Syphilis

Syphilis is a systemic infection caused by *Treponema pallidum*, a microaerophilic spirochete that infects only humans and a few primates. The infection is usually acquired through sexually contact with infected lesions or body fluids; less commonly, transplacentally from mother to unborn child; and, rarely, through blood transfusion, accidental inoculation, or puncture with contaminated instruments such as those used for tattooing.

**Etiology**

The cause of syphilis is a motile, corkscrew-shaped, prokaryotic bacterium with a flexible, helically coiled cell wall. *T. pallidum* measures between 6 and 15 µm in length, and 0.10 to 0.18 µm in width. It has tapered ends between which are 6 to 14 regularly spaced tight spiral coils. When fixed, the spirals impart a wave-like configuration. Under dark-field microscopic examination, the treponemes resemble strings of beads with a characteristic rotator motion and a flexion and back-and-forth squiggle. This motion is said to be characteristic of virulent treponemes and to facilitate penetration through the tissue. However, in fluid medium, the bacteria lack locomotion, which distinguishes them from most saprophytic treponemes. Replication occurs through fission, with an interval of 30 to 33 hours between divisions.

The spirochete has three main components. The protoplast is the central part of the treponeme and contains the genome and the organelles responsible for metabolism. The axial filament (flagelum) consists of six to eight elastic fibrils twisted around the protoplast. It imparts the helicoid shape and contributes to the spirochete’s mobility. The outer envelope contains a heteropolymer peptidoglycan macromolecule that preserves the organism’s shape, protects fragile cytoplasm against injury, and filters large molecules.

**Immunology**

*T. pallidum* penetrates mucosal surfaces and abraded skin of humans. Chemotactic factors attract neutrophils to the inoculation site. Skin breakdown results in a chancre, initiating the primary stage. In more mature chancre, neutrophils are replaced by lymphocytes that, through secretion of lymphokines, attract and activate macrophages that ingest and destroy the organisms. Consistent with a T helper 1 predominant local cellular response, the lesions contain IL-1, IFN-γ, IL-10 and IL-12. Plasma cells are also present in the infiltrate and a humoral response is elicited. Antibodies to *T. pallidum* are detectable at the time or shortly after the chancre appears. Production of immunoglobulin M (IgM) precedes that of IgG. The combined humoral and cell-mediated immune responses appear to eliminate the spirochetes locally, resulting in the end of the primary stage.

After a few weeks, proliferation of spirochetes markedly increases, and the disease becomes generalized. During this secondary stage, antibody levels skyrocket in response to the huge numbers of organisms. The antibody response modifies the appearance of the secondary syphilis lesions, which would otherwise resemble primary chancre. At this time, resistance to new infection develops, although delayed-type hypersensitivity to *T. pallidum* becomes unexpectedly
deficient. This suppression of cell-mediated immunity allows proliferation of the organisms despite rising antibody levels.

The secondary stage is followed by an asymptomatic stage called latency. During this period, delayed-type hypersensitivity reappears. In the tertiary stage, the immune response results in the formation of granulomas, although treponemes are rarely detected, even by immunofluorescence.

Immunity to re-infection develops only in untreated patients. After treatment, most re-infected patients develop typical chancres.

The means by which some treponemes resist the immune attack, which effectively clears practically every organism from early lesions, is unknown. Possible explanations include inhibition of cell-mediated responses, refuge of treponemes in anatomic sites (central nervous system, eye, aorta, bone, lymph node) that shield the organisms from detection by the immune system, and protection by the slimy mucopolysaccharide coat surrounding the spirochetal cell wall.

**Natural history of disease**

Syphilis has been described as an on-and off- and on-again disease.

Early syphilis includes the primary stage (chancre), secondary disease (mucocutaneous lesions and lymphadenopathy, with or without organ involvement) and subsequent clinical relapses.

Latent disease is subdivided into early (less than 1 year) and late (1 year or longer) stages.

Tertiary (late) disease can present with cutaneous, cardiovascular or neurologic involvement.

**Clinical findings**

*Primary syphilis*

At the site of treponemal penetration, after an incubation period that ranges from 10 to 90 days (average 3 weeks), a dusky red macule appears that grows into a papule and becomes a chancre by ulcerating in the center. The length of incubation period varies inversely with the number of inoculated treponemes. The chancre is round or oval, measures approximately 1 cm in diameter, has sharply demarcated, regular, raised, firm, non-tender, rubbery borders. The smooth, ham-colored ulcer base may be covered with yellowish crust or grayish slough. Untreated, chancre persists from 1 to 6 weeks; it resolves within 1 to 2 weeks after treatment and heals without scarring.

Multiple chancres may be present in up to 47 percent of cases, and edema, phimosis, erosive balanitis, lymphangitis and thrombophlebitis of the dorsal vein may be found.

In men, the commonly involved locations are the glans, the coronal sulcus, and the foreskin. Chancre in the urethral orifice have been reported to cause an inflammatory Phimosis that may eventuate in penile gangrene. Retraction of the foreskin with a chancre in its mucosal surface causes the foreskin to flip briskly, a sign known as the Dory flop.

In women, the labia, fourchette, urethra and perineum are affected in descending order of frequency. Chancre in women tend to have an edematous
rather than a cartilaginous induration. Edema induratium is a unilateral labial swelling with rubbery consistency and intact surface, characteristic of a deep-seated chancre in this site. Chancres may develop in the cervix, but are rarely detected. Kissing chancres are common in areas of skin-to-skin contact such as the vulva.

Approximately two-thirds of extragenital chancres occur above the neck, and one-half of these are seen on the lips, the perioral region or in the oral cavity. The rest appears on the fingers, breasts, trunk, abdomen and extremities. Chancres on the fingers may be painful. Anorectal primary syphilis is often asymptomatic and underdiagnosed and should be considered in any at-risk person with rectal pain, bloody stools, anal fissures, or a precipitously appearing mass or ulcer in the anorectal area.

In 70 percent to 80 percent of all primary syphilis cases, enlarged, rubbery, movable, non-tender, non-suppurative, discrete lymph nodes – scleradenitis appear during the first week of infection.

Secondary syphilis
Lesions of secondary syphilis erupt 3 to 12 weeks after the appearance of the chancre but may develop months later or in up to 15 percent of case, before the chancres disappears. The secondary stage usually recedes in 2 to 12 weeks.

Patients with secondary syphilis may experience symptoms such as malaise, appetite loss, fever, headache, stiff neck, lacrimation, myalgias, arthralgias, nasal discharge and depression. However, between 80 percent or 95 percent of cases present with a skin eruption, which invariably is the salient diagnostic feature of the infection.

Most eruptions are macular and/or papular. Nodular and pustular eruptions occur infrequently. Early on, the lesions of secondary syphilis often have a symmetric pattern and become polymorphic later. With or without treatment, non-ulcerated secondary lesions heal without scarring after 2 or 12 weeks.

Macular eruption (roseola syphilitica) consists of 0.5 to 2 cm, pink, discrete, non-scaling, oval macules which predominately involve the trunk and flexor aspects of the upper extremities. The face is usually spared, but any area, including the palms and soles may be involved.

Papular eruptions represent an evolution of the macular lesions toward papules and plaques, as some macules become palpable and develop a dark coppery hue. Lesions are often present on the genitalia, face palms and soles. Papular eruptions include papulosquamous, follicular, lenticular and annular varieties. They may be generalized or grouped, aggregated and localized to defined sites. A thin white ring of scales on the surface of a lesion (Biett’s collarette) is a valuable diagnostic sign.

Pustular eruptions include several several morphologic variants. In miliary pustular eruptions, small acuminate pustules resolve with depressed pigmented scars. In acneiform, varioliform or obtuse eruptions there are large acuminate perifollicular pustules. In impetiginoid or eanthymiform eruptions, flat pustules become confluent and covered with a large crust called carapace.
Malignant syphilis (lues maligna) presents with widespread papulopustules or nodules that become necrotic or break down into ulcers covered by layers of rupioid crusts resembling an oyster shell. The eruption is associated with toxicity, fever, arthralgias and occasionally hepatitis. Oral ulcers and mucous patches may develop. Most patients are immunocompromised or in poor health.

Pigmentary changes may remain after healing of lesions. On the sights of the neck, an interesting pattern consisting of hypopigmented macules superimposed on linear pigmented reticulated patches has been called *leukoderma colli syphiliticum* or the Necklace of Venus.

Mucous membrane lesions are extremely infectious. The three manifestations are condyloma lata, mucous patches and pharyngitis. The last two heal spontaneously within 2 to 3 weeks, but condyloma may persist for months.

*Condylomata lata* consists of flesh colored or hypopigmented macerated papules or plaques. Their surface may be smooth, papillated or covered with cauliflower-like vegetations. The common sites are the genital and anal areas and less frequently the oral commisures, face, axillae, inframammary folds, and toe webs.

*Mucous patches* are painless, shallow, rounded erosions covered with gray macerated scaling. Lesions may occur anywhere in the mouth but are more common on the tongue and lips. The tonsils and epiglottis may be affected. Mucous patches also arise on the glans penis, inner vulva and anus.

*Pharyngitis* of variable severity may occur in up to one-fourth of cases, although soreness is rare. Diffuse redness of the pharynx, palate and tonsils may be very mild or severe with edema and erosions.

Hair loss may be the only sign of secondary syphilis. It may be either patchy, diffuse or both. The more characteristic type consists of small irregular patches of non-scarring alopecia throughout the scalp but predominantly on the occipital and parietal regions. Occasionally the eyebrows, beard and other hair bearing areas are affected.

**Latent syphilis**

The secondary stage is followed by an asymptomatic stage with no clinical findings; the only evidence of disease is reactive serologic testing. Latency may remain indefinitely, be interrupted by a relapse of secondary syphilis or progress to the tertiary stage. Because latent syphilis is a diagnosis of exclusion, careful examination for mucocutaneous lesions and organ involvement is required. In addition, ultrasound evaluation of the aorta to exclude cardiovascular disease and cerebrospinal fluid (CSF) examination for neurosyphilis should be considered if the history or physical findings suggest these diagnoses.

For therapeutic and epidemiologic purposes, the latent stage is divided into early (less than 1 year) and late (1 year or longer) stages. The duration of the infection should be determined by history and previous serologic tests.

In clinical practice, patients who were adequately treated but who continue to have low titers of nontreponemal tests are commonly seen. If adequate previous treatment or lack of reinfection cannot be confirmed, these patients should be
assumed to be infected and treated. A record of nontreponemal test titer and the administered therapy should then be given to the patient.

**Tertiary syphilis**

Approximately one-third of patients with untreated latent syphilis develop tertiary syphilis, while the other two-thirds remain in perpetual latency. The three principle presentations during this stage are late benign syphilis, cardiovascular disease and neurosyphilis.

*Late benign syphilis* includes any symptomatic syphilitic manifestation after the secondary and relapsing stages that does not involve the cardiovascular and nervous systems. The lesions are caused by a cell-mediated inflammatory response to a small number of treponemes present in the affected tissues.

The more commonly involved organs are the skin, mucous membranes and bones, but gummas may appear in practically any organ.

**Late benign syphilis of the skin**

Tertiary skin lesions can be divided into two types: granulomatous nodules and gummas. Precocious lesions develop within the first 2 years after resolution of the secondary stage and late lesions at any time after that. Most of the lesions develop within 3 to 7 years, but gummas have appeared as long as 60 years after infection. The longer the interval before appearance of the skin lesions, the more solitary and destructive is the process.

Nodular and noduloulcerative lesions tertiary lesions are superficial, firm, painless, dull-red, shiny, flat cutaneous nodules that measure several millimeters to 2 cm in size. The nodular occur into grouped configuration. The skin overlying the lesions breaks down, resulting in irregular ulcers covered with crust. The lesions are most commonly seen on the arms, back and face. Even without treatment, the granulomas heal after several years, leaving atrophic scars with increased or decreased pigmentation.

Gummas are non-tender pink to dusky-red nodules or plaques that vary in size from millimeters to many centimeters in diameter. They may arise anywhere in the body but are more common on the scalp, forehead, buttocks and presternal, supraclavicular or pretibial areas. The nodule is initially firm but develops a gummy consistency due to accumulation of necrotic tissue. Gummas may grow horizontally as well as vertically. As the central gumma heals, new lesions may develop on the periphery, forming scalloped borders. In contrast to noduloulcerative lesions, gummas are deeper and more destructive, they heal with scars. The lesions are rarely contagious.

**Mucous membrane lesions of late benign syphilis**

Discrete gummas may involve mucous membranes, especially the palate, nasal mucosa, tongue, tonsils and pharynx. The lesions ulcerate and are disfiguring. Destruction of the nasal cartilage and bone (saddle nose) and perforation of the nose and palate are disease hallmarks.

**Cardiovascular syphilis**

Presumably, during the early stages of syphilis, treponemes invade the aortic wall, where they can remain dormant indefinitely. The treponemes have a predilection for the aortic vasa vasorum and cause chronic, low-grade
inflammation that eventuates in an obliterative endarteritis with gradual necrosis of the muscular and elastic tissues and scarring.

The most common complications of cardiovascular syphilis are aortitis, aortic aneurysm, aortic valve incompetence, coronary ostial stenosis, and myocardial gummatous disease. Clues to the syphilitic etiology are the relative young age of the patient, absence of ateriosclerotic changes, reactive syphilis serology, poor response to vasodilators and concomitant aortic regurgitation.

**Neurosyphilis**

Hematogenous invasion of the meninges by *T. pallidum* occurs early in syphilis. About 25 percent of patients with untreated primary or secondary syphilis do not clear the spirochetes from the CNS, and the organisms presumably remain dormant. It has been assumed that the development of CNS disease depends primarily on the host’s immunologic response to the infection.

Neurosyphilis is divided into asymptomatic, meningeal, meningovascular, parenchymatous and gummatous disease.

In clinical practice, an unusual combination of signs and symptoms may be present, resulting in a puzzling neurologic picture.

The diagnosis of neurosyphilis should be strongly considered in an young adult with a stroke, new seizure disorder, confusional syndrome or dementia. Detection relies on detection of clinical manifestations, serum serologic tests, CSF examination and radiographic scans.

**Congenital syphilis**

The definition of congenital syphilis was recently updated; however, because most infants have no clinical or serologic evidence of syphilis at birth and develop abnormalities months to years later, all potentially infected infants should be treated with penicillin. Mothers usually transmit the infection to the fetus transplacentally and possibly during delivery through contact with an infectious genital lesion.

**Definition of Congenital Syphilis**

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<tr>
<th>Type</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Confirmed</td>
<td>An infant in whom <em>Treponema pallidum</em> is identified in lesions, placenta,</td>
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<td>umbilical cord, or autopsy tissue.</td>
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<td>Presumptive</td>
<td>Any infant whose mother was untreated or treated with antibiotics other</td>
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<td>than penicillin before delivery, regardless of findings in the infant or</td>
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<td>Any infant or child with a reactive treponemal test for syphilis and any</td>
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<td>one of the following:</td>
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<td>- Evidence of congenital syphilis on physical examination or x-ray of long</td>
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<td>- Presence in the cerebrospinal fluid of lymphocytosis and elevated protein</td>
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<td>(without other cause).</td>
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<td>- Reactive cerebrospinal fluid VNRL</td>
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<td>- Infant rapid plasma reagin fourfold higher than mother (both drawn at</td>
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<td>birth) or Reactive immunoglobulin M-treponemal antibody test in serum</td>
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<td>Syphilitic</td>
<td>Stillbirth.</td>
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<td>A fetal death in which the mother had untreated or inadequately treated</td>
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<td>syphilis at delivery of a fetus after a 20-week gestation or of a fetus</td>
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<td>weighing &gt; 500 g.</td>
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*Congenital syphilis includes cases of perinatally acquired syphilis in infants and children, as well as syphilitic Stillbirths.*
Approximately 25 percent of infants from mothers with untreated primary or secondary syphilis die in utero. Of those infants born, almost one-half develop the disease, another one-fourth are seropositive without clinical manifestations and only one-fourth are not infected.

Syphilis remains the most common cause of nonimmune hydrops fetalis. Such infants are born with pallor, edema and a bloated abdomen.

Prenatal syphilis is divided into early (first 2 years) and late (after 2 years) stages.

Early prenatal syphilis: This stage is comparable to the secondary stage of acquired syphilis because treponemes disseminate throughout fetus. Without treatment almost one-half of symptomatic infants die. Infants are born premature or small for dates. They are irritable and cry feebly. In descending order of frequency, the manifestations found are low birth weight, hepatosplenomegaly, anemia, jaundice, thrombocytopenia, skin lesions, respiratory distress, rhinitis and pseudoparalysis. Rhinitis (“snuffles”) usually develops in the second to third week of life and may be earliest clinical sign. Initially thin, a mucoid nasal discharge, teeming with spirochetes, can become purulent or bloody. The nasal septum may become perforated. If untreated, flattening of the nasal bridge results in the characteristic saddle of fleur de lis nose.

Mucocutaneous lesions are like secondary syphilis manifestations, usually consist of an eruption of cooper to red colored macules and papules, with or without scale, predominantly on the palms and soles and diaper area. Condylomata lata may also be present. Commonly known as syphilitic pemphigus, the presence of blisters on palms and soles is a sign of severe disease. Ulcerations around the mouth, nose and anus may heal with rhagades (Parrot’s lines), depressed linear scars that persist to adulthood and radiate from the orifice like spokes of a wheel.

Lymphadenopathy occurs in one-half of the cases but may not be prominent.

Bone disease, although usually asymptomatic, is the most common early manifestation. The most frequently observed osseous lesion, osteochondritis, is diagnosed by its characteristic radiographic sawtooth appearance in the metaphysis. Pain from osteochondritis of the long bones, is exacerbated by movement, so the child keeps affected limb still, a sign known as pseudoparalysis of Parrot.

Late prenatal syphilis: Manifestations appear after the age of 2 years and can be divided into 2 groups: malformations (stigmata) and active pathologic processes.

Diagnostic tests

Dark-field microscopy is a diagnostic test of choice in chancreles and moist lesions of secondary syphilis, especially condylomata lata and mucous patches. The test is invalid for oral lesions because saprophytic treponemes that cannot be differentiated from T.pallidum are common in the mouth. In such case a lymph node aspirate can be examined by dark-filed microscopy.
**Direct fluorescence antibody test**
The lesional exudate is smeared on a glass slide and stained with fluorescence labeled anti-T.pallidum immunoglobulin. In contrast to dark field microscopy, the smear can be held for later evaluation and oral and anal lesions can be examined because only T.pallidum is stained. The sensitivity of the test is greater than 90 percent.

**Serology**
Serologic tests for the syphilis are divided into two main types. The simpler cardiolipin-based nontreponemal tests are used for screening and to follow therapeutic response. The more elaborate T.pallidum-based treponemal tests are used for diagnostic confirmation and to improve diagnosis of early, congenital and neurosyphilis.

A presumptive diagnosis of syphilis is made by a reactive nontreponemal test, such as the RPR or the VDRL, confirmed by a treponemal test, such as the microhemagglutination assay with T.pallidum or the FTA-ABS test (fluorescent treponemal antibody absorption).

**Interpretation of Serologic Tests**

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<tr>
<th>RPR</th>
<th>MHA-TP</th>
<th>CAPTIA (IgM) EIA</th>
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- No syphilis or incubating syphilis
- Early primary syphilis
- Primary or secondary syphilis
- Early infection
- Late secondary or latent syphilis
- Biologic false-positive, late syphilis
- Late infection, treated syphilis, or false-positive treponemal test
- Re-infection, relapse

**Sensitivity and Specificity of Serologic Tests**

<table>
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<th>Test</th>
<th>Sensitivity (%)</th>
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<tr>
<td>VDRL</td>
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<tr>
<td>Rapid plasma reagin</td>
<td>80 (74-87)</td>
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<tr>
<td>Fluorescent treponemal antibody-absorption</td>
<td>86 (81-100)</td>
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<tr>
<td>Microhemagglutination assay w/ Treponema pallidum antigen</td>
<td>98 (93-100)</td>
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<tr>
<td>Capta syphilis (IgM) enzyme immunoassay</td>
<td>92 (85-99)</td>
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Note: For explanation of serologic tests, see text.

**Treatment**
Parenteral penicillin is the treatment of choice for all stages of syphilis. A concentration of penicillin above 0.018mg/L is considered treponemical.

The recommended doses of long-acting benzathine penicillin provide treponemical levels for 3 to 4 weeks.
Parenteral penicillin is the only treatment with documented efficacy of neurosyphilis, HIV infection and pregnancy.

Tetracyclines, erythromycin and third-generation cephalosporins have strong antitreponemal activity in experimental and clinical trials but are less effective than penicillin.

**Primary and secondary syphilis (without neurologic, ophthalmologic and auditory involvement)**

A single dose of benzathine penicillin G, 2.4 millions units intramuscularly, is the preferred treatment.

**Penicillin allergy** Patients with uncomplicated syphilis may be treated with doxycycline 100 mg orally twice daily for 2 weeks; tetracycline 500mg orally four times daily; erythromycin 500mg orally four times daily; ceftriaxone 250mg daily or 1g every other day intramuscularly or intravenously for 8 to 10 days is an alternative.

**Follow-up** patients should be re-examined clinically and serologically at 6 and 12 months.

**Early latent syphilis**

A single dose of benzathine penicillin G, 2.4 million units intramuscularly is the recommended treatment.

**Penicillin allergy** if the patient is neither pregnant nor HIV-infected, treat with doxycycline 100 mg orally twice daily for 4 weeks.

**Late latent syphilis**

Benzathine penicillin G, 2.4 million units intramuscularly 1 week apart for three doses, is the treatment of choice.

**Penicillin allergy** Doxycycline 100mg orally twice daily or tetracycline 500 mg orally four times daily for 28 days may be prescribed.

**Follow-up** Quantitative nontreponemal serologic tests should be repeated at 6, 12 and 24 months. After treatment, the patient should be re-evaluated for neurosyphilis.

**Tertiary syphilis (cardiovascular, late benign syphilis)**

Benzathine penicillin G, 2.4 million units intramuscularly 1 week apart for three doses, is the treatment of choice.

**Penicillin allergy** if the patient is not HIV infected and the CSF is negative, treat with doxycycline 100mg orally twice daily for 2 weeks.

**Neurosyphilis**

The treatment of choice is aqueous crystalline penicillin G 18 to 24 million units administered daily as 3.5 to 4.0 million units intravenously every 4 hours for 10 to 14 days.

Alternatively, treatment with a single injection of procaine penicillin G 2.4 million units intramuscularly daily and probenecid 500mg orally every 6 hours for 10 to 14 days.

**Penicillin allergy** Desensitize and treat with penicillin.

**Follow-up** Re-examine the CSF every 6 months until normal.
Treatment in pregnancy
The penicillin regimen appropriate to the stage of the disease should be used. In primary, secondary and early latent syphilis a second benzathine penicillin injection 1 week later is recommended.

Penicillin allergy: Desensitize and treat with penicillin.

Screening: Pregnant women should be screened at their initial prenatal visit, and those with seropositive results should be considered infected unless treatment can be verified and sequential serologic antibody titers convincingly demonstrate an appropriate response. Screening should be repeated in the third trimester and again at delivery.

Prenatal syphilis
Neonatal period: Aqueous penicillin G 50,000 units/kg intravenously every 12 hours for the first 7 days of life and every 8 hours for the next 3 days, or procaine penicillin G 50,000 units/kg intramuscularly daily for 10 to 14 days.

Postneonatal period: Benzathine penicillin G 50,000 units/kg (up to 2.4 million units) intramuscularly if CSF examination is negative. If positive, aqueous penicillin G, 50,000 units/kg, every 4 to 6 hours, intravenously for 10 to 14 days.

Follow-up:
- Seropositive infants or infants born to mothers who were seroactive at delivery must be re-examined clinically and serologically every 2 to 3 months until the test becomes nonreactive or the titer has decreased fourfold;
- If the reactive test result was caused by passive transplacental transfer, nontreponemal antibody titers should decrease by 3 months and disappear by 6 months of age;
- If the child was infected and treated, the serologic decline may be slower;
- If the titers are stable or increasing after 8 to 12 months of age, the child should be re-evaluated (including CSF analysis) and retreated with a 10-day course of intramuscularly penicillin G.

Treatment of sex partners and persons exposed to syphilis
Examine the exposed person and do a serologic test. Treat the contact if there is clinical or serologic evidence of disease; treat prophylactically for primary syphilis if:
- The exposure occurred within 90 days preceding the sex partner’s diagnosis of early syphilis;
- The exposure occurred more than 90 days before the sex partner’s diagnosis of early syphilis, but serologic tests are not immediately available, and reliability is uncertain;
- The evaluation of a long-term sex partner of a person with latent syphilis demonstrates possible transmission serologically or clinically.