

Manifestations of Syphilis

Bernard M. Karnath, MD

S yphilis is a sexually transmitted disease (STD) caused by the *Treponema pallidum* spirochete, named because of its resemblance to a twisted thread (*Treponema*) and pale color (*pallidum*).¹ The term *syphilis* originates from the poem “Syphilis, sive Morbus Gallicus” by Girolamo Fracastoro, an Italian physician and poet (1478–1553), in which the fictional shepherd in the poem, Syphilus, is a victim of the disease.^{2,3}

T. pallidum is transmitted by direct sexual contact (oral, anal, vaginal) or vertically across the placenta from mother to fetus. Syphilis can manifest in several ways. In the pre-antibiotic era, syphilis was often called “the great imitator” because its signs and symptoms are similar to those of various other diseases.^{4,5} This article reviews the manifestations of syphilis in its various stages and briefly discusses laboratory evaluation and treatment.

EPIDEMIOLOGY

Syphilis rates have recurrently peaked and troughed in approximately 10-year cycles since reporting began in the United States in 1941.^{6,7} In the United States, the most recent syphilis epidemic occurred in 1990,^{6,7} while reported cases of syphilis reached their lowest level in 2000 (**Figure 1**).⁸ However, the epidemiology of syphilis has changed in recent years primarily as a result of increasing cases among men who have sex with men. Consequently, the male to female case ratio increased from 1.5 in 2000 to 5.3 in 2003.⁸ Ethnic disparities in syphilis exist, with incidence rates 5 times greater in African-American persons as compared with white persons in recent years.⁸ The rates of syphilis cases in the United States are highest in the South.⁸

STAGES OF DISEASE

The clinical course of syphilis is divided into 4 stages—primary, secondary, and tertiary stages in which characteristic manifestations occur and a latent stage in which the patient is asymptomatic but seropositive (**Table**).⁹ The latent stage occurs with the resolution of the secondary stage. Identifying the appropriate stage of disease

FEATURES OF SYPHILIS

- Syphilis is a sexually transmitted disease caused by the bacterium *Treponema pallidum*.
- Syphilis manifests in 4 stages: primary, secondary, latent, and tertiary stages.
- During the primary stage of syphilis, a characteristic painless ulceration called a *chancre* appears at the site of inoculation.
- In secondary syphilis, a nonpruritic, symmetric, papular rash appears, which can involve the palms of the hands and soles of the feet.
- Patients with latent syphilis have serologic evidence of infection without signs or symptoms of disease.
- Syphilis is known to facilitate HIV transmission, and therefore all patients with syphilis should be tested for HIV infection. Conversely, with the high rates of syphilis and HIV coinfection, routine screening for syphilis in HIV-infected patients is recommended.
- Penicillin is the treatment of choice for all stages of syphilis. In penicillin-allergic patients, doxycycline, tetracycline, azithromycin, and ceftriaxone are options depending on the stage of disease.

is important because it affects duration of treatment.¹⁰ Physical examination should include evaluation of the skin, scalp, oropharynx, and genital and anal areas. Because syphilis can involve the neurologic system at almost any stage,¹¹ a neurologic examination is important, and if eye involvement is suspected, ophthalmologic examination is required as well. Of note, examiners must use contact precautions when examining a patient with primary or secondary syphilis.

Dr. Karnath is an associate professor of medicine, University of Texas Medical Branch at Galveston, Galveston, TX.

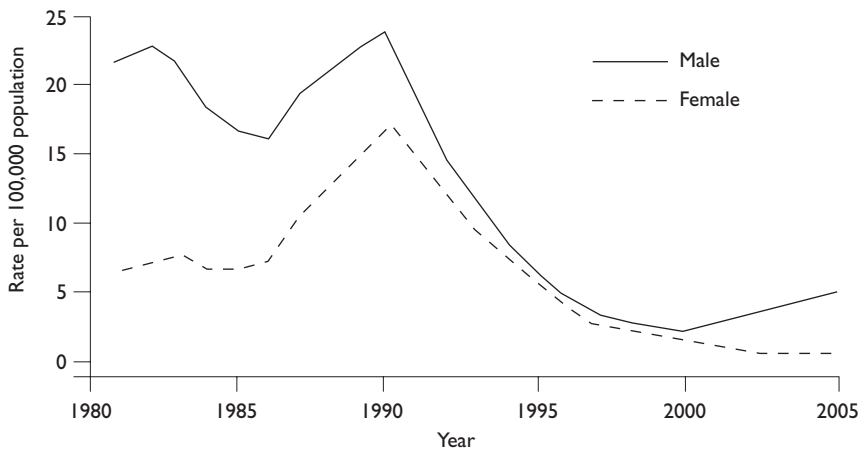


Figure 1. Rates of syphilis in the United States, 1980–2005. (Reproduced from Centers for Disease Control and Prevention. Trends in reportable sexually transmitted diseases in the United States, 2006. National surveillance data for Chlamydia, gonorrhea, and syphilis. Available at www.cdc.gov/std/stats/trends2006.htm#syphilistrends. Accessed 13 Oct 2008.)

Table. Time Course of Untreated Syphilis

| | Duration | Manifestations |
|-------------------|--|---|
| Incubation period | 3 wk | |
| Primary stage | 6 wk | Chancre formation, inguinal lymphadenopathy |
| Secondary stage | Months (variable) | Skin eruptions, fever, malaise, alopecia, generalized lymphadenopathy |
| Latent stage | Early (< 1 yr*); late (≥ 1 yr*) | Asymptomatic, seropositivity |
| Tertiary stage | Years | Gummas in various organs, cardiovascular involvement |
| Neuro-syphilis | Years, although can present in any stage | Meningitis, uveitis, tabes dorsalis |

*After initial infection.

Primary Syphilis

Primary syphilis is acquired by direct contact with open lesions of an individual with syphilis. *T. pallidum* is transmitted through small abrasions in the skin. The initial manifestation of primary syphilis is called a *chancre*, a painless skin ulceration at the point of exposure, often on the penis, vagina, or rectum and usually ranging in size from 0.3 to 3.0 cm (Figure 2).¹ The average time from exposure to the appearance of the chancre is 3 weeks.¹² The chancre may persist for 4 to 6 weeks and usually heals spontaneously even without treatment. Inguinal lymphadenopathy can occur. A diagnosis of primary syphilis is often missed because the initial lesion goes undetected by the patient.⁵ This may be the result of an atypical location versus an atypical morphology of the initial lesion.¹³

Other bacterial STDs such as chancroid, granuloma inguinale, lymphogranuloma venereum (LGV), and

genital herpes can present with genital lesions and should be considered in the differential diagnosis. These bacterial STDs are less common than syphilis, with an incidence of fewer than 100 annual cases in recent years.^{14,15} Chancroid presents with the combination of a nonindurated painful genital ulcer and tender suppurative inguinal adenopathy. The causative organism in chancroid is *Haemophilus ducreyi*. Culture of the organism is not highly sensitive and requires special medium (ie, Nairobi medium). Granuloma inguinale, caused by *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*), presents with a painless ulcerative lesion without regional lymphadenopathy.¹⁶ Primary LGV (causative organism, *Chlamydia trachomatis*) begins as a small, painless papule or pustule that may erode to form a small ulcer, which usually heals rapidly. The second stage of LGV presents with tender inguinal lymphadenopathy. *Chlamydia* serologies with complement fixation titers of greater than 1:64 support the diagnosis. Genital herpes is a chronic viral infection that classically presents with painful vesicles or small ulcers typically 1 to 3 mm in size.

Secondary Syphilis

Secondary syphilis is the result of hematogenous dissemination of *T. pallidum*, which subsequently causes systemic symptoms. This stage typically occurs 6 to 8 weeks after the primary infection.¹³ Manifestations of secondary syphilis can mimic many other diseases, and cutaneous manifestations are common. Manifestations include a generalized rash, fever, malaise, myalgias, alopecia, and generalized lymphadenopathy.^{3,13} The initial rash of secondary syphilis begins as a faint exanthem with macular pink lesions that are asymptomatic and are often overlooked.³ The rash is not pruritic, and lesions are oval macules of varying size (0.5–1 cm).⁵ After



Figure 2. Chancre of primary syphilis. (Reprinted with permission from Zetola NM, Engelman J, Jensen TP, Klausner JD. Syphilis in the United States: an update for clinicians with an emphasis on HIV coinfection. *Mayo Clin Proc* 2007;82:1093.)



Figure 3. Papular rash of secondary syphilis. This rash occurs after the initial macular exanthem, which is often overlooked. (Reprinted with permission from Wolff K, Johnson RA, Suurmond R. *Fitzpatrick's color atlas and synopsis of clinical dermatology*. 5th edition. New York: The McGraw-Hill Companies, Inc; 2005: 919.)

a few days, a symmetric papular eruption can appear (**Figure 3**).³ In 50% to 80% of cases, the papular rash of secondary syphilis involves the palms of the hands and the soles of the feet (**Figure 4**).¹² The differential diagnosis includes pityriasis rosea, drug eruptions, psoriasis, lichen planus, scabies, and acute febrile exanthems.¹⁷ Serologic testing may be necessary to exclude syphilis in patients with a papular rash. Alopecia related to secondary syphilis is classically described as patchy with a moth-eaten appearance.^{1,13} Manifestations of secondary syphilis usually resolve without treatment, at which time the disease enters a latent stage.

Latent Syphilis

Because transmission usually occurs during the primary and secondary stages when lesions are present, it is important to diagnose and treat syphilis early. Latent syphilis is defined as having serologic evidence of infection without signs or symptoms of disease. Latent syphilis can be classified as early or late depending on the time frame from initial infection (early, < 1 yr and late, ≥ 1 yr¹⁶). The distinction is important because it affects treatment duration (*see* Treatment section).

Tertiary Syphilis

Tertiary (late) syphilis generally occurs 5 to 20 years after initial infection and can present with mucocutaneous, cardiac, ophthalmologic, neurologic, or osseous abnormalities.⁴ Tertiary disease will develop in approximately one third of untreated individuals, manifesting



Figure 4. Plantar rash of secondary syphilis. A similar rash can occur on the palms of the hands. (Reprinted with permission from Wöhrl S, Geusau A. Clinical update: syphilis in adults. *Lancet* 2007; 369:1912.)

as gummatous (benign) syphilis, cardiovascular syphilis, or neurosyphilis.¹⁶

The incidence of late gummatous syphilis has declined dramatically since the introduction of antimicrobial agents.¹⁸ Gummas present as painless, firm nodules on various organs (skin, liver, spleen, bone). Gummas involving the skin form in the hypodermal layer as

granulomatous lesions, and their morphology ranges from nodules to plaques.¹⁸ Gummas on the skin often ulcerate and can lead to scar formation and disfigurement.¹³ On the organs, gummas are a form of granuloma (a nodule of inflammatory cells) that become hyalinized and undergo fibrous degeneration, which eventually scar and become fibrous nodules.

Cardiovascular syphilis is extremely rare. Syphilitic aortitis manifests more than 10 to 20 years after the primary infection. Syphilitic aneurysms are the most frequent complication of syphilitic aortitis, commonly occurring in the ascending aorta and complicated by aortic insufficiency.¹⁹ The prognosis for patients with syphilitic aneurysms is extremely poor with a 2-year mortality rate of approximately 80%.²⁰

Neurosyphilis

Neurosyphilis can occur at almost any stage of syphilis.¹⁶ Classic syndromes of neurosyphilis are now much less common in the antibiotic era,²¹ likely due to inadvertent antibiotic treatment of early stages of syphilis while treating other infections.²¹

Neurologic findings are varied in neurosyphilis. Early neurosyphilis can present with meningeal and meningovascular involvement within weeks to years of primary infection.²² Meningovascular neurosyphilis can compromise the vascular supply of the central nervous system, resulting in infarctions. Meningeal syphilis can present with syphilitic meningitis and manifest with headache, nausea, vomiting, and neck stiffness in the absence of fever.¹² Seizures can also occur. Cranial neuropathies are a component of early meningovascular neurosyphilis. The most common ocular finding of neurosyphilis is uveitis.²³ Ocular changes may include the Argyll Robertson pupil, which is unresponsive to light but constricts with accommodation or convergence (ie, the pupil only constricts when the eye focuses on a close object).²⁴

Late neurosyphilis tends to affect the brain and spinal cord parenchyma and occurs years to decades after initial exposure.^{12,22} Because parenchymatous neurosyphilis directly involves the central nervous system parenchyma, a wide range of clinical syndromes result. Signs and symptoms include loss of deep tendon reflexes, impaired vibratory sensation, impaired proprioception, ataxia, and psychiatric manifestations (eg, psychosis, delirium, dementia).

First identified by Romberg, tabes dorsalis is a progressive degenerative process affecting the posterior columns of the spinal cord, leading to an ataxic wide-based gait.²⁵ Romberg's sign, in which swaying is observed while the patient stands erect with feet together

and eyes closed, was once synonymous with tabes dorsalis.²⁵ A positive Romberg's sign suggests that ataxia is sensory in nature and therefore dependant on loss of proprioception. Once the most common manifestation of neurosyphilis, tabes dorsalis is now rarely seen since the introduction of antibiotics.²¹

LABORATORY EVALUATION

T. pallidum cannot be cultured in vitro, and microscopic testing is difficult. Thus, serologic testing is the standard for diagnosis of syphilis. Serologic testing initially may be negative in the primary stages of disease and may not become positive for 1 to 2 weeks after the appearance of the chancre.²⁶ At this point, diagnosis is clinical, and dark field microscopy is used to evaluate for the characteristic morphology and movements of *T. pallidum* in exudate collected from the chancre. Dark field microscopy is positive in all secondary syphilis lesions except for the macular exanthem.²⁷ However, dark field microscopy is not widely available.²⁸ Nontreponemal tests, such as VDRL and rapid plasma reagent (RPR), are nonspecific and are useful only for initial screening and posttreatment follow-up. False-positive results may occur in patients with autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis.²⁹ Reactive VDRL or RPR tests should be confirmed with specific treponemal testing, including fluorescent treponemal antibody absorption (FTA-ABS) and the microhemagglutination assay for *T. pallidum*. Syphilis is known to facilitate HIV transmission. All patients with syphilis should be tested for HIV infection, and, conversely, patients with HIV should be routinely screened for syphilis.^{26,30,31}

In the presence of positive serologic tests and neurologic manifestations as discussed above, the evaluation of neurosyphilis requires a lumbar puncture and evaluation of the cerebrospinal fluid (CSF). CSF analysis will reveal mononuclear pleocytosis and increased protein, and a VDRL test will be reactive. In the absence of neurologic findings, a serum RPR of 1:32 or greater is a helpful cutpoint when deciding whether lumbar puncture is indicated, especially in the HIV-infected patient.^{32,33} Additionally, in HIV-infected patients, some specialists recommend performing a lumbar puncture if the patient has a serum CD4+ count of 350 cells/ μ L or less.³³

TREATMENT

Recommended treatment for primary, secondary, and early latent syphilis is a single dose of benzathine penicillin G, 2.4 million units intramuscularly.¹⁶ Alternative treatments for penicillin-allergic patients include a 2-week course of doxycycline 100 mg orally

twice daily, tetracycline 500 mg orally 4 times daily, or erythromycin 500 mg orally 4 times daily.¹⁶ Data on the efficacy of single-dose azithromycin are lacking and treatment failures have been reported.³⁴ Resistance with macrolide antibiotics has also been reported.³⁴

The recommended treatment for late latent syphilis of undetermined duration and tertiary syphilis is benzathine penicillin G, 2.4 million units intramuscularly once weekly for 3 consecutive weeks.¹⁶ Alternative treatment is doxycycline 100 mg orally twice daily or tetracycline 500 mg orally 4 times daily for 4 weeks. Recommended treatment for neurosyphilis is aqueous crystalline penicillin G, 2 to 4 million units intravenously every 4 hours for 10 to 14 days.¹⁶

Penicillin allergy poses a problem in the treatment of syphilis. For treatment of neurosyphilis, it has been suggested that penicillin-allergic patients be desensitized in order to receive standard drug therapy.³⁵ To desensitize a patient, penicillin is given in a controlled manner in gradually increasing doses, which allows the patients to tolerate the medication without an allergic reaction. Desensitization should not be performed in a patient with a history of certain reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Ceftriaxone can be used as an alternative agent, although a 10% risk of cross-reactivity exists.³⁶ Although successful treatment of neurosyphilis has been reported with a 14-day regimen of ceftriaxone, it remains to be validated in large clinical trials.³⁴

Within several hours after beginning antibiotic treatment for syphilis, the Jarisch-Herxheimer reaction may develop. This reaction manifests with fever, chills, and rigors and can occur as early as 2 hours after exposure to an antibiotic.³⁷ Although often mistaken for an allergic reaction, the reaction is actually a febrile inflammatory response.³⁸ The Jarisch-Herxheimer reaction can occur in any stage of syphilis but is more common during the secondary stage.³⁷ The Jarisch-Herxheimer reaction is hypothesized to be due to endotoxin release that occurs as treponemal organisms are killed versus activation of the cytokine cascade, thus resulting in fever, chills, and rigors.³⁷ The Jarisch-Herxheimer reaction is self-limited and treatment is supportive with antipyretic and anti-inflammatory agents. Antibiotic treatment should be continued.^{37,38} The Jarisch-Herxheimer reaction has been noted in the treatment of other spirochete diseases, including Lyme disease and leptospirosis.

With satisfactory treatment of early syphilis, most patients will become seronegative within 1 year.²⁶ However, a fourfold decrease in nontreponemal titers at 3 to 6 months is considered a satisfactory treatment response in all stages of syphilis. For example, a change

from 1:32 to 1:8 on RPR testing would be considered a fourfold decrease in titers.^{1,39} However, the FTA-ABS will remain positive for life in most patients despite treatment.²⁶

For neurosyphilis, follow-up should include lumbar puncture with CSF evaluation repeated every 6 months until the cell count is normal. Changes in the VDRL-CSF or CSF protein occur more slowly than cell counts, and persistent abnormalities are less important than decreasing cell count. If the cell count has not decreased after 6 months, retreatment should be considered.¹⁶

CONCLUSION

Syphilis is an STD caused by the bacterium *T. pallidum*. Signs and symptoms of syphilis are similar to other diseases, and history and physical examination are essential to rule out other diagnoses. Syphilis facilitates HIV transmission and is especially common among men who have sex with men. Thus, all patients with syphilis should be tested for HIV infection, and, conversely, patients with HIV should be routinely screened for syphilis. Penicillin is the treatment of choice for all stages of syphilis, especially neurosyphilis. Treatment failures have been reported with alternative antibiotics.

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Corresponding author: Bernard M. Karnath, MD, 301 University Boulevard, Galveston, TX 77555; bmkarnath@utmb.edu.

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