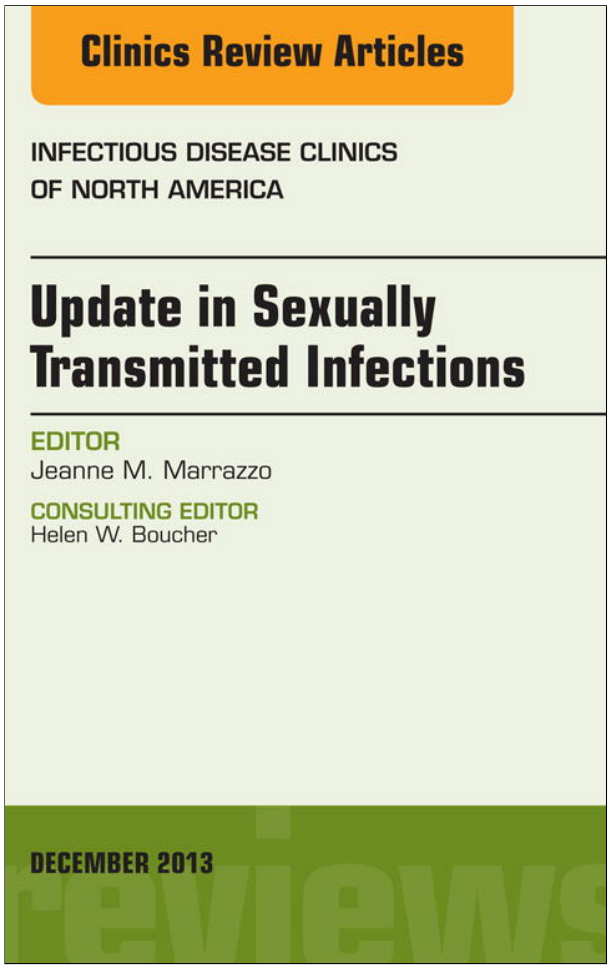

Syphilis in the Modern Era
An Update for Physicians

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KEYWORDS

• Sexually transmitted disease • Syphilis • *Treponema pallidum* • Chancre
• Men who have sex with men • Benzathine penicillin G

KEY POINTS

- Syphilis is common among men who have sex with men and is associated with HIV acquisition.
- Syphilis can cause a wide range of systemic manifestations.
- Penicillin G remains the treatment of choice for all stages of syphilis.
- Syphilis partner services and presumptive treatment of contacts based on exposure history is essential to prevent syphilis reinfection and control the spread of disease.

ETIOLOGY AND PATHOGENESIS

Syphilis is caused by infection with the spirochetal bacterium *Treponema* subspecies *pallidum*. *T pallidum* is a highly motile coiled organism with tapering ends and 6 to 14 spirals. Of uniform cylindrical shape, the bacteria measure approximately 6 to 15 μm in length and 0.25 μm in width. *T pallidum* is a slowly metabolizing organism with an average multiplication time of approximately 30 hours. Humans are the only host for the organism.[1] Most cases of syphilis are transmitted by sexual contact (vaginal, anogenital, and orogenital), but it can also be spread congenitally (in utero or less

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commonly during passage through the birth canal).[2–4] Rare cases of acquisition through blood products have also been reported.[5–7] On skin-to-skin contact the motile spirochetes enter through areas of microtrauma of the skin or mucosa, multiplying locally with resultant systemic dissemination within 24 hours. The phospholipid-rich outer membrane of the spirochete contains few surface-exposed proteins; this may help it evade the host immune system. The primary pathologic lesion, found at all stages of the disease, is an obliterative endarteritis that leads to many of the clinical manifestations of syphilis. Histologic examination of a chancre is characterized by an intense infiltrate of plasma cells, with scattered macrophages and lymphocytes. A granulomatous reaction can also occur.[8]

EPIDEMIOLOGY

Infectious syphilis reached a historic low in the United States in 2000, with only 9756 primary and secondary cases (2.1 per 100,000 persons) compared with approximately 100,000 cases (71 per 100,000 persons) in 1946.[9] In response to declining syphilis incidence, the Centers for Disease Control and Prevention released "The National Plan to Eliminate Syphilis from the United States" in 1999.[10] However, starting in 2001, rates of primary and secondary syphilis have continued to rise, with an epidemic resurgence among men who have sex with men (MSM) (**Fig. 1**).[9,11] In 2011, there were 13,970 primary and secondary syphilis cases in the United States (4.5 per 100,000 persons), and 72% of cases for which there was information about gender of sex partners were among MSM. Reversal in the control of syphilis in disenfranchised, low socioeconomic black heterosexual subpopulations has also been observed in major metropolitan areas in the Southeast of the United States.[9] In San Francisco and many other large urban areas that have experienced increases in the incidence of syphilis among MSM, approximately two-third of cases occur in HIV-infected men; HIV incidence among HIV-uninfected men with syphilis is high.[12–15] Similar trends in syphilis have been reported throughout Europe in cities with large populations of MSM.[16,17]

The syphilis epidemic among MSM has been attributed to individual, network, and population level factors, including (1) a decrease in safer sex practices secondary to HIV prevention fatigue, antiretroviral treatment optimism, and an increase in recreational drug use, especially methamphetamines and erectile dysfunction

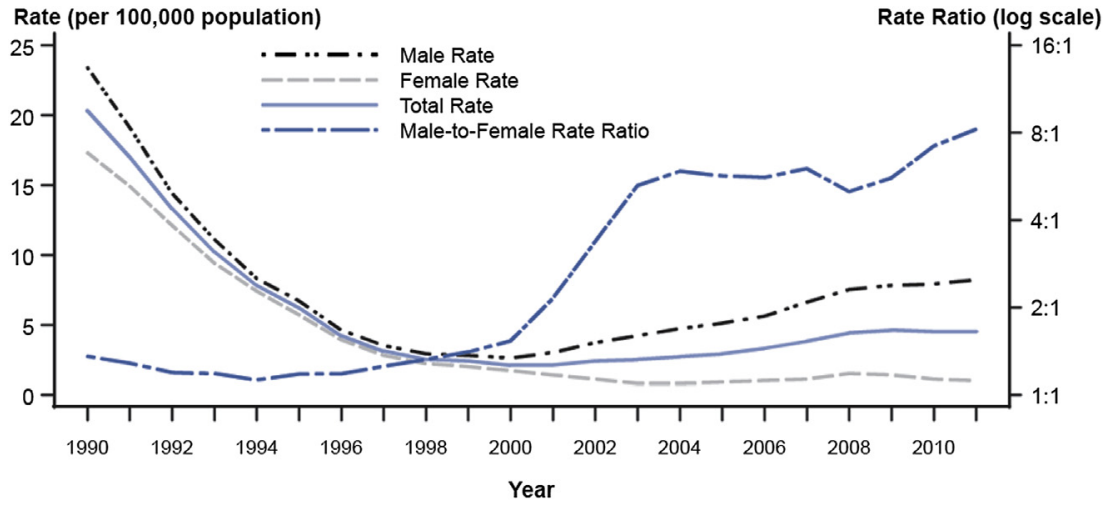

Fig. 1. Primary and secondary syphilis—rates by sex and male-to-female rate ratios, United States, 1990–2011. (*From* Centers for Disease Control and Prevention, December 2012. Available at: http://www.cdc.gov/std/stats11/figures/38.htm. Accessed June 21, 2013.)

medications; (2) harm-reduction strategies like serosorting (selective unprotected sex with partners of the same HIV-serostatus) and oral sex, which may decrease the risk of HIV transmission but can facilitate syphilis transmission; (3) rising use of the Internet as a meeting venue, which has revolutionized sexual networks and facilitated sex partnering, leading to increased number of sex partners, including anonymous partners who cannot be reached for partner services; and (4) decreasing AIDS mortality, which has increased the size of the population at risk for syphilis.[13,18–26] Rising antiretroviral coverage suppresses individual and community HIV viral load and prevents HIV but not syphilis transmission. This may partially explain the divergence between HIV and syphilis rates among MSM that is occurring in some municipalities.[27,28] If other biomedical HIV-prevention strategies, for instance pre-exposure prophylaxis, become more widespread, the divergence between syphilis and HIV epidemiology may further widen.

Syphilis is endemic throughout the developing world. Regional data from the World Health Organization demonstrate that approximately 5% of pregnant women seeking antenatal care services in the Western Pacific, Sub-Saharan Africa, South Asia, and South America have evidence of recent syphilis infection. This results in a substantial burden of adverse pregnancy outcomes, such as miscarriages, stillbirths, and newborns with congenital syphilis infection. An estimated 1.4 million pregnancies are affected annually worldwide. Globally, congenital syphilis is more common than perinatal HIV infection.[29]

The well-documented increase of syphilis in China has intensified global concern about syphilis. An aggressive venereal disease control policy of the Chinese government during the 1950s to 1970s effectively eliminated syphilis, but recent data show a 250- to 1000-fold increase in adult and congenital cases, respectively, in the last decade.[30] This is thought to be caused by several sociopolitical, economic, and cultural factors, including skewed sex ratios in some communities, a large rural-to-urban migrant population, expanding demand for commercial sex, stigma related to same sex behaviors, and low use of sexual health services.[31]

HISTORICAL PERSPECTIVE

Current understanding of the natural course of syphilis infection among untreated individuals is largely based on historical data from the preantibiotic era. The Oslo Study was a large prospective natural history study in which Boeck observed approximately 2000 patients with primary and secondary syphilis admitted to the Oslo Clinic from 1891 to 1910.[32] From 1932 to 1972 in Macon County, Alabama, the US Public Health Service conducted the infamous Tuskegee Syphilis Study to observe untreated syphilis infection among African American men. Treatment was withheld from study participants even after the discovery of penicillin. Lessons learned from the Tuskegee Study have shaped modern standards regarding research ethics and informed consent.[33] In 2008, Susan Reverby, a historian and expert on the Tuskegee Study, discovered that the US Public Health Service exposed several hundred Guatemalans, many of whom were prisoners, sex workers, or patients in a mental institution, to syphilis in an undocumented research project in 1946 to 1948. The horrific ethical violations that transpired led to an official apology from the United States to the Guatemalan government and an investigation by the Presidential Commission on Bioethical issues. Those studies provide important reminders that the quest for answers in biomedical research can blind researchers to moral concerns and the rights of study participants, and underscore the importance of bioethics training, community advisory boards, and institutional review boards.[34,35]

CLINICAL FEATURES

Early Syphilis

Early syphilis, which includes the primary, secondary, and early latent stages of infection, is defined as syphilis of less than 1 year's duration. That designation is based on the observation that infectivity declines after the first year.

Primary syphilis

Primary syphilis presents 1 week to 3 months (median, 21 days) after exposure with a painless lesion, a chancre, at the site of inoculation and nontender regional lymphadenopathy. The lesion starts as a papule and rapidly forms an ulcer that is typically nonexudative with a clean base (Fig. 2). Primary lesions are most commonly found on the external genitalia, but can develop on any site of exposure including the perineum, cervix, anus, rectum, lips, oropharynx, and hands (Figs. 3 and 4). Multiple chancres can occur and are more common in patients with HIV infection (Fig. 5). Without treatment, the chancre usually heals on its own within 1 to 3 weeks.[36] Primary syphilis must be differentiated from other causes of genital ulcer disease including other infectious causes (herpes simplex virus, chancroid, lymphogranuloma venereum, and pyogenic ulcers) and noninfectious causes (trauma, neoplasia, and fixed drug eruptions). Herpetic ulcers, unlike chancres, are usually superficial, vesicular, nonindurated, and painful. Chancroid, caused by *Haemophilus ducreyi*, is rare in the United States and is typically nonindurated, painful, and exudative with a necrotic base.

Secondary syphilis

The timing of onset of the secondary stage of syphilis is highly variable. It typically occurs 2 to 8 weeks after the disappearance of a chancre, but in some cases the primary chancre may still be present. Many patients do not recall a history of a primary lesion. Secondary syphilis typically presents with rash, fever, headache, pharyngitis, and lymphadenopathy, but has a wide range of possible systemic manifestations including hepatitis, glomerulonephritis, periostitis, and early neurologic complications, such as uveitis and meningitis.[36]

The cutaneous manifestations of secondary syphilis are diverse. The classic exanthem of secondary syphilis is a diffuse maculopapular rash that often, but not always, involves the palms and soles (Fig. 6) and scrotum (Fig. 7). However, the rash can also be papular, annular, or pustular, and can have a fine overlying scale. Other mucocutaneous manifestations include (1) condylomata lata (moist heaped-up broad plaques found in intertriginous areas, such as the perianal area, vulva, and inner thighs; Fig. 8); (2) mucous patches (gray, superficial erosions or plaques on the buccal mucosa and tongue, under the prepuce, and on the inner labia; Fig. 9); (3) split papules (fissured, nodular lesions at the angle of the lips and in the nasolabial folds; Fig. 10); and (4)

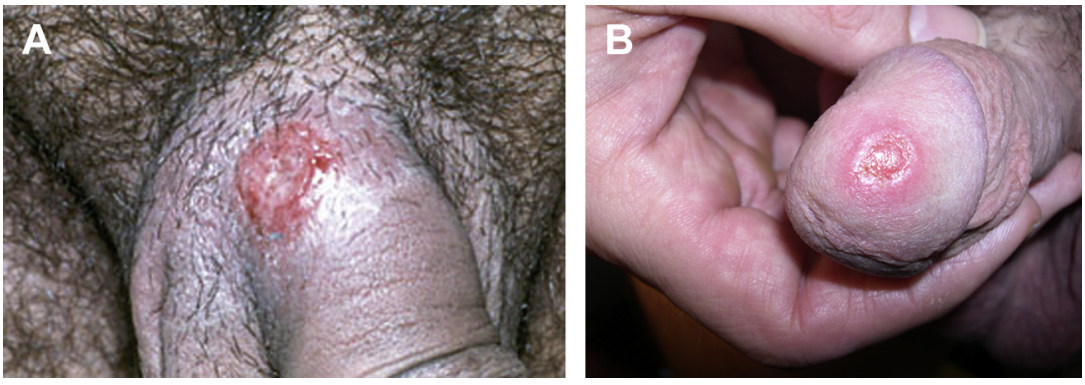

Fig. 2. (*A, B*) Penile chancres.

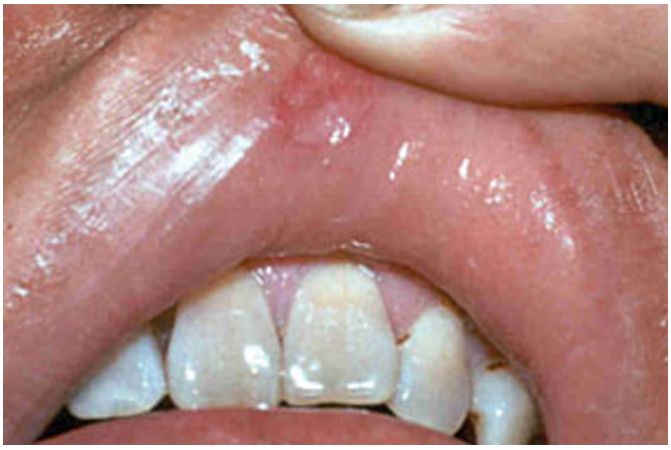

Fig. 3. Chancre on lip.

patchy alopecia (thinning of hair, eyebrows, and beard caused by syphilitic involvement of the hair follicle). The cutaneous lesions of syphilis, particularly the nonkeratinized mucocutaneous lesions (condylomata lata and mucous patches), contain large concentrations of spirochetes and are highly infectious.

Invasion of the central nervous system (CNS) is common during secondary syphilis, and may be asymptomatic or may manifest as an aseptic meningitis, with headache, neck stiffness, and a lymphocytic pleocytosis of cerebrospinal fluid (CSF). The meningeal inflammation is often basilar, leading to unilateral or bilateral cranial nerve abnormalities, particularly of cranial nerves II, III, VI, VII, and VIII.

The diverse manifestations of secondary syphilis earn it the name "the great imitator." Other diseases that should be considered in the differential diagnosis of fever, rash, pharyngitis, and lymphadenopathy include mononucleosis (acute Epstein-Barr virus infection); acute HIV infection; and other viral syndromes. The condylomata lata of secondary syphilis should be distinguished from condylomata acuminata (multiple, small, raised genital warts caused by human papilloma virus). Mucous patches can be mistaken for oral candidiasis. Other infections that cause a rash involving the palms and soles include Rocky Mountain spotted fever; meningococcemia; measles; and certain coxsackievirus infections (hand-foot-and-mouth disease).

Early latent syphilis

Without treatment, the manifestations of secondary syphilis generally resolve within a few weeks. The disease then enters a latent phase, characterized by a lack of clinical

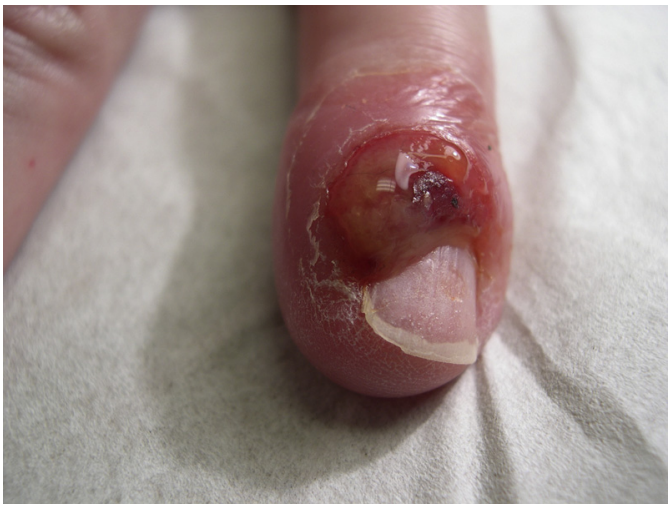

Fig. 4. Chancre on finger.

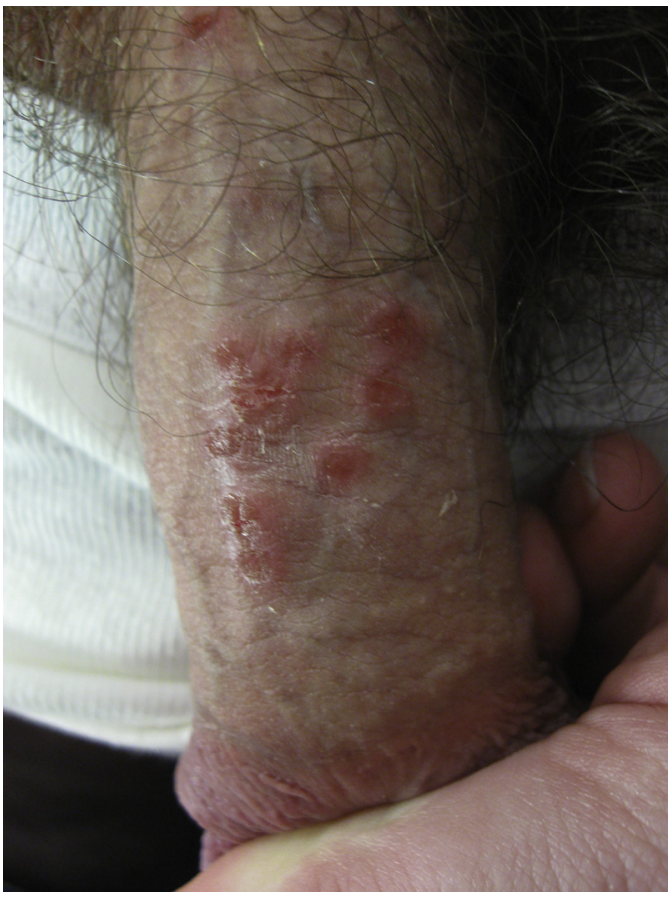

Fig. 5. Multiple penile chancres.

signs of syphilis but positive serologic tests. Observational studies have shown that recrudescent secondary syphilis symptoms can occur in untreated patients up to 5 years after their initial presentation, but generally these relapses occur within the first year. Early latency has therefore been defined as the asymptomatic period during the first year after initial syphilis infection. A patient who is found to have a reactive serologic test for syphilis can be diagnosed as having early latent syphilis if, during the prior year, they had (1) a documented nonreactive serologic test or fourfold or greater increase in titer of a nontreponemal test; (2) unequivocal symptoms of primary or

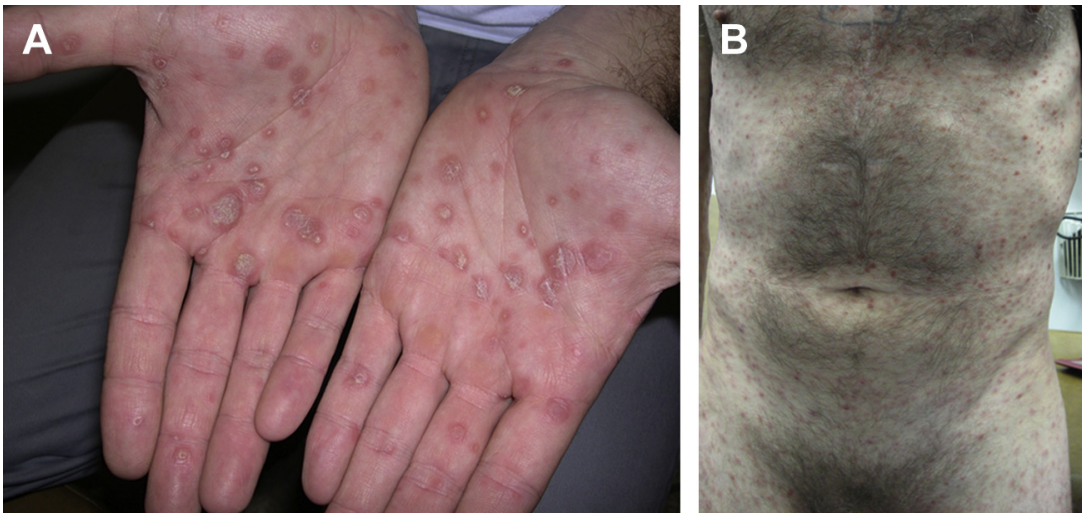

Fig. 6. (*A*) Palmar rash of secondary syphilis. (*B*) Truncal rash of secondary syphilis.

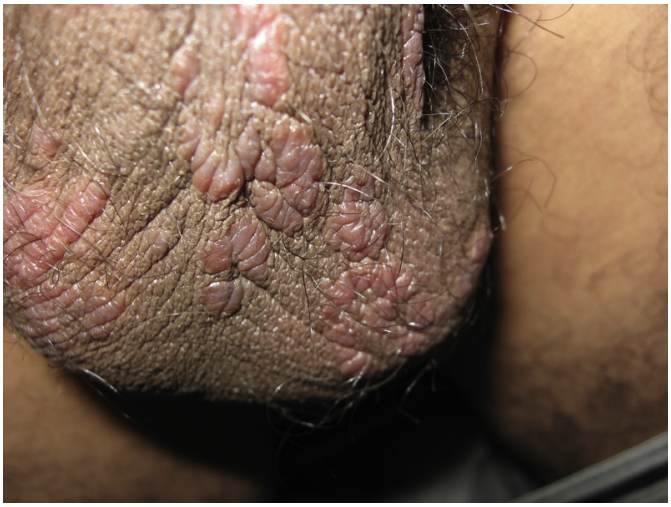

Fig. 7. Papulosquamous scrotal rash of secondary syphilis.

secondary syphilis; or (3) a sex partner documented to have primary, secondary, or early latent syphilis.[37]

Late Syphilis

Late latency is the asymptomatic phase of syphilis greater than 1 year after syphilis infection. Late latent syphilis, unlike early latent syphilis, is not thought to be infectious (except in pregnant women in whom transmission may occur), and requires a longer duration of treatment compared with early latent syphilis (see section on treatment).

Tertiary syphilis

Tertiary syphilis, or late symptomatic syphilis, has become very uncommon in the antibiotic era. In tertiary syphilis, endarteritis leads to cellular necrosis, fibrosis, sclerosis, scarring, and loss of normal tissue parenchyma. The three most common manifestations of tertiary disease are (1) neurologic; (2) cardiovascular; and (3) gummatous (or late benign) syphilis.

Late neurologic complications of syphilis As described previously, acute syphilitic meningitis can occur early in syphilis infection and is a well-described feature of secondary syphilis. Late neurologic complications of syphilis, which present after long periods of latency, are caused by meningovascular and/or parenchymal damage. Vascular involvement leading to focal ischemia can present with a myriad of neurologic deficits including hemiparesis, aphasia, and focal or generalized seizures.

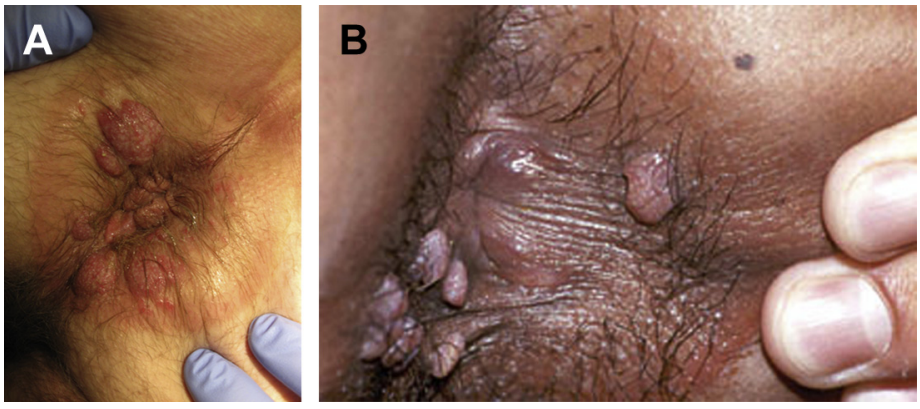

Fig. 8. (*A, B*) Perianal condylomata lata.

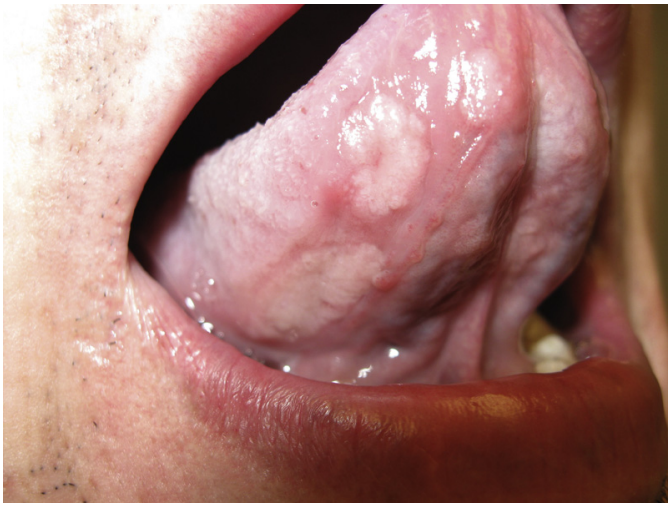

Fig. 9. Mucous patches on the tongue.

Classic late neurologic manifestations attributed to parenchymal damage include general paresis and tabes dorsalis.

General paresis, also known as general paralysis of the insane, is a meningoencephalitis with direct invasion of the cerebrum by *T pallidum*. The encephalitis is chronic and usually manifests in middle to late adulthood after a 15- to 20-year incubation period. A wide range of manifestations include progressive dementia with changes in personality, affect, sensorium, intellect, and speech. Defects in judgment, emotional lability, grandiose delusions, megalomania, depression, catatonia, amnesia, and hyperreflexia have been described. The Argyll Robertson pupil, a small, often irregularly shaped pupil that constricts on accommodation but not to light, is a classic though uncommon feature of general paresis.

Tabes dorsalis, syphilitic involvement of the posterior columns of the spinal cord, impacted about one-third of patients with late neurologic manifestations of syphilis in the preantibiotic era, but is now a very rare condition. The incubation period ranges from 20 to 25 years. Clinical symptoms include lightning pains, paresthesias, decreased reflexes, abnormalities in peripheral sensation, difficulty walking, and bladder and bowel dysfunction. Patients often have a positive Romberg sign. A classic description of tabes dorsalis includes patients who walk with their heels landing hard on the floor, knees positioned outward with their feet slapping.[36]

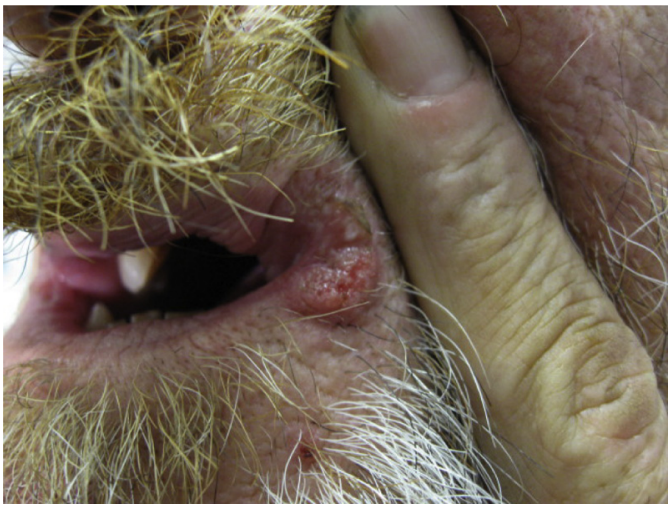

Fig. 10. Split papule.

Cardiovascular syphilis Endarteritis of the vaso vasorum of the aorta can lead to aortitis and aneurysm formation. This usually involves the ascending aorta, which in turn can cause dilation of the aortic ring, aortic regurgitation, or ascending aortic aneurysms.[8] Following the ascending aorta, the transverse aorta and then the descending arch are the next most common sites involved. Chronic inflammation of the coronary arteries can lead to narrowing and stenosis of the coronary ostia, which can ultimately lead to myocardial ischemia, infarction, and congestive heart failure.

Gummatous (or late benign) syphilis Gummatous disease is extremely uncommon and is characterized by indolent destructive lesions of the skin, soft tissue, and bony structures. Although those lesions are destructive, they respond rapidly to treatment. Visceral organs, bones, and the CNS can also be involved. The differential diagnosis of lesions of the skin and mucous membranes is broad and depends on the local epidemiology of other infectious diseases and neoplasms. Conditions to consider in the differential diagnosis of gummatous-appearing skin lesions include Hodgkin disease, mycosis fungoides, tuberculosis, systemic lupus erythematous, fungal infections, sarcoid, and granuloma annulare.

Congenital syphilis

The manifestations of congenital syphilis are variable and include asymptomatic disease, spontaneous abortion, intrauterine growth restriction, neonatal disease, and neonatal death. The fetus is usually infected transplacentally. Congenital infection is most likely to be acquired in the setting of maternal early syphilis; however, it has been documented at any stage of syphilis. Some of the classic features of neonatal disease include rhinitis (snuffles), which typically occurs early in the course of the disease, and rash, hepatitis, splenomegaly, and perichondritis or periostitis. Untreated neonates who survive neonatal syphilis enter a latent period. The perichondritis and periostitis can lead to deformities of the nose (saddle nose) and of the metaphyses of the lower extremities (saber shin). Other late manifestations of congenital syphilis include peg-shaped central incisors (Hutchinson teeth); frontal bossing; and recurrent arthropathy.[2,38]

Prevention and early detection of congenital syphilis depends on routine screening of pregnant women for syphilis. All pregnant women should be screened at the first prenatal visit. Women who are at high risk for syphilis infection should be screened again in the third trimester and at delivery (see diagnostic approach).[37]

DIAGNOSIS

Treponema pallidum cannot be cultivated in artificial media, is too slender to be observed by light microscopy, and fails to take up traditional Gram stains. It can be visualized using darkfield microscopy, which uses refracted light on a darkened background to identify the spirochete in clinical specimens; however, this technique is not widely available in clinical practice. Although polymerase chain reaction has been used to amplify genetic elements of *T pallidum* in clinical specimens, there are no current Food and Drug Administration cleared molecular amplification assays in use in routine clinical practice. The clinical diagnosis of syphilis is based on the characteristic findings of the skin and mucous membranes and is confirmed with serologic assays measuring antibodies to nontreponemal (rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL] tests) and treponemal antigens (treponemal pallidum particle agglutination, fluorescent treponemal absorption, enzyme immunoassays [EIA], and chemiluminescence immunoassays).

Nontreponemal tests use a laboratory-prepared lecithin-cholesterol antigen to detect treponemal-directed antibody in the patient serum specimen. Nontreponemal

tests have a sensitivity of approximately 86% in primary syphilis and 100% in secondary syphilis.[39] Nontreponemal tests are 98% specific, with false-positives associated with older age; autoimmune disease (eg, lupus); other infections (eg, bacterial endocarditis, rickettsial infection); chronic liver disease; intravenous drug use; and recent vaccination. Nontreponemal tests can be performed quantitatively and response to treatment is demonstrated by declining nontreponemal titers over time.

In traditional syphilis screening algorithms, treponemal-specific tests are used to confirm the diagnosis of syphilis and to rule out false-positives in the setting of a positive nontreponemal test. The fluorescent treponemal antibody absorbed (FTA-ABS), *T pallidum* particle agglutination (TPPA), and *T pallidum* hemagglutination assay use true treponemal antigens as a key reagent. Unlike nontreponemal antibody tests, which decline in titer with treatment, treponemal-specific tests typically remain reactive for the remainder of the life of the individual irrespective of the success of treatment. Like nontreponemal tests, their sensitivity is lower in primary disease, although they may become reactive before nontreponemal tests in the earliest stages of primary infection. They are 100% sensitive and 99% specific in secondary disease.[39] By law, diagnosing clinicians and laboratories in the United States are required to report reactive laboratory tests for syphilis (treponemal and nontreponemal) to public health authorities.

Some clinical laboratories and blood banks have begun to use a treponemal EIA in place of a nontreponemal assay as a more cost-effective initial screening test for syphilis. A positive treponemal EIA identifies persons with a history of treated syphilis and those with untreated or incompletely treated syphilis. If the treponemal EIA is positive, a nontreponemal test should be obtained to determine the titer for monitoring response to treatment. This is known as "reverse sequence screening." If the nontreponemal test is nonreactive, a second treponemal-specific antibody test (TPPA or FTA-ABS) should be obtained because the initial EIA result could be a false-positive.[37] Although the specificity of the available syphilis EIAs is generally high, the positive predictive value of the test depends on the prevalence of syphilis in the population being screened. In low-prevalence settings, up to 40% of EIA-positive, RPR-negative specimens may be false-positives.[40,41] If two treponemal-specific antibody tests are positive and the nontreponemal test is nonreactive, this could represent latent infection, a previously treated case or, less likely, very early syphilis infection. In that situation, providers should closely examine the patient for any signs of primary syphilis and attempt to document prior treatment; sexually transmitted disease control programs within local or state health departments can often assist in this effort. If that is not possible, the diagnosis and treatment of latent syphilis should be considered.

Primary Syphilis

Evaluation of a patient who presents with a genital ulcer should include (1) sexual, medical, and medication history; (2) oral, skin (trunk, upper and lower extremities, palms and soles, scrotum), genital, and anal examination; (3) darkfield microscopic examination of suspicious lesions if available (serous exudate from a chancre can be examined for the presence of spirochetes); (4) serum nontreponemal tests like the RPR or VDRL and treponemal tests like the TPPA or FTA-ABS (because treponemal-specific tests may be more sensitive in early disease); (5) herpes simplex virus culture or polymerase chain reaction in a swab of an ulcer; and (6) serology for HIV infection (particularly essential if syphilis is diagnosed).

Secondary Syphilis

A rash of any type in a sexually active individual should be considered as potential syphilis until proved otherwise, particularly if it is bilaterally symmetric. The typical

rash of secondary syphilis does not yield moist specimens for darkfield examination; however, if condylomata lata are present, and darkfield microscopy is available, these can be swabbed and examined directly for spirochetes. Nontreponemal tests are highly sensitive in secondary syphilis. A prozone phenomenon can occur when the antitreponemal antibody titer is so high that the characteristic agglutination reaction that produces a reactive specimen cannot occur. When the clinical suspicion for secondary syphilis is high and the nontreponemal test is negative, the test should be repeated with additional dilutions, usually 1:10.

Tertiary Syphilis

Serologic tests are usually reactive in tertiary syphilis; titers of nontreponemal tests can range from low to very high titers, but are usually lower than in early syphilis. In patients with neurologic findings concerning for late neurosyphilis and positive serum nontreponemal and treponemal antibody tests, the CSF should be examined. In addition, the CSF should be examined in a patient diagnosed with any other form of tertiary syphilis (cardiovascular or gummatous). A positive CSF VDRL establishes the diagnosis of neurosyphilis.

CSF Analysis: Indications and Interpretation

Syphilis can involve the CNS at any stage of disease. Asymptomatic invasion of the CNS is common in early syphilis, and abnormalities of the CSF have been found in up to 40% of patients with untreated secondary syphilis.[36,42] The clinical significance of those findings is unclear, because most patients with early syphilis respond appropriately to standard therapy. The CSF should therefore be examined in any patient with syphilis and any neurologic or ophthalmic symptoms or signs (cognitive dysfunction, motor or sensory defects, visual or auditory symptoms, cranial nerve palsies, meningismus). A CSF examination should also be considered in patients who fail to respond to therapy with an appropriate decline in nontreponemal antibody titer.[37] Although CSF abnormalities are more common in HIV-infected persons with syphilis and RPR titers greater than or equal to 1:32 and/or CD4 T-cell counts less than or equal to 350 cells/mm^3, in the absence of neurologic symptoms, there is no evidence that CSF examination in such persons is associated with improved clinical outcomes.[43,44]

Lymphocytic pleocytosis (10–500 WBC/mm^3) and elevated CSF total protein are characteristic of the acute, syphilitic meningitis seen in early syphilis. Fewer cells are seen in the CSF in late neurosyphilis, including syphilitic cerebrovascular disease, general paresis, and tabes dorsalis. An absence of white blood cells in the CSF excludes the diagnosis of neurosyphilis. In the setting of a reactive serum nontreponemal and treponemal antibody test, a reactive CSF VDRL confirms the diagnosis of neurosyphilis. However, the CSF VDRL, particularly in early syphilitic meningitis, is not highly sensitive. The role of other serologic tests in the CSF is uncertain. The CSF FTA-ABS has a high false-positive rate, but is more sensitive than the CSF VDRL. The CSF FTA-ABS can be used to exclude neurosyphilis in at-risk patients with an abnormal CSF and a negative CSF VDRL.

Congenital Syphilis

The diagnosis of congenital syphilis rests on the identification of syphilis in the mother, and a combination of clinical, radiologic, and laboratory findings in the infant. All infants born to mothers with reactive nontreponemal and treponemal test results should be screened for congenital syphilis by performing a quantitative nontreponemal antibody test on infant serum (not umbilical cord blood, which can become contaminated

with maternal blood). The infant should be examined carefully for signs and symptoms of syphilis. If clinically indicated, the work-up may include long-bone radiographs; chest radiograph; liver function tests; cranial ultrasound; ophthalmologic examination; auditory examination; and CSF analysis for VDRL, cell count, and protein.[2,37] The evaluation and management of congenital syphilis should be made in consultation with a pediatric infectious diseases specialist.

TREATMENT

Penicillin G remains the treatment of choice for all stages of syphilis. The treatment regimen (route of administration and duration) depends on the stage of disease (**Table 1**). Early syphilis (ie, primary, secondary, or early latent) can be treated with a single injection of 2.4 million units of intramuscular penicillin G benzathine; patients coinfected with HIV do not require additional doses of penicillin.[37,45–47] A nontreponemal antibody test should be obtained on the day of treatment to establish a baseline titer for monitoring response to therapy. Late syphilis (late latent syphilis and syphilis of unknown duration) is treated with penicillin G benzathine, 2.4 million units intramuscular weekly for a total of three injections given a week apart without missing any doses.[37,48] A lapse of more than 14 days requires restarting treatment. Neurosyphilis is treated with intravenous aqueous penicillin G, 2.4 million units every 4 hours for 10 to 14 days. Intravenous treatment should be followed by penicillin G benzathine, 2.4 million units intramuscularly weekly for 3 weeks. Patients with syphilitic uveitis or other ocular manifestations should be treated according to the recommendations for neurosyphilis.[37]

Approximately 10% of patients self-report a history of a penicillin allergy, but the rates of true penicillin allergy are likely much lower.[49] Other antibiotics have efficacy and can be used, if necessary, in the setting of penicillin allergy. Doxycycline is effective for early stage syphilis (100 mg orally twice daily for 14 days) and for late syphilis (100 mg orally twice daily for 28 days).[37,48,50] Daily ceftriaxone (1–2 g daily either IM or IV for 10–14 days) can be used as an alternative to penicillin,[51,52] and the risk of penicillin cross-reactivity with third-generation cephalosporins is negligible.[53] A randomized controlled trial conducted among HIV-uninfected patients outside the United States found that oral azithromycin administered at a dosage of 2 g was equivalent to benzathine penicillin G, 2.4 million units intramuscularly, for the treatment of early syphilis.[54] However, given documented cases of azithromycin treatment failures and evidence of *T pallidum* resistance to azithromycin in the United States, there is limited role for azithromycin in the treatment of syphilis in the United States.[55,56]

FOLLOW-UP

Patients with early stage syphilis, particularly those with high titer secondary syphilis, should be counseled about the possibility that they may experience a Jarisch-Herxheimer reaction after treatment. This immune-mediated process occurs within 2 to 24 hours of receiving penicillin G and is characterized by the acute onset of fever, headache, and myalgias. Peripheral leukocytosis and transaminitis can also occur. It occurs in 50% to 75% of patients with primary and secondary syphilis, is more common in patients with higher baseline nontreponemal titers, and is less common in patients with a history of treated syphilis.[57] The reaction is usually self-limited and can be managed with antipyretics and nonsteroidal anti-inflammatory medications. In pregnant women, the reaction may trigger preterm labor or other complications, so close monitoring in collaboration with the patient's obstetrician is essential, but this should not prevent or delay treatment.

Table 1
Treatment for syphilis

Syphilis Stage or Diagnosis	Primary Therapy	Alternative Therapy	Comment
Primary, secondary, and early latent syphilis	Penicillin G benzathine, 2.4 million units IM as a single dose	Doxycycline, 100 mg PO twice daily for 14 d Or Ceftriaxone, 1–2 g either IM or IV daily for 10–14 d Or Tetracycline, 100 mg PO four times daily for 14 d	—
Late latent syphilis	Penicillin G benzathine, 2.4 million units IM once weekly for 3 wk	Doxycycline, 100 mg PO twice daily for 28 d Or Tetracycline, 100 mg PO four times daily for 28 d	—
Neurosyphilis	Penicillin G aqueous, 18–24 million units IV daily (3–4 million units q 4 h or by continuous infusion) for 10–14 d	Procaine penicillin, 2.4 million units IM daily *plus* probenecid, 500 mg PO four times daily, both for 10–14 d Or Ceftriaxone, 2 g either IM or IV daily for 10–14 d	Follow-up treatment with 3 additional weekly injections of penicillin G benzathine, 2.4 million units IM
Tertiary syphilis (not neurosyphilis)	Penicillin G benzathine, 2.4 million units IM once weekly for 3 wk	—	Cerebrospinal fluid evaluation should be performed before therapy

The response to treatment should be assessed by the resolution of clinical manifestations and by the decline in nontreponemal antibody titers over time. Successful therapy is determined by a fourfold decline in the nontreponemal antibody test (eg, 1:32–1:8). When monitoring response to treatment, the same nontreponemal test (either RPR or VDRL) should be followed serially because of variation in nontreponemal antibody titer according to test type. Ideally, all patients with syphilis should have follow-up titers measured at 3, 6, 9, 12, and 24 months posttreatment. Titers can rise transiently in the first few weeks after treatment, so retesting before 3 months is not recommended.[58] In early stage syphilis a fourfold decline should occur within 6 to 12 months of treatment. In late syphilis this decline can take 12 to 24 months.

Across studies, between 15% and 27% of patients with early syphilis fail to achieve a fourfold decline in titer after 12 months, irrespective of HIV infection status.[43,45,59] In addition, some patients achieve a fourfold decline but continue to have a "high" titer (eg, 1:32). The biologic and clinical significance of a lack of decline in titer or persistent "high" titer despite fourfold decline are unclear. Those cases may be caused by syphilis reinfection or less likely treatment failure. Repeat syphilis infections are common,[60] and by following serial nontreponemal antibody titers, it is easier to distinguish reinfection from treatment failure. Because treatment failure may be the result of unrecognized CNS infection, CSF examination can be considered if a fourfold decline in titer is not observed within the expected interval. If the CSF is abnormal, the patient should be treated for neurosyphilis. If the CSF is normal, optimal treatment is unclear and some experts recommend that treatment be reinitiated with penicillin G benzathine, 2.4 million units weekly for 3 weeks.[37] In a study of 82 HIV-negative patients who failed to achieve a fourfold decline 6 months after treatment of primary syphilis, retreatment with one additional dose of penicillin G benzathine, 2.4 million units, led to a serologic cure in only 27%.[61]

Whether HIV-infected patients with syphilis have a slower decline in nontreponemal antibody titer than HIV-uninfected patients is unclear, because results have varied between studies.[45,46,62,63] Given the possibility of slower titer decline, most experts recommend following up asymptomatic HIV-infected patients for a full 12 months for early syphilis and 24 months for late latent syphilis before making a determination of treatment failure.

PREGNANCY AND CONGENITAL SYPHILIS

Pregnant women with syphilis who are allergic to penicillin should be desensitized and treated with penicillin according to the guidelines listed previously.[37] In pregnant women the Jarisch-Herxheimer reaction can precipitate uterine contractions, fetal distress, or premature labor; thus, pregnant women should be treated in a monitored setting.[2,64] Treatment of neonates with proved or probable congenital syphilis should be done in consultation with a pediatric infectious diseases specialist.

PUBLIC HEALTH RESPONSE: MANAGEMENT OF SEX PARTNERS

Providers can work together with local health departments to prevent the spread of syphilis. Presumptive and confirmed cases of syphilis should be reported within 1 working day of diagnosis. Staff in public health departments are then able to contact and notify sex partners, and provide testing and treatment as appropriate. Internet partner notification (ie, using email and chat room "handles" to notify partners) can augment syphilis case management and is an important tool in the modern syphilis epidemic.[65] For patients exposed to early syphilis within the past 3 months the proper management includes examination; nontreponemal testing (stat, if available); and

immediate treatment with penicillin regardless of serologic test results. For patients exposed to early syphilis who are beyond the 3-month incubation period, treatment depends on clinical examination findings and serologic test results. Presumptive treatment of contacts based on exposure history is essential to prevent reinfection and control the spread of disease.

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