Consensus Statement

2019 Chinese Expert Consensus Statement on diagnosis and treatment of syphilis

The incidence and prevalence of sexually transmitted diseases (STDs) is still high in China. To guide the prevention measures and management of these STDs, we had published several guidelines on diagnosis and treatment of these diseases during 2007 to 2014. Since then, much had changed in epidemic trends of STDs and technological development. Today, the need for a new view on the prevalence, mechanism, diagnosis, and treatment of these STDs is urgent. Thereafter, we renewed the last version of the 2014 Chinese guidelines on diagnosis and treatment of STDs. The current guidelines are hopefully to be referenced in clinical practice of diagnosis, treatment, prevention, and control of venereal diseases by the clinicians working in the departments of dermatology, obstetrics and gynecology, urology, preventive medicine and other related disciplines. The chapters are the part of the guidelines on diagnosis and treatment of syphilis.

Syphilis, caused by Treponema pallidum subsp pallidum (T. pallidum), is a chronic, systemic human disease transmitted through sexual contact. The disease is classified as acquired or congenital. Acquired syphilis is divided into early and late syphilis. Early syphilis is defined as syphilis of ≤2 years induration since infection, which induces the primary, secondary and early latent syphilis stages. Late syphilis is defined as syphilis of >2 years duration since infection, including the late benign syphilis, cardiovascular syphilis, and late latent syphilis, etc. All cases with unknown duration are defined as late latent syphilis. Congenital syphilis is divided into early congenital syphilis (<2 years of age) and late congenital syphilis (≥2 years of age).

Manifestations and diagnosis

Primary syphilis

1. Epidemiological history
The patients usually have unprotected sex contact with one or several partners, a subset of whom are infected or might have had a diagnosis of syphilis in the past.

2. Clinical features
2.1 Chancre: The primary syphilis lesion appears at the site of venereal contact, usually in the genitals, after an average incubation period of 3 weeks (range: 2–4 weeks). The primary chancre begins as a raised papule and then quickly grows to a typical chancre, a round or oval, painless, indurated chancre. The chancre usually is solitary, occasionally multiple. The chancre has a clear base, without an exudate.

2.2 Indolent enlargement of lymph nodes: The indolent enlargement of lymph nodes, unilaterally or bilaterally, appears at the inguinal region or nearby the lesions. These lymph nodes are isolated in mild tenderness. The skin over these lymph nodes usually appears normal without red, swollen, or hot, sometime with light tenderness.
3. Laboratory diagnosis

3.1 Darkfield microscopy examination (DFME), argentic staining, and polymerase chain reaction (PCR): The three methods can be used to directly demonstrate *T. pallidum*. DFME and argentic staining are methods for chancres, erosive cutaneous lesions, and lymph nodes, which can directly demonstrate treponemes. PCR can be performed for the detection of *T. pallidum* DNA from specimens of any lesion exudate, tissue or body fluid.[1]

3.2 Non-treponemal serological tests: Positive. Non-treponemal serological tests includes the Venereal Diseases Research Laboratory test (VDRL), the Rapid Plasma Reagin test (RPR), and the Toluidine Red Unheated Serum Test (TRUST), etc. If the duration is less than 6 weeks, the tests may be negative. In this case, the tests should be repeated after 6 weeks.

3.3 Treponemal test: Positive. Treponemal serological tests include *T. pallidum* Haemagglutination test (TPHA), *T. pallidum* Passive Particle Agglutination test (TPPA), Fluorescent Treponemal Antibody absorption test (FTA-ABS test). Treponemal Enzyme Immunoassay (EIA), Chemiluminescence Immunoassay (CIA), IgG immunoblot test for *T. pallidum*. If the duration is less than 4 weeks, the tests may be negative. In this case, the tests should be repeated after 4 weeks.

4. Diagnostic classification

4.1 Probable case: The case has epidemiological history and clinical features, and meets the item of 3.2 or 3.3 of laboratory tests.

4.2 Confirmed case: The case has epidemiological history and clinical features, and meet the item of 3.1 of laboratory tests. Or the case has epidemiological history and clinical features, and meets the items of 3.2 and 3.3 of laboratory tests.

Secondary syphilis

1. Epidemiological history

The patients usually have unprotected sex contact with one or several partners, a subset of whom are infected or might have had a diagnosis of syphilis in the past, or have a history of blood transfusion.

2. Clinical features

Syphilis was acquired ≤2 years, with or without a diagnosis of primary syphilis previously. The clinical features of secondary syphilis commonly appear at 4–6 weeks after onset of chancre. The clinical manifestations include the below.

2.1 Cutaneous or mucosal lesions: The lesion of secondary syphilis likely mimics lesions of other skin disease and may be difficult to distinguish. It may be present as macular rash, papules, scales, and pustule, etc., involving the head, the face, the entire trunk, and the extremities. The rash in palms of the hands and soles of the feet are generally reddish brown and scaly. Symmetric papules and plaques with a collarette of scale on palm and sole, as well as condyloma lata and moist
papule in the moist regions of the anogenital area, are characteristic lesion of secondary syphilis. In addition, mucus patches in the oropharynx, nodular lesion in nasal mucosa, and “moth-eaten” patchy alopecia also are common. The skin rash are usually non-itching, and mostly different in different patients, however, commonly only one type of lesion is present in one patient. Additionally, the skin lesion in the relapse of secondary syphilis is few and weird. Annular lesion, arciform lesion, and curveform lesion are commonly observed.

2.2 Generalized lymphadenopathy is often observed in most patients.

2.3 Other systemic manifestations, such as periosteal inflammation, hepatitis, splenomegaly, periostitis, arthritis, meningitis, auricular and ophthalmic abnormalities, meningeovascular syphilis also can be observed in secondary syphilis.

3. Laboratory diagnosis
3.1 DFME, argentinc staining, and PCR: The three methods can be used to directly demonstrate *T. pallidum*. DFME and argentinc staining can find the presence of treponema in serous exudates from condyloma lata, moist papule, and mucus patches. PCR can be performed for the detection of *T. pallidum* DNA. Because *T. pallidum* in the mucus patches in the oropharynx is difficultly to distinguish from other commensal spirochetes of the oral cavity, DFME and argentinc staining is not recommended.

3.2 Non-treponemal serological tests: Positive.

3.3 Treponemal serological test: Positive.

4. Diagnostic classification
4.1 Probable case: The case has epidemiological history and clinical features, and meets the item of 3.2 or 3.3 of laboratory tests.

4.2 Confirmed case: The case has epidemiological history and clinical features, and meets the item of 3.1 of laboratory tests. Or the case has epidemiological history and clinical features, and meets the items of 3.2 and 3.3 of laboratory tests.

*Tertiary syphilis (late syphilis)*

1. Epidemiological history
The patients usually have unprotected sex contact with one or several partners, a subset of whom are infected or might have had a diagnosis of syphilis in the past, or have a history of blood transfusion.

2. Clinical features
Syphilis was acquired ≥2 years, with or without diagnosis of primary syphilis or secondary syphilis previously. The clinical manifestation includes the following:
2.1 “Benign” late syphilis

2.1.1 Cutaneous or mucosal lesions: Nodular lesions usually involving in the skin of head, face, and extensor extremities, Gummas are common in late syphilis. It usually located in the skin, oral cavity, throat, and other organs. The gummas in the upper palate and nasal might lead to perforation of the septum and of the soft palate, usually in the midline, characterized by saddle nose deformity.

2.1.2 Syphilis of bone.

2.1.3 Syphilis of other viscera: Late syphilis also might be involved in respiratory tract, digestive tract, liver, spleen, urogenital system, endocrine glands, and muscle, etc.

2.2 Cardiovascular syphilis: Cardiovascular syphilis may manifest simple aortitis, aortic insufficiency, aortic aneurysm, coronary artery stenosis, and angina, etc.\(^2\)\(^-\)\(^4\)

3. Laboratory diagnosis

3.1 Non-treponemal serological tests: Positive.

3.2 Treponemal serological test: Positive.

4. Diagnostic classification

4.1 Probable case: The case has epidemiological history and clinical features, and meets the item of 3.1 or 3.2 of laboratory tests.

4.2 Confirmed case: The case has epidemiological history and clinical features, and meets the items of 3.1 and 3.2 laboratory tests.

Neurosyphilis

1. Epidemiological History
The patients usually have unprotected sex contact with one or several partners, a subset of whom are infected or might have had a diagnosis of syphilis in the past, or have a history of blood transfusion.

2. Clinical features
2.1 Asymptomatic neurosyphilis: No clinical features of neurosyphilis.

2.2 Syphilitic meningitis: It may occur in early syphilis. The manifestations may be present as meningitis symptom, such as fever, headache, nausea, vomiting, papillary edema, neck rigidity, and positive meningeal irritation signs. The clinical features of cranial nerve inflammation are characterized by vision loss, diplopia, ptosis, facial paralysis, and hearing loss. Hemiplegia, aphasia, and seizures may be observed in meningovascular syphilis. Meningitis and polyradiculopathy are also observed in meningovascular syphilis, including limb weakness, paresthesia, paresis, paraplegia, incontinence, back pain, sensation loss, and muscular atrophy.\(^5\)
2.3 Meningovascular syphilis: It may occur in early syphilis, but mostly in late syphilis. Occlusive cerebrovascular syndrome are the most common manifestations, including hemiparesis, hemiplegia, and aphasia, etc. The manifestation of spinal cord infarction may be present as diffuse pain, delayed paralysis, spasmodic paralysis, paraplegia, urinary and fecal incontinence, deep sensory deficit and sensory ataxia below the lesion level, paralysis of lower motor neurons at corresponding segments, decreased muscle tone, and muscular atrophy, etc.\textsuperscript{[6,7]}

2.4 Parenchymatous neurosyphilis: Usually occur in late stage of neurosyphilis, is the manifestation of chronic meningoencephalitis due to direct invasion of the cerebrum by treponemes. The clinical features are present as psychiatric manifestations and neurologic symptoms, characterized by the below:

2.4.1 General paresis: The most common features are mental and behavioral abnormalities. The psychiatric manifestations may be present as defects in judgment, emotional lability, depression, grandiose delusions, megalomania, dementia, and delusions. The neurologic manifestation also is observed in general paresis. The neurologic manifestation may be present as pupillary abnormalities, dysarthria, flattening of the facial lines, tremors of the facial muscles, tongue, and hands, seizures, stroke, and nutrition disorder.\textsuperscript{[8,9]}

2.4.2 Tabes dorsalis: The clinical features are due to the involvement of the posterior cord of the spinal cord and the posterior root of the spinal nerve. Common manifestations include paresthesia and lightning pains, characterized by Argyll Robertson pupil, lightning pains in the lower extremities, sensory abnormalities or loss, reduction or absence of tendon reflexes, reduction of muscle strength in low extremities, uroschisis, Charcot’s joint, optic atrophy, and visceral crisis, etc.\textsuperscript{[10,11]}

2.4.3 Gummatous syphilis: Cerebral gumma resembles the manifestations of intracranial tumors, characterized by seizure and signs of increased intracranial pressure, such as headache, nausea, vomiting, papillary edema, stiff neck. Spinal gumma may lead to paraplegia, incontinence, loss of sensation below the damaged plane, among other symptoms.\textsuperscript{[12,13]}

2.5 Ocular syphilis: It may occur in all stages of syphilis. Ocular syphilis may be involved in all structures of both eyes, including cornea, sclera, iris, choroid, vitreous body, retina, and optic nerve. Ocular syphilis may occur alone, or with tabes dorsalis or paralytic dementia. The clinical features are present as eyelid droop, limited eye movement, bulbous conjunctival congestion, visual field defect, distortion of vision, discoloration of vision, darkening of vision, flashes in the eyes, floating objects in the eyes, diplopia, decreased vision, and blindness, etc.\textsuperscript{[14,15]}

2.6 Auricular syphilis: Common manifestations are presented as reduced hearing, deafness, with or without tinnitus, which are also the symptom or sign of neurosyphilis. Deafness may be accompanied by syphilitic meningitis.\textsuperscript{[16,17]}

Due to the different involvement of sites of nervous system, the manifestations of neurosyphilis are complex and various, sometime overlap or compound.
3. Laboratory tests
3.1 Non-treponemal serological tests: Commonly positive in late syphilis, rarely negative in the patient in the late stage.

3.2 Treponemal serological test: Positive.

3.3 Examination of cerebrospinal fluid (CSF)
3.3.1 Abnormalities of CSF routine examination: the number of white blood cells is equal or more than $5 \times 10^6$/L (in person co-infected with human immunodeficiency virus [HIV], $>20 \times 10^6$/L), the elevated protein concentration is more than 500 mg/L, except other known causes for these abnormalities.

3.3.2 CSF tests for neurosyphilis: Positive FTA-ABS test with or without positive CSF VDRL. If the CSF FTA-ABS test and CSF VDRL are unavailable, they can be replaced with CSF TPPA test and CSF RPR (or CSF TRUST) test.$^{[18]}$ Recently, CSF PCR and the level of CSF CXCL13 are currently considered to help establish a diagnosis of neurosyphilis.$^{[19,20]}$

4. Diagnostic classification
4.1 Probable case: The case has an epidemiological history and clinical manifestation of neurosyphilis, and meets the items of 3.1, 3.2, and 3.3.1 of laboratory tests, without other known causes for these laboratory tests abnormalities.

4.2 Confirmed case: The case has an epidemiological history and clinical manifestation of neurosyphilis, and meets the items of 3.1, 3.2, and 3.3 of laboratory tests.

**Latent syphilis**

1. Epidemiological history
The patients usually have unprotected sex contact with the sex partner, and either of several sex partners or sex partner who had been infected with syphilis in the past or history of blood transfusion.

1.1 Early latent syphilis: In the past two years, the case has been in the following situations: (1) Has high risk sex contact in the recent two years, and never has high risk sex contact two years ago. (2) With similar manifestation of primary or secondary syphilis, but never been diagnosed as syphilis and treated with anti-syphilis medicine. (3) Sex partners have history of syphilis.

1.2 Late latent syphilis: Occur after two years from the infection of syphilis. All cases with unknown duration are defined as late latent syphilis.

2. Clinical features
No clinical manifestation of syphilis.

3. Laboratory diagnosis
3.1 Non-treponemal serological tests are commonly positive in latent syphilis.
3.2 Treponemal serological tests are mostly positive in latent syphilis.

3.3 Examination of CSF: Usually negative in latent syphilis. If the examination of the CSF is available, it is recommended to rule out asymptomatic neurosyphilis.

4. Diagnostic classification
4.1 Probable case: The case has no clinical features and never been received diagnosis and treatment for syphilis, but meet the item of 3.1 or 3.2 of laboratory tests.

4.2 Confirmed case: The case has no clinical features and never been received diagnosis and treatment for syphilis, but meet the items of 3.1 and 3.2 of laboratory tests. If the examination of the CSF is available, it is recommended to rule out asymptomatic neurosyphilis

Congenital syphilis

1. Epidemiological history
The mother is a patient with syphilis.

2. Clinical features
2.1 Early congenital syphilis: Within the first 2 years of life. The infants usually have poor development. The clinical features are similar to those of acquired secondary syphilis. The skin lesions usually present as erythema, papules, condyloma planum, blisters – bullae. Rhinitis, laryngitis, osteomyelitis, osteochondritis, and ossitis also may be observed in early congenital syphilis. Additional clinical features include generalized lymphadenopathy, hepatosplenomegaly, and anemia, etc.[22]

2.2 Late congenital syphilis: Symptoms of syphilis occur after two years of age. Late congenital syphilis corresponds to acquired tertiary syphilis. Inflammatory lesions and marked clinical manifestation commonly are observed in late congenital syphilis. The inflammatory lesions include interstitial keratitis, gumma in nose and palate, Clutton’s joints, neural deafness, and osteoperitis in tibia, etc. Marked clinical manifestations include high cranium, saddle-nose, saber shin, Higouménaki’s sign, Hutchinson teeth, and skin radially chapped around mouth, etc.[22,23]

2.3 Latent congenital syphilis: Untreated congenital syphilis with no clinical manifestation, negative of serological test and examination of CSF. Within the first 2 years of life is defined as early latent congenital syphilis, and occurring after two years of age is defined as late latent congenital syphilis.

3. Laboratory diagnosis
3.1 DFME, argentie staining, and PCR: DFME and argentie staining can show the presence of treponema in skin and mucous lesion as well as tissue specimens. The examination of T. pallidum DNA by PCR is usually positive.

3.2 Non-treponemal serological tests: positive. Congenital syphilis is highly likely if one of the
below situations occurs: (1) the infant’s nontreponemal antibody titer is fourfold or greater than the mother’s serum; (2) the infant’s nontreponemal antibody titer remains increase within the follow up three months.

3.3 Treponema serological test: positive. Positive IgM testing can confirm the diagnosis of congenital syphilis, but negative IgM testing cannot exclude treponema infection. [24,25]

4. Diagnostic classification
4.1 Probable case: All the infants born by the mother with syphilis but untreated before. Or all the stillbirth and abortion cases without enough evidence to confirm fetal transmission of syphilis.

4.2 Confirmed case: The case has one of the below tests or follow-up scenarios: (1) DFME or argentinc staining finds the presence of treponema in skin lesion, mucous lesion, and tissue specimens. Or the PCR testing is positive. (2) The test of IgM antibody in infants’s sera is positive. (3) The infant’s nontreponemal antibody titer is fourfold or greater than the mother’s serum, and the treponemal test is positive. (4) The infant’s nontreponemal test at birth is negative, or the antibody titer is less fourfold than the mother’s serum, but the nontreponemal test during follow up changed to positive, or the antibody titer increased, may accompanied by the clinical features appear and positive treponemal test. (5) The infant’s treponemal test remains positive at 18 months after born by the mother with syphilis.

Management

General principles
1. Diagnosed early, treated correctly, the earlier the treatment, the greater the efficacy.
2. Adequate dose of drug, regular treatment. Irregular treatment may increase the recurrent risk of syphilis and promote process of late syphilis.
3. Follow up for an adequately long period after treatment.
4. All patients with syphilis should receive consulting and tests for HIV infection.
5. All sex partners should be examined and treated for syphilis at the same time.

Treatment regimens
1. Early syphilis (primary, secondary, and early latent syphilis)
   
   Recommended regimen: Benzathine penicillin G 2.4 million units intramuscularly (IM) in both buttocks, 1 dose or 2 doses of 2.4 million units each at 1-week intervals. Or procaine penicillin 800,000 units IM daily for 15 days. [26]

   Alternative regimen: Ceftriaxone 500 mg–1 g, IM or intravenously (IV) daily for 10 days. [26]

   Penicillin allergy: Doxycycline 100 mg twice daily, orally for 15 days. Macrolides are no longer be used as treatment for patients with allergy to penicillin due to high resistance rate in China. [27,28]

2. Late syphilis (Tertiary syphilis of skin, mucous, and bone, late latent and unknown duration
syphilis, and recurrent secondary syphilis)

**Recommended regimen:** Benzathine penicillin G 2.4 million units IM in both buttocks separately, 3 doses in total, once weekly. Or procaine penicillin 800,000 units IM daily for 20 days (defined as a course of treatment), when it is necessary, repeating a course of treatment after a 2-week interval.

**Penicillin allergy:** Doxycycline 100 mg twice daily, orally for 30 days.

3. **Cardiovascular syphilis**
   If with heart failure, heart failure should firstly be managed until heart function recover. The drug of penicillin should be injected initially at a small dose to avoid Jarisch-Herxheimer reaction, which may lead to the aggravation of heart failure or death.

**Recommended regimen:** Aqueous crystalline penicillin G 100,000 units IM at first day, one time. Aqueous crystalline penicillin G 100,000 units IM at second day, two times. Aqueous crystalline penicillin G 200,000 units IM at third day, two times. From forth day, following the below regimen: procaine penicillin 800,000 units IM daily for 20 days (defined as a course of treatment), repeating a course of treatment after a 2-week interval. Or Benzathine penicillin G 1.2 million units IM in each buttock, total 3 doses, once weekly. All person with cardiovascular syphilis should be tested to exclude neurosyphilis. If co-infected with neurosyphilis, treated with the recommended regimens of neurosyphilis.\(^{29}\)

**Penicillin allergy:** Doxycycline 100 mg twice daily, orally for 30 days.

4. **Neurosyphilis, ocular and auricular syphilis**

**Recommended regimen:** Aqueous crystalline penicillin G 18–24 million units daily IV (3–4 million units every 4 hours) for 10–14 days, if necessarily, following with Benzathine penicillin G 2.4 million units IM weekly, total 3 doses. Or Procaine penicillin 2.4 million units IM once daily and Probenecid 500 mg orally four times a day, for 10–14 days, if necessarily, following with Benzathine penicillin G 2.4 million units IM weekly, total 3 doses.\(^{30,31}\)

**Penicillin allergy:** Doxycycline 100 mg twice daily, orally for 30 days.

**Other management considerations:** Due to involvement of multiple systems, particularly the vital organs, the clinical manifestations of neurosyphilis are complex, various, and serious, which evoke the necessity and importance of multiple disciplinary treatment (MDT). MDT, usually composed of the departments of dermatology and venereology, neurology, psychiatry, ophthalmology, clinical laboratory, infectious disease, and imaging, will decide on a treatment regimen for neurosyphilis that is more scientific, reasonable, standard, and individual.

5. **Congenital syphilis**

5.1. **Early congenital syphilis (<2 years of age)**

Infants with abnormal examination of CSF:
**Recommended regimen:** Aqueous crystalline penicillin G 100,000–150,000 units/kg IV daily, administered as 50,000 units/kg per dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for 10-14 days. Or procaine penicillin G 50,000 units/kg per dose IM in a single daily dose for 10-14 days.\textsuperscript{32,33}

**Infants with normal examination of CSF:** Benzathine penicillin G 50,000 units IM in both buttocks separately for single dose. If the examination of CSF is not available, treat as the infants with abnormal examination of CSF.

**Penicillin allergy:** There is no best alternative treatment so far, if not a history of ceftriaxone allergy, ceftriaxone (normal examination of CSF 125 mg, abnormal examination of CSF 250 mg) IM daily for 10–14 days, be aware of possible cross-allergic reactions with penicillin.

5.2. Late congenital syphilis (≥2 years of age)

**Recommended regimen:** Procaine penicillin 50 000 units/kg IM daily for 10 days defined as a course of treatment (the dose of penicillin should be less than that of adults in the same stage of syphilis).

**Penicillin allergy:** There is no best alternative treatment so far, in absence of a history of ceftriaxone allergy, ceftriaxone 250 mg IM daily for 10–14 days, be aware of possible cross-allergic reactions with penicillin. Tetracycline is prohibited for children < 8 years old.

6. Gestational syphilis

All pregnant patients diagnosed during the pregnancy should receive treatment with Benzathine penicillin G 2.4 million units IM in both buttocks separately, 3 doses in total, once weekly. After treatment, the nontreponemal test should be checked monthly to monitor effectiveness, recurrence and reinfection of the disease. Pregnant patients are recommended to receive only one course of anti-syphilis therapy.\textsuperscript{34} All pregnant patients should be timely treated as soon as they are found no recommended treatment before. In the case of the pregnant woman is allergic to penicillin, there is no the best alternative regimens. Some studies suggest that ceftriaxone can be used for treatment of pregnant women with syphilis and prevent congenital syphilis,\textsuperscript{35} thereafter, if the women without a history of ceftriaxone allergy, ceftriaxone can be used carefully, but more attention should be paid to the cross-allergic reaction. In the background of the very high rate of macrolides resistance in *T. pallidum* in China, erythromycin can be used only in the situation that *T. pallidum* is confirmed to be sensitive to macrolides by molecular methods. More careful clinical and serologic follow-up is also required. In addition, erythromycin cannot treat an infected fetus because it cannot pass through the placenta. The mother should be treated again with doxycycline when being stop breastfeeding.

7. Management of co-infection with HIV

7.1 All patients with HIV infection should be screened by serological tests for syphilis.

7.2 If the serological tests cannot confirm the diagnosis of syphilis, immunofluorescence testing or silver staining testing can be used to exam the presence of *T. pallidum* in the skin tissue.
7.3 Although the current theory that syphilis co-infected with HIV may be more likely lead to neurosyphilis remains controversial, many experts suggest the examination of CSF for all syphilis patients with HIV infection to exclude neurosyphilis.\[36,37\]

7.4 It remains uncertain whether the doses of drugs or the course of treatment should be increased in those syphilis patients co-infected with HIV infection.\[38,39\] However, primary and secondary and latent syphilis patient with HIV infection are suggested the examination of CSF to exclude neurosyphilis. If examination of CSF is not available, the treatment should be given as for neurosyphilis.

7.5 Close monitor and regular follow-up visits are required after treatment.

8. Jarisch-Herxheimer reaction
Jarisch-Herxheimer reaction also called hyperbolic response after treatment, usually occurs within the first a few hours after the initiation of any therapy for syphilis and resolves within 24 hours. The clinical symptom is similar to the symptom of influenza including fever, chills, general discomfort, headache, muscle and bone pain, nausea, and palpitations, etc.\[40\] The Jarisch-Herxheimer reaction occurs most frequently among persons with early syphilis, and may lead to chancre swelling and the rash of secondary syphilis more prominent.\[41\] Patients with primary and secondary syphilis should be informed about this possible reaction before antisyphilis treatment and how to manage it if it occurs. It usually required no special management if no severe complications. Jarisch-Herxheimer reaction occurs rarely in persons with late syphilis, however, usually is more serious, particularly in patients with cardiovascular syphilis and neurosyphilis. Patients with symptomatic neurosyphilis may have markedly severe reactions such as epileptic persistence. Accordingly, hospitalization of patients with late syphilis is recommended to timely manage the possible symptoms. In addition, Jarisch-Herxheimer reaction may lead to early labor or cause fetal distress in pregnant women,\[42\] but this should not prevent or delay therapy. In the above situation, treatment for syphilis should be given, accompanied by medical monitoring and management. It is recommended that the antisyphilis treatment of pregnant patients with early syphilis should be given under the monitor of doctor. If it is available, hospitalization at the first day is recommended to timely manage symptoms. In order to prevent Jarisch-Herxheimer reaction, the regimen of prednisone 20–30 mg oral twice daily for 2–3 days is suggested. However, it is unclear that whether the recommended regimen can prevent the occurrence of Jarisch-Herxheimer reaction.

Follow-up and treatment evaluation
After recommended treatment, regular follow-up should be performed, including clinical and serological evaluation. Early syphilis patients should receive follow-up for no less than 2 years and up to three years. The first follow-up evaluation should be at 3-month after treatment, then every 3 months for the first year, and at 6-month intervals for up to 2–3 years post treatment. The assessment criteria of effective treatment include the skin lesion and clinical symptoms disappear, and the titer of a nontreponemal serological test should decline by more than or equal to 4 fold (e.g., from 1:32 to 1:8) within 3–6 months after treatment. The nontreponemal serological test will
mostly return to negative within 1 year among patients with primary syphilis, and within 2 years among patients with secondary syphilis. If the nontreponemal serological test reverts from negative to positive or the titer is increased by 4-fold, it is defined as serological reactivation. If clinical symptoms reappear (usually accompanied by increased nontreponemal serological titer), it is defined as clinical reactivation. In the above two circumstances, reinfection should be first excluded before diagnosis of reactivation. After excluding neurosyphilis, the patients with reactive syphilis should be retreated with double amount (2 course of treatment, 2-week interval between courses of treatment).

In a few syphilis patients, the titer of nontreponemal serological test may decline, but it usually does not return to negative, and remain positive within certain period (even through life), in which case, defined as serofast. The mechanism of serofast remains unclear. For patients in serofast status, the reinfection should be first excluded, and a close evaluation of the clinical signs and serological tests should be provided to early diagnose cardiovascular syphilis and neurosyphilis, including HIV infection test, examination of cardiovascular and nervous system, and examination of CSF. After the above system infection has been ruled out, regular follow-up is required including the general examination and serological tests. If the titer rises, retreatment should be given.

Late syphilis should be followed up for 3 years or longer, i.e., every 3 months for the first year, and at 6-month intervals for up to 3 years or longer. If no clinical manifestations of reactivation and neurosyphilis, cardiovascular syphilis, and other visceral syphilis can be excluded, patients with serofast do not need to be treated again. However, regularly repeated serological examination should be provided for 3 years or longer before terminating follow-up.

In neurosyphilis, serological tests and CSF examination should be performed every 3–6 months after treatment. The CSF cell count can sensitively indicate the effectiveness of therapy. If CSF pleocytosis is initially present, CSF examination should be performed at 3-month intervals until the cell count is normal. The changes in the CSF-VDRL or CSF protein also can be used to evaluate the effectiveness of therapy, however, these changes occur more slowly, and persistent abnormalities might be less important. If the CSF cell count has not decreased after 3 months, or if the CSF cell count or protein is not normal after 2 years, repeat therapy should be considered. However, in many patients after repeat therapy, the CSF cell count or protein persist abnormal. In some patients with aortic insufficiency, coronary artery stenosis, toxic aortic aneurysm and symptomatic neurosyphilis, clinical symptoms and signs may persist after recommended treatment.

Management of sex partners
All sex partners of persons with syphilis should be notified and accordingly given examination and treatment. For patients with primary or secondary syphilis, sex partners within the past 3 months or 6 months should be notified, respectively. Sex partner notification may have to extend up to 1 years for patients in early latent syphilis. For patients with late latent syphilis, spouse and all sex partners in the past should be notified. Both the mother of an infant with congenital syphilis
and her sex partner should be examined for syphilis. If serological tests in sex partners are positive, treatment should be given immediately, if serologic test results are negative, a total of 3 reexaminations after 4 weeks monthly are recommended. In patients with syphilis as well as their sex partners, if the follow-up examinations are uncertainly performed, presumptive treatment is recommended immediately. Due to the markedly strong infectivity of early syphilis, all persons who have had sexual contact with a person with early syphilis within 3 months who receives a diagnosis are recommended to receive presumptive treatment for syphilis, regardless of the serological results.

References


