to 8 weeks after primary syphilis infection. The presentation of secondary syphilis is diverse. The disseminated treponemal infection has multisystem manifestations. Patients may describe constitutional symptoms including fever, malaise, myalgia, fatigue, or arthralgia. They may also notice generalized lymphadenopathy. These features may be mistaken for an intercurrent viral illness or primary HIV infection. There may be a generalized symmetric macular, papular, or maculopapular, diffuse rash, typically affecting the palms of the hands and plantar aspects of the feet. The rash may also occur on the trunk and scalp. Occasionally the papules may ulcerate. There may be generalized mucosal ulceration, causing "snail-track” ulcers on the buccal mucosa, and erosions on the genitalia. There may be flesh-colored wart-like lesions in the genital area, known as condylomata lata. Patchy alopecia may develop.

Uncommon presentation includes specific organ involvement. Symptoms of headache, meningismus, hearing loss, seizures, or neuropathy suggest neurologic involvement. Neurosyphilis may occur at any stage of infection with syphilis, and may occur in up to 10% of patients with untreated syphilis.[15] Visual changes due to syphilitic iritis, uveitis, and choroidoretinitis may initially present to ophthalmologic services.[25] The vasculitis due to secondary syphilis may cause a nephrotic syndrome, glomerulonephritis, or hepatitis.

Up to 25% of people who have untreated secondary syphilis go on to develop relapsing episodes of secondary syphilis. Symptoms include rash and fever. These relapsing episodes rarely occur more than 1 year after acquiring syphilis.

Latent syphilis

Latent syphilis is defined as positive serology in the absence of clinical features of syphilis. Early latent syphilis is defined as asymptomatic infection that is diagnosed on the basis of positive serology alone, acquired <1 year previously (according to the Centers for Disease Control and Prevention [CDC]) or <2 years previously (according to the World Health Organization [WHO]).[4] [5]
Syphilis infection

Late latent syphilis is defined as asymptomatic infection that is acquired >1 year previously (CDC) or >2 years previously (WHO). The patient is not known to have been seronegative within the past year (CDC) or past 2 years (WHO).

Signs and symptoms of tertiary syphilis

It is estimated that 15% to 40% of patients with untreated syphilis progress to tertiary syphilis (late symptomatic disease). Tertiary syphilis is characterized by chronic, end-organ complications, often many years after initial infection. The diagnosis may be suspected from a past history of features of earlier-stage disease and the presence of risk factors.

Neurosyphilis may involve damage to the dorsal columns of the spinal cord, causing a syndrome known as tabes dorsalis. Features of tabes dorsalis include:

- Ataxia
- Loss of anal and bladder sphincter control
- Argyll-Robertson pupils
- Areflexia
- Dorsal column loss (loss of vibration and proprioception/position sense)
- Romberg sign.

Brain involvement causes a range of syndromes, including cognitive and motor impairment, which are sometimes grouped under the broad term "general paresis". Features of general paresis may include:

- Personality change
- Memory impairment
- Altered mood
- Confusion
- Seizures
- Tremor
- Argyll-Robertson pupils.

A neurology or psychiatric consultation is required if neurosyphilis or brain involvement is suspected.

Cardiovascular syphilis usually affects the aortic root, causing an aortitis, which results in aortic regurgitation. Angina may arise as a result of coronary ostial stenosis. Aortic medial necrosis may cause aortic aneurysm. The cardiac murmur of aortic regurgitation and/or symptoms and signs of heart failure or aortic aneurysm on clinical exam require a cardiology consult.

Gummatous syphilis (also known as benign tertiary syphilis) affects skin and visceral organs, causing organomegaly and infiltrative or destructive lesions, as well as perforation or collapse of affected structures. Gumma lesions consist of granulomatous rubbery tissue with a necrotic center. The destructive lesions may gradually replace normal tissue. Gummata are an extremely rare manifestation of late syphilis, with the commonest presentation being chronic skin ulceration and nodular infiltration.

HIV coinfection

Syphilis is an important facilitator of HIV transmission. MSM are at particular risk of coinfection with HIV. The presence of HIV may alter the presentation of syphilis.
Syphilis infection

Diagnosis

- Primary syphilis: larger, painful multiple ulcers.
- Secondary syphilis: genital ulcers more common and higher titers with rapid plasma reagin (RPR) testing and Venereal Disease Research Laboratory (VDRL) testing.
- Possibly more rapid progression to neurosyphilis.
- Serologic responses to infection may be atypical.[25]

Signs and symptoms of congenital syphilis

Congenital syphilis occurs when the fetus acquires the infection transplacentally from the mother. This may result in miscarriage, stillbirth, or neonatal death.[2] Intrauterine features such as hydrops may be detected on fetal ultrasound scanning. Postnatal manifestations are divided into early and late stages; early manifestations occur in the first 2 years of life, and late manifestations occur after 2 years of age.

The diagnosis of congenital syphilis is suspected, taking into account various factors, including:[5]

- Identification of syphilis in the mother
- Adequacy of maternal treatment
- Presence of clinical, laboratory, or radiographic evidence of syphilis in the infant (testing should include paired maternal and neonatal nontreponemal serologic titers using the same test, preferably conducted at the same laboratory).

Most clinical signs are not visible at birth, but usually develop within 3 months. A highly infectious rhinitis, which may be purulent or blood-stained, may persist and is one of the earliest signs. Other early signs (occurring within 2 years) include hepatosplenomegaly, glomerulonephritis and nephrotic syndrome, generalized lymphadenopathy, central nervous system (CNS) involvement (including cerebrospinal fluid [CSF] abnormalities and syphilitic meningitis), and bone involvement (e.g., osteochondritis).[6][28] A neonatal skin rash may occur and may be similar to the rash of secondary syphilis in adults. It may also be more widespread, bullous or papulonecrotic, or desquamating. Initially, the rash may be vesicular with small blisters appearing on the palms and plantar surfaces of the feet. An erythematous or maculopapular rash, which is often copper-colored, may subsequently appear on the face, palms, and plantar surfaces of the feet. Necrotizing funisitis (inflammation of the umbilical cord) is virtually diagnostic of congenital syphilis and is found usually in preterm infants who are stillborn or die within a few weeks of birth. The umbilical cord has a specific appearance known as the “barberpole” cord as a result of inflammation of the matrix of the umbilical cord.[6][29]

[Fig-9]

[Fig-10]

Untreated congenital syphilis may present late (after 2 years of age). It is important to distinguish late congenital syphilis from postnatally acquired syphilis, as the latter raises the suspicion of child sexual abuse and should be investigated further.[30]

Late congenital syphilis has several distinct findings, including:[28]

[Fig-11]

[Fig-12]

[Fig-13]

[Fig-14]
Syphilis infection

Diagnosis

• Interstitial keratitis
• Peg-shaped central incisors, notched at the apex (Hutchinson teeth)
• Eighth cranial nerve deafness
• Frontal bossing of the skull
• Anterior bowing of the shins (Saber shins)
• Saddle nose deformity
• Clutton joints (symmetric painless knee swelling).

Interstitial keratitis, Hutchinson teeth, and eighth cranial nerve deafness are collectively known as Hutchinson triad.

Initial investigations for acquired syphilis*

Microscopic tests:

Culture of *Treponema pallidum* in vitro is not possible. Dark-field microscopy of the skin lesion can provide a definitive diagnosis of syphilis, but this test is not usually available outside specialist settings. The lesion is cleansed and abraded with a gauze pad until serous exudates appear, which are then collected onto a glass slide for microscopic analysis. Identification of *T pallidum* from the sample allows for immediate diagnosis. A single negative result does not exclude infection as collection of the treponemes is operator-dependent. A lesion is considered negative for *T pallidum* if microscopy on three different days is negative.[31] [32] Sensitivity of dark-field microscopy for genital ulcers is 74% to 86% and specificity is 85% to 100%. [31] [33] [34] [35]

For secondary syphilis, dark-field microscopy may be positive from skin or ulcerative anogenital lesions. However, gummata in tertiary syphilis have few, if any, identifiable *T pallidum* organisms. If available, dark-field microscopy should also be performed on any lesions or nasal discharge in infants with possible congenital syphilis.

Serologic tests:

Serology testing is the most commonly used method for diagnosing syphilis. It should be performed in all patients with signs or symptoms of syphilis (e.g., a painless anogenital ulcer). Serology testing requires the use of both treponemal (specific) and nontreponemal (nonspecific) tests. The most common approach is to use a treponemal test as the initial serologic test, followed by a nontreponemal test if the treponemal test is positive (i.e., a “reverse sequence screening algorithm”).[36] This approach reduces time and costs compared with using a nontreponemal test as the initial serology test.[36] [37]

Treponemal tests include:[10]

• Treponemal enzyme immunoassay (EIA)
• *T pallidum* particle agglutination assay (TPPA)
• *T pallidum* haemagglutination assay (TPHA)
• Fluorescent antibody absorption (FTA-ABS)
• Immunocapture assay (ICA).

Treponemal tests are antigen-based tests and work by detecting antibodies to *T pallidum*. A patient with a positive treponemal test result will remain positive for life, irrespective of current or past infection. Therefore, a positive result alone cannot distinguish between an active infection (i.e., currently untreated or incompletely treated) and a past (treated) infection. Another limitation is that false-positive results may
Syphilis infection occur in the presence of diseases caused by nonsexually transmitted treponemal infections (e.g., yaws, pinta, bejel). False-negative results may occur in incubating and early primary syphilis.[38]

A nontreponemal test should always be undertaken following a positive treponemal test to confirm a diagnosis and provide evidence of active disease or re-infection. Nontreponemal tests include:[5] [39] [40]

- RPR test
- VDRL test

The RPR test is usually the test of choice due to ease of use and interpretation. Nontreponemal tests work by detecting the antibody response to the release of cardiolipin during syphilis infection. These tests can provide a quantitative measure of disease activity (titer) and can be used to monitor treatment response.[41] [42] [43] [44] [45] RPR and VDRL titers decrease or become nonreactive with effective treatment. A titer of ≥32 is rarely seen in adequately treated infection. Despite adequate treatment, some patients maintain a persisting low level positive antibody titer (known as a serofast reaction).[46] False positives may occur due to the presence of a variety of medical conditions, such as pregnancy, autoimmune disorders, and other infections. A false-negative test may occasionally occur in an undiluted specimen (the prozone phenomenon).

If the nontreponemal test is negative, then a different treponemal test should be performed to confirm the results of the initial treponemal test.[5]

The same nontreponemal test should be used sequentially when monitoring treatment response. This is because results obtained from one test are not directly comparable with that of the next nontreponemal test. 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), signifies a clinically significant difference between two nontreponemal test results.

There is evidence that the majority of patients with HIV who are treated for syphilis will have persistently positive nontreponemal titers (i.e., they are serofast), despite a fourfold decrease in titers as a result of treatment.

Incubation periods (usual time after infection that the test becomes positive) for treponemal and nontreponemal tests are as follows.

**Treponemal tests**

- EIA: 3 weeks
- TPPA: 4-6 weeks
- TPHA: 4-6 weeks.

**Nontreponemal tests**

- RPR: 4 weeks
- VDRL: 4 weeks.

Patients with secondary syphilis will have strongly positive syphilis serologic tests. Delayed seroreactivity or false-negative nontreponemal serology may rarely occur if there is HIV coinfection.[25] [47] [48]

Patients with early or late latent syphilis may be detected as part of screening blood tests (e.g., prior to blood donation). EIA is the serologic treponemal test generally used for screening.[49] In late latent syphilis, treponemal tests are always positive.
In tertiary syphilis, positive serology will suggest a diagnosis already suspected from the history and clinical signs.

**Other initial investigations for acquired syphilis**

Line immunoassay (LIA) serologic tests (e.g., INNO-LIA Syphilis test) can be used to confirm syphilis infection following initial serologic treponemal testing. A single LIA test can confirm infection, making it more convenient than traditional methods of serologic confirmation, which usually require performing multiple assays. Studies evaluating the performance of LIA tests for syphilis infection have demonstrated higher sensitivity and specificity compared with FTA-ABS and TPHA serology tests.[50] [51]

**Emerging investigations**

Compared with current tests (e.g., serology, dark-field microscopy), polymerase chain reaction (PCR) testing for *T. pallidum* using samples taken directly from ulcerative lesions has been found to be moderately sensitive (70% to 80%) and highly specific (>90%) for diagnosing primary and secondary syphilis.[52] The CDC considers PCR testing a valid method for diagnosing primary and secondary syphilis, and its use is likely to increase.[53]

Point of care (POC) serologic testing with either treponemal or combination treponemal/nontreponemal tests has been assessed in the setting of high-risk regions, where rapid and early diagnosis may be more important than accuracy. Several clinical trials have shown promise[54] and POC testing has been recommended as part of the Pan American Health Organization strategy to diagnose and treat syphilis.[55]

**Further investigations for acquired syphilis**

A lumbar puncture and CSF examination should be performed in any patient with clinical evidence of neurosyphilis (e.g., headache, meningismus, ophthalmic or auditory symptoms, cranial nerve palsies, motor or sensory deficits, seizures, or cognitive dysfunction).[5] CNS involvement can occur at any stage of syphilis and can range from asymptomatic meningeal involvement to dementia and sensory neuropathy. A computed tomography or magnetic resonance imaging brain scan should be performed first if there is concern regarding raised intracranial pressure (i.e., mainly to ensure that undertaking a lumbar puncture is safe). A lumbar puncture is also indicated if syphilis of unknown duration is diagnosed in the presence of HIV coinfection. Neurosyphilis is suggested by:[24]

- CSF white blood cell (WBC) count >10 cells/mm³ (10 × 10⁶ cells/L)
- CSF protein >50 mg/dL (0.50 g/L)
- A positive CSF VDRL test.

The CSF will also demonstrate a positive TPHA, TPPA, or FTA-ABS treponemal test.[24] [56] [57] [58] A nonreactive CSF-TPHA test result usually excludes neurosyphilis. Neurologic involvement is unlikely at CSF TPHA or TPPA titers <1:320. CSF examination should be repeated every 6 months until the CSF WBC count is normal if elevated on the initial sample.

[VIDEO: Diagnostic lumbar puncture in adults: animated demonstration ]

A chest x-ray should be performed in people with syphilis of unknown duration, and in those who have had syphilis for more than 2 years, whether or not they have had cardiac symptoms. This may detect possible aortic aneurysm or aortic calcification. Any patient with suspected aortic regurgitation, heart failure, or aortic aneurysm will require both a chest x-ray and echocardiogram.
All patients with syphilis should be tested for HIV. In geographic areas in which the prevalence of HIV is high, patients who have primary syphilis should be retested for HIV after 3 months, even if the first HIV test result is negative.[5] Hence a low threshold for the testing and treatment of syphilis in patients with HIV is advisable.

Initial investigations for congenital syphilis

The CDC has published recommendations concerning serologic tests required in the diagnosis of congenital syphilis.[5] Syphilis serology should be performed on all pregnant women at the first prenatal visit.[5] Serology should be repeated again early in the third trimester and at delivery if serology has been positive, or if there is high maternal risk of syphilis acquisition. The syphilis serologic status of the mother should be determined during pregnancy and prior to discharge of the infant from the hospital.[5] Any woman who delivers a stillborn infant should be tested for syphilis. All pregnant women who have syphilis should also be tested for HIV. All infants who are born to mothers with positive serology require a nontreponemal test (VDRL or RPR), which should be performed on the infant's serum rather than on umbilical cord blood.

Further investigations for congenital syphilis

Pregnant women with syphilis or suspected of having syphilis require a fetal ultrasound scan. The presence of fetal or placental syphilis (e.g., hepatomegaly, ascites, hydrops fetalis) indicates a greater risk of treatment failure for congenital syphilis.[65] After birth, lumbar puncture with CSF analysis for WBC count, protein (and VDRL), complete blood count, and other tests as clinically indicated (e.g., chest x-ray, cranial ultrasound, long-bone x-rays, liver function tests, auditory brainstem response) are recommended by the CDC in the following cases:[5]

- Infants (aged <1 month) with confirmed or highly probable disease plus:
  - An abnormal physical exam that is consistent with congenital syphilis or
  - A serum quantitative nontreponemal serologic titer that is fourfold higher than the mother’s titer or
  - A positive dark-field or fluorescent antibody test of body fluid.
- Infants (aged <1 month) who have a normal physical exam and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer plus:
  - The mother was not treated, was inadequately treated, or has no documentation of having received treatment or
  - The mother was treated with erythromycin or other nonpenicillin regimen or
  - The mother received treatment <4 weeks before delivery.
- Children aged >1 month with reactive serologic tests and at risk of congenital syphilis. These children should also have an HIV test.

Risk factors

[VIDEO: Venepuncture and phlebotomy: animated demonstration ]

[VIDEO: Diagnostic lumbar puncture in adults: animated demonstration ]
Syphilis infection

**Diagnosis**

**Strong sexual contact with an infected person**
- The risk of acquiring syphilis after sex with someone with primary or secondary syphilis is between 30% and 60%.[13] [14]

**men who have sex with men (MSM)**
- At higher risk, particularly if they are also HIV coinfected, use illicit drugs such as methamphetamine, or have multiple, casual sexual partners.[16] [17]
- In 2017, more than half (57.9%) of all reported cases of primary and secondary syphilis in the US occurred in MSM.[9]

**illicit drug use**
- Association due to the exchange of sex for money or drugs, particularly crack cocaine.[18] [19]

**commercial sex workers**
- Association due to the exchange of sex for money or drugs, particularly crack cocaine.[18] [19]

**multiple sexual partners**
- A risk factor for all STIs.
- Important in syphilis epidemiology.[16]

**people with HIV or other STIs**
- Suggests unprotected sexual intercourse, which increases the risk of STIs.
- All patients who have an STI should have syphilis screening, as should patients at higher risk of STIs, irrespective of where they are seen.

**syphilis during pregnancy (risk for congenital syphilis)**
- The fetus acquires the infection from the infected mother.
- This may result in miscarriage, stillbirth, or neonatal death.[2]
- Prenatal screening aims to identify and treat asymptomatic infected women, thus preventing transplacental transmission.[20]

**History & examination factors**

**Key diagnostic factors**

**anogenital ulcer (common)**
- Initially a macule, developing into a papule and then ulcerating to form a chancre.[Fig-2]
- Classically appears in the anogenital area 14 to 21 days after exposure (primary infection).
- Usually indurated, solitary, and painless.[Fig-3]
- May not always be noticed by the patient and examining physician, and it heals spontaneously.
- Atypically may be multiple and painful. Coinfection with genital herpes or chancroid may cause painful ulceration. HIV coinfection may be associated with multiple ulcers.
- Erosions on the genitalia may also occur in secondary syphilis.
lymphadenopathy (common)
- Moderately enlarged, rubbery regional lymphadenopathy associated with the classical syphilitic ulcer (chancre) in primary infection.
- Generalized lymphadenopathy may occur with secondary syphilis.

diffuse rash (common)
- Symmetric macular, papular, or maculopapular rash in secondary syphilis.
  - Often widespread with mucous membrane involvement.
  - May desquamate.
  - Usually nonitchy, over the trunk, palms, soles, and scalp.
  - In dark-skinned patients may cause pruritus.
  - May accompany a history of constitutional symptoms such as fever and malaise.
  - Onset is usually 6 to 12 weeks after exposure.
  - Up to 25% of people who have untreated secondary syphilis develop relapsing episodes of rash and fever.
  - Rash also occurs in congenital syphilis.

constitutional symptoms (common)
- Such as fever, malaise, myalgia, fatigue, and arthralgia with secondary syphilis.
- May be mistaken for primary HIV infection or another intercurrent viral illness.
- Up to 25% of people who have untreated secondary syphilis develop relapsing episodes of rash and fever.

fatigue (common)
- As a result of cardiovascular syphilis (tertiary disease), which may lead to heart failure.
- May also be a constitutional symptom in secondary syphilis.

rhinitis (congenital syphilis) (common)
- A sign of early congenital syphilis (occurring <2 years of age).
- Discharge may be purulent and bloody.

hepatosplenomegaly (congenital syphilis) (common)
- A sign of early congenital syphilis (occurring <2 years of age).
- Usually associated with other signs of disseminated infection (rash, mucous membrane ulceration).

patchy alopecia (uncommon)
- May develop in secondary syphilis.

condylomata lata (uncommon)
- Slightly raised, or flat, round, or oval papules covered by gray exudates.
- A sign of secondary syphilis.
- May be present within moist areas of the perineum.
- May be mistaken for genital warts.
memory impairment, altered mood, confusion, or dementia (uncommon)

- Possible signs of neurosyphilis.
- Brain involvement in tertiary syphilis causes a range of syndromes, including cognitive and motor impairment, which are sometimes grouped under the broad term "general paresis".

visual disturbance (uncommon)

- Visual impairment may be a presenting feature of syphilitic iritis or uveitis, occurring in secondary infection.

Argyll-Robertson pupils (uncommon)

- Bilaterally small, irregular pupils, which do not constrict when exposed to bright light, but do constrict in response to accommodation.
- A feature of tabes dorsalis occurring in tertiary syphilis.

loss of sense of vibration, proprioception, and position sense (uncommon)

- Dorsal column loss is a feature of tabes dorsalis, occurring in tertiary syphilis.

ataxia (uncommon)

- A feature of tabes dorsalis occurring in tertiary syphilis.

loss of anal and bladder sphincter control (uncommon)

- A feature of tabes dorsalis occurring in tertiary syphilis.

positive Romberg sign (uncommon)

- A feature of tabes dorsalis occurring in tertiary syphilis.

diastolic murmur (uncommon)

- Possible sign of cardiovascular syphilis (tertiary disease).
- Diastolic murmur at the left sternal edge indicates aortic regurgitation, which may be due to aortitis caused by cardiovascular syphilis.

rubbery lesions/nodules with a necrotic center (uncommon)

- A sign of gummatous syphilis (also known as benign tertiary syphilis).
- Affects skin and visceral organs.
- The destructive gumma may gradually replace normal tissue.

miscarriage, stillbirth, or neonatal death (congenital syphilis) (uncommon)

- Signs of congenital syphilis.[66]

premature labor and intrauterine growth retardation (congenital syphilis) (uncommon)

- Signs of early congenital syphilis.

neonatal skin rash (congenital syphilis) (uncommon)

- May occur in early congenital syphilis (occurring <2 years of age).
- This rash may be similar to the rash of secondary syphilis in adults. It may also be more widespread, bullous or papulonecrotic, or desquamating.
Syphilis infection

Diagnosis

- Initially the rash may be a vesicular rash with small blisters appearing on the palms and plantar surfaces of the feet. An erythematous or maculopapular rash, which is often copper-colored, may subsequently appear on the face, palms, and plantar surfaces of the feet. The rash may also affect the mouth, genitalia, and anus.

[Fig-9]

- **tibial bowing (congenital syphilis) (uncommon)**
  - A sign of late congenital syphilis (occurring >2 years of age).
  - Due to neonatal osteochondritis in congenital syphilis.

[Fig-10]

- **craniofacial malformation (congenital syphilis) (uncommon)**
  - A sign of late congenital syphilis (occurring >2 years of age).
  - Including frontal bossing, high cranium, and saddle nose.

- **tooth abnormalities (congenital syphilis) (uncommon)**
  - A sign of late congenital syphilis (occurring >2 years of age).
  - Hutchinson teeth (peg-shaped incisors, notched at the apex), mulberry molars dome-shaped with small cusps at the apex.
  - Poorly mineralized teeth.

[Fig-13]

- **necrotizing funisitis (congenital syphilis) (uncommon)**
  - Necrotizing funisitis (inflammation of the umbilical cord) is virtually diagnostic of congenital syphilis. Usually found in preterm infants who are stillborn, or die within a few weeks of birth.
  - The umbilical cord has a specific appearance known as the “barberpole” cord as a result of inflammation of the matrix of the umbilical cord.[6] [29]

Other diagnostic factors

- **mouth ulcer (common)**
  - May coexist with genital ulceration.
  - Occurs in both primary and secondary infection.
  - In secondary infection the mouth ulcers (snail track ulcers) will usually be coexistent with other symptoms or signs, such as rash, fever.

- **asymptomatic with positive serology (latent syphilis) (common)**
  - Latent syphilis is defined as positive serology in the absence of clinical features of syphilis.
  - Ulcers in primary syphilis may not be noticed by the patient and examining physician.

- **tremor (uncommon)**
  - Possible sign of tertiary disease with brain involvement.
  - Brain involvement in tertiary syphilis causes a range of syndromes, including cognitive and motor impairment, which are sometimes grouped under the broad term "general paresis".

- **headache (uncommon)**
• May indicate neurologic involvement.
• May occur with neck stiffness.

meningismus (uncommon)
• May indicate neurologic involvement.

eye pain (uncommon)
• May be a presenting feature of syphilitic iritis or uveitis, occurring in secondary infection.

hearing loss (uncommon)
• The eighth cranial nerve is the most commonly affected cranial nerve in neurosyphilis.
• Hearing loss may be a symptom and a sign of both early and late neurosyphilis.
• Deafness may also occur as a result of late congenital syphilis (occurring >2 years of age).

seizures (uncommon)
• Suggest neurologic involvement.

peripheral edema (uncommon)
• Occurs with nephrotic syndrome that may develop due to vasculitis in secondary syphilis.

jaundice (uncommon)
• May indicate hepatitis, due to vasculitis in secondary syphilis.

peripheral neuropathy (uncommon)
• Sign of neurosyphilis.
• Usually affecting lower limbs.

areflexia (uncommon)
• May occur in all forms of neurosyphilis.

angina (uncommon)
• As a result of cardiovascular syphilis (tertiary disease).

dyspnea (uncommon)
• As a result of cardiovascular syphilis (tertiary disease), which may lead to heart failure.
• Aortic aneurysm caused by syphilis almost always affects the thoracic aorta (usually the ascending part of the thoracic aorta), resulting in heart failure.

organomegaly (uncommon)
• Lesions in gummatous syphilis may cause organomegaly, and become infiltrative or destructive.

skin or visceral organ perforation or collapse of structure (uncommon)
• May occur as a result of gummatous syphilis.

neonatal neurologic abnormalities (congenital syphilis) (uncommon)
• May include a wide range of problems such as seizures, meningitis, obstructive hydrocephalus, and cranial nerve palsies.
## Diagnostic tests

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>dark-field microscopy of swab from lesion</strong></td>
<td>coiled spirochete bacterium with a corkscrew appearance and motility</td>
</tr>
<tr>
<td>• Performed to identify <em>Treponema pallidum</em>.</td>
<td></td>
</tr>
<tr>
<td>• Can provide a definitive diagnosis of syphilis, but is not usually</td>
<td></td>
</tr>
<tr>
<td>available outside specialist settings.</td>
<td></td>
</tr>
<tr>
<td>• The lesion is cleansed and abraded with a gauze pad until serous</td>
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<tr>
<td>exudates appear, which are collected onto a glass slide for</td>
<td></td>
</tr>
<tr>
<td>microscopic analysis.</td>
<td></td>
</tr>
<tr>
<td>• A single negative result does not exclude infection; ideally 3</td>
<td></td>
</tr>
<tr>
<td>negative examinations on different days are required.</td>
<td></td>
</tr>
<tr>
<td>• Primary syphilis: sensitivity of dark-field microscopy is 74% to</td>
<td></td>
</tr>
<tr>
<td>86%, specificity is 85% to 100%.[33]</td>
<td></td>
</tr>
<tr>
<td>• Secondary syphilis: dark-field microscopy may be positive from</td>
<td></td>
</tr>
<tr>
<td>ulcerative anogenital lesions.</td>
<td></td>
</tr>
<tr>
<td>• Gummata in tertiary syphilis have few, if any, identifiable</td>
<td></td>
</tr>
<tr>
<td><em>T pallidum</em> organisms.</td>
<td></td>
</tr>
<tr>
<td><strong>serum treponemal enzyme immunoassay (EIA)</strong></td>
<td>positive</td>
</tr>
<tr>
<td>• A treponemal serology test.</td>
<td></td>
</tr>
<tr>
<td>• A patient with a positive treponemal test result will remain</td>
<td></td>
</tr>
<tr>
<td>positive for life. Therefore, a positive result alone cannot</td>
<td></td>
</tr>
<tr>
<td>distinguish between an active infection or past (treated)</td>
<td></td>
</tr>
<tr>
<td>infection.</td>
<td></td>
</tr>
<tr>
<td>• The most common approach is to use a treponemal test as the initial</td>
<td></td>
</tr>
<tr>
<td>serologic test, followed by a nontreponemal test to confirm</td>
<td></td>
</tr>
<tr>
<td>diagnosis and provide evidence of active disease or reinfection</td>
<td></td>
</tr>
<tr>
<td>(i.e., a &quot;reverse sequence screening algorithm&quot;).[36]</td>
<td></td>
</tr>
<tr>
<td>• False-positive results may occur with other nonsexually transmitted</td>
<td></td>
</tr>
<tr>
<td>treponemal infection (e.g., yaws, pinta, bejel).</td>
<td></td>
</tr>
<tr>
<td>• False-negative results may occur in incubating and early primary</td>
<td></td>
</tr>
<tr>
<td>syphilis. It usually takes 3 weeks for an EIA IgG/IgM test to</td>
<td></td>
</tr>
<tr>
<td>become positive after infection with <em>Treponema pallidum</em>.</td>
<td></td>
</tr>
<tr>
<td>• EIA is the test generally used for screening.[3]</td>
<td></td>
</tr>
<tr>
<td>• Primary syphilis: EIA sensitivity 82% to 100%, and specificity</td>
<td></td>
</tr>
<tr>
<td>97% to 100%.[67]</td>
<td></td>
</tr>
<tr>
<td>• Secondary syphilis: EIA sensitivity is 100%.[67]</td>
<td></td>
</tr>
<tr>
<td>• Late latent syphilis: EIA sensitivity is 98% to 100%.[67]</td>
<td></td>
</tr>
<tr>
<td><strong>serum Treponema pallidum particle agglutination (TPPA)</strong></td>
<td>positive</td>
</tr>
<tr>
<td>• A treponemal serology test.</td>
<td></td>
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<td>(i.e., a &quot;reverse sequence screening algorithm&quot;).[36]</td>
<td></td>
</tr>
<tr>
<td>• Primary syphilis: TPPA sensitivity 85% to 100%, and specificity</td>
<td></td>
</tr>
<tr>
<td>98% to 100%.[68] [69]</td>
<td></td>
</tr>
<tr>
<td>• Secondary and late latent syphilis: TPPA sensitivity 98% to 100%.[69]</td>
<td></td>
</tr>
<tr>
<td><strong>serum Treponema pallidum hemagglutination (TPHA)</strong></td>
<td>positive</td>
</tr>
<tr>
<td>• A treponemal serology test.</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Serum fluorescent treponemal antibody absorption (FTA-ABS) test</td>
<td>positive</td>
</tr>
<tr>
<td>Immunocapture assay</td>
<td>positive</td>
</tr>
<tr>
<td>Line immunoassay (LIA) serologic test</td>
<td>positive</td>
</tr>
<tr>
<td>Serum rapid plasma reagin (RPR) test</td>
<td>positive</td>
</tr>
</tbody>
</table>

- A patient with a positive treponemal test result will remain positive for life. Therefore, a positive result alone cannot distinguish between an active infection or past (treated) infection.
- The most common approach is to use a treponemal test as the initial serologic test, followed by a nontreponemal test to confirm diagnosis and provide evidence of active disease or reinfection (i.e., a "reverse sequence screening algorithm").[36]
- FTA-ABS is used less often than TPHA and TPPA because it is less specific.

- A treponemal serology test.
- A patient with a positive treponemal test result will remain positive for life. Therefore, a positive result alone cannot distinguish between an active infection or past (treated) infection.
- The most common approach is to use a treponemal test as the initial serologic test, followed by a nontreponemal test to confirm diagnosis and provide evidence of active disease or reinfection (i.e., a "reverse sequence screening algorithm").[36]
- LIA serologic tests (e.g., INNO-LIA syphilis test) can be used to confirm syphilis infection following initial serologic treponemal testing. A single LIA test can confirm infection, making it more convenient than traditional methods of serologic confirmation (which usually require multiple assays). Studies evaluating the performance of LIA tests for syphilis infection have demonstrated higher sensitivity and specificity compared with FTA-ABS and TPHA serology tests.[50] [51]

- A nontreponemal serology test.
- Provides a quantitative measure of disease activity and can be used to monitor treatment response (RPR titers decrease or become nonreactive with effective treatment).
- The most common approach is to use a treponemal test as the initial serologic test, followed by a nontreponemal test to confirm diagnosis and provide evidence of active disease or reinfection (i.e., a "reverse sequence screening algorithm").[36]
- A titer of ≥32 is rarely seen in adequately treated infection.
- Despite adequate treatment, some patients maintain a persisting low level positive antibody titer (known as a serofast reaction).[46]
<table>
<thead>
<tr>
<th>Test</th>
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</thead>
<tbody>
<tr>
<td>• False positives may occur due to the presence of a variety of medical conditions (e.g., pregnancy, autoimmune disorders, and infections).</td>
<td></td>
</tr>
<tr>
<td>• A false-negative test may occasionally occur in an undiluted specimen (the prozone phenomenon).</td>
<td></td>
</tr>
<tr>
<td>• Primary syphilis: RPR sensitivity 70% to 73%. [10] [70]</td>
<td></td>
</tr>
<tr>
<td>• Secondary syphilis: RPR sensitivity is 100%. [70]</td>
<td></td>
</tr>
<tr>
<td>• Preferred test over the serum Venereal Disease Research Laboratory test.</td>
<td></td>
</tr>
</tbody>
</table>

**serum Venereal Disease Research Laboratory (VDRL) test**

| • A nontreponemal serology test. | positive |
| • Provides a quantitative measure of disease activity and can be used to monitor treatment response (VDRL titers decrease or become nonreactive with effective treatment). |        |
| • The most common approach is to use a treponemal test as the initial serologic test, followed by a nontreponemal test to confirm diagnosis and provide evidence of active disease or reinfection (i.e., a “reverse sequence screening algorithm”). [36] |        |
| • A titer of ≥32 is rarely seen in adequately treated infection. |        |
| • Despite adequate treatment, some patients maintain a persisting low level positive antibody titer (known as a serofast reaction). [46] |        |
| • False positives may occur due to the presence of a variety of medical conditions (e.g., pregnancy, autoimmune disorders, and infections). |        |
| • A false-negative test may occasionally occur in an undiluted specimen (the prozone phenomenon). |        |
| • Primary syphilis: VDRL sensitivity 44% to 76%. [70] |        |
| • VDRL is positive in 77% of cases of late latent syphilis. [10] |        |
| • VDRL sensitivity in secondary syphilis is 100%. [70] |        |
# Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>lumbar puncture, cerebrospinal fluid (CSF) analysis</em></td>
<td>WBC count &gt;10 cells/mm³; CSF protein &gt;50 mg/dL; CSF VDRL positive; CSF TPHA/TPPA/FTA-ABS positive</td>
</tr>
<tr>
<td>• Indicated for any patient with clinical evidence of neurologic involvement (e.g., cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsy, features of meningitis).</td>
<td></td>
</tr>
<tr>
<td>• Indicated if syphilis of unknown duration exists in the presence of HIV coinfection.</td>
<td></td>
</tr>
<tr>
<td>• Indicated in any child with congenital syphilis and neurologic symptoms or signs.[5]</td>
<td></td>
</tr>
<tr>
<td>• An elevated CSF WBC count and positive CSF Venereal Disease Research Laboratory (VDRL) suggests neurologic involvement.[24]</td>
<td></td>
</tr>
<tr>
<td>• Some patients with neurosyphilis have an isolated elevated CSF WBC count and negative rapid plasma reagin/VDRL.</td>
<td></td>
</tr>
<tr>
<td>• Neurosyphilis is unlikely at CSF <em>Treponema pallidum</em> hemagglutination assay (TPHA)/ <em>T pallidum</em> particle agglutination assay (TPPA) titers &lt;1:320.</td>
<td></td>
</tr>
<tr>
<td>• A nonreactive CSF-TPHA test result usually excludes neurosyphilis.</td>
<td></td>
</tr>
<tr>
<td>• [VIDEO: Diagnostic lumbar puncture in adults: animated demonstration]</td>
<td></td>
</tr>
<tr>
<td><em>chest x-ray</em></td>
<td>possible widened thoracic aorta, aortic calcification</td>
</tr>
<tr>
<td>• May detect possible thoracic aortic aneurysm or aortic calcification.</td>
<td></td>
</tr>
<tr>
<td>• Required in people with symptoms or signs of aortic regurgitation, heart failure, or aortic aneurysm.</td>
<td></td>
</tr>
<tr>
<td><em>echocardiogram</em></td>
<td>may show evidence of heart failure, aortic regurgitation, or thoracic aortic aneurysm</td>
</tr>
<tr>
<td>• Required if cardiovascular syphilis is strongly suspected (e.g., a patient has symptoms or signs of aortic regurgitation, heart failure, or aortic aneurysm).</td>
<td></td>
</tr>
<tr>
<td><em>CT brain</em></td>
<td>usually normal</td>
</tr>
<tr>
<td>• Performed before lumbar puncture to exclude elevated intracranial pressure, to ensure that undertaking a lumbar puncture will be safe.</td>
<td></td>
</tr>
<tr>
<td>• Elevated intracranial pressure is rarely caused by syphilis itself.</td>
<td></td>
</tr>
<tr>
<td><em>MRI brain</em></td>
<td>usually normal</td>
</tr>
<tr>
<td>• Performed before lumbar puncture to exclude elevated intracranial pressure, to ensure that undertaking a lumbar puncture will be safe.</td>
<td></td>
</tr>
<tr>
<td>• Elevated intracranial pressure is rarely caused by syphilis itself.</td>
<td></td>
</tr>
<tr>
<td><em>HIV test</em></td>
<td>positive or negative</td>
</tr>
<tr>
<td>• All patients with syphilis should be tested for HIV.</td>
<td></td>
</tr>
<tr>
<td>• In geographic areas in which the prevalence of HIV is high, patients who have primary syphilis should be retested for HIV after 3 months even if the first HIV test result is negative.[5]</td>
<td></td>
</tr>
<tr>
<td><em>fetal ultrasound scan</em></td>
<td>may show hepatomegaly, ascites, hydrops fetalis, intrauterine growth retardation</td>
</tr>
<tr>
<td>• Should be performed on all pregnant women with syphilis or suspected of having syphilis.</td>
<td></td>
</tr>
<tr>
<td>• Presence of fetal or placental syphilis indicates a greater risk of treatment failure for congenital syphilis.[65]</td>
<td></td>
</tr>
<tr>
<td><em>CBC</em></td>
<td>may show anemia, thrombocytopenia,</td>
</tr>
<tr>
<td>• Performed in infants with possible congenital syphilis.</td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>Result</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td><strong>Test</strong></td>
<td><strong>Result</strong></td>
</tr>
<tr>
<td><strong>cranial ultrasound</strong></td>
<td><strong>leukopenia, possible neutrophilia</strong></td>
</tr>
<tr>
<td>• May be indicated in infants with suspected congenital syphilis.</td>
<td>may demonstrate craniofacial malformation</td>
</tr>
<tr>
<td><strong>long-bone x-rays</strong></td>
<td><strong>may demonstrate osteochondritis</strong></td>
</tr>
<tr>
<td>• May be indicated in infants with suspected congenital syphilis.</td>
<td>performed if osteochondritis suspected.</td>
</tr>
<tr>
<td><strong>liver function tests</strong></td>
<td><strong>aspartate aminotransferase and alanine aminotransferase may be elevated</strong></td>
</tr>
<tr>
<td>• May be indicated in infants with suspected congenital syphilis.</td>
<td>performed if clinical findings suggestive of liver involvement (e.g., hepatomegaly).</td>
</tr>
<tr>
<td><strong>evoked auditory potentials</strong></td>
<td><strong>may detect deafness</strong></td>
</tr>
<tr>
<td>• May be indicated in infants with suspected congenital syphilis.</td>
<td>performed if clinically indicated.</td>
</tr>
<tr>
<td><strong>audiometry</strong></td>
<td><strong>may detect hearing deficit</strong></td>
</tr>
<tr>
<td>• Neurosyphilis may involve cranial nerves (particularly the 8th cranial nerve).</td>
<td></td>
</tr>
</tbody>
</table>

**Emerging tests**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treponema pallidum polymerase chain reaction (PCR) (sample taken directly from ulcerative lesions)</strong></td>
<td>positive</td>
</tr>
<tr>
<td>• <em>T pallidum</em> PCR has been shown to have moderate sensitivity (70% to 80%) and high specificity &gt;90% in the diagnosis of primary or secondary syphilis, when compared with adequate reference tests (e.g., serology, dark-field microscopy).</td>
<td>positve</td>
</tr>
<tr>
<td>• The Centers for Disease Control and Prevention considers PCR testing a valid method for diagnosing primary and secondary syphilis, and its use is likely to increase.</td>
<td>positve</td>
</tr>
<tr>
<td><strong>point of care (POC) testing with either treponemal or combination treponemal/nontreponemal antibody</strong></td>
<td>positive; however, a positive result for treponemal antibodies alone does not distinguish between current, past, or treated infection</td>
</tr>
<tr>
<td>• POC syphilis testing has been assessed in the setting of high-risk regions, where rapid and early diagnosis may be more important than accuracy. Several clinical trials have shown promise and POC testing has been recommended as part of the Pan American Health Organization strategy to diagnose and treat syphilis.</td>
<td>positve; however, a positive result for treponemal antibodies alone does not distinguish between current, past, or treated infection</td>
</tr>
</tbody>
</table>
## Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Genital herpes             | • There may be a history of fever, genital blisters or sores, and lymphadenopathy with first-episode herpes simplex.  
  • The patient may describe previous episodes of genital ulceration.  
  • On physical exam there are typically multiple, painful vesicular or ulcerative lesions on or around the genitals or rectum.                                                                 | • Isolation of herpes simplex virus (HSV) from lesions in cell culture confirms the diagnosis, although the sensitivity is low, and decreases as lesions heal. Viral culture isolates will identify if HSV-1 or HSV-2 is causative.[5]  
  • Increasingly, polymerase chain reaction is supplanting culture as the test of choice to diagnose and type HSV.                                                                 |
| Chancroid                  | • Characterized by painful genital ulcers and painful inguinal lymphadenopathy. Lesions of primary syphilis are typically not painful.  
  • Usually occurs in discrete outbreaks.  
  • On physical exam there may be an erythematous papule, pustule, or painful ulcer, as well as painful unilateral inguinal lymphadenopathy (bubo formation), which may rupture.                       | • *Haemophilus ducreyi* is identified on specialist culture medium, which is not widely commercially available and has a sensitivity of <80%.[71]  
  • Polymerase chain reaction testing is up to 100% sensitive but is not universally approved.[71][72]  
  • Therefore a positive diagnosis of chancroid is suggested by the presence of painful genital ulcers with no evidence of syphilis or herpes simplex virus.[5]                                                                 |
| Primary HIV infection      | • Not preceded by genital ulceration.  
  • However, genital ulceration may be present at the same time as primary HIV infection and the rash associated with the ulceration.                                                                                                           | • Laboratory tests positive for HIV, including antigen (P24 antigen) tests.                                                                                                                                               |
| Other acute viral exanthemas | • Not preceded by genital ulceration.                                                                                                                                                                                                     | • Laboratory tests positive for specific virus.                                                                                                                                                                         |
| Scabies                    | • Skin lesions usually pruritic.  
  • Typical distribution: interdigital, wrists, nipples, ankles, buttocks.                                                                                                                                                                  | • Diagnosis is usually clinical, but skin scrapings and microscopy for *Sarcoptes scabiei* may be performed.                                                                                                          |
| Eczema                     | • Skin lesions usually absent on palms and plantar aspects of feet.                                                                                                                                                                      | • Diagnosis is usually clinical.  
  • Skin biopsy can be undertaken to confirm diagnosis.                                                                                                                                                                   |
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psoriasis</strong></td>
<td>• Skin lesions usually absent on palms and plantar aspects of feet.</td>
<td>• Diagnosis is usually clinical.</td>
</tr>
<tr>
<td></td>
<td>• Not associated with signs of systemic infection.</td>
<td>• Skin biopsy can be undertaken to confirm diagnosis.</td>
</tr>
<tr>
<td><strong>Lichen planus</strong></td>
<td>• Skin lesions usually absent on palms and plantar aspect of feet.</td>
<td>• Diagnosis is usually clinical.</td>
</tr>
<tr>
<td></td>
<td>• Not associated with signs of systemic infection.</td>
<td>• Skin biopsy can be undertaken to confirm diagnosis.</td>
</tr>
<tr>
<td><strong>Genital warts</strong></td>
<td>• Pink lumps, in genital and/or perianal skin and mucous membranes. Not necessarily confined to opposing membranes. Not associated with other signs of secondary syphilis (rash, constitutional symptoms, generalized lymphadenopathy).</td>
<td>• Diagnosis is usually clinical.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Exclusion of syphilis (negative syphilis serology).</td>
</tr>
<tr>
<td><strong>Alzheimer dementia</strong></td>
<td>• Progressive dementia. • No specific differentiating symptoms and signs compared with neurosyphilis. • Less likely to have a history of possible signs and symptoms of earlier stages of syphilis infection.</td>
<td>• Exclusion of syphilis (negative syphilis serology).</td>
</tr>
<tr>
<td><strong>Vascular dementia</strong></td>
<td>• Progressive dementia. • Multi-infarct dementia often associated with other evidence of arteriopathy. • Less likely to have a history of possible signs and symptoms of earlier stages of syphilis infection.</td>
<td>• Exclusion of syphilis (negative syphilis serology).</td>
</tr>
</tbody>
</table>
Step-by-step treatment approach

The treatment of syphilis infection is curative with appropriate antibiotics. Prompt diagnosis and antibiotic therapy is important because of the possibility of long-term complications, either from untreated infection or from prolonged infection of unknown duration. Parenteral penicillin-G is the first-line drug treatment for all stages of syphilis, as recommended by the Centers for Disease Control and Prevention (CDC).[5] The preparation (i.e., benzathine, procaine, aqueous), dose, and length of treatment are determined by the stage and clinical manifestations of the disease.[3] [5] [91] [92]

Without neurosyphilis

Treatment may follow diagnostic test results or may be empiric. Empiric therapy may be considered in those with suspected early infection (a rash or ulceration) before results of serology are available. This approach may be appropriate if there are concerns regarding re-attendance. Sexual contacts of patients with confirmed syphilis should be screened and offered presumptive treatment if follow-up may be problematic. The benefits of empiric therapy (prompt therapy) and risks (potentially unnecessary treatment) should be discussed with the patient.

The first-line treatment for primary, secondary, and early latent syphilis (without neurosyphilis) is intramuscular benzathine penicillin-G as a single dose.[5] If the patient is allergic to penicillin and is not pregnant, oral doxycycline may be offered as a first-line treatment. Adherence and patient compliance may influence treatment outcome if oral therapy is administered. Single-dose azithromycin is used in some centers, but is not recommended by the CDC due to concerns regarding macrolide resistance.[93] [94] [95]

Treatment of latent syphilis is intended to prevent late complications. The first-line treatment of late latent and tertiary (gummatous and cardiovascular) syphilis (without neurosyphilis) is intramuscular benzathine penicillin-G given as three doses over 2 weeks (days 0, 7, 14). Oral doxycycline may be offered as a first-line treatment to patients with penicillin allergy. Patients who have symptomatic gummatous syphilis or cardiovascular syphilis should undergo cerebrospinal fluid (CSF) examination before treatment is started.

Untreated cardiovascular (latent) syphilis may be asymptomatic, or cause aortic aneurysm (mainly thoracic), aortic regurgitation, angina, or stenosis of coronary ostia. Antibiotic therapy for cardiovascular syphilis does not reverse cardiovascular disease, which may continue to progress after treatment. This is because the underlying pathology of medial necrosis of the aortic wall has been established. Discussion with a cardiologist is advised.

Neurosyphilis

Central nervous system involvement can occur at any stage of syphilis, and can range from asymptomatic meningeal involvement to dementia and sensory neuropathy. First-line treatment for neurosyphilis is intravenous aqueous penicillin-G. Second-line treatment is intramuscular procaine penicillin plus oral probenecid. Some specialists administer intramuscular benzathine penicillin-G once weekly for up to 3 weeks after the treatment regimen for neurosyphilis has been completed, to ensure the duration of treatment is comparable with that of late syphilis in the absence of neurosyphilis.

Penicillin desensitization is recommended for all patients with penicillin hypersensitivity and neurosyphilis. The evidence for the use of nonpenicillin regimens is relatively weak. However, high-dose doxycycline is used by some clinicians in this situation.[96]
Penicillin allergy skin testing identifies patients at high risk for penicillin reactions. Skin reagents used should include major and minor allergens.[97] Patients who are skin-test negative can receive penicillin therapy. However, some clinicians perform desensitization without skin testing, particularly if the skin reagents for both minor and major determinants of penicillin allergy are not available. Acute desensitization can be performed in patients who have a positive skin test to one of the penicillin determinants, and should be performed in a hospital setting. Oral or intravenous desensitization can be performed, and is usually completed in 4 hours, following which the first dose of penicillin is administered.[98]

**Infection in pregnancy**

Parenteral penicillin-G is the only recommended treatment in pregnancy. Pregnant patients who are allergic to penicillin should be desensitized and treated with penicillin. Pregnant women should receive penicillin-based treatment according to their stage of syphilis, although some specialists recommend that women presenting in the third trimester with early syphilis should receive two injections of benzathine penicillin-G rather than one.

Sonographic fetal assessment for congenital syphilis is performed. The presence of fetal or placental syphilis (e.g., hepatomegaly, ascites, and hydrops fetalis) indicates a greater risk of treatment failure for congenital syphilis.[65] Pregnant women should be advised of the possibility of the Jarisch-Herxheimer reaction. Jarisch-Herxheimer reaction may be complicated by fetal distress and premature labor. Specialist care by an obstetrician is recommended.

**Coinfection with HIV**

Syphilis is an important facilitator of HIV transmission. Most clinicians treat HIV-positive and HIV-negative patients with the same penicillin regimens, according to the stage of syphilis. For example, first-line treatment of primary and secondary syphilis among patients with HIV coinfection is with a single dose of intramuscular benzathine penicillin-G.[5] However, duration of therapy may be prolonged in patients with HIV and neurosyphilis.

People with HIV infection and primary or secondary syphilis should be assessed clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy.[5] Although of unconfirmed benefit, some specialists recommend performing CSF analysis 6 months after therapy either routinely or if nontreponemal titers do not decrease fourfold within 6-12 months of therapy. Patients with primary or secondary syphilis and HIV coinfection who are allergic to penicillin should receive antibiotic therapy as recommended for penicillin-allergic, HIV-negative patients.

**Congenital syphilis**

All infants born to mothers with reactive nontreponemal and treponemal tests should have nontreponemal serology (Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR] tests) performed on infant serum. False-positive results may occur if umbilical cord blood is sampled, due to contamination of umbilical cord blood with maternal blood.

When infants aged >1 month test positive for syphilis, clinicians should review maternal records and serology results to determine if the infection is congenital or acquired.[5]

If there is evidence of effective treatment (and no reinfection) of the mother, a normal physical exam of the infant, and the infant's VDRL/RPR is less than fourfold higher than the mother’s, then no treatment
is indicated. Infants with an abnormal physical exam or a VDRL/RPR that is fourfold or greater than the mother’s titer should be fully evaluated and treated.

First-line treatment of congenital syphilis is intravenous aqueous penicillin-G or intramuscular procaine penicillin-G.[5] Intramuscular benzathine penicillin-G is recommended if a nontreponemal test in the infant is nonreactive and there is low likelihood of infectivity.[5] Discussion with an obstetric specialist and neonatologist is recommended. Intramuscular benzathine penicillin-G is infrequently used in resource-rich countries. Close clinical and serologic follow-up by a pediatric specialist is recommended.

### Potential adverse effects of therapy

Patients should be warned of possible reactions to treatment, such as the Jarisch-Herxheimer reaction and iatrogenic procaine reaction.

Jarisch-Herxheimer reaction is an acute febrile illness that can occur within the first 24 hours after initiation of antibiotic treatment for syphilis. Symptoms include acute fever, headache, and myalgia, usually in patients with early syphilis. Corticosteroid therapy may be considered to prevent potential serious consequences of Jarisch-Herxheimer reaction in nonpregnant patients with cardiovascular syphilis or neurosyphilis.[3] However, evidence of effectiveness is unclear and it is not routinely recommended in the US.

Iatrogenic procaine reaction (procaine psychosis, procaine mania, Hoigné syndrome) may occur if intramuscular procaine penicillin-G is mistakenly administered intravenously. Patients may develop penicillin allergic responses, including anaphylactic shock.[90]

### Treatment details overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

<table>
<thead>
<tr>
<th>Initial</th>
<th>( summary )</th>
</tr>
</thead>
<tbody>
<tr>
<td>adults with suspected early infection or sexual contacts of patients with confirmed infection</td>
<td>1st consideration of empiric antibiotics</td>
</tr>
</tbody>
</table>
### Acute

#### adults without neurosyphilis

<table>
<thead>
<tr>
<th></th>
<th>1st</th>
<th>adjunct</th>
</tr>
</thead>
<tbody>
<tr>
<td>without penicillin allergy</td>
<td>intramuscular benzathine penicillin-G</td>
<td>prednisone</td>
</tr>
<tr>
<td>with penicillin allergy: nonpregnant</td>
<td>oral doxycycline</td>
<td>prednisone</td>
</tr>
<tr>
<td>with penicillin allergy: pregnant</td>
<td>desensitization</td>
<td>postdesensitization intramuscular benzathine penicillin-G</td>
</tr>
</tbody>
</table>

#### adults with neurosyphilis

<table>
<thead>
<tr>
<th></th>
<th>1st</th>
<th>adjunct</th>
</tr>
</thead>
<tbody>
<tr>
<td>without penicillin allergy</td>
<td>intravenous aqueous penicillin-G</td>
<td>subsequent intramuscular benzathine penicillin-G</td>
</tr>
<tr>
<td></td>
<td>adjunct</td>
<td>prednisone</td>
</tr>
<tr>
<td></td>
<td>2nd</td>
<td>intramuscular procaine penicillin-G plus oral probenecid</td>
</tr>
<tr>
<td>with penicillin allergy</td>
<td>desensitization</td>
<td>postdesensitization penicillin-G</td>
</tr>
<tr>
<td></td>
<td>adjunct</td>
<td>prednisone</td>
</tr>
<tr>
<td></td>
<td>2nd</td>
<td>high-dose oral doxycycline</td>
</tr>
<tr>
<td></td>
<td>adjunct</td>
<td>prednisone</td>
</tr>
</tbody>
</table>

#### congenital syphilis

<table>
<thead>
<tr>
<th></th>
<th>1st</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>intravenous aqueous penicillin-G or intramuscular procaine penicillin-G</td>
</tr>
<tr>
<td></td>
<td>2nd</td>
</tr>
<tr>
<td></td>
<td>intramuscular benzathine penicillin-G</td>
</tr>
</tbody>
</table>
Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

<table>
<thead>
<tr>
<th>Initial</th>
<th>1st consideration of empiric antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>adults with suspected early infection or sexual contacts of patients with confirmed infection</td>
<td></td>
</tr>
</tbody>
</table>

Primary options

» penicillin G benzathine: 2.4 million units intramuscularly as a single dose

Secondary options

» doxycycline: 100 mg orally twice daily

Empiric therapy may be considered in those with suspected early infection (a rash or ulceration) before results of serology are available. Empiric therapy may be appropriate if there are concerns regarding re-attendance. The benefits of empiric therapy (prompt therapy) and risks (potentially unnecessary treatment) should be discussed with the patient.

» Intramuscular benzathine penicillin-G as a single dose is given. If the patient is allergic to penicillin and is not pregnant, oral doxycycline may be offered.

» Sexual contacts of patients with confirmed syphilis should be screened and offered presumptive treatment if follow-up may be problematic.

» Treatment course: 14 days (doxycycline)
## Treatment

### Acute adults without neurosyphilis

<table>
<thead>
<tr>
<th>without penicillin allergy</th>
<th>1st intramuscular benzathine penicillin-G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary options</td>
<td></td>
</tr>
<tr>
<td>» penicillin G benzathine: primary/secondary/early latent syphilis (first, second, and third trimesters): 2.4 million units intramuscularly as a single dose; primary/secondary/early latent syphilis (alternative dosing for third trimester): 2.4 million units intramuscularly as a single dose, repeat in 1 week; late-latent/tertiary gummatous syphilis/cardiovascular syphilis: 2.4 million units intramuscularly once weekly for 3 weeks</td>
<td></td>
</tr>
</tbody>
</table>

» The first-line treatment for primary, secondary, and early latent syphilis (without neurosyphilis) is intramuscular benzathine penicillin-G as a single dose. Note that the dose may be split and administered at two discrete injection sites.

» The first-line treatment of late latent and tertiary (gummatous and cardiovascular) syphilis (without neurosyphilis) is intramuscular benzathine penicillin-G given as three doses over 2 weeks (days 0, 7, 14).

» Patients who have symptomatic gummatous syphilis or cardiovascular syphilis should undergo cerebrospinal fluid examination before treatment is started.

» Pregnant women should receive penicillin-based treatment according to their stage of syphilis. Some specialists recommend that women presenting in the third trimester with early syphilis should receive two injections of benzathine penicillin-G, rather than one.

» Most clinicians treat HIV-positive and HIV-negative individuals with the same penicillin regimens, according to the stage of syphilis.

» Antibiotic therapy for cardiovascular syphilis does not reverse cardiovascular disease, which may continue to progress after treatment. Discussion with a cardiologist is advised.

### Adjunct prednisone

Treatment recommended for SOME patients in selected patient group

| Primary options            |                                          |
| » prednisone: 40-60 mg orally once daily for 3 days; start 24 hours before penicillin |
### Acute

<table>
<thead>
<tr>
<th>with penicillin allergy: nonpregnant</th>
<th>1st oral doxycycline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>- doxycycline: 100 mg orally twice daily</td>
<td></td>
</tr>
<tr>
<td>- If the patient is allergic to penicillin, the first-line treatment in nonpregnant patients is oral doxycycline.</td>
<td></td>
</tr>
<tr>
<td>- Adherence and patient compliance may influence treatment outcome if oral therapy is administered.</td>
<td></td>
</tr>
<tr>
<td>- Patients who are allergic to penicillin, with primary or secondary syphilis and HIV coinfection, should receive antibiotic therapy as recommended for penicillin-allergic, HIV-negative patients.</td>
<td></td>
</tr>
<tr>
<td>- Antibiotic therapy for cardiovascular syphilis does not reverse cardiovascular disease, which may continue to progress after treatment. Discussion with a cardiologist is advised.</td>
<td></td>
</tr>
<tr>
<td>- Treatment course: 14 days for primary/secondary/early latent syphilis; 28 days for late latent/tertiary gummatous syphilis/cardiovascular syphilis.</td>
<td></td>
</tr>
<tr>
<td><strong>adjunct prednisone</strong></td>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>- prednisone: 40-60 mg orally once daily for 3 days; start 24 hours before doxycycline</td>
<td></td>
</tr>
<tr>
<td>- Corticosteroid therapy may be considered to minimize the risk of Jarisch-Herxheimer reaction in nonpregnant patients with neurosyphilis.[3] However, evidence of effectiveness is unclear and it is not routinely recommended in the US.</td>
<td></td>
</tr>
</tbody>
</table>
Syphilis infection

Treatment

### Acute

- **with penicillin allergy:** 1st desensitization
  - **Jarisch-Herxheimer reaction** is an acute febrile illness that can occur within the first 24 hours after initiation of antibiotic treatment for syphilis. Symptoms include acute fever, headache, and myalgia, usually occurring in patients with early syphilis.

- **Pregnant**
  - Penicillin desensitization is recommended for all patients with penicillin hypersensitivity in pregnancy. The evidence for the use of nonpenicillin regimens is relatively weak.

- **Penicillin allergy skin testing** identifies patients at high risk for penicillin reactions. Skin reagents used should include major and minor allergens. Those who are skin-test negative can receive penicillin therapy. However, some clinicians perform desensitization without skin testing, particularly if the skin reagents for both minor and major determinants of penicillin allergy are not available.

- Acute desensitization can be performed in patients who have a positive skin test to one of the penicillin determinants, and should be performed in a hospital setting. Oral or intravenous desensitization can be performed, and is usually completed in 4 hours, following which the first dose of penicillin is administered.

### Plus

- **postdesensitization intramuscular benzathine penicillin-G**
  - Treatment recommended for ALL patients in selected patient group

### Primary options

- **penicillin G benzathine:**
  - Primary/secondary/early latent syphilis (first, second, and third trimesters): 2.4 million units intramuscularly as a single dose; primary/secondary/early latent syphilis (alternative dosing for third trimester): 2.4 million units intramuscularly as a single dose, repeat in 1 week; late-latent/tertiary gummatous syphilis/cardiovascular syphilis: 2.4 million units intramuscularly once weekly for 3 weeks

  - Desensitization is usually completed in 4 hours, following which the first dose of penicillin is administered.

  - Some specialists recommend that women in the third trimester with early syphilis should receive two intramuscular injections of benzathine penicillin-G rather than one.
**Syphilis Infection**  

**Treatment**  

### Acute

<table>
<thead>
<tr>
<th>Adults with neurosyphilis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>without penicillin allergy</strong></td>
<td><strong>1st</strong></td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» penicillin G sodium: 18-24 million units/day intravenously given in divided doses every 4 hours (or by continuous infusion)</td>
<td></td>
</tr>
<tr>
<td>» Central nervous system involvement can occur at any stage of syphilis and can range from asymptomatic meningeal involvement to dementia and sensory neuropathy. First-line treatment for neurosyphilis is intravenous aqueous penicillin-G.</td>
<td></td>
</tr>
<tr>
<td>» Pregnant women should receive penicillin-based treatment according to their stage of syphilis.</td>
<td></td>
</tr>
<tr>
<td>» Most clinicians treat HIV-positive and HIV-negative patients with the same penicillin regimens, according to the stage of syphilis. Duration of therapy may be prolonged in patients with HIV and neurosyphilis.</td>
<td></td>
</tr>
<tr>
<td>» Treatment course: 10-14 days.</td>
<td></td>
</tr>
<tr>
<td><strong>adjunct</strong></td>
<td>subsequent intramuscular benzathine penicillin-G</td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» penicillin G benzathine: 2.4 million units intramuscularly once weekly</td>
<td></td>
</tr>
<tr>
<td>» Some specialists administer benzathine penicillin-G once weekly for up to 3 weeks after the intravenous aqueous penicillin-G regimen for neurosyphilis has been completed.</td>
<td></td>
</tr>
<tr>
<td>» This ensures the duration of treatment is comparable with that of late syphilis in the absence of neurosyphilis.</td>
<td></td>
</tr>
<tr>
<td><strong>adjunct</strong></td>
<td>prednisone</td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Acute

<table>
<thead>
<tr>
<th>2nd</th>
<th>intramuscular procaine penicillin-G plus oral probenecid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» penicillin G procaine: 2.4 million units intramuscularly once daily</td>
<td></td>
</tr>
<tr>
<td>-and-</td>
<td></td>
</tr>
<tr>
<td>» probenecid: 500 mg orally four times daily</td>
<td></td>
</tr>
</tbody>
</table>

- Second-line treatment for neurosyphilis is intramuscular procaine penicillin-G plus oral probenecid.

- Most clinicians treat HIV-positive and HIV-negative patients with the same penicillin regimens according to the stage of syphilis. Duration of therapy may be prolonged in patients with HIV and neurosyphilis.

- Pregnant women should receive penicillin-based treatment according to their stage of syphilis.

<table>
<thead>
<tr>
<th>adjunct</th>
<th>prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td></td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» prednisone: 40-60 mg orally once daily for 3 days; start 24 hours before penicillin</td>
<td></td>
</tr>
</tbody>
</table>

- Corticosteroid therapy may be considered to minimize the risk of Jarisch-Herxheimer reaction in nonpregnant patients with neurosyphilis. However, evidence of effectiveness is unclear and it is not routinely recommended in the US.

- Jarisch-Herxheimer reaction is an acute febrile illness that can occur within the first 24 hours after initiation of antibiotic treatment for syphilis. Symptoms include acute fever, headache, and myalgia, usually occurring in patients with early syphilis.

- Prednisone 40-60 mg orally once daily for 3 days; start 24 hours before penicillin

- Jarisch-Herxheimer reaction may be considered to minimize the risk of Jarisch-Herxheimer reaction in nonpregnant patients with neurosyphilis. However, evidence of effectiveness is unclear and it is not routinely recommended in the US.
Acute

<table>
<thead>
<tr>
<th>with penicillin allergy</th>
<th>1st desensitization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Penicillin desensitization is recommended for all patients with neurosyphilis who have penicillin hypersensitivity. The evidence for the use of nonpenicillin regimes is relatively weak.</td>
</tr>
<tr>
<td></td>
<td>Penicillin allergy skin testing identifies patients at high risk for penicillin reactions. Skin reagents used should include major and minor allergens.[97] Those who are skin-test negative can receive penicillin therapy. However, some clinicians perform desensitization without skin testing, particularly if the skin reagents for both minor and major determinants of penicillin allergy are not available.</td>
</tr>
<tr>
<td></td>
<td>Acute desensitization can be performed in patients who have a positive skin test to one of the penicillin determinants, and should be performed in a hospital setting. Oral or intravenous desensitization can be performed, and is usually completed in 4 hours, following which the first dose of penicillin is administered.[98]</td>
</tr>
<tr>
<td>plus postdesensitization penicillin-G</td>
<td></td>
</tr>
<tr>
<td>Treatment recommended for ALL patients in selected patient group</td>
<td></td>
</tr>
<tr>
<td>Primary options</td>
<td></td>
</tr>
<tr>
<td>penicillin G sodium: 18-24 million units/day intravenously given in divided doses every 4 hours (or by continuous infusion)</td>
<td></td>
</tr>
<tr>
<td>Secondary options</td>
<td></td>
</tr>
<tr>
<td>penicillin G procaine: 2.4 million units intramuscularly once daily -and- probenecid: 500 mg orally four times daily</td>
<td></td>
</tr>
<tr>
<td>adjunc subsequent postdesensitization intramuscular benzathine penicillin-G</td>
<td></td>
</tr>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» <a href="#">penicillin G benzathine</a>: 2.4 million units intramuscularly once weekly</td>
<td></td>
</tr>
<tr>
<td>» Some specialists administer benzathine penicillin-G once weekly for up to 3 weeks after the treatment regimen for neurosyphilis has been completed (only if first-line intravenous therapy was chosen as the initial therapy).</td>
<td></td>
</tr>
<tr>
<td>» This ensures the duration of treatment is comparable with that of late syphilis in the absence of neurosyphilis.</td>
<td></td>
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<tr>
<td><strong>adjunct</strong></td>
<td>prednisone</td>
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<td>Treatment recommended for SOME patients in selected patient group</td>
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</tr>
<tr>
<td><strong>Primary options</strong></td>
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</tr>
<tr>
<td>» prednisone: 40-60 mg orally once daily for 3 days; start 24 hours before penicillin</td>
<td></td>
</tr>
<tr>
<td>» Corticosteroid therapy may be considered to minimize the risk of Jarisch-Herxheimer reaction in nonpregnant patients with neurosyphilis. However, evidence of effectiveness is unclear and it is not routinely recommended in the US.</td>
<td></td>
</tr>
<tr>
<td>» Jarisch-Herxheimer reaction is an acute febrile illness that can occur within the first 24 hours after initiation of antibiotic treatment for syphilis. Symptoms include acute fever, headache, and myalgia, usually occurring in patients with early syphilis.</td>
<td></td>
</tr>
<tr>
<td><strong>2nd</strong></td>
<td>high-dose oral doxycycline</td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» doxycycline: 200 mg orally twice daily</td>
<td></td>
</tr>
<tr>
<td>» The evidence for the use of nonpenicillin regimens is relatively weak. However, high-dose doxycycline is used by some clinicians in this situation.</td>
<td></td>
</tr>
<tr>
<td>» Treatment course: 28 days.</td>
<td></td>
</tr>
<tr>
<td><strong>adjunct</strong></td>
<td>prednisone</td>
</tr>
<tr>
<td>Treatment recommended for SOME patients in selected patient group</td>
<td></td>
</tr>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» prednisone: 40-60 mg orally once daily for 3 days; start 24 hours before doxycycline</td>
<td></td>
</tr>
</tbody>
</table>
### Acute

- Corticosteroid therapy may be considered to minimize the risk of Jarisch-Herxheimer reaction in nonpregnant patients with neurosyphilis.\[3\] However, evidence of effectiveness is unclear and it is not routinely recommended in the US.

- Jarisch-Herxheimer reaction is an acute febrile illness that can occur within the first 24 hours after initiation of antibiotic treatment for syphilis. Symptoms include acute fever, headache, and myalgia, usually occurring in patients with early syphilis.

### Congenital Syphilis

#### 1st Intravenous Aqueous Penicillin-G or Intramuscular Procaine Penicillin-G

**Primary Options**

- **Penicillin G Sodium**: 100,000 to 150,000 units/kg/day intravenously, administered as 50,000 units/kg/dose every 12 hours during the first 7 days of life and then every 8 hours thereafter

  OR

- **Penicillin G Procaine**: 50,000 units/kg intramuscularly once daily

  *All infants born to mothers with reactive nontreponemal and treponemal tests should have nontreponemal serology (Venereal Disease Research Laboratory or rapid plasma reagin tests) performed on infant serum. False-positive results may occur if umbilical cord blood is sampled, due to contamination of umbilical cord blood with maternal blood.*

- **First-line treatment of congenital syphilis is intravenous aqueous penicillin-G or intramuscular procaine penicillin-G.\[5\] [99]** Discussion with an obstetric specialist and neonatologist is recommended. Subsequently, close clinical and serologic follow-up by a pediatric specialist is recommended.

  *Treatment course: 10 days.*

- **Postnatally-acquired syphilis raises the suspicion of child sexual abuse, which should be investigated further.\[30\]**

#### 2nd Intramuscular Benzathine Penicillin-G

**Primary Options**

- **Penicillin G Benzathine**: 50,000 units/kg intramuscularly as a single dose
Syphilis infection

**Acute**

- Recommended if a nontreponemal test in the infant is nonreactive and there is low likelihood of infectivity.\[5\] [99]

- Covers possible incubating syphilis with close serologic follow-up.

- Discussion with an obstetric specialist recommended.

- Intramuscular benzathine penicillin-G is infrequently used in resource-rich countries. Close clinical and serologic follow-up by a pediatric specialist is recommended.

- Postnatally-acquired syphilis raises the suspicion of child sexual abuse, which should be investigated further.\[30\]
Emerging

Azithromycin#

Azithromycin may be an option in special circumstances only when local susceptibility to azithromycin is likely.[100] Data regarding resistance to azithromycin for treating syphilis in specific settings are not available, and will likely remain unknown. The World Health Organization Guideline Development Group notes concerns about the risk of azithromycin resistance in *Treponema pallidum*. [100]

Ceftriaxone

Ceftriaxone has been used to treat late latent syphilis and neurosyphilis. However, there is no clear consensus regarding the optimal duration of treatment. Results from meta-analyses have found ceftriaxone to be noninferior to penicillin in terms of cure rates, relapse rates, and serofast rates.[101] [102] In patients with penicillin allergy, there is a low risk of allergic reaction with ceftriaxone due to cross-sensitivity, and it may be given in patients with no history of anaphylaxis.
**Recommendations**

**Monitoring**

Nontreponemal tests are repeated to monitor active infection and treatment response. Titers should decline fourfold within 6 months after treatment of primary or secondary syphilis and within 12-24 months after treatment of latent or late syphilis.

Venereal Disease Research Laboratory or rapid plasma reagin titers should be measured monthly after treatment for 3 months, and then every 3 months thereafter. The same nontreponemal test should be used sequentially when monitoring treatment response. This is because results obtained from one test are not directly comparable with that of the other, nontreponemal test.

With effective treatment, nontreponemal tests should become negative. However, some patients who have received adequate treatment become serofast, maintaining a low-level positive titer. This is their baseline titer from which reinfection is assessed.

Following treatment for neurosyphilis, cerebrospinal fluid (CSF) examination should be repeated every 6 months until the white blood cell (WBC) count is normal (if elevated on the initial sample). Retreatment is considered if the WBC count has not decreased after 6 months or if the CSF remains abnormal after 2 years.[5]

**Patient instructions**

Patients should be informed that future treponemal-specific testing will reveal previously treated syphilis infection.

Before receiving antibiotic treatment, all patients should be advised of the possibility of the Jarisch-Herxheimer reaction occurring, particularly those patients with early syphilis. The reaction may occur within the first 24 hours after antibiotic therapy due to the rapid killing of treponemes. It is characterized by acute fever, headache, and myalgia. In pregnant women this may cause fetal distress and premature labor.

Patients with primary syphilis should be advised to avoid sexual activities (including oral sex) until the lesions have resolved. Specifically, abstinence from sexual activity is recommended for at least 2 weeks after the lesions of primary syphilis have fully healed, and until 2 weeks after therapy is complete.[3]

Social stigma remains regarding syphilis infection and there may be patient concern about future disclosure issues (e.g., prenatal screening).

Contact tracing of sexual partners should be undertaken to identify asymptomatic patients at risk of syphilis. [CDC: syphilis - fact sheet]
**Complications**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jarisch-Herxheimer reaction</td>
<td>short term</td>
<td>high</td>
</tr>
</tbody>
</table>
| Occurs within the first 24 hours after antibiotic therapy due to the rapid killing of treponemes.  
Characted by acute fever, headache, and myalgia, usually in patients with early syphilis.  
The likelihood of reaction is high in early syphilis but low in late syphilis. However, all patients should be advised of a possible reaction prior to receiving antibiotic treatment.  
In pregnant women, Jarisch-Herxheimer reaction may cause fetal distress and premature labor.  
Treatment is supportive with oral fluids, acetaminophen, and nonsteroidal anti-inflammatory drugs.  
Corticosteroid therapy may be considered to minimize the risk of a Jarisch-Herxheimer reaction in nonpregnant patients with cardiovascular syphilis or neurosyphilis.[3] However, the evidence of effectiveness is unclear and it is not routinely recommended in the US. | short term | medium      |
| allergic reaction to penicillin            | short term| medium     |
| May arise in patients not previously known to be allergic.  
In patients with penicillin allergy, alternative treatment options may be offered, dependent on the stage of syphilis.  
Penicillin allergy skin testing and desensitization may be required (e.g., in the treatment of pregnant women).  
Penicillin-allergic responses may include urticaria, angioedema, and anaphylaxis.  
Treatment of allergic reaction is determined by the severity of the reaction. | short term | medium     |
| iatrogenic procaine reaction               | short term| low        |
| Occurs when intramuscular procaine penicillin-G (e.g., used to treat neurosyphilis) is mistakenly administered intravenously.  
Patients may develop penicillin allergic responses, including anaphylactic shock.[90] | long term | medium     |
| HIV infection                              | long term | medium     |
| Syphilis facilitates the acquisition of HIV. | variable | medium     |
| asymptomatic progression of disease        | variable | medium     |
| Organ-specific complications can occur in untreated infection of unknown duration.  
Specialist opinion should be sought depending on the nature of the complication (e.g., ophthalmology specialist opinion for ocular infection, cardiovascular specialist opinion for aortic regurgitation). | variable | medium     |
Prognosis

Natural course of infection
Treatment is curative once antibiotic treatment is completed. However, reinfection may occur if there is further exposure to syphilis.

The natural course of organ-specific involvement is determined by the stage of syphilis at diagnosis and whether appropriate treatment has been administered. Follow-up of organ-specific complications requires specialist opinion (e.g., cardiology assessment of aortic regurgitation; neurology assessment of tabes dorsalis).

Serology test results
Treponemal-specific tests remain reactive lifelong; therefore, they are unable to differentiate between current (active) and past infections. Nor can they be used to monitor response to treatment.

Patients should be informed that future treponemal-specific testing will reveal previously treated syphilis infection.

Nontreponemal tests show a decline in titers or become nonreactive (negative) with effective treatment and are, therefore, used as a quantitative marker of treatment response. Titers should decline fourfold within 6 months after treatment of primary or secondary syphilis, and within 12-24 months after treatment of latent or late syphilis.[104]
# Diagnostic guidelines

## International

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Published by</th>
<th>Last published</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening for syphilis infection in pregnancy [88]</strong></td>
<td>US Preventive Services Task Force</td>
<td>2018</td>
</tr>
<tr>
<td><strong>Syphilis infection in nonpregnant adults and adolescents: screening [73]</strong></td>
<td>US Preventive Services Task Force</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Sexually transmitted diseases treatment guidelines, 2015 [5]</strong></td>
<td>Centers for Disease Control and Prevention</td>
<td>2015</td>
</tr>
<tr>
<td><strong>Recommendations for partner services programs for HIV infection, syphilis, gonorrhea, and chlamydial infection [78]</strong></td>
<td>Centers for Disease Control and Prevention (CDC)</td>
<td>2008</td>
</tr>
<tr>
<td><strong>WHO guideline on syphilis screening and treatment for pregnant women [89]</strong></td>
<td>World Health Organization</td>
<td>2017</td>
</tr>
<tr>
<td><strong>WHO guidelines for the treatment of Treponema pallidum (syphilis) [4]</strong></td>
<td>World Health Organization</td>
<td>2016</td>
</tr>
<tr>
<td><strong>2014 European guideline on the management of syphilis [90]</strong></td>
<td>International Union against Sexually Transmitted Infections (IUSTI)</td>
<td>2014</td>
</tr>
<tr>
<td><strong>UK national guideline on the management of sexually transmitted infections and related conditions in children and young people [49]</strong></td>
<td>British Association for Sexual Health and HIV</td>
<td>2010</td>
</tr>
</tbody>
</table>
# Treatment guidelines

## International

**Sexually transmitted diseases treatment guidelines, 2015**  
*Published by:* Centers for Disease Control and Prevention (CDC)  
*Last published:* 2015

**Recommendations for partner services programs for HIV infection, syphilis, gonorrhea, and chlamydial infection**  
*Published by:* Centers for Disease Control and Prevention  
*Last published:* 2008

**WHO guideline on syphilis screening and treatment for pregnant women**  
*Published by:* World Health Organization (WHO)  
*Last published:* 2017

**WHO guidelines for the treatment of Treponema pallidum (syphilis)**  
*Published by:* World Health Organization  
*Last published:* 2016

**Barrier methods for contraception and STI prevention**  
*Published by:* Faculty of Sexual and Reproductive Healthcare (UK)  
*Last published:* 2015

**UK national guidelines on the management of syphilis**  
*Published by:* British Association for Sexual Health and HIV  
*Last published:* 2015

**2014 European guideline on the management of syphilis**  
*Published by:* International Union against Sexually Transmitted Infections  
*Last published:* 2014

**UK national guideline on the management of sexually transmitted infections and related conditions in children and young people**  
*Published by:* British Association for Sexual Health and HIV  
*Last published:* 2010
Online resources

1. USPSTF: syphilis infection in pregnant women - screening (external link)
2. USPSTF: Syphilis infection in nonpregnant adults and adolescents: screening (external link)
3. CDC: sexually transmitted disease surveillance, 2017 (external link)
4. NSC: the UK NSC recommendation on syphilis screening in pregnancy (external link)
5. CDC: syphilis - fact sheet (external link)
Key articles

- British Association for Sexual Health and HIV (BASHH). UK national guidelines on the management of syphilis. December 2015 [internet publication]. Full text


- World Health Organization. WHO guideline on syphilis screening and treatment for pregnant women. 2017 [internet publication]. Full text


References


49. British Association for Sexual Health and HIV (BASHH). United Kingdom national guideline on the management of sexually transmitted infections and related conditions in children and young people - 2010. 2010 [internet publication]. Full text


55. Pan American Health Organization (PAHO). Guidance on syphilis testing in Latin America and the Caribbean: improving uptake, interpretation, and quality of testing in different clinical settings. 2015 [internet publication]. Full text


76. The World Health Organization. The use of rapid syphilis tests. 2006 [internet publication].


81. World Health Organization, Department of Reproductive Health and Research. The global elimination of congenital syphilis: rationale and strategy for action. 2007 [internet publication].  Full text


89. World Health Organization. WHO guideline on syphilis screening and treatment for pregnant women. 2017 [internet publication].  Full text


103. Faculty of Sexual and Reproductive Healthcare. Barrier methods for contraception and STI prevention. August 2015 [internet publication]. [Full text]


Figure 1: Electron micrograph of *Treponema pallidum* on cultures of cotton-tail rabbit epithelium cells

*CDC/Dr David Cox; used with permission*
Figure 2: A primary vulvar syphilitic chancre due to Treponema pallidum bacteria

CDC: PHIL image ID 5340; used with permission
Figure 3: A penile chancre located on the proximal penile shaft: primary syphilitic infection

CDC/ Dr Gavin Hart; Dr NJ Fiumara; used with permission
Figure 4: Gummatous lesions on the dorsal surface of the left hand

CDC/Susan Lindsley; used with permission
Figure 5: Secondary syphilitic papulosquamous rash on the torso and upper body

CDC/Susan Lindsley; used with permission
Figure 6: Secondary syphilitic lesions on the face

CDC: PHIL image ID 3500; used with permission
Figure 7: Secondary syphilis presenting pigmented macules and papules on the skin

CDC/Susan Lindsley; used with permission
Figure 8: Secondary syphilitic lesions of vagina

CDC/J. Pledger; used with permission
Figure 9: This was a case of congenital syphilis resulting in the death of this newborn infant

CDC: PHIL image ID 3510; used with permission
Figure 10: This newborn presented with symptoms of congenital syphilis that included lesions on the soles of both feet

CDC: PHIL image ID 4148; used with permission
Figure 11: Interstitial keratitis

CDC/Susan Lindsley; used with permission
Figure 12: Peg-shaped, notched central incisors (Hutchinson teeth)

CDC/Robert E. Sumpter; used with permission
Figure 13: Osteoperiostitis of the tibia ("saber shins")

CDC/Robert E. Sumpter; used with permission
Figure 14: Clutton joints

CDC/Richard Deitrick; used with permission
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