Chapter 6

Syphilis

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Additional information is available at the end of the chapter

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Abstract

Syphilis is a sexually transmitted disease caused by the spirochete *Treponema pallidum*. It is transmissible by sexual contact, from mother to fetus, via blood transfusion, and occasionally by direct contact with infectious lesions. It has been a major public health problem both before the antibiotic era and now, with the increase of acquired immunodeficiency states and unprotected sex. The clinical manifestations of the disease can mimic many other infections and immune-mediated diseases; thus, it may be difficult to make early diagnosis. After the discovery of penicillin in the twentieth century, the spread of the disease has been largely controlled, but up to now, it has not been fully eradicated. In this chapter, overall information about the disease including the epidemiology, clinical presentation forms, pathophysiological mechanisms, and latest diagnostic and treatment approaches are reviewed.

Keywords: syphilis, clinical stages of syphilis, neurosyphilis, congenital syphilis, diagnosis of syphilis, treatment of syphilis

1. Introduction

Syphilis is an infectious sexually transmitted disease caused by the spirochete microorganism *Treponema pallidum*. Syphilis is transmissible by sexual contact with infectious lesions, from mother to fetus in utero, via blood product transfusion, and occasionally through breaks in the skin that come into contact with infectious lesions. Unprotected sex is the major risk factor for the acquisition of syphilis, especially among men who have sex with men (MSM). It is an intermittently active disease with primary, secondary, latent, and tertiary stages.

Syphilis is a disease with great historical importance and has played a major role in medicine for over a century. The disease was named after an afflicted shepherd named Syphilus in 1530. It is known to be "the great impostor," particularly because the manifestations can mimic

many other infections and immune-mediated diseases. For this reason, the historical Sir William Osler once remarked "The physician who knows syphilis knows medicine." Many famous people throughout the history are thought to have suffered from syphilis, including Bram Stoker, Henry VIII, and Vincent van Gogh. After the discovery of penicillin in the twentieth century, the spread of the disease has been largely controlled, but up to now, it has not been fully eradicated.

The responsible microorganism *T. pallidum* is a fragile spiral bacterium. It can survive only briefly outside of the body; thus, transmission almost always requires direct contact with the infectious lesions. Incubation time from exposure to development of primary lesions, which occur at the primary site of inoculation, is approximately 3 weeks but can range from 10 to 90 days. Regardless of the stage of disease and location of lesions, histopathologic hallmarks of syphilis include endarteritis and a plasma cell-rich infiltrate. Secondary syphilis develops about 4–10 weeks after the primary lesion. During this stage, the spirochetes multiply and spread throughout the body, and variable mucocutaneous lesions and systemic manifestations may be observed. During the secondary infection, the immune reaction is at its peak, and antibody titers are high.

Latent syphilis is a stage at which the features of secondary syphilis have subsided, but the patient is still seropositive. About one-third of untreated patients at this stage develop tertiary syphilis, whereas the rest remain asymptomatic. Tertiary syphilis is rather rare and mainly involves the cardiovascular and central nervous system, developing over months to years and involving slow inflammatory damage to tissues.

The morbidity of syphilis ranges from minor symptoms of the early stages to the more significant systemic symptoms of secondary syphilis and neurological and cardiovascular consequences of tertiary disease. Latent syphilis can persist for years, causing significant morbidity and mortality if left untreated. The prevalence of the disease continues to increase due to the emergence of the AIDS epidemic, since genital ulcers may facilitate the sexual transmission of HIV, and HIV-seropositive patients have an increased risk for rapid progression to neurosyphilis. Approximately one-third of patients left untreated will develop late complications such as cardiovascular, neurosyphilis, or gummatous syphilis. Mortality rates are higher among these groups, up to 20% for tertiary syphilis, and late complications appear more commonly in men than in women [1]. On the other hand, for primary and secondary syphilis, the prognosis is rather good with appropriate treatment since *T. pallidum* is highly sensitive to penicillins.

2. Epidemiology

Syphilis is a worldwide-distributed disease and is particularly encountered in countries with low socioeconomic status. The rates of primary and secondary syphilis decreased dramatically worldwide with the introduction of penicillin treatment after the Second World War. It is estimated that worldwide in 2012, there were 18 million prevalent cases of syphilis in adolescents and adults aged 15–49 and 5.6 million new cases [2]. The global incidence rate was 1.5 cases per 1000 females and 1.5 cases per 1000 males. According to the same

report, the highest prevalence was in the African region, followed by the Southeast Asian and Western Pacific regions. In the United States, from 2005 to 2014, the overall number of reported primary and secondary syphilis cases increased significantly from 8724 to 19,999 [3, 4]. In 2015, a total of 23,872 primary and secondary syphilis cases were reported, and the national rate increased by 19% to 7.5 cases per 100,000 population [5]. The rise in the rate of reported syphilis cases is primarily attributable to increased cases among men who have sex with men (MSM). The increasing incidence of syphilis in this population is due in part to rising rates of risky sexual behaviors, such as anonymous sex, unprotected sex (oral and anal), sex with multiple partners, and/or sex under the influence of drugs, especially methamphetamine. Concomitant HIV and syphilis infections are prevalent since they have similar modes of transmission, and infection with one may enhance the acquisition and transmission of the other among MSM. Available data suggest that approximately 50% of MSM with primary and secondary syphilis are HIV-infected, compared with 10% of men who have sex with women and 3.9% of women [6]. One long-term study conducted among US military personnel found that 5.8% of 4239 patients with newly diagnosed HIV infection also had serologic evidence of syphilis [7]. The rate of reported primary and secondary syphilis cases remains highest among Blacks, with the overall rate of syphilis being highest in Black men. As an example, in 2015, the rate of reported cases per 100,000 population was 39.0 in Black men, 16.6 in Hispanic men, and 7.6 in White men. Similar ethnical percentages apply among women as well [5].

Congenital syphilis is also a significant public health problem, complicating an estimated one million pregnancies per year throughout the world [8]. The incidence of congenital syphilis reflects the rate of syphilis in women of childbearing age who received no prenatal care or treatment for syphilis before or during pregnancy. In the United States, the rate of congenital syphilis among infants <1 year of age fluctuated between 8 and 12 cases per 100,000 live births between 2005 and 2015 [9]. The rate of congenital syphilis is increased among infants born to mothers with HIV infection. However, the contribution of maternal coinfection with syphilis and HIV to vertical transmission of either syphilis or HIV is not completely understood.

3. Pathophysiology

T. pallidum, the causative organism of syphilis, was first identified in 1905 by Schaudinn and Hoffmann [10]. It is a bacterium from the order *Spirochaetales*, a treponeme which causes human disease. *T. pallidum* is approximately 6–20 microns long and 0.1–0.18 microns in width, making it impossible to be visualized under direct light microscopy. With dark-field microscopy, casting an oblique light, *T. pallidum* is a corkscrew-shaped organism with wound spirals. It exhibits a characteristic rotary motion with flexing and back-and-forth movement, all of which are considered to be diagnostic. It cannot survive outside an animal host, nor can it be cultured in vitro for extended time period.

The organism has lipid-rich outer membrane with uniform-sized transmembrane proteins and periplasmic flagella. Inoculation and penetration of the microorganism occur via mucosal

surfaces and abraded skin, followed by attachment to host cells and multiplication. Despite a slow estimated dividing time of 30 hours, the spirochete evades early host immune responses and establishes the initial ulcerative lesion, the chancre, disseminating to the regional lymph nodes and internal organs [11, 12].

3.1. Primary stage

The primary lesion develops 10–90 days after infection (3 weeks on average) as a papule, followed by necrosis and well-circumscribed ulceration that is firm to palpation (chancre), as well as enlarged regional lymph nodes. *T. pallidum* elicits innate and adaptive cellular immune responses in the skin and blood. At this stage, Th1-predominant cellular response with activation of macrophages is observed around the lesion [13]. Compared with peripheral blood, lesional fluids were enriched with CD4+ and CD8+ T cells, activated monocytes, macrophages, and dendritic cells. Many of these dendritic cells also express HIV coreceptors (e.g., CCR5 and DC-SIGN), which may help explain the epidemiologic link between syphilis and HIV transmission [14]. Several pathogenic mechanisms including an antigenically inert treponemal cell surface, resistance to phagocytosis, and downregulation of the local host immune response have been considered for this stage. After acquisition of *T. pallidum*, humoral immune responses also lead to the development of a variety of antibodies, effectively providing the resolution of the primary chancre, even in the absence of therapy, while widespread dissemination of spirochetes occurs at the same time, leading to subsequent clinical manifestations of secondary or tertiary syphilis.

3.2. Secondary stage

The secondary stage is characterized by dissemination and multiplication of the microorganism in different tissues in up to 6 months after the local lesion. This stage follows primary syphilis in almost every patient in the absence of appropriate treatment. Various lesions may occur due to circulating immune complexes, human fibronectin, antibodies, and complements with accompanying systemic signs [15].

3.3. Latency

Latency is the period between healing of the clinical lesions and appearance of late manifestations, lasting for many years. Weakened immunity with aging may result in the reactivation of a small number of treponemes that had survived in sequestered sites. Alternatively, a partially immune hypersensitive host may react to the presence of treponemes, causing a chronic inflammatory response. About 70% of untreated individuals will remain in this stage for the rest of their lives and are immune to new primary infection. This period is divided into early (1 year or less) and late (more than 1 year) latency with positive serology for specific antibodies without clinical signs or symptoms. Infectivity may occur intermittently due to the presence of treponemes in the peripheral bloods, and thus pregnant women at this stage may infect the fetus in utero.

3.4. Tertiary stage

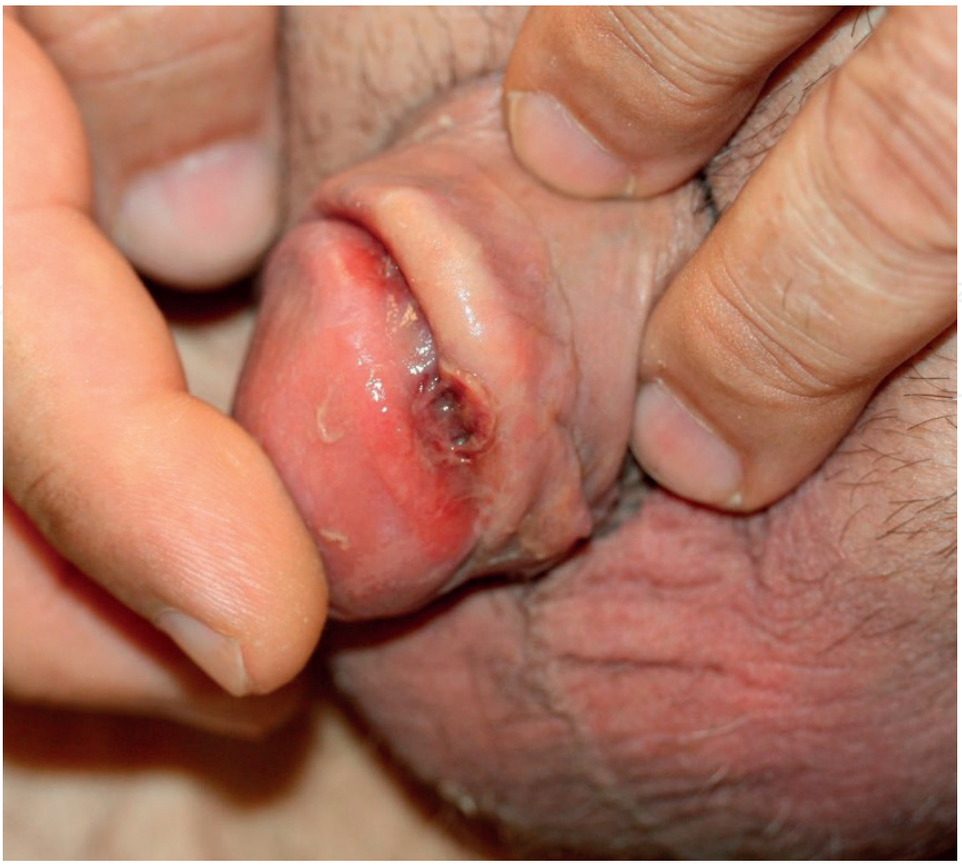
At this stage the number of organisms decrease, but a high cellular immune response arises. Signs of late syphilis can be observed in approximately one-third of untreated individuals several months to years after being infected. The microorganisms may invade the central nervous and cardiovascular systems as well as other organs characterized pathologically by the presence of granulomas, a result of delayed-type cellular hypersensitivity reaction. Studies with human subjects who were inoculated cutaneously with small numbers of live *T. pallidum* found that gummas developed only in those who had previous syphilis [16]. This suggests that development of gummas requires an immune response insufficient to be protective but substantial enough to cause tissue damage and granuloma formation in the reinfected host. Small vessel vasculitis is also a common manifestation of this stage with the presence of lymphocytes and plasma cells infiltrating blood vessels and perivascular tissues.

4. Clinical features

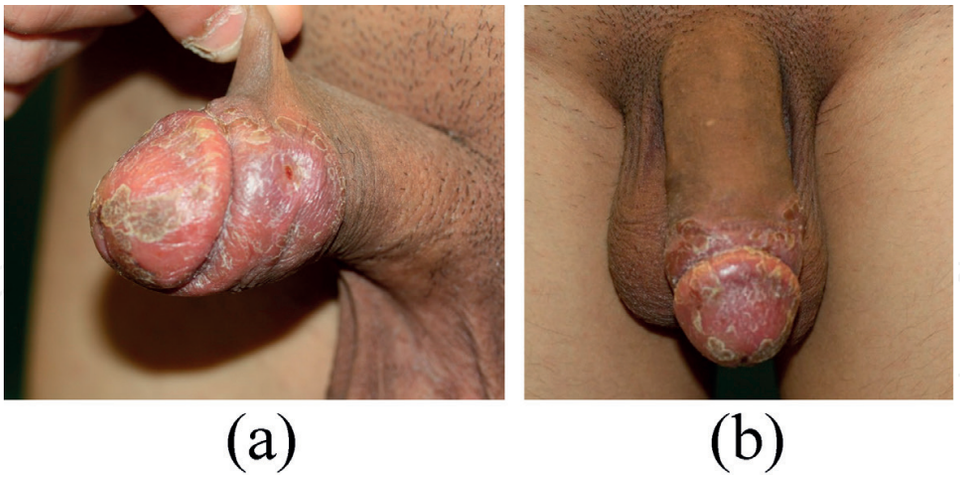
Syphilis is an intermittent disease with primary, secondary, and tertiary stages as well as a latent period of variable length, preceding the onset of tertiary syphilis. According to the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO), e*arly syphilis* includes the primary and secondary stages (CDC, acquired <1 year previously; WHO, acquired <2 years previously), and *late syphilis* extends from late latency (CDC, acquired >1 year previously; WHO, acquired >2 years previously) through the tertiary stage.

4.1. Primary syphilis

Following acquisition of *T. pallidum*, the chancre usually begins as a painless papule and progresses to a round or oval ulcer with raised and indurated margin. (**Picture 1**) The ulcer generally has a non-exudative base and is associated with mild to moderate regional, usually bilateral lymphadenopathy. The median incubation period before the chancre appears is 21 days [17]. Untreated chancres heal in 3–6 weeks with the help of local immune responses. The lesions usually occur on the genitalia (**Picture 2**), but occasionally patients may develop chancres at other sites of inoculation. Cervical, anal, perianal, rectal, or posterior pharynx chancres may go unrecognized, and thus in these cases, syphilis is more frequently diagnosed during the secondary stage. The chancre represents an initial local infection, but syphilis quickly becomes systemic with widespread dissemination of the spirochete. The presence of treponemes by dark-field microscopic examination of fluid from the surface of the chancre is the most sensitive and specific method for the diagnosis of primary syphilis. Cardiolipin, a component of mammalian cells, is modified by treponemes, and antibodies to cardiolipin can be measured by the rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) assay in about 80% of individuals at the onset of clinical symptoms. Alternatively, antibodies to surface proteins of *T. pallidum* detected by hemagglutination assays (*T. pallidum*



Picture 1. Primary syphilis chancre with indurated margin.



Picture 2. Syphilis chancre in subacute phase with crusts and desquamation.

hemagglutination assay [TPHA], micro-hemagglutination assay for antibodies to *T. pallidum* [MHA-TP]) or fluorescent treponemal antibody absorption (FTA-ABS) assay are present in 90% of patients with primary syphilis. Since antibodies usually remain positive for life, a differentiation between primary syphilis and an earlier infection may not be possible, and dark-field examination should be performed.

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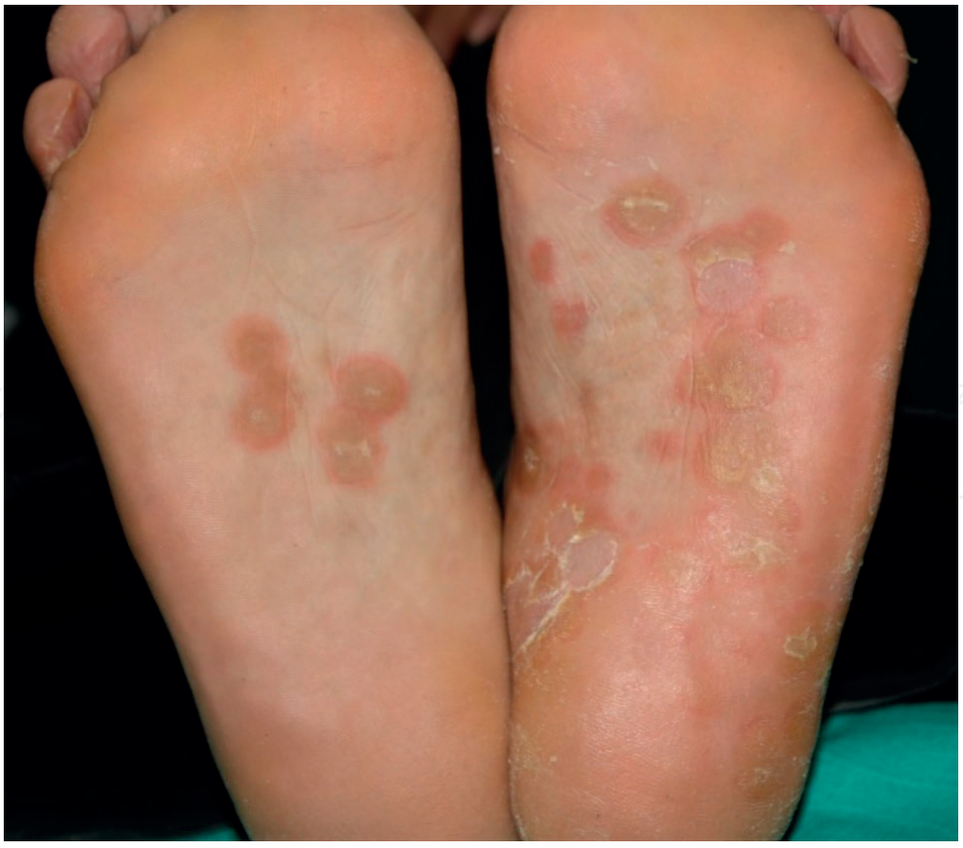
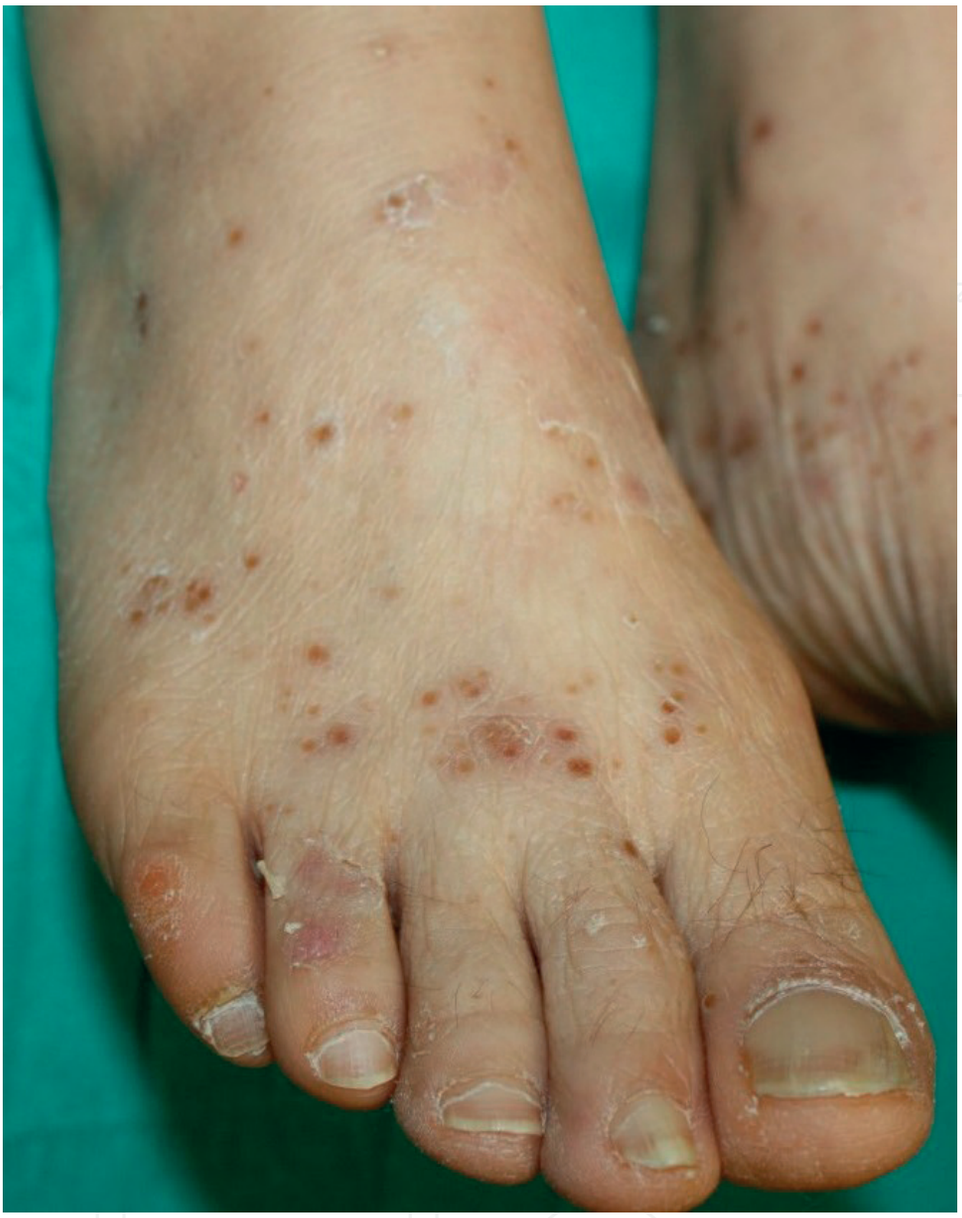
4.2. Secondary syphilis

The secondary stage of the disease results from the hematogenous and lymphatic dissemination of treponemes in 3–10 weeks, observed in approximately 25% of individuals with untreated infection [18]. It is characterized by both mucocutaneous and systemic manifestations. Prodromal symptoms include fever, malaise, anorexia, sore throat, lymphadenopathy, weight loss, myalgia, and headache. These clinical manifestations probably reflect the immunologic response resulting from widespread dissemination of *T. pallidum*.

Secondary syphilis has a vast variety of signs and symptoms. Most commonly encountered clinical presentation is generalized, non-pruritic papulosquamous eruption. The rash is very characteristic; however, in one series of 105 patients with secondary syphilis, more than 20% of the patients did not notice their lesions [19]. It is a diffuse, symmetric macular or papular eruption involving the entire trunk and extremities, including the palms and soles (**Picture 3** and **4**). Involvement of the palms and soles is an important clue for the diagnosis of secondary syphilis [20]. Individual lesions are discrete copper, red, or reddish-brown and measure 0.1–2 cm in diameter, with or without scales. (**Picture 5**) Pustular syphilis can be seen as small pustular syphilis, large pustular syphilis, flat pustular syphiloderm, or pustular-ulcerative syphilis. Superficial, painless aphthae-like lesions or gray plaques may be observed in mucosal areas. Large, raised, gray to white lesions called "condylomata lata" are often observed in the



Picture 3. Symmetrical plantar eruptions of secondary stage syphilis.



Picture 4. Red to brownish papules on the extensor face of extremities, in secondary stage disease.

moist mucosal regions of the anogenital area or the mouth. These lesions occur most often in areas near to the primary chancre and may show direct spread of organisms from the primary ulcer. Malignant syphilis (lues maligna) is a rare entity with disseminated chancre-like lesions, particularly observed in case of immunodeficiency states such as AIDS [21]. Additional clinical findings include annular or figurate plaques with central hyperpigmentation on the face; non-scarring and reversible "moth-eaten" alopecia on the scalp, eyebrows, or beard; granulomatous nodules and plaques, or crusted necrotic lesions. Lesions resolve over weeks to months without treatment, except for lues maligna. Occasionally, about 20% of untreated patients experience relapsing episodes of secondary syphilis, which can occur for up to 5 years after their initial infection.

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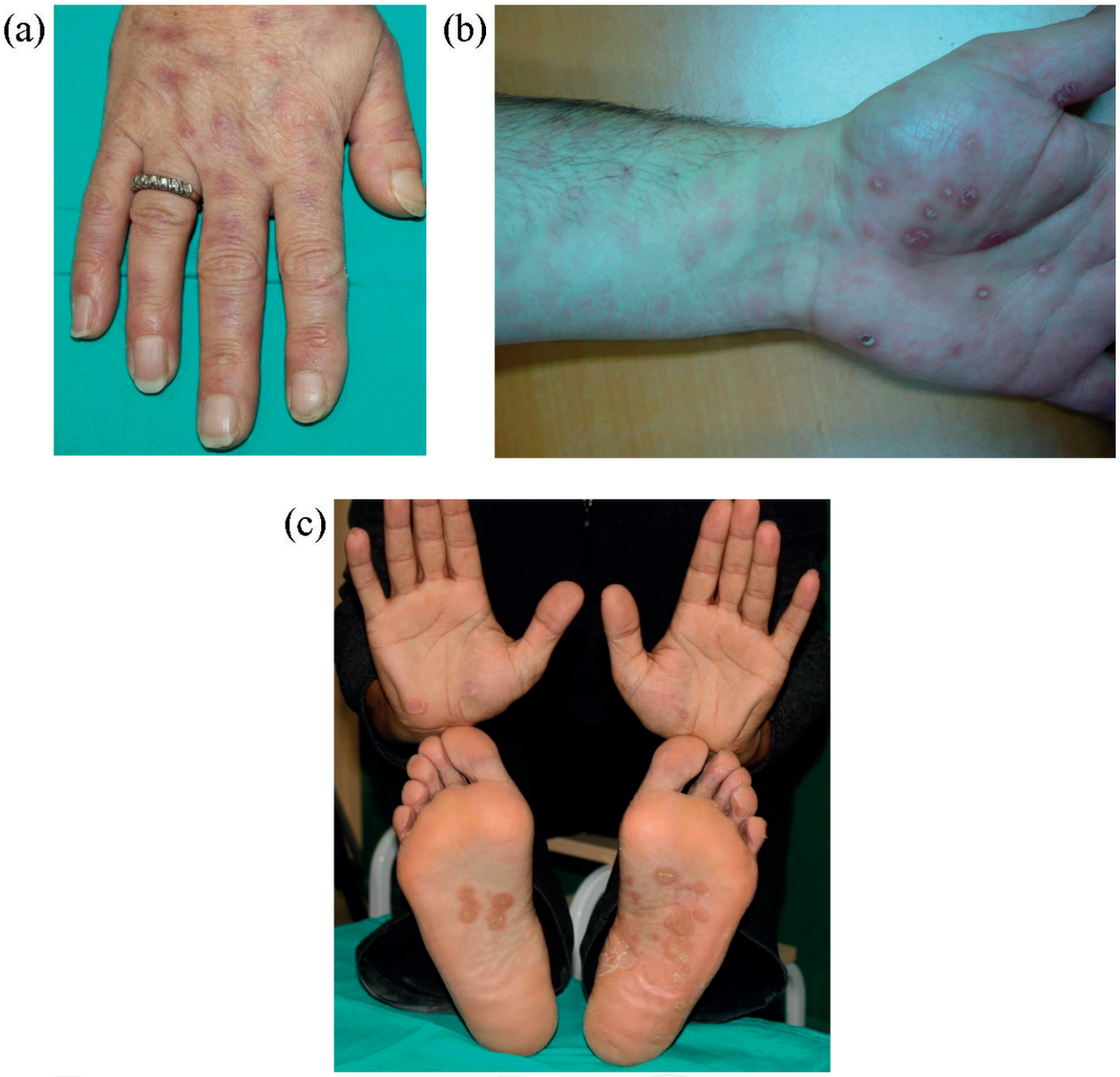

Picture 5. Brown to purple macules and papules, scattered in flexor or extensor face of distal extremities.

Most patients with secondary syphilis have lymph node enlargement with palpable nodes present in the posterior cervical, axillary, inguinal, and femoral regions. Epitrochlear lymphadenopathy is particularly characteristic for the diagnosis. These nodes are generally minimally tender, firm, and rubbery in consistency. Systemic findings of secondary syphilis include syphilitic hepatitis, extensive ulceration of gastrointestinal tract, synovitis, osteitis, periostitis, transient albuminuria, nephrotic syndrome, or acute nephritis with hypertension and acute renal failure [22, 23].

For the detection of secondary syphilis, dark-field examination of serous exudates from skin or mucosal lesions could be performed. On the other hand, serological tests are more useful at this stage. Cardiolipin and specific antibodies are always positive in patients with secondary

syphilis, except for a temporary negative non-treponemal test in case of prozone phenomenon or HIV infection.

4.3. Latent syphilis

After a period of 3–12 weeks, untreated secondary syphilis typically resolves spontaneously, followed by an asymptomatic state called latent syphilis. The diagnosis at this stage can only be made based on a positive serology. About 90% of relapses occur within the first year, referred as early latent stage. After 1 year, the patients enter the late latent stage, lasting for months to years.

About one-third of infected individuals have a nonreactive RPR test and no reactivation for the rest of their lives, and only the specific antibody assays (e.g., MHA-TP, FTA-ABS) remain positive. For another one-third of patients, antibodies against cardiolipin (e.g., RPR, VDRL) persist together with a positive MHA-TP or FTA-ABS assay without any symptoms. The remaining one-third, however, progresses to tertiary syphilis. For the cases without any medical history regarding the presence of clinical symptoms in the past weeks or months and previous treatments, differentiation between early and late latency is not possible. This group of patients is accepted as having late latent syphilis. This distinction is particularly important because patients with late latent disease are not considered infectious to their recent sexual contacts since they do not have lesions that can transmit disease. In contrast, patients with early latent syphilis may have transmitted *T. pallidum* to their sexual partners through lesions that were recently active, but are no longer present. Differentiating early from late latent disease also has implications for treatment approaches. Response of latent syphilis to treatment is indicated by a decline in the RPR or VDRL titer.

4.4. Tertiary (late) syphilis

Approximately 25–40% of patients with untreated syphilis can develop late disease, and symptoms may appear at any time from 1 to 30 years after primary infection [24]. Tertiary syphilis has a variable range of manifestations that appear months to years after initial infection. Involvement of the skin, bones, CNS, heart, and major vessels is pathognomonic. Half of the patients with tertiary syphilis develop only gummatous lesions, while the remaining have either cardiovascular disease or neurological manifestations. A confirmed case of late syphilis with clinical manifestations requires the demonstration of *T. pallidum* in late syphilitic lesions by special stains, polymerase chain reaction, or equivalent direct molecular methods. A probable case is diagnosed when characteristic abnormalities or lesions are noted along with a reactive treponemal serological test. All patients with a suspicion of tertiary syphilis should undergo lumbar puncture and CSF examination for detection of neurosyphilis.

4.4.1. Gummatous syphilis

The most common feature of late syphilis is gummas, which are locally destructive lesions in the skin, bones, liver, and other organs. The gummas in the skin are nodular or nodulouloulcerative granulomatous lesions with a round, irregular, or serpiginous shape, remaining for

weeks to months, and eventually heal with scar tissue. A subcutaneous gumma may become necrotic, resulting in ulceration of the skin or mucous membranes as well as destruction of underlying bones. Gummatous lesions of the bones are usually accompanied by periostitis and osteitis. Clinical manifestations include pain, swelling, and limited range of motion. Other sites that can be affected by gummas include the tongue and oral cavity, upper respiratory tract, myocardium, and gastrointestinal and nervous systems.

4.4.2. Cardiovascular syphilis

Cardiovascular syphilis has a late onset, with a latent period of 15–30 years. During the early stage of the disease, vasa vasorum of the proximal aorta is affected, and transmural inflammatory lesions leading to endarteritis of the vessels develop. The disease typically involves the ascending thoracic aorta resulting in dilatation and aortic valve regurgitation. Vasculitis of the vasa vasorum leads to weakening of the wall of the aortic root [25]. The onset is insidious, and most patients present with an asymptomatic murmur or with left heart failure. Syphilis may also involve the coronary arteries, resulting in narrowing and thrombosis.

4.4.3. Neurosyphilis

Neurosyphilis is the infection of the central nervous system by *T. pallidum*, and although it is typically a manifestation of tertiary syphilis, it can occur at any stage of the disease. It was common in the pre-antibiotic era, occurring in 25–35% of patients with syphilis; however, nowadays, it is most frequently seen in patients with HIV infection [26–28]. Within this group of patients, lower peripheral CD4+ T cell counts are closely linked to have symptomatic neurosyphilis [29]. Early in the course, the disease involves cerebrospinal fluid, meninges, and vasculature, while later on brain and spinal cord parenchyma are also affected.

4.4.3.1. Early neurosyphilis

The disease process begins with the invasion of the cerebrospinal fluid; however, this does not always result in persistent infection, and spontaneous resolution may occur after transient meningitis. Failure to clear organisms from the CSF results in "asymptomatic neurosyphilis," and individuals with this form of neurosyphilis are at risk for subsequent forms of symptomatic neurosyphilis [30]. The diagnosis of asymptomatic neurosyphilis is based on the identification of CSF abnormalities, including a lymphocytic pleocytosis, elevated protein concentration, and a reactive CSF-VDRL. Patients with asymptomatic neurosyphilis, regardless of CSF-VDRL reactivity, should be treated for neurosyphilis to prevent progression to symptomatic disease. Symptomatic meningitis occurs mostly within the first year after infection, and patients may have headache, confusion, nausea and vomiting, and stiff neck. Visual acuity may be impaired if there is concomitant uveitis, vitritis, retinitis, or optic neuropathy. The CSF abnormalities are more severe than those seen in asymptomatic meningitis. Cerebrovascular syphilis is, on the other hand, an infarction secondary to syphilitic endarteritis, which can result in hemiparesis or hemiplegia. This form of neurosyphilis may present as an ischemic stroke in a young person.

4.4.3.2. Late neurosyphilis

Parenchymatous neurosyphilis is observed at this stage, which is due to the direct invasion of the cerebrum by treponemes. General paresis and tabes dorsalis are the hallmarks of late neurosyphilis, and if untreated it can progress to death. General paresis (paretic neurosyphilis) is a progressive condition, usually developing 10–25 years after the infection. Initial findings include deficits in memory, judgment, and personality changes, and severe dementia may be seen in progression [31]. Common abnormal neurological findings include dysarthria; facial and limb hypotonia; intentional tremors of the face, tongue, and hands; and reflex abnormalities. Tabes dorsalis is a disease of the posterior columns of the spinal cord and dorsal roots. It has the longest latent period between primary infection and onset of symptoms with the interval averaging about 20 years. Most frequent symptoms are sensory ataxia and lancinating pains, which are sudden pain attacks affecting the limbs, back, or face. Pupillary irregularities are among the most common signs in patients with tabes dorsalis, and the Argyll Robertson pupil accounts for approximately half of these. Diplopia, loss of vibratory and position sense, reduced reflexes in the legs, ataxia, and sphincter dysfunction are other symptoms of tabes dorsalis.

In patients with known syphilis, a lumbar puncture with CSF examination should be performed if neurologic or ophthalmic signs or symptoms appear in any stage of the disease, if there is evidence of active tertiary syphilis affecting other parts of the body, and if there is a treatment failure including the failure of serum non-treponemal tests to fall appropriately. In addition to the clinical findings, the diagnosis of neurosyphilis is based upon reactive blood and CSF serologies, which are almost always positive with elevation of pressure, protein concentration, and immunoglobulin levels as well as a mononuclear pleocytosis. The presence of specific antitreponemal antibodies in the CSF is mandatory, but the specificity is low since IgG antibodies can diffuse into the CSF or result from contamination of the CSF by blood. CSF to serum IgG ratio divided by CSF to serum albumin ratio gives the CSF-IgG index, and a value of greater than 0.7 indicates IgG synthesis in the brain due to local inflammation. The presence of nonspecific antibodies, e.g., a positive VDRL test or RPR assay in CSF, is observed in most cases.

4.5. Congenital syphilis

Congenital syphilis occurs when the spirochete *T. pallidum* is transmitted from a pregnant woman to her fetus. Infection can result in stillbirth, prematurity, or a wide spectrum of clinical manifestations, and only severe cases are clinically apparent at birth. If a child has physical, laboratory, or radiographic signs of congenital syphilis and was born to a mother with untreated, inadequately, or suboptimally treated syphilis, this condition is defined as congenital syphilis. It is a significant public health problem, complicating an estimated one million pregnancies per year throughout the world [8]. Most cases develop because the mother received no prenatal care or treatment for syphilis before or during pregnancy. Among women with untreated early syphilis, 40% of pregnancies result in spontaneous abortion [32]. Congenital syphilis is generally acquired through transplacental transmission of spirochetes

in the maternal bloodstream or, occasionally, through direct contact with an infectious lesion during birth [33].

4.5.1. Early congenital syphilis

Infants generally present with symptoms during the neonatal period or within the first 3 months of life. Typical manifestations are cachexia and skin lesions similar to those of acquired secondary syphilis. Bloody or purulent mucinous nasal discharge, perioral and perianal fissures, anemia, thrombocytopenia, syphilitic pneumonitis, hepatitis, nephropathy, lymphadenopathy, and hepatosplenomegaly may also be observed. Osteochondritis of skeletal bones may result in pseudoparalysis of Parrot due to reduced movement of the extremities due to pain.

4.5.2. Late congenital syphilis

This clinical entity of childhood or adolescent period corresponds to tertiary syphilis in adults. In about one-third of children, an interstitial keratitis is seen; this finding together with typical dental abnormalities (Hutchinson's teeth) and neural deafness forms the Hutchinson triad.

The initial evaluation for congenital syphilis in infants and children should include a quantitative VDRL or RPR titer, physical examination for evidence of congenital syphilis, dark-field microscopic examination or direct fluorescent antibody staining of suspicious lesions or body fluids, and, for newborns, pathologic examination of the placenta and umbilical cord with specific fluorescent antitreponemal antibody staining. IgG antibodies which are present in the bloodstream of the child may have been acquired transplacentally from the mother. A serum titer for a non-treponemal test that is fourfold higher than the mother's titer is suggestive of infection, but infected neonates may have lower titers. FTA-ABS-19S-IgM test to detect 19S-antibodies and IgM-capture ELISA test have high sensitivity for these cases. Additionally, detection of spirochetemia by PCR can improve the sensitivity of the diagnosis of congenital syphilis in neonates. In late congenital syphilis, diagnosis is based on clinical findings in association with reactive serologic tests.

5. Syphilis and pregnancy

Syphilis remains an important health concern for women at childbearing age. Failure to detect or adequately treat maternal disease often results in serious consequences for the fetus. Clinical features and diagnostic approaches are similar to normal population. All pregnant women should be screened for syphilis at the first prenatal visit, and the test should be repeated during the third trimester (28–32 weeks of gestation) and again at delivery in women who are at high risk for syphilis. Vertical transmission of syphilis can occur at any time during pregnancy and at any stage of the disease. Treatment of maternal syphilis at least 30 days before delivery is the most important factor influencing the risk of congenital infection. Penicillin remains the gold standard for the treatment of syphilis in pregnant patients as well.

Penicillin desensitization is indicated for infected pregnant women with documented penicillin allergy as alternative drugs are not as safe or effective as penicillin.

6. Syphilis and HIV

Genital ulcerative diseases, such as syphilis, can increase the risk of both sexual and perinatal HIV transmission [34]. This is mostly because of the lack of an epithelial barrier due to ulceration of the skin or mucous membranes, large numbers of macrophages and T cells with receptors for HIV, and production of cytokines by macrophages stimulated by treponemal lipoproteins. Patients with HIV are at increased risk for neurosyphilis, especially if they have a CD4 count <350 cells/ml and/or a RPR titer of ≥1:32; however, unless neurologic symptoms are present, CSF examination in HIV patients has not been associated with improved clinical outcomes [35]. Clinical manifestations of syphilis and treatment approaches are similar for HIV-infected and HIV-noninfected patients; however, serologic responses appear slower in these patient groups.

7. Workup and laboratory diagnosis

Patients presenting with suspicious signs and symptoms of syphilis, pregnant women, commercial sex workers, sexually active men who have sex with men, and HIV-infected individuals should be routinely screened for syphilis. All patients with positive syphilis serology should also be tested for HIV infection.

The diagnosis of syphilis is based on the direct detection of treponemes or treponemal DNA by microscopy or molecular biologic techniques as well as various serologic tests. There are two types of serologic tests for syphilis: against cardiolipin (non-treponemal tests) antigens and treponemal antigens (treponemal tests). These tests rely upon a humoral immune response to infection. Thus, the use of serologic testing may be limited in patients with advanced immunosuppression or early disease.

7.1. Direct detection of *T. pallidum*

T. pallidum cannot be routinely cultured in vitro; thus, microscopic examination or molecular assays are used to detect the microorganism directly. With careful collection of serous fluid containing specimens, movement of spirochetes can be visualized by dark-field microscopy. Direct fluorescent antibody (DFA) testing can be also used to detect the organism; however, neither of these complex tests is routinely performed nor available in clinical settings. Alternatively, some laboratories have developed polymerase chain reaction (PCR)-based assays to detect *T. pallidum* DNA target sequences from clinical specimens. According to various studies, the sensitivity and specificity of PCR method from lesional specimens are relatively high, up to 95 and 98%, respectively [36–40]. However, PCR tests are not suitable for

screening asymptomatic individuals, since the sensitivity of PCR testing tends to be much lower in blood and cerebrospinal fluid specimens (approximately 24–32%) [36].

7.2. Non-treponemal tests

They are based upon the reactivity of serum from infected patients to a cardiolipin-cholesterol-lecithin antigen and include venereal disease research laboratory (VDRL), rapid plasma regain (RPR), unheated serum reagin (USR), reagin screen test (RST), and toluidine red unheated serum test (TRUST). All these tests measure IgG and IgM antibodies against this lipoprotein-like material released from damaged host cells and treponemes. Titers of these antibodies correlate with disease activity and are used for screening and monitoring the treatment. These quantitative tests are performed even in case of a positive dark-field examination, to obtain a baseline for the follow-up of the treatment process. A fourfold decrease in the antibody titer indicates successful treatment, while a fourfold increase indicates relapse or reinfection. In the case of early and efficacious treatment, non-treponemal assays usually become negative over time. Although these screening tests are nonspecific, and therefore not definitive, they have traditionally been used for initial syphilis screening due to their relatively low cost and ease of performance.

7.3. Treponemal tests

The major indication for treponemal tests is confirmation of reactive non-treponemal tests. However, nowadays, they have been automated, with fast and easy use, and as a result, these tests are increasingly used as an initial screening test rather than as confirmatory tests. They are based upon the detection of antibodies directed against specific treponemal antigens and thus tend to be more specific than non-treponemal tests. The sensitivity varies with the stage of syphilis: between 70 and 100% in primary syphilis, 100% in secondary and latent syphilis, and about 95% in late syphilis [41]. Treponemal tests are qualitative only and are reported as "reactive" or "nonreactive." These tests cannot differentiate between antibodies to *T. pallidum* and other treponemes or spirochetes, and they generally remain positive for lifetime; thus, they are not used for monitoring the response to treatment.

T. pallidum hemagglutination assay (TPHA), micro-hemagglutination assay for *T. pallidum* (MHA-TP), and *T. pallidum* particle agglutination (TPPA) tests: these tests measure antibodies directed against surface proteins of *T. pallidum* attached to rabbit erythrocytes as antigen carriers. Positive result shows previous or active syphilis but disease activity cannot be determined.

Fluorescent treponemal antibody absorption (FTA-ABS): This test shows the reaction of serum and whole treponeme and forming of antigen-antibody complexes with the help of fluorescein isothiocyanate. IgM and IgG can be selectively differentiated.

FTA-ABS-19S-IgM test: Fraction of IgM antibody is measured, with a higher specificity. This test is used for differentiation of relapsing disease from reinfection or in case of congenital syphilis.

*S*olid-phase hemadsorption assay (SPHA) or IgM ELISA: This test is used for the detection of specific IgM antibodies that attach to the solid phase of microtiter plates by reacting with the treponemal antigen on rabbit erythrocytes as antigen carriers. IgM antibodies can also be measured by the ELISA technology. They are used for the diagnosis of congenital syphilis, neurosyphilis, and reinfection.

T. pallidum enzyme immunoassay (TP-EIA)

In late 2014, the US Food and Drug Administration granted a Clinical Laboratory Improvement Amendments waiver permitting the use of a rapid (10-minute) finger-stick treponemal-based antibody test called the Syphilis Health Check (SHC) [42]. But exact sensitivity and specificity of this test have not been established yet. In **Table 1** types and different properties of both treponemal and non-treponemal tests are summarized.

Serologic testing to diagnose syphilis should include the use of both non-treponemal and treponemal tests [43]. Traditional serologic testing algorithms for syphilis involve initial screening with a non-treponemal test. A reactive result is then confirmed with a treponemal test, such as FTA-ABS. If the non-treponemal test is negative and patient is asymptomatic, no further testing is necessary. If both tests are reactive and the patient has no history of previous disease, the results are consistent with a new infection, and appropriate treatment should be prompted. However, for patients with a history of treated syphilis in the past with positive treponemal and non-treponemal results, the need for treatment depends upon the patient's clinic and the non-treponemal titer. This may indicate a new infection, an evolving response to recent treatment, treatment failure, or the presence of a serofast state. In case of a new infection, non-treponemal test reveals a fourfold or greater increase in titer from the individual's prior posttreatment test. If the patient has persistently reactive but low titer

Treponemal tests		**Non-treponemal tests**	
• *Treponema pallidum* hemagglutination assay (TPHA) • Micro-hemagglutination assay for *Treponema pallidum* (MHA-TP) • *T. pallidum* particle agglutination assay (TPPA) • Fluorescent treponemal antibody absorption (FTA-ABS) • FTA-ABS-19S-IgM test • Solid-phase hemadsorption assay (SPHA) • IgM ELISA • *T. pallidum* enzyme immunoassay (TP-EIA)	• Possible false negativity in early-stage disease • May remain positive for lifetime • Not useful for monitoring treatment response • Possible false positivity (autoimmune diseases, HIV infection, hypergammaglobulinemia) • High sensitivity and specificity	• Venereal disease research laboratory (VDRL) • Rapid plasma regain (RPR) • Unheated serum reagin (USR) • Reagin screen test (RST) • Toluidine red unheated serum test (TRUST)	• Possible false negativity in early-stage disease • Useful for monitoring treatment response • May become negative with early treatment • Possible false negativity (prozone phenomenon, HIV) • Possible false positivity (pregnancy, autoimmune diseases, drug use, lymphomas, malaria, vaccinations, cirrhosis, antiphospholipid syndrome) • Low cost and ease of performance

Table 1. Serological tests for diagnosis of syphilis.

non-treponemal test despite adequate treatment, it is considered as a serofast state. All other cases are regarded as treatment failures and should be retreated properly.

Alternatively, a popular novel approach uses treponemal tests such as TP-EIA as a screening method, followed by a non-treponemal test for confirmation. With this reverse order, there is an increase in false positivity rates but also an increase likelihood of catching patients with very early or late latent syphilis.

In case of a positive but usually low titer non-treponemal test followed by a negative one during screening, the patient is generally considered to have a false-positive syphilis result. It is estimated that 1–2% of the United States population has false-positive non-treponemal test results [44]. False-positive tests may be observed during pregnancy, acute febrile illness such as endocarditis or rickettsial disease, recent immunization, autoimmune disorders (particularly systemic lupus erythematosus), intravenous drug use, chronic liver disease, and in case of HIV disease [41].

If the patient has a positive treponemal and negative non-treponemal test, clinical symptoms should be investigated, and treatment should be administered in case of a positive finding. However, if there are no clinical signs or symptoms and repeated treponemal test is also positive, treatment for late latent syphilis is recommended. Another possibility is false-positive treponemal test which can be seen in case of spirochetal infections, malaria, and leprosy [45].

Negative non-treponemal test together with possible clinical signs and symptoms may point out early syphilis, prior to antibody formation or can be due to prozone effect [46]. In such cases of early primary syphilis, fluorescent treponemal antibody absorption (FTA-ABS) is thought to be the most sensitive method. Prozone reaction is also a major cause of a false-negative non-treponemal test. High titers of antibodies, usually in secondary syphilis, interfere with clumping of antigen-antibody complexes and make the visualization of the agglutination impossible. This phenomenon is usually associated with pregnancy, HIV coinfection, and neurosyphilis [47].

8. Pathology

Ulceration and dermal infiltrate of plasma cells, lymphocytes, and histiocytes are observed in primary syphilis. Spirochetes may also be detected with Warthin-Starry stain. In case of secondary syphilis, dermal infiltrates can be perivascular, lichenoid, diffuse, or nodular, with necrotic or ulcerated epidermis. In tertiary syphilis, tuberculoid granulomas, endothelial swelling, and vascular proliferation are present together with plasma cells.

9. Differential diagnosis

For primary syphilis, all conditions causing genital ulcers should be taken into consideration. These most commonly include genital herpes, chancroid, lymphogranuloma venereum, Behçet's disease, and fixed drug eruption. In case of secondary syphilis, cutaneous findings may resemble viral exanthems, guttate psoriasis, pityriasis rosea, lichen planus, pityriasis lichenoides

chronica, maculopapular drug eruptions, or nonspecific nummular eczema. Recurrent aphthous stomatitis, oral lichen planus, herpangina, candidiasis, and hand,foot, and mouth disease should be considered in case of mucosal involvement. Genital mucosa findings of secondary stage may mimic HPV-related lesions such as condyloma lata, bowenoid papulosis, or squamous cell carcinoma. Gummatous lesions of tertiary syphilis can be mistaken for lupus vulgaris, leishmaniasis, deep fungal infections, mycosis fungoides, and sarcoidosis.

10. Treatment

A non-treponemal serologic test should be obtained before initiating therapy (preferably on the first day of treatment) to establish the pretreatment titer and adequacy of serological response. Parenteral penicillin G is the treatment of choice for all stages of the disease [16, 43, 48]. A penicillin level of >0.018 mcg/l is considered treponemicidal, and this level of antimicrobial should be present in serum and/or CSF [49]. The dosage and duration of treatment depend upon the stage of the disease. For patients without neurosyphilis, penicillin G benzathine is the preferred formulation, and it is given via intramuscular route. In case of penicillin allergy, rechallenging or desensitization can be tried initially. Alternative antimicrobial agents include tetracyclines and cephalosporins. Azithromycin should be used only if other agents are not available, because treatment failures due to macrolide-resistant *T. pallidum* have been reported [50, 51]. The CDC and International Union against Sexually Transmitted Infections (IUSTI) currently recommend that HIV-infected individuals receive the same syphilis regimens as HIV-negative patients. Stage of the disease and treatment options are summarized in **Table 2**.

10.1. Early syphilis

The goals of treatment are to prevent long-term adverse outcomes and reduce transmission. A diagnosis of early syphilis implies that *T. pallidum* infection occurred within the previous year and consists of primary, secondary, and early latent syphilis. A single dose of 2.4 million units of penicillin G benzathine (intramuscular) is the standard therapy for early syphilis [48, 50, 52]. No resistance against penicillin G has been reported up to now, and clinical cure rates are 90 to 100% for both HIV-uninfected and HIV-infected persons. First-line alternative to penicillin is doxycycline (100 mg PO twice daily), for 14 days. Oral amoxicillin (3 g) with probenecid (500 mg) can also be used, twice daily for 14 days. One to two grams of parenteral ceftriaxone for 10–14 days and a single 2 g dose of azithromycin are other alternatives [53–55]. *Jarisch-Herxheimer* reaction is an acute febrile reaction frequently accompanied by headache and myalgias within the first 24 hours of penicillin treatment and is most common among patients with early syphilis.

10.2. Late syphilis

This includes tertiary and late latent syphilis, with longer duration of treatment. Penicillin G benzathine (2.4 million units intramuscularly) once weekly for three weeks is the standard

	Clinical stage	Recommended treatment regimen	Alternative treatment regimen
Early syphilis	• Primary • Secondary • Early latent (acquired <1 year previously)	• Penicillin G benzathine 2.4 million units IM, single dose	• Procaine penicillin, 1.2 million units, for 10 days • Doxycycline 100 mg orally twice daily for 14 days • Ceftriaxone 1–2 g daily IM or IV for 10–14 days • Tetracycline 500 mg orally four times daily for 14 days • Azithromycin, 2 g orally, single dose • Amoxicillin 3 g plus probenecid 500 mg, orally twice daily for 14 days
Late syphilis	• Late latent (acquired >1 year previously or of unknown duration) • Cardiovascular and gummatous syphilis • Retreatment of primary, secondary, or latent syphilis after treatment failure	• Penicillin G benzathine 2.4 million units IM once weekly for 3 weeks	• Procaine penicillin, 1.2 million units IM for 20 days • Doxycycline 100 mg orally twice daily for 28 days • Ceftriaxone 2 g daily IM or IV for 10–14 days • Tetracycline, 500 mg orally for 28 days
Neurosyphilis	• Early neurosyphilis • Late neurosyphilis	• Penicillin G 3–4 million units IV every 4 hours (18–24 million units by continuous infusion) for 10–14 days • Penicillin G procaine 2.4 million units IM daily plus probenecid 500 mg orally four times daily, for 10–14 days	• If possible, patients allergic to penicillin should be desensitized and treated with IV penicillin • Ceftriaxone, 2 g IM or IV for 10–14 days

Table 2. Stage of the disease and treatment options.

therapy for late syphilis [43]. If the patient misses a dose or more than 14 days have elapsed since the prior dose, the course should be reinitiated [56]. Patients with gummatous or cardiovascular infection should have a CSF examination prior to therapy to assess for neurosyphilis. Administration of 40–60 mg of prednisolone daily for 3 days beginning 24 hours before treatment for any form of cardiovascular syphilis may be advised [57]. Alternative regimens for late syphilis include doxycycline (100 mg PO twice daily for 28 days) or ceftriaxone (2 g IV or IM daily for 10–14 days); however, as there are limited data on the efficacy of these regimens in late syphilis, close monitoring is mandatory [58].

10.3. Neurosyphilis

These patients should generally be treated with intravenous therapy due to the fact that higher doses are necessary to produce measurable cerebrospinal fluid levels of the drug [59]. Preferred regimen is IV penicillin G (3–4 million units IV every 4 hours or 18–24 million units per day by continuous infusion) for 10–14 days. If the patient has late syphilis, together with neurosyphilis, a single dose or three doses of penicillin G benzathine (2.4 million units IM) may be administered after this course of therapy, for longer duration of effect. If the patient is allergic to penicillin, desensitization or rechallenge is strongly advised, so that the standard IV regimen can be used instead of an alternative regimen. Procaine penicillin plus probenecid, ceftriaxone, oral amoxicillin with probenecid, or doxycycline are other alternatives with limited success rates.

11. Follow-up

Patients should be monitored clinically and with laboratory testing to ensure that they are responding appropriately to therapy. A fourfold decline in the non-treponemal titer, equivalent to a change of two dilutions, is considered as good response to therapy. In a systematic review that included data from 20 studies, a fourfold or greater decline in non-treponemal titers was associated with younger age, higher baseline non-treponemal titers, and earlier syphilis stage [60].

If non-treponemal titers do not decline fourfold or if there is a fourfold increase after initial decline, this is considered as treatment failure. Since drug resistance to penicillin has not been described, treatment failure is likely due to poor adherence with the treatment regimen, treatment with an alternative agent, immunocompromised status, or undiagnosed neurosyphilis. It is also important to distinguish this treatment failure from reinfection.

In patients with early syphilis, serologic testing should be performed 6 and 12 months following treatment and at any time if clinical symptoms recur. Patients with late syphilis should undergo follow-up serologic testing at 6, 12, and 24 months. In case of abnormal CSF findings, a CSF examination is recommended at a 6-month interval until cell counts are normal and the CSF-VDRL is negative.

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