

# A 19-Year-Old Man Presenting With Rash on His Trunk, Hands, and Feet

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TARGET AUDIENCE	CME INFORMATION	CREDIT
<p>The January/February Clinical Case of the Month is intended for general practitioners, medicine subspecialists including infectious disease, clinical pharmacology, allergy and immunology specialists, emergency medicine physicians, dermatologists, and pathologists.</p>	<p>The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) <i>AMA PRA Category 1 Credit</i><sup>™</sup>. Physicians should only claim credit commensurate with the extent of their participation in the activity.</p>	
<p>EDUCATIONAL OBJECTIVES</p> <p>The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be better able to understand the pathophysiology, prognosis, clinical presentation, and treatment of syphilis. Estimated time to complete this activity is one (1) hour.</p>	<p>DISCLOSURE</p> <p>Mr. Courville, Drs. Crowe, and Engel have nothing to disclose. Dr. Lopez discloses that he is a member of the <i>Journal</i> Board of Trustees. Dr. Lopez is also on the <i>Journal</i> Editorial Board.</p>	<p>ORIGINAL RELEASE DATE      EXPIRATION DATE 1/31/2008                              1/31/2009</p>

A 19-year-old man presented with a rash of three weeks duration. The rash began as “itchy red bumps” on the abdomen and lower back. The patient scratched the bumps before they ulcerated. The patient also noted flu-like symptoms and a sore throat at the time that the rash first appeared. The patient went to a local community hospital and was treated with a corticosteroid injection for a presumed inflammatory reaction. A few days later he noticed the rash involved the palms of his hands and the soles of his feet. The patient was seen by a dermatologist and was given an anti-pruritus medication that did not alleviate the symptoms. Over the following two weeks, the rash changed from a papular to a macular eruption and the patient decided to visit an outpatient health clinic for further evaluation.

A review of the patient’s sexual history revealed that he had unprotected sexual intercourse with a previous partner for several months prior to the development of the rash. In retrospect, the patient thought that this partner may have been developing a pruritic rash at the time. The patient practiced receptive and insertive anal and oral intercourse with men only. He has had three partners in the previous 12 months and denied any history of sexually transmitted diseases.

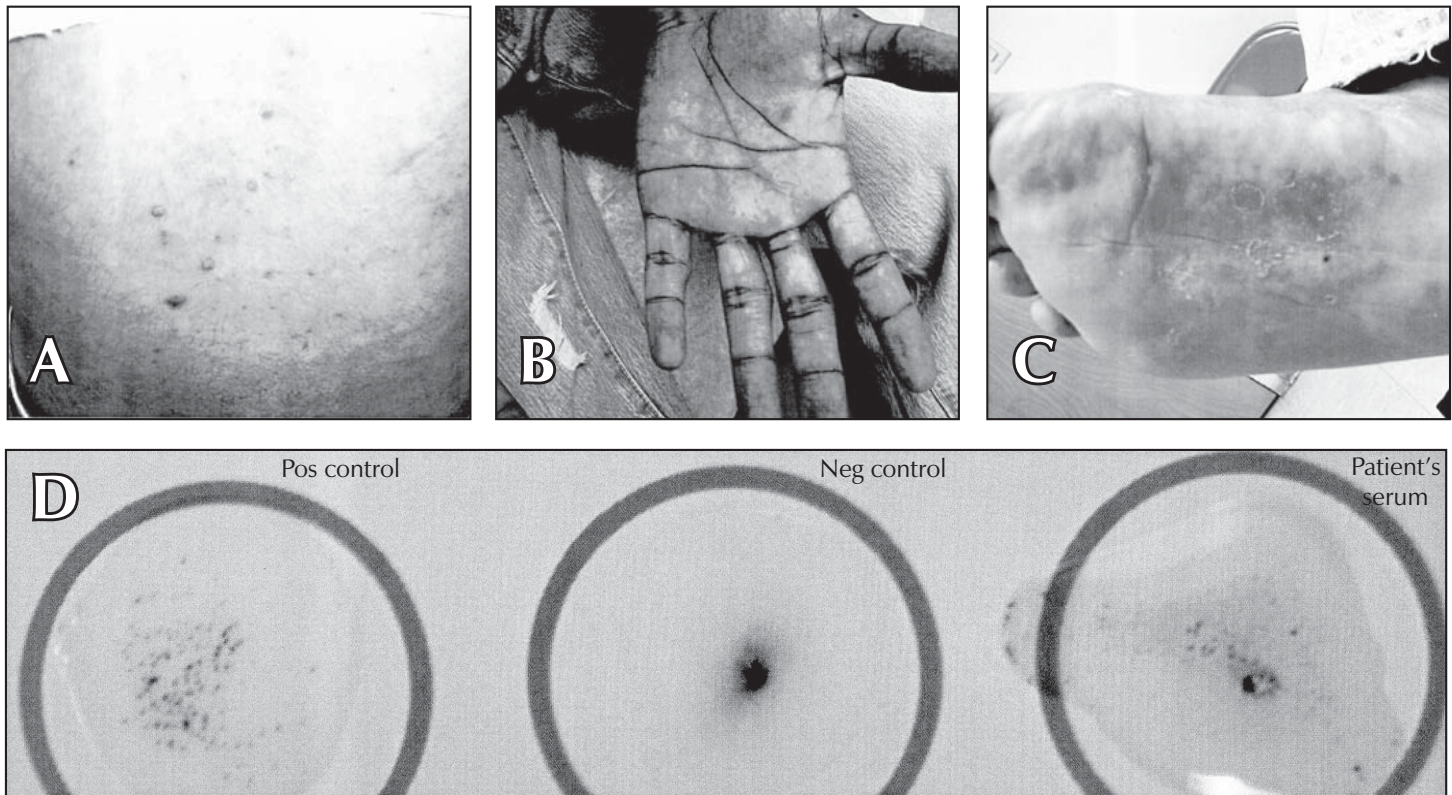
A review of his social history revealed that he smoked six to seven cigarettes a day and drank three alcoholic beverages weekly. He denied illicit drug use.

On physical exam, the patient was alert and oriented to person, place, and time. He was not in any apparent distress. A 3-mm, non-tender ulcer was noted on the left tonsillar fossa. Skin exam revealed a diffuse hyper-pigmented rash consisting of papules and macules on his lower back (Figure 1A), abdomen, palms of his hands (Figure 1B), and soles of his feet (Figure 1C). Genital exam did not demonstrate penile lesions, penile discharge, testicular masses, or abnormal lymphadenopathy.

Laboratory evaluation revealed a negative HIV test (Uni-Gold<sup>™</sup>, Trinity Biotech, Wicklow, Ireland), but the serum agglutination assay for rapid plasma reagin (Sure-Vue<sup>®</sup> RPR, Fisher Healthcare, Houston, Texas) was positive (Figure 1D).

The patient was diagnosed with secondary syphilis and treated with one dose of benzathine penicillin G, 2.4 million units given intramuscularly. He was instructed to refrain from sexual activity for two weeks. He was counseled about safe sexual practices and smoking cessation. The patient was also referred to disease management case workers to help locate his sexual partners for treatment.

Laboratory evaluation of the initial serum collection demonstrated a positive fluorescent treponemal antibody test and a Venereal Disease Research Laboratory (VDRL) test titer of 1:16. On subsequent follow-up visits, the patient’s VDRL test titer decreased to 1:4 and then 1:2 at one month and two months post treatment.



**Figure 1.** Clinical findings of case patient. A. Macular-papular rash of secondary syphilis on the back of the patient. B. Presence of macules on the palm. C. Presence of hyperpigmented macules on the plantar surface of the foot. D. Serum agglutination assay for rapid plasma reagin (Sure-Vue® RPR, Fisher Healthcare, Houston, Texas). Positive control on left, negative control in middle, and positive patient's serum on right.

## INTRODUCTION

Syphilis, caused by the bacterium *Treponema pallidum*, is a preventable and curable sexually transmitted disease. When untreated, syphilis is a disease that is divided into stages based on acute and chronic manifestations. The reservoir for *T. pallidum* is humans. Syphilis is most commonly transmitted by sexual activity but can be transmitted transplacentally to the fetus during pregnancy or by blood transfusion.

## HISTORY

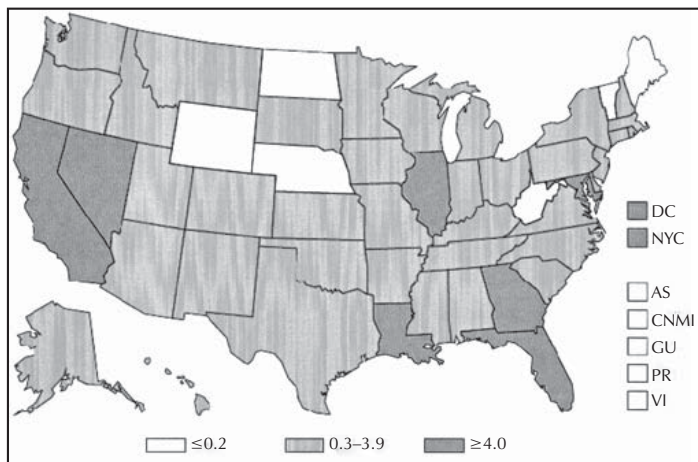
The first recognized European epidemic of syphilis occurred in the late 1400s in Naples and was called "The Great Pox".<sup>1,2</sup> During the 19th century, syphilis was known as "The Disease of the Century". During that century, there was a 5%-20% life-time risk for acquiring syphilis. Of infected people 6% developed neurosyphilis,<sup>3</sup> which would often result in tabes dorsalis, producing a high-stepping gait described as "walking on cotton," or general paresis of the insane. In 1822, Antoine-Laurent Bayle became the first physician to attribute the psychiatric symptoms of neurosyphilis to chronic inflammation of the meninges.<sup>3</sup> F.R. Schaudinm and P.E. Hoffman discovered the causative agent of syphilis in 1905 and named it *Spirochaeta pallida*.<sup>2</sup> The Wasserman test (complement fixation) was developed

in 1906 as a means to diagnose syphilis.<sup>2</sup> In 1943, John Mahoney demonstrated that penicillin was an effective therapy for primary syphilis.<sup>4</sup>

## EPIDEMIOLOGY

After the introduction of penicillin in 1940 and through education and treatment of sexual contacts, cases of syphilis declined until 1980. However, the incidence of syphilis increased through the 1980s and peaked in the early 1990s due to budget cuts for public health programs for syphilis.<sup>5</sup> The incidence of syphilis then decreased starting in 1994 and in 2000 was the lowest since official reporting began in 1941.<sup>6</sup> However, the incidence of primary and secondary syphilis has been continually increasing since 2000, characterized by HIV co-infection, high risk sexual behavior, and incarceration in correctional institutions.<sup>7</sup> Furthermore, the number of cases among women increased in 2004, and the male-to-female ratio decreased in 2005 suggesting that heterosexuals may be increasingly infected with syphilis.<sup>7</sup>

In 2005, the southern United States continued to have the highest case rate of primary and secondary syphilis (3.8 cases per 100,000 population per year), more than any other region in the United States (Figure 2).<sup>7</sup> In 2005, Louisiana ranked 3rd among 50 states, the District of Columbia, and three territories in case rates of primary and secondary syphilis. Louisiana had 6.2 cases of primary and secondary



**Figure 2.** National incidence of syphilis. \*Per 100,000 population per year. In 2005, the overall US rate of primary and secondary syphilis was 3.0 cases per 100,000 population, which is above the *Healthy People 2010* objective of 0.2 cases per 100,000 population per year. Six states (Maine, Nebraska, North Dakota, Vermont, West Virginia, and Wyoming) reported rates at or below the national objectives. Syphilis, primary and secondary incidence\* - United States, 2005. (MMWR 2007/vol. 54/No. 53)

syphilis per 100,000 population compared to the US national rate of 3.0 cases per 100,000 population per year.<sup>5,6</sup> Within the state, case rates are highly clustered in a few parishes (Figure 3).<sup>5</sup>

### MANIFESTATIONS OF SYPHILIS

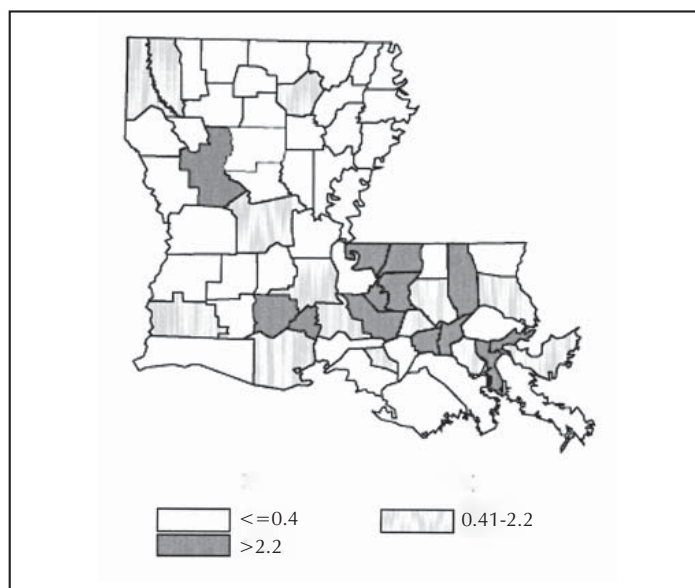
Manifestations of syphilis follow a stepwise progression described by clinical stages. The stages include 1) incubation period 2) primary infection 3) secondary infection 4) latent infection (early and late) and 5) tertiary infection.<sup>8-10</sup>

The incubation period begins with inoculation of the *Treponema pallidum* spirochete via a break in the dermis or mucous membrane. Once the spirochete is beneath the epithelium, it replicates and spreads to regional lymph nodes. The duration of the incubation period ranges from 10 days to 90 days depending on inoculation size and previous exposure to the pathogen.<sup>8-10</sup>

The hallmark of primary syphilis is a chancre, typically the first clinical manifestation of infection.<sup>8-11</sup> The chancre begins as a red, painless papule approximately 0.5 to 2 cm in diameter that soon ulcerates to develop the classic indurated, nontender ulcerative lesion. It is usually not purulent and is classically associated with moderate firm and painless regional lymphadenopathy. Because the chancre erupts wherever the spirochete invades the epithelium, it can present on almost any surface of the body. Men most commonly present with chancres on the penis, but chancres can also present in the oral cavity, anal canal, and rectum. Lesions in women are recognized less often as they commonly develop the painless lesions on the labia or cervix, as well as lesions in the oral cavity, anal canal, and rectum.<sup>9-11</sup> The clinical picture of primary syphilis can be confusing as there are variants of this presentation. For example, atypical chancres have been reported to present as painful, pruritic

lesions with ragged, irregular edges, as well as lesions that do not demonstrate induration.<sup>12,13</sup> Histopathologically, the chancre is characterized by an infiltration of plasma cells, a concentric endothelial and fibroblastic proliferative thickening of small blood vessels, and eventually almost pathognomonic obliterative endarteritis. The chancre heals spontaneously in four to six weeks.<sup>10,11</sup> HIV-infected patients have been reported to present more often with multiple ulcers or with concomitant manifestations of primary and secondary syphilis when compared to HIV-negative patients.<sup>14,15</sup>

Soon after inoculation, the spirochete proliferates and disseminates widely via lymphatics to the bloodstream. This extensive spirochetemia is the basis for the systemic, florid manifestations of the secondary stage of the illness. The clinical signs and symptoms of the secondary stage typically appear about four to ten weeks after the appearance of the chancre, but occasionally, secondary syphilis can emerge coincident with the appearance of a chancre. The delay before the onset of disseminated syphilis findings is due to the capability of the host immune response to modify the progression of infection. Thus, the duration of this delay is affected by the immunocompetency of the host and the virulence of the spirochete. The initial finding in disseminated syphilis is a generalized macular rash. A few days following the eruption of the rash, papular lesions appear in a symmetrical pattern. This maculopapular eruption involves the trunk and extremities including the palms of the hands and soles of the feet. The lesions are generally scaly, or psoriatic, in nature, but they can also be smooth, or less commonly, pustular. Involvement of the hair follicles can lead to alopecia. Malignant syphilis (*maligna lues*) can occur and is defined as disseminated lesions that resemble primary chancres. Condyloma lata,



**Figure 3.** Incidence of syphilis per 100,000 population per year by parish in Louisiana -2005. (<http://www.cdc.gov/std/syphilis2005/>)

another manifestation of secondary syphilis, are gray or white, wart-like plaques that commonly evolve from other secondary lesions such as papules that then undergo breakdown with extension of infection into surrounding tissue. These plaques typically present in moist areas and areas of trauma, such as axilla and groin, that are conducive to the replication of spirochetes and thus are teeming with spirochetes.

Constitutional symptoms such as low-grade fever, malaise, weight loss, headache, pruritus, sore-throat, and myalgia are commonly seen with dissemination. The disseminated phase features a generalized lymphadenopathy that differs from the lymphadenopathy of the primary stage in that it involves all lymphatic structures. It occurs when the infection spreads beyond the satellite lymph nodes, or buboes, of the primary infection. The lymph nodes are typically firm and painless. Epitrochlear lymph node enlargement can be a distinct finding in treponemal infection.<sup>10,11</sup>

Neurological involvement during the disseminated phase may occur in as many as 40% of patients.<sup>10,11</sup> Cerebrospinal fluid (CSF) abnormalities may include pleocytosis, an increased protein concentration, positive CSF-VDRL titer, or the presence of spirochetes in the absence of other CSF abnormalities. The most common symptomatic manifestation of early central nervous system syphilis is acute syphilitic meningitis.<sup>8,17</sup> Headaches, meningismus, cerebrovascular accidents, and cranial nerve involvement have been described. Vision loss, internuclear ophthalmoplegia, nystagmus, deafness, tinnitus, or facial weakness are common manifestations of cranial nerve involvement. Syphilitic paraplegias (Erb's paralysis) and amyotrophic meningomyelitis characterized by asymmetrical paraparesis, hyperreflexia, Babinski's sign, sphincter disturbances, spastic neurogenic bladder, and minimal back pain may occur.<sup>8,10</sup> Acute syphilitic meningitis is most often benign even without treatment in that it will remit along with most other findings of the secondary stage. However, cranial nerve palsies may persist.<sup>16</sup> Clinically, infection of the central nervous system warrants the same treatment strategy regardless of the stage of presentation.<sup>8,16</sup>

Due to the ability of *T. pallidum* to disseminate, every organ can be involved during secondary syphilis. Liver involvement has been described as either subclinical hepatitis or symptomatic hepatitis. Ocular involvement can present as pan- or anterior uveitis or iritis. Gastrointestinal (GI) involvement has been described and can present as an ulcer or infiltration of the wall of the GI tract. Skeletal involvement includes, but is not limited to, osteitis, synovitis, or periosteitis. Renal involvement typically manifests itself as the deposition of treponemal antigen, immunoglobulin, and complement in the glomeruli presenting the picture of immune-complex glomerulonephritis.<sup>10,11</sup> The manifestations of disseminated disease typically resolve within three months of their onset. Immunologically, the resolution of symptoms marks the

ability of the host immune system to overcome the vast dissemination of spirochetes.<sup>10,11</sup>

Latent syphilis is characterized by serological reactivity in the absence of clinical manifestations. Latent syphilis is arbitrarily subdivided into early and late forms. Early latent syphilis is the phase of latency in which the individual is still infectious and during which a recurrence of symptoms and infectious lesions may occur. The infectious phase of syphilis endures for approximately four years after inoculation with the spirochete. However, in terms of treatment, early latent syphilis is defined as the absence of clinical manifestations within the first 12 months of infection. Late latent syphilis is syphilitic infection greater than one year or of unknown duration in the absence of clinical symptoms. The infectivity of a patient with late latent syphilis is markedly reduced from secondary syphilis, and the possibility of relapse is less likely. In the late latent phase, there remains significant risk of transmitting the bacteria through the placenta to the fetus during pregnancy.<sup>8,9,16</sup>

Tertiary syphilis, or late syphilis, is the chronic inflammation of any particular organ that leads to sequelae years after the initial infection. Tertiary syphilis is subdivided into late neurological, cardiovascular, gummatous, and sometimes leuitic osteitis.

Neurosyphilis can technically occur at any stage of disease as proven by early CNS infiltration of spirochetes during the secondary disseminated stage. Neurosyphilis should be more accurately subdivided into acute neurosyphilis and late neurosyphilis. Acute neurosyphilis generally remits with resolution of other manifestations of secondary syphilis. Late neurosyphilis can also be subdivided into asymptomatic and symptomatic forms.

Asymptomatic neurosyphilis is the most common form of neurosyphilis.<sup>10,17</sup> The diagnosis of asymptomatic neurosyphilis is given to patients who have no clinical manifestation of neurologic involvement but who have one or more CSF abnormalities: lymphocytic pleocytosis, an elevated protein concentration, a decreased glucose concentration, or a positive nontreponemal test.<sup>16</sup>

Symptomatic late neurosyphilis can be either meningovascular or parenchymatous neurosyphilis. Meningovascular neurosyphilis is due to inflammatory-associated endarteritis obliterans within the small blood vessels of the brain, meninges, and spinal cord leading to infarction. Meningovascular neurosyphilis can present as hemiplegia, seizures, aphasia, or other manifestations ranging from focal neurological deficits to progressive neurological deficits. It can be differentiated from the classical syndromes of stroke or cerebral emboli, which are more sudden in onset. The vascular syndromes of syphilis usually progress over days and are often preceded by a prodrome of headache, vertigo, insomnia, or psychiatric disturbances lasting weeks to months. The time lapse for meningovascular neurosyphilis is approximately 5-12 years after initial infection.

Parenchymatous neurosyphilis is not an inflammatory process but rather a degenerative process in which

the spirochete has damaged the cortical or spinal cord-associated nerve cells. This parenchymal involvement includes atrophy and fibrosis and can present in a number of ways. General paresis, or dementia paralytica, characterizes the syndrome of cortical involvement and manifests as personality changes, affect changes, hyperactive reflexes, Argyll-Robertson pupils, illusions, megalomania, memory loss, deficiencies in judgment, and slurred speech. This disorder is typically fatal within a few months to three or four years.<sup>17,18</sup> Spinal cord degeneration presents as the syndrome of tabes dorsalis, resulting from demyelination of the posterior columns and the dorsal root ganglia. Patients may present with shooting pains down both legs (lightening pains), paresthesias, bladder and fecal incontinence, loss of position and vibratory sense, wide-based gait, diminished reflexes, and cranial nerve involvement such as optic atrophy. Parenchymatous disease develops about 15-25 years after initial infection.<sup>8,10,17,18</sup>

Cardiovascular syphilis is the result of endarteritis obliterans of the vasa vasorum of the aorta. The result of this inflammation is progressive medial necrosis and loss of elastic tissue resulting in aneurysm. Luetic aneurysms most commonly involve the proximal aorta and aortic arch. Complications of such aneurysms include aortic regurgitation, coronary artery stenosis, and encroachment of the aneurysm on the recurrent laryngeal nerve, trachea, superior vena cava, and main-stem bronchi. Time from primary infection to onset of cardiovascular syphilis is 15-30 years.

Gummatous syphilis, or late benign syphilis, has the gumma as its hallmark. Gummas are granulomatous, indolent, locally destructive lesions of soft tissue or bone. Cutaneous manifestations range from nodules to deep-seated lesions that lead to ulceration. They can appear in the liver as gummatous hepatitis causing low-grade fever, epigastric pain, tenderness, and eventually cirrhosis (hepar

lobatum). Fractures can occur when gummas involve the bone, and upper respiratory tract perforation can occur when they are in the palate. Trauma can predispose to the development of gummas. These lesions begin as nodules that grow slowly before eventually undergoing central coagulative necrosis with softening and involution of the lesion. Ultimately fibrosis occurs with deep scarring.<sup>10,17</sup>

## DIAGNOSIS

The diagnosis of syphilis can be made by either direct detection of *T. pallidum* or by serological methods. Darkfield examinations and direct fluorescent antibody tests of lesion exudates or tissue are definitive methods for diagnosing early syphilis.<sup>16</sup> Identification of motile spirochetes using darkfield microscopy of material from lesions of primary and secondary syphilis has a sensitivity of 97%.<sup>19</sup> Direct fluorescent antibody testing (DFA-Tp) of lesion can be a valuable testing modality when darkfield microscopy is not possible. DFA-Tp methodology can be used on dried specimens, making the need for a fresh sample with readily available laboratory personnel less vital. Unfortunately, neither darkfield microscopic examination nor DFA-Tp testing are feasible to perform routinely. DNA amplification may be useful in the diagnosis of early syphilis with initial studies demonstrating 94.7% sensitivity and 98.6% specificity.<sup>20</sup>

Serological tests for syphilis continue to be the mainstay of diagnosis. Serodiagnosis utilizes a two step mechanism.<sup>21,22</sup> Patients are first screened with a non-treponemal test such as the rapid plasma reagin (RPR) or the Venereal Disease Reference Laboratory (VDRL) tests. Confirmatory testing is then done on specimens with positive screening tests by utilizing either a *T. pallidum* agglutination assay (TPPA), a *T. pallidum* haemagglutination assay (TPHA), or an enzyme immunosorbant assay (EIA).

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## TREATMENT

Over the last 500 years various treatment strategies for syphilis have been used including mercury, arsenic, and deliberate infection with malaria. The current drug of choice, penicillin, has been utilized for over 50 years. The effectiveness of penicillin in the treatment of syphilis was established through decades of experience prior to the advent of randomized control trials. To date, no comparative trials have been conducted that sufficiently guide an optimal course of therapy with penicillin.

Parenterally administered penicillin G is the treatment of choice for all stages of syphilis. The treatment duration, dosage, and preparation of penicillin G (ie, benzathine, aqueous procaine, or aqueous crystalline) depend on the stage and clinical presentation of disease.<sup>16</sup>

### Primary, Secondary, and Early Latent Syphilis

The recommended adult regimen for the treatment of primary, secondary, and early latent syphilis is benzathine penicillin G, 2.4 million units IM as one dose (Table). Serologic and clinical follow up should occur 6 to 12 months following treatment. Nontreponemal titers that do not decline fourfold after six months may reflect treatment failure. If treatment failure is suspected, patients should be evaluated for HIV infection and, in some expert opinion, undergo CSF examination to rule out neurosyphilis. Guidelines for re-treatment are unclear, but many specialists recommend weekly IM benzathine penicillin G, 2.4 million units, for three weeks.

Alternative therapies for patients who are penicillin-allergic include tetracycline 500 mg QID for 14 days, doxycycline 100 mg BID for 14 days, or ceftriaxone 1g IM or IV daily for 8-10 days. Ceftriaxone has been shown to be equivalent to penicillin in small studies, but "the usefulness of ceftriaxone remains to be validated in larger clinical trials".<sup>23</sup> Azithromycin had gained popularity as an alternative to penicillin, but the discovery of macrolide-resistant mutations in large US cities such as San Francisco, Seattle, and Baltimore has raised concern. While ceftriaxone appears to be a clinically efficacious alternative for some experts, the "routine use of azithromycin cannot be recommended".<sup>23</sup>

### Latent Syphilis

The recommended adult regimen for the treatment of late latent syphilis and latent syphilis of unknown duration is benzathine penicillin G, 2.4 million units IM administered one time a week for three weeks (Table). Quantitative serologic testing should be done at 6, 12 and 24 months after treatment. For patients without evidence of CSF infection, re-treatment should be initiated "if a) titers increase fourfold, b) an initially high titer ( $\geq 1:32$ ) fails to decline at least fourfold within 12-24 months of therapy, or c) signs or symptoms attributable to syphilis develop".<sup>16</sup> CSF examination should occur for any of the above mentioned criteria as well as for ophthalmic or neurologic symptoms,

**Table. Treatment of Syphilis.**

#### *Recommended Adult Regimen#*

#### **Primary, Secondary, and Early Latent Syphilis**

Benzathine penicillin G 2.4 million units IM once

Alternate regimens for penicillin-allergic patients:

- 1) Doxycycline 100 mg orally twice daily for 14 days\*<sup>^</sup>
- 2) Tetracycline 500 mg orally four times a day for 14 days\*<sup>^</sup>
- 3) Ceftriaxone 1 gram IM or IV daily for 8-10 days\*<sup>^</sup>
- 4) Pregnant patients: desensitize to penicillin and treat with penicillin

#### **Late Latent Syphilis, Latent Syphilis of Unknown Duration, and Tertiary Syphilis**

Benzathine penicillin G 7.2 million units administered as 2.4 million units IM weekly for 3 weeks

Alternate regimens for penicillin-allergic patients:

- 1) Doxycycline 100 mg orally twice daily for 28 days\*<sup>^</sup>
- 2) Tetracycline 500 mg orally four times a day for 28 days\*<sup>^</sup>
- 3) Pregnant patients: desensitize to penicillin and treat with penicillin

#### **Neurosyphilis**

Aqueous crystalline penicillin G 18-24 million units per day, administered as 3-4 million units IV every 4 hours or continuous infusion, for 10-14 days

Alternative regimens:

- 1) Procaine penicillin 2.4 million units IM once daily for 10-14 days PLUS probenecid 500 mg orally four times a day for 10-14 days
- 2) Penicillin allergy: Ceftriaxone 2 grams daily either IM or IV for 10-14 days\*<sup>^</sup>
- 3) Pregnant patients: desensitize to penicillin and treat with penicillin

#Sexually transmitted diseases treatment guidelines, 2006. *MMWR* 55:No. RR-11, August 2006.

\*The use of alternatives to penicillin has not been well studied in HIV-infected patients.

<sup>^</sup> Patients with penicillin allergy whose compliance with therapy or follow-up cannot be ensured should be desensitized and treated with penicillin.

active tertiary syphilis, or HIV infection with late latent syphilis or syphilis of unknown duration.<sup>16</sup>

The efficacy of penicillin alternatives in the treatment of latent syphilis is poorly documented. For the treatment of early latent syphilis, the penicillin substitutes used for primary and secondary syphilis are acceptable. The treatment of late latent syphilis or syphilis of unknown duration may include doxycycline 100mg BID or tetracycline 500mg QID, each for 28 days. Evidence suggests that ceftriaxone is an effective alternative to penicillin, but data are limited on the dosage and duration of therapy.<sup>16</sup>

### Tertiary Syphilis

The recommended adult regimen for the treatment of tertiary syphilis is benzathine penicillin G, 7.2 million units administered as 2.4 million units IM weekly for three weeks (Table).

The CSF of patients with tertiary syphilis (cardiovascular syphilis or gumma) should be evaluated prior to treatment. Some experts recommend that cardiovascular syphilis be treated with the same regimen as neurosyphilis. Data are limited regarding the follow-up of patients with tertiary syphilis.<sup>16</sup>

### Neurosyphilis

The recommended regimen for the treatment of neurosyphilis in adults is aqueous crystalline penicillin G, 18-24 million units daily, administered as continuous infusion or as 3-4 million units IV every four hours, for 10-14 days (Table). Compliant patients may be treated with an alternative regimen that includes procaine penicillin, 2.4 million units IM daily, plus probenecid, 500 mg orally every six hours, both for 10-14 days.

The duration of treatment for neurosyphilis is shorter than that of latent syphilis, therefore some experts recommend an additional 2.4 million units IM weekly for up to three weeks. CSF evaluation should be repeated every six months until the cell count is normal if a pleocytosis was present at diagnosis. Re-treatment may be considered if the cell count has not decreased after six months or if the CSF is abnormal after two years.<sup>16</sup>

If cross-reactivity is not a concern in penicillin-allergic patients, ceftriaxone 2 g daily IM/IV for 10-14 days is acceptable. There is insufficient data to recommend other alternative regimens for the treatment of neurosyphilis. If there is concern of severe penicillin allergy, skin testing and desensitization should be performed.<sup>16</sup>

### Syphilis in Pregnancy

All women should be screened for syphilis by serological tests during the early stages of pregnancy if possible. No infant should leave the hospital without having the maternal serological status for syphilis determined at least once during pregnancy.<sup>16</sup> Pregnant women should be treated with penicillin G for syphilis in any stage, as it is the only treatment with documented efficacy during pregnancy.

If patients are penicillin-allergic, they should receive skin testing and desensitization if necessary.<sup>16</sup>

### Treatment of Sexual Partners

Syphilis may be transmitted only in the presence of mucocutaneous lesions, which are uncommon following one year of infection. Sexual partners exposed to syphilis in any stage need clinical and serologic evaluation. Individuals who were exposed within 90 days prior to the diagnosis of primary, secondary, or early latent syphilis in a sexual partner should be treated presumptively, even if the exposed individual is seronegative. Individuals who were exposed > than 90 days prior to the diagnosis of primary, secondary, or early latent syphilis in a sexual partner should be treated presumptively if follow-up is questionable or serologic tests are not immediately available. Exposed sex partners can be treated for early latent syphilis presumptively if the patient with syphilis of unknown duration has high non-treponemal titers (ie,  $\geq 1:32$ ). Long-term partners of patients with latent syphilis should be evaluated and treated accordingly.<sup>16</sup>

## CONCLUSIONS

The incidence of primary and secondary syphilis is increasing, and today's health care worker/physician needs to be aware of the clinical manifestations, diagnosis, and treatment of this disease. Penicillin remains the standard of care for all stages of syphilis. Syphilis is a preventable and curable disease, but without continued interventions to treat and prevent this sexually transmitted disease, this entity will continue to flourish in our communities.

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For each question, choose the one answer that is most correct.

1. All of the following are true concerning syphilis except
  - a. Syphilis is most commonly transmitted by sexual activity but can be transmitted transplacentally to the fetus during pregnancy or by blood transfusion.
  - b. The incidence of primary and secondary syphilis has been continually increasing since 2000, characterized by HIV co-infection, high-risk sexual behavior, and incarceration in correctional institutions.
  - c. The hallmark of primary syphilis is a chancre, typically the first clinical manifestation of infection.
  - d. The reservoir for syphilis infections is the mosquito.
2. True/False:  
Due to the ability of *T. pallidum* to disseminate, every organ can be involved during secondary syphilis.
3. All of the following are true concerning syphilis except
  - a. Latent syphilis is characterized by serological reactivity in the absence of clinical manifestations.
  - b. Neurosyphilis can occur only in the secondary stage of syphilis when dissemination of the organism is most pronounced.
  - c. The diagnosis of syphilis can be made by either direct detection of *T. pallidum* or by serological methods.
  - d. Parenterally administered penicillin G is the treatment of choice for all stages of syphilis.
4. True/False:  
Pregnant women should be treated with penicillin G for syphilis in any stage, as it is the only treatment with documented efficacy during pregnancy.