BULLETIN OF STOMATOLOGY AND MAXILLOFACIAL SURGERY
Volume 21, N 8

DOI: 10.58240/1829006X-2025.21.-466

REVIEW ARTICLE

SYPHILIS: ETIOLOGY, EPIDEMIOLOGY, CLASSIFICATION, DIAGNOSIS, AND STANDARD THERAPIES.NARRATIVE REVIEW

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Received: *Aug 17. 2025;* ***Accepted:*** *Sep 7, 2025;* ***Published:*** *Sep 20, 2025*

ABSTRACT

Syphilis is a chronic venereal infectious disease and *Treponema pallidum* is the causative micro-organism. The transmission is by sexual contact, via transfusion of blood product, from the mother to fetus, and through the contact of infectious lesions with a break in the skin. Different periods of activity and latency, systemic dissemination, and sever complications in inadequately treated patients or patients that remain without treatment may occurs. In untreated patients, the progression through primary, secondary, latent, to tertiary stages can occur. Different arrays of tests are available for syphilis diagnosis, but can always be confirmed serologically. Since 1943 syphilis has been treated with penicillin, but syphilis still remains the most important health problem in the developing and developed areas. The present review gives an overview of syphilis, its epidemiological data, various clinical manifestations, different diagnostic methods and treatment approaches for every clinical type.

Keywords: Sexually transmitted diseases; Syphilis; Treponemal disease; Treponema pallidum

INTRODUCTION

The term syphilis was used in 1530, and also called 'lues' in Latin. It is infectious venereal disease and *Treponema pallidum* is the causative micro-organism. It is highly contagious systemic bacterial infection. After the contact, the incubation period is about 3 to 4 weeks, but it sometimes vary from 1 to 12 weeks, this depend on virulence and number of the micro-organism, and the host response. [1] Syphilis is characterized by different periods of activity and latency, systemic dissemination, and sometimes it may progress to a different severe acute complication [2] In case of untreated syphilis, it can progress from primary, secondary, latent, to the tertiary stages. Signs and symptoms are different from patient to others depending on the infection stages. The diagnosis can always be confirmed serologically with histopathological and immunohistochemical characteristic. [3]

Syphilis has been effectively treated with penicillin, but its prevalence has been increased in the world, and now considered a re-emerging disease mostly among patients bellow the age of 25 years, and mostly in middle and low-income countries. [4]

Its prevalence has also started to increase in Americas and Europe, and can occurs in patients with male to male sex. [5,6] Comparing with other countries, it has a relatively low percentage in Iraq, in which the infection occurs mostly in males and in the age group more than 50 years. [7]

The present review gives an overview of syphilis etiology, its epidemiological data, various clinical manifestations, different diagnostic methods and appropriate treatment approaches for each clinical form of patients with different syphilitic stages.

ETIOLOGY

The causative micro-organism of syphilis is a filamentous, anaerobic, highly mobile, gram-negative, spiral *Treponema pallidum*. The contact with an infected patient during sexual activity is the most common way of spread, and through blood products transmission, or donation of organ. The *Treponema pallidum* can also enter the person body through minor cuts in the mucous membrane or skin. It can also be pass to the babies from infected mother during childbirth or pregnancy. Generally, it is not possible to get infection through toilet seats, or sharing the eating utensils, because the treponema cannot live outside body and die very quickly.[8]

Syphilis is highly contagious in the primary, secondary and in the latent early stages.[9] During sexual activity treponema can inter the host by small abrasions in the mucus membrane or skin. Inside the epithelium, *Treponema pallidum* then multiplies and invades the blood stream and lymphatic vessels. Macrophages can participate in phagocytosis of the *Treponema pallidum*. But, the immune response of the host is insufficient to destroy all the pathogens. [10]

EPIDEMIOLOGY

In the world, nearly more than twelve million cases of syphilitic infection per year.[1] Other found, there are about six million new cases of syphilis every year in patients with age 15-49 years, and about 300000 neonatal and fetal deaths are caused by syphilis, and 215000 infants are with a high risk of early death. [4]

In Iraq, syphilitic deaths reached 137 or 0.09% of total deaths, with a mortality rate of 0.18/100000 people. [11] In the National Blood Transfusion, Baghdad city/Iraq, a total of 178,966 healthy blood donors were included in the study. Number of infected persons was 1233 (0.69%), 1208 (98%) for males and 25(2%) for females. [12] In Basrah, a study conducted between 2019 and 2021 on 197,898 blood donors showed that the syphilis seroprevalence rates was 0.38% in 2019, 0.47% in 2020, and 0.36% in 2021. with marked declined trend.[13] Other study among persons which planning to marry in Iraq/Baqubah city found that among 15135 couples with the age of 20 to 70 years, attending to blood Bunk-Teaching Hospital, only 22 persons were seen positive for syphilis. [7]

In Saudi Arabia, a cross-sectional research revealed that out of 1183254 studied persons only (0.45%) were found as seropositive for syphilis, 33 patients were non-Saudi; and 21 patients were Saudi, with 30 males, and 22 married from the total number. This research revealed that the percentage of the involved patients by infection was low among the studied population and more than half of the syphilis positive cases were foreigners.[14]

In Africa, the highest prevalence was seen, and the values were ranged from (0.2 to1.8) percent. [4] From 2015 to 2018, participants were shared in five surveys in Tanzania, Uganda, Ethiopia, Zimbabwe, and Zambia. The study revealed that (57·6%) of the participants were females, and (42·4%) of the participants were males. Population-based syphilis prevalence was 0·9% in Zimbabwe and Tanzania, 3·0% in Zambia, and 2·1% in Uganda. Nearly 1027615 participants had active syphilitic infection across the mentioned countries, and the syphilis incidence was higher among patients with HIV in Ethiopia than in Zambia.[15]

In United States, it was found an increase in syphilitic infection incidence. In 2000, there were 5973 reported cases (2.12/ 100000). Also, several cases were reported in 2016, 58.1% were among men which had sex with the infected men, 13.9% were seen in men which had sex with woman, 11.0% were seen in women, and 16.9% were seen in men without any data of sex partners. [16] In 2017, there were 3064 reported cases (9.5/100000). Rates of syphilitic infection are high in male with 16.9/100000 males in comparison to female patients, with 2.3 cases of males/100000 females.[17] In 2017, 918 reported congenital syphilis in new born babies with a rate of 23.3 cases/ 100000 of lived births.[18] Then the incidence increased from 1.26 patients/100000 in 2017 to 4.88 patients/100000 in 2022, then declined to 2.47 patients/100000 by 2024. [19] In Brazil, it affects mainly young adults and adolescents, ages of 15 to 25 years, but it also seen in other age groups. In this study, syphilis has no predilection for gender, racial, or socioeconomic class. [20] In HIV-positive patients, it was found that the prevalence was seen more than 300-times greater. [21]

In Europe, the syphilis prevalence was seen higher in southern and eastern areas than in western ones. The overall rate is six/ 10000 of the population. Syphilis was seen eight times higher in men than in women. Most of the infections were seen in patients of (25) years and older; The younger people which aged 15-24 years represented only 13% of the patients with syphilis. Nearly (62%) of the patients were seen in men to men sex. [22] Countries like Germany, Belgium and France showed increases more than 50% of the cases. The lowest reported percentage was seen in Croatia with one infected patient/ 100000 of the screened population, and the highest percentage was reported in Denmark with 13.7 infected patients/ 100000 of the screened population. [23]

Russia found that there was an increase in syphilis prevalence during 1978 to 1979 with 28 cases/100000 of the screened population. But the incidence rises to 263 infected patients/100000 in 1996 [24]. This may be due to a decline in economy. The travelling with other cities like china can also raise the incidence of syphilitic infection. [24,25]

In India, between 1980 to 2000, the congenital syphilis incidence was significantly decreased due to the good care in the prenatal period. [26] Among 250 patients in

Bengal, a study found that a significant decrease in the prevalence of syphilis from (10.8%) in (2004) to (3.6%) in (2008). [27] In 2015 a study found a significant decrease in rate of syphilis in North India, but a significant rise in rates were seen in drug users, HIV-seropositive patients, and pregnant women.[28] Ankita *et al* found that of the 78 syphilitic patients, 78.2% were males, 19.2% were females, and 2.6% were transgender, and most of them were young adults of 21 to 30 years. About 2/3 of the infected patients were married and about 1/3 of the cases had HIV infection. [29] In China, the incidence of syphilis has increased since 1990 to 2010, and was seen higher in urban areas, and in sex workers and in men with men sex. [30]

The rate of syphilitic infection among the low-risk groups in 2000 to 2005 were seen nearly (0.3–0.6%) while the rates in a high-risk groups were (7–15%). [31] Zeng *et al* research revealed that syphilis incidence in people with HIV was 18.6%. They also found that the syphilis the prevalence was less in women with HIV than that in men with HIV. [32]

CLASSIFICATION

A. Acquired syphilis:

Based on the time from its initial infection and the progression of the infection, it is classified into stages. The stages are:

Primary syphilis

Clinically, this stage manifested as painless indurated ulcerative chancre, nearly 2 cm in diameter, which appears about 10 to 90 days after the contact with infectious patient. Chancres are mostly seen on the vagina, penis, and rectum, but may also occur at any place in which the direct contact with the infectious areas occurs. [33] It started as macule, then papule, and then changed into round or oval red or greyish ulcer with indurated edges. Microscopically, it presents as ulceration of the mucosa, with a base of dense inflammatory infiltrate (Figure-1). Chancre can be associated with regional non-tender or tender lymphadenopathy.[34] In case of no treatment, after three to six weeks the primary lesion spontaneously resolves without any scarring. [33,34]

Secondary syphilis

In this stage, the manifestation occurs from (4 to 8) weeks after chancre emergence. Commonly the signs include macular skin rash seen on feet soles and hands palms (Figures-2 A, B). The lesions appear brown or red; and may appears similar to eczema or psoriasis us a scaly hyperpigmented lesion. [35]

In contrast to the primary syphilitic stage, the secondary syphilitic lesions of the oral cavity are painful, multiple, and associated with generalized painless lymphadenopathy, migraine, fatigue, fever, sore throat, and weight loss. [36]

The oral mucosa is usually affected by several clinical forms and called mucous patches[37], that appears as elevated plaques and sometimes become ulcerated and covered by white or a gray pseudo membrane (Figure-2C). Similar to the primary stage, the histopathological picture of the secondary stages usually demonstrates a focal ulcerations and dense lymphocytes and plasma cells infiltration in lamina propria. [38]

Latent syphilis

When the clinical signs of the secondary syphilis disappear, the latent stage started, which follows the untreated secondary stage. This latent stage is referring to infection in patients who have no clinical manifestations, but the syphilitic patients have a positive serologic test. [39]

Latent syphilitic infection is classified into two stages. The early latent syphilis is that which was acquired in the previous year. While the late latent syphilis is that which acquired more than one year prior. During the early stages, latent syphilis is contagious, but not during the late latent stage. Pregnant women in early or late stage, can transmit the infection to fetus and affect the brain, heart, nerves, bones, and other parts of the body.[40] Latent syphilis can stay for several years, and about (60%) of the untreated patients in the late latent stage can appears without any symptom. At this stage, in case of appropriate therapy is given, the progression from late latent syphilis to tertiary stage will be prevented. [41]

Tertiary syphilis

Tertiary syphilis appears in about 1/3 of the untreated syphilitic patients, after a period of several years. The symptoms vary from patient to patient and depend on the organs which are affected. [42]

Neurosyphilis causes damage to the central nervous system, potentially causing blindness, loss of co-ordination, dementia, stroke, numbness, deafness, trigeminal neuropathy, and paralysis.[43]

Cardiovascular syphilis can cause endarteritis and may cause aortic aneurysms, coronary-artery stenosis, aortic insufficiency, heart failure, myocarditis, and damage to heart valves. Gummatous syphilis is granulomatous destruction of different visceral organs, most commonly the liver. [43]

The oral complications are gumma development and syphilitic leukoplakia with a danger of oral squamous cell carcinoma. In general, gummas will emerge on the palate and tongue, parotid gland, and the alveolus. At first, gumma shows one or multiple swelling as a necrotic granulomatous lesion. Then the swellings form ulcerations, with zones of breakdown, with possible bone destruction, and palatal perforation (Figure -3A). The zones of ulceration tend to heal, the resultant scarring on the tongue can cause fissuring. [44]

Syphilitic leukoplakia (Figure- 3B) is white patch with a raised corrugated nonhomogeneous surface in oral mucosa. It cannot be removed and can become potentially

malignant. A relationship between oral squamous cell carcinoma and tertiary syphilis has been proposed for a long time. [45]

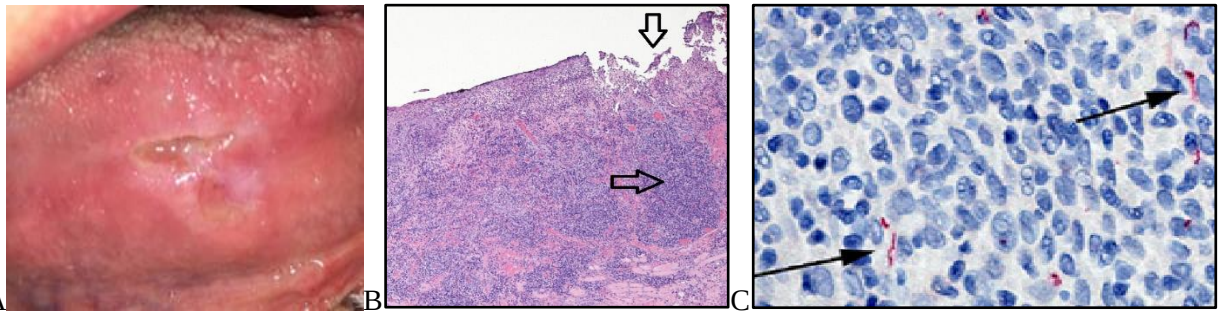


Figure 1. Patient with primary syphilis: (A) Ulceration on the surface of the tongue. Mucosal biopsy of patient with primary syphilis: (B) Exhibiting mucosal ulceration (upper arrow) overlying the lamina propria which contain a dense inflammatory infiltrate (lower arrow), 40x magnification. [46] (C) Treponema pallidum immunohistochemical stain (black arrows) revealed spirochetal organisms, 1000x magnification. [46]

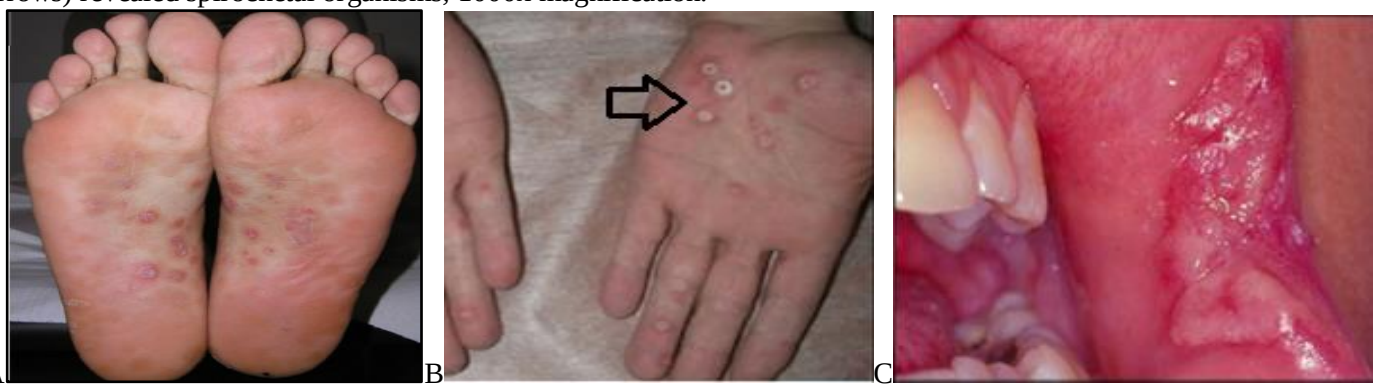


Figure 2. Patient with secondary syphilis: (A,B) Palmoplantar sites appears as red papules with a central scales, arrow. [38] (C) Mucous patches appear as a slightly elevated plaques, covered with a white pseudo membrane in the labial mucosa. [37]

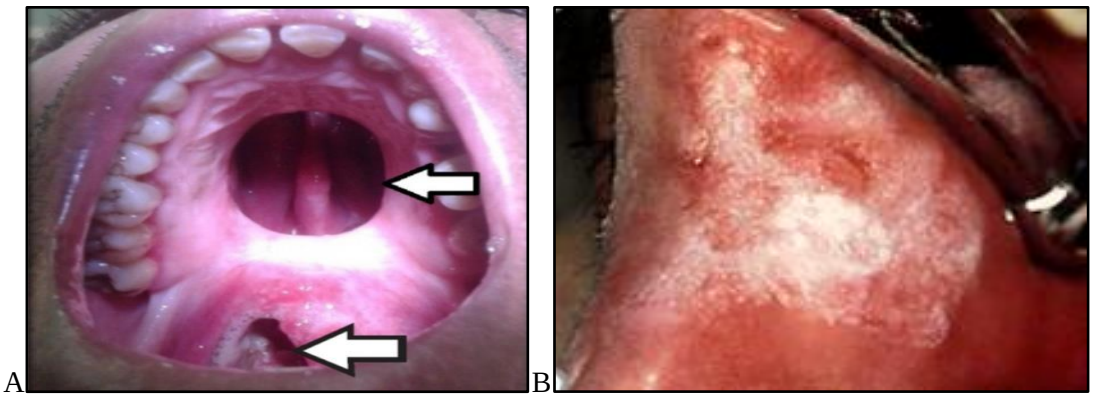


Figure 3. Patient with tertiary syphilis: (A) Palate showing two perforation due to destruction caused by syphilitic gummas [47]. (B) Clinical features of the leukoplakia-like form of oral tertiary syphilis [37].

A. Congenital syphilis:

Treponema transmission from the mother to the fetus causes congenital syphilis. Through transplacental or hematogenous routes, the transmission occurs. The transmission also can occur through the blood transfusions. Neonatal death, miscarriage or prematurity can occur if the transmission of *Treponema pallidum* is happened during the first trimester of pregnancy. [48]

If the transmission occurs in the second or third trimester of pregnancy, at birth, most of the infants from mothers with untreated syphilis may have no any laboratory or clinical evidence of *Treponema pallidum* infection, but they can

develop the manifestations several months or years later, if the syphilitic infection is untreated. [48] For this reason, the congenital syphilis can be classified into:

Early congenital syphilis

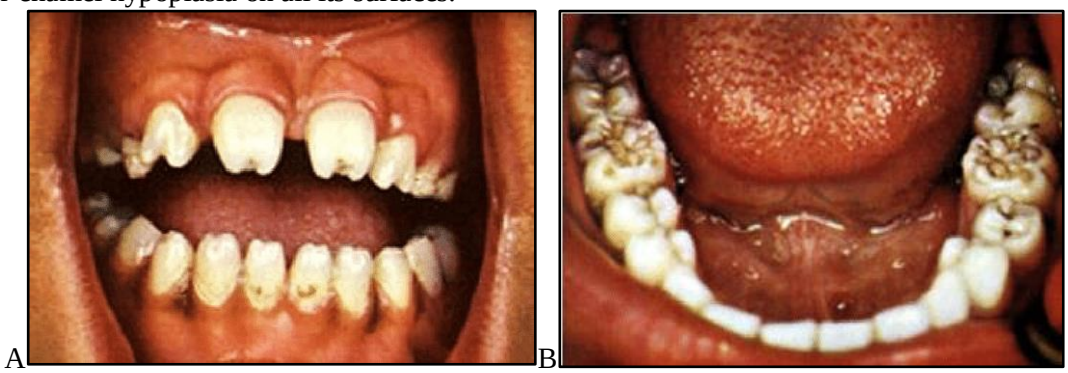
Clinically, the manifestations appear equal or less than two years of age, and include rash of the skin, cataracts, osteochondritis, splenomegaly, nephrotic syndrome, gastrointestinal malabsorption, pancreatitis, myocarditis, adenopathy, and hypopituitarism. [48]

Late congenital syphilis

Clinically, the manifestations appear more than two years of age, and include Hutchinson's incisors, Mulberry molars, seizures, atrophy of optic nerve, cranial nerve palsies, interstitial keratitis, hydrocephalus, bossing of frontal bone, short maxilla, saddle nose, high palatal arch, mandibular protuberant, and synovitis of the joints. Regarding the dental defects, they are mostly affecting the permanent incisors (Hutchinson's incisors) and first molars (Mulberry teeth) due to infection of the tooth buds by *Treponema pallidum* (Figure 4). Hutchinson's teeth and Mulberry molar may occur together. [49]

The incisors incisal edge clinically may have a notched edge, which is more common in the permanent maxillary central incisor than the lateral incisors, and on case this notch is not present and the tooth has a narrow incisal edge, the tooth is named a screwdriver incisor. [50,51] Mulberry molars contain multiple small enamel cusps associated with the permanent first molars. [49]

During pregnancy, all infected pregnant women must be treated, otherwise the born baby must be screened for the presence of the infection and treated. [51] Syphilitic canine is less frequently seen and the canines is usually exhibiting a linear enamel hypoplasia on all its surfaces. [49]



A B

Figure 4. Congenital syphilis (A) Notched screw driver shaped incisors. (B) Mulberry molars. [49]

DIAGNOSIS

Dermatologists mostly diagnose the syphilis by observing the clinical and sexual history, different laboratory investigations and sometimes radiology. The diagnosis of syphilis can be directly by microscopy, or indirectly by different serologic tests [33].

A. Direct diagnosis by microscopic observation

Darkfield microscopy

Treponema pallidum can only survive inside the body, so it is difficult to cultivated it by *in vitro* investigation. Direct diagnosis is done by detection of the micro-organism by dark field microscopy of *treponemal pallidum* in the serous exudate taken from a lesion which is a good specimens' sources for darkfield testing.[52] The *Treponema pallidum* is spiral-shaped organism that is 0.1–0.2 μm wide, and 6–15 μm long, and can be visualized only by darkfield microscopy which is useful for visualizing live, unstained *Treponema pallidum.* Dark field microscopy is a rapid method for detection of *Treponema*, especially in the early period of the primary syphilis, in which all the serological tests may be negative. It enhances contrast by illuminating the specimen at oblique angles, making the organism appear bright against a dark background. [52,53]

Histopathology

The histopathological characteristics of primary syphilis are nonspecific and characterized by the presence of ulcerations with a chronic inflammatory cells infiltration in lamina propria, so the biopsy and histopathologic examination must be always performed with the serologic test. In addition to that, the silver-based stains can highlight both the spirochetes and the melanin granules (Figure 5A) resulting in a difficulty in interpreting the images. [38]

Immunohistochemistry

Immunohistochemistry can be used to diagnose syphilis. It involves staining tissue samples with antibodies specific to *Treponema pallidum* to identify its presence. [54] Skin biopsy showed spirochetes in both epidermis and dermis; and shows a perivascular invasion in underlying connective tissue stroma (Figure- 5 B, C, D). [55]

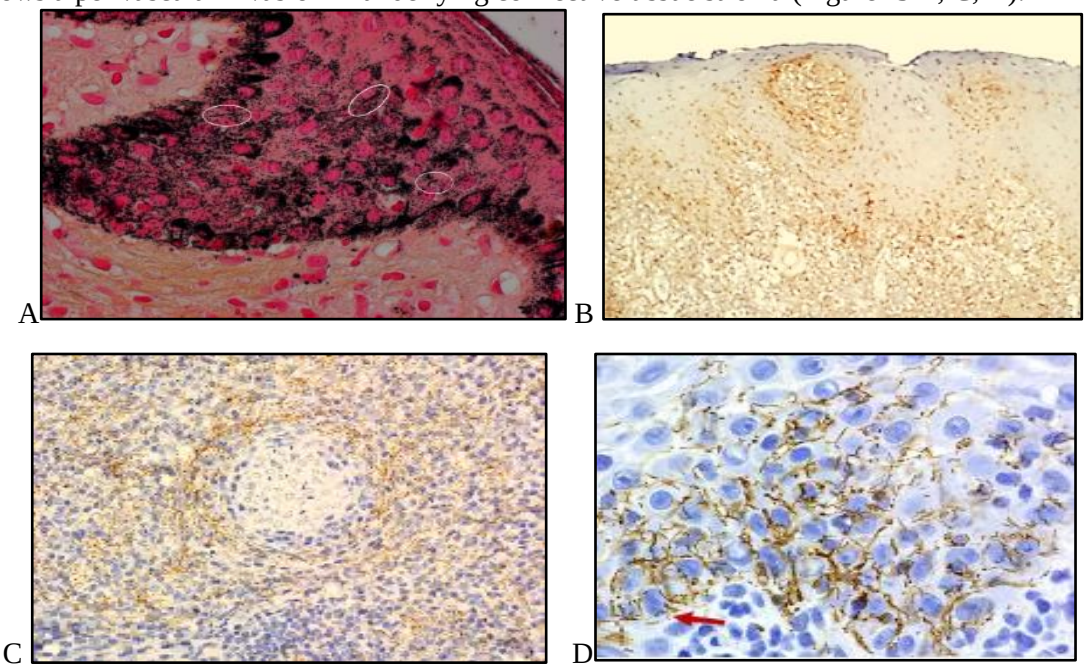


Figure 5 (A) Silver nitrate stain highlights the spirochetes as seen in the white circles and the melanin granules (400x magnification) [38]. (B) *Treponema pallidum* reveals positive staining in the epidermal-dermal junction (Immunohistochemistry ×100) [56], (C) *Treponema pallidum* surrounding blood vessels in the deeper stroma, (Immunohistochemistry ×400). [55] (D) Positive staining for coiled spirochetes (Immunohistochemistry x1000). [55]

Indirect diagnosis by serological tests

The two categories are, non-treponemal tests in which it detects the non-treponemal antibody, and treponemal tests for detection of specific treponemal antibody. [56]

Nontreponemal tests

These tests involve both rapid plasmas regain test and venereal disease research laboratory test. Both can detect the antibodies to lecithin, cardiolipin, and cholesterol as a measure of the tissue damage. In case of reactivity of the nontreponemal test, the laboratory assesses the amount of antibody as a titer. The titers monitoring can also use to assess the response to treatment. In successfully treated persons, this test becomes non-reactive in about three months. [57]

Treponemal tests

This measure the IgG and IgM which are the specific antibodies which works against *Treponema pallidum*. They are more more sensitive than nontreponemal tests during the early period of infection. The IgG and IgM are detected 14 days after infection. Some of the developed *treponema pallidum* tests are the fluorescent treponemal antibody absorption test, the *Treponema pallidum* particle agglutination test, and the *Treponema pallidum* hemagglutination test. More recent *treponema pallidum* assays are chemiluminescence immunoassay and enzyme immunoassay. [58]

Regardless of the stage, all the patients with syphilitic infection must undergo both the treponemal and the nontreponemal tests. Because every type of test has its limitations and may be insufficient for the diagnosis. Other medical conditions like autoimmune diseases, the false-positive nontreponemal test can be also associated; therefore, every patient with a positive nontreponemal test should also receive a treponemal test in order to confirm the diagnosis of infection. [59]

STANDARD THERAPIES

Once syphilis has been diagnosed, the treatment must be straightforward. The treatment is usually intra muscular benzathine penicillin, which is a long-acting form of the antibiotic. Benzathine penicillin G is the best recommended treatment for syphilitic infection in every stage. It inactivating an enzyme which is important for the *Treponemal* cell wall growth and repair. Without this enzyme, *Treponema* experience cell lysis from osmotic pressure. Assessment of the treatment efficacy, a follow-up with laboratory testing is required. [38]

Sexual partner in the last 90 days must be informed of the possibility of the infection and must be informed about the importance of evaluation for any sign suggestive of syphilitic infection complications. Treatment of the sex partners is important to decrease the risk of re-

infection.[60,61] The WHO (2016) recommendations treatment for syphilis infection are: [62]

- **In primary, secondary, and early latent stages of syphilis:** The recommended treatment is benzathine penicillin Gm 2.4 million units, IM in a single dose.
- **In late latent and tertiary syphilitic infection:** The recommended treatment is benzathine penicillin G, 2.4 million units, IM once a week for three weeks.
- **In tertiary syphilis after several years:** The recommended treatment is benzathine penicillin G, 2.4 million units, IM once a week for three weeks.
- **In neurosyphilis and ocular syphilis:** The recommended treatment is aqueous penicillin G, 18–24 million units /day, IV for 10–14 days.
- **In congenital syphilis:** The recommended treatment is aqueous benzyl penicillin, 100 000–150 000 units /kg/day, IV for 10–15 days.
- **In pregnant:** The recommended treatment is benzathine penicillin G, 2.4 million units, once IM in a single dose.
- **In the presence of benzathine penicillin allergy:** The recommended treatment is doxycycline,100 mg, orally twice daily for 14 days.

CONCLUSION

Syphilis is a bacterial contagious infection, caused by the gram-negative anaerobic bacteria named *Treponema pallidum* which transmitted by the direct contact with an infected patient during the sexual activity, transmission can also occur via blood products or organ donation. Nearly more than twelve million new cases per year in the world present. The epidemiology in Islamic countries is less than the others. The acquired syphilis is divided in to primary, secondary, latent, and tertiary stages, and the clinical manifestations and complications depend on the syphilitic stage. Congenital syphilis occurs if the *Treponema* is transmitted from the infected mother to the fetus. Syphilis diagnosis is by observing patient clinical and sexual history, directly by tissue microscopic examination, or indirectly by different serologic tests. Treatment is usually by intramuscular benzathine penicillin, but also depend on the condition of the patient. Follow-up by different laboratory testing is important to assess the treatment efficacy.

DECLARATIONS

Funding No funding to declare.

Conflict of interest

The authors declare no conflict of interest.

Authors' Contributions

All authors contributed equally to drafting the manuscript.

Competing Interests

The authors declare that they have no conflict of interest.

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