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Syphilis: A clinical perspective

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Abstract

Syphilis is a chronic sexually and vertically transmitted infection caused by *Treponema pallidum* subspecies pallidum, known for its varied clinical manifestations and ability to cross biological barriers. Prevalence is highest in Africa and low- and middle-income countries, with a resurgence in men who have sex with men in high-income countries. Syphilis has several phases: incubation (up to 90 days), primary phase, secondary phase, latent phase and tertiary phase. Primary syphilis begins with a painless chancre and regional lymphadenopathy. The secondary phase includes rash, fever and generalized lymphadenopathy. The latent phase is asymptomatic, and the tertiary phase may cause neurosyphilis and cardiovascular syphilis. Ocular and otic manifestations may also occur. Syphilis is diagnosed with serological tests: nontreponemal (RPR, VDRL) for initial diagnosis and monitoring, and treponemal (FTA-ABS, TPPA) for confirmation. Microscopy and PCR are also useful. In neurosyphilis, CSF is analyzed. Penicillin G is the treatment of choice for all stages of syphilis. Alternatives such as doxycycline are used in allergy sufferers. Prevalence has increased in certain groups, requiring additional strategies.

Keywords: Syphilis; Chancre; *Treponema pallidum*; Treponemal tests

1. Introduction

Syphilis is a chronic, systemic, sexually and vertically transmitted infection with multiple stages, caused by the spirochete *Treponema pallidum subspecies pallidum*. It is considered the most virulent subspecies, being the only one capable of crossing both the blood-brain and placental barriers (1). *T. pallidum* measures approximately 0.2um in diameter with a length ranging from 6 to 20um. Taking these measurements into account, they are not visible by light microscopy, but are better visualized by dark field microscopy or phase contrast microscopy. For many years, it has been called the "great impostor" or "great imitator" due to its varied clinical manifestations (1). It was first described in Europe in the early 16th century, suggesting its entry from North America by Columbus and his crew, but contemporary evidence suggests that it was more likely imported from Africa through contact with cases of yaws, as mentioned in 1679 by Thomas Sydenham (2). In 1906, the American Journal of Syphilis, Gonorrhea and Veneral Disease, identified the causative agent initially called Spirochaeta pallida.

2. Epidemiology

Currently, there are data from the WHO in 2012 where it estimates a prevalence of syphilis of 17.7 million adults between 15 and 49 years worldwide, and an estimated 6.3 million new cases in 2016 (2). The highest prevalence is recorded in Africa and more than 60% of new patient diagnoses occurred in low- and middle-income countries. High-income countries have a low prevalence of syphilis among heterosexual men and women, but a resurgence is being observed among men who have sex with men, especially associated with HIV infection (2). In the United States, the

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number of reported syphilis cases has increased since the early 2000s, with preliminary information for 2021 indicating that there were more than 171,000 cases of all stages of syphilis, representing a 68% increase from 2017 (3).

3. Etiology

Treponema pallidum subsp. pallidum is part of a family of spirochetes and is related to other pathogens causing non-venereal diseases such as *T. pallidum subsp. endemicum (bejel)*, *T. pallidum subsp. pertenue (yaws)* and *T. carateum (pinta)* with clinical and microbiological differences. It has a size that varies from 6 to 20 µm in length and is 0.2 µm in diameter with its characteristic endoflagellate spiral body surrounded mainly by its cytoplasmic membrane, and an external membrane stabilized by layers of peptidoglycan(4).

In part, the difficult research on its morphology and pathogenesis has been explained by its slow growth in traditional cultures due to the absence of the tricarboxylic acid cycle and an electron transport chain that implies an inefficient metabolism and replication in aerobic conditions; added to the fact that they are not tolerant to desiccation, and high temperatures explains why their infectious capacity is lost in a few hours or days and their efficient transmission requires close personal contact (5).

Despite these striking metabolic limitations, *T. pallidum* has virulence factors that grant sufficient competence to invade and survive in a wide variety of tissues and organs; among which are its corkscrew motility, chemotactic capacity mainly through the TpF1 protein that activates the IL-8 and TLR5 signaling pathway (6), its capacity for antigenic variation, low content of outer membrane protein, host component adhesion capabilities and its ability to cause damage through the Tp0750 and Tp0751 proteins that participate in the degradation of proteins, such as those involved in blood coagulation and the integrity of the basement membrane (7).

4. Risk factors

There are many risk factors for syphilis, the most frequently reported is infection by Human Immunodeficiency Virus (HIV), and being much more variable are other sociodemographic and clinical characteristics such as smoking, use of illicit drugs, number of sexual partners, single marital status, lack of fixed address, men who have sex with men; where their levels of association vary according to the selected population (8)(9).

The main risk factors in immunosuppressed patients due to human immunodeficiency virus infection has been described and are presented in **Table 1** (10).

Table 1 Risk factors in patients with HIV

Risk factor	**RR**
Age 18-30 years	1.33
Black race	1.62
MSM	3.11
Recent diagnosis	5.51
RR: Risk ratio MSM: Man who has sex with man HIV: Human immunodeficiency virus.	

5. Pathophysiology

Infection by *T. pallidum* initially consists of penetration of intact mucous membranes or injured skin, where it reaches the lymphatic system and spreads throughout the body via the bloodstream. At the site of inoculation, and when the concentration of bacteria reaches 10^7 CFU, the primary lesion of syphilis called chancre occurs, which is usually accompanied by locoregional adenopathy (11). The outer membrane of *T. pallidum* lacks lipopolysaccharides and has a phospholipid composition markedly different from the outer membranes of typical gram-negative bacteria; consequently, the lack of pathogen-associated molecular patterns (PAMPs) exposed in the surface allows the spirochete to avoid the host's innate surveillance mechanisms, facilitating local replication and early dissemination. Its limited surface antigenic capacity promotes evasion of adaptive immune responses, facilitating persistence (11). Transmission of venereal syphilis occurs during sexual contact with an actively infectious partner; exudate containing as few as 10 organisms can transmit the disease. Spirochetes enter mucous membranes directly or through abrasions in the skin,

which is less keratinized in the perigenital and perianal areas; they adhere to epithelial cells and extracellular matrix components; in this case, fibronectin and laminin are key substrates for these interactions (11). Spirochetes penetrate the extracellular matrix and intercellular junctions by “stop-and-go” movements that coordinate adherence with motility and are propelled by back-and-forth ondulating waves generated by flagellar rotation and presumably assisted by the proteolytic activity of the outer membrane protein TP0751 (palilysin) (11). Organisms are taken up by dendritic cells, which then travel to draining lymph nodes to present treponemal antigens to naïve B and T cells. Opsonic antibodies are subsequently produced that markedly enhance spirochete uptake and degradation by phagocytes, releasing lipopeptides and other PAMPs to bind to Toll-like receptors lining the inside of the phagosome and antigenic peptides for presentation to locally recruited T cells. These activated cells secrete gamma interferon (IFNy), which promotes clearance by macrophages but also enhances the production of tissue-damaging cytokines such as tumor necrosis factor and IL-6 (11).

6. Natural history

The natural history of the disease is classically divided into the following phases: 1) an incubation period that can last up to 90 days; 2) a primary phase, characterized by a chancre at the inoculation site, associated with regional lymphadenopathy; 3) a florid and disseminated phase (secondary syphilis), typically characterized by generalized rash, mucocutaneous lesions and lymphadenopathy that can affect any organ such as the central nervous system (CNS); 4) an asymptomatic latent period that can last for years and in which the disease is only detectable by reactive serological analysis, 5) one third of untreated people experience a tertiary reactivation phase that can affect the ascending aorta, cause neurosyphilis or granulomatous necrotizing lesions (gum) in any organ (1) (figure 1).

Syphilis being a chronic sexually transmitted disease, can manifest itself through different clinical stages, each of which manifests with a different set of symptoms that affect multiple organ systems (1).

7. Clinical manifestations

First, the primary syphilis, which typically begins 2 to 6 weeks after the initial infection is characterized by the appearance of the chancre. This is usually painless, with a clean base and indurated edges, and may be present at the site of exposure to *Treponema pallidum*, including the genital area, mouth, or perianal region. In addition, regional lymphadenopathy may be observed and spontaneously disappears if not treated, although the bacteria remain in the body, progressing to the next phase, which corresponds to secondary syphilis with onset between 2 and 8 weeks after the disappearance of the chancre and is characterized by systemic dissemination of the bacteria. Patients experience a generalized skin rash that notably affects the palms and soles, mucocutaneous lesions, fever, fatigue, generalized lymphadenopathy, patchy alopecia, and in some cases, mild hepatitis and nephritis. This stage is especially notable for the wide range of symptoms, justifying the term "great imitator," as it can be confused with several infectious or autoimmune diseases. Once the secondary manifestations subside, the infection becomes asymptomatic and enters the latent syphilis stage, in which it is only detected by serological tests. It is classified as early latent (less than one year since infection) and late (more than one year). Although symptoms are absent, the infection can reactivate, particularly in the early latent phase, and remains transmissible. Tertiary syphilis is the advanced stage that occurs in approximately one third of untreated patients and can appear 10 to 30 years after the initial infection. It is characterized by severe complications, such as neurosyphilis and cardiovascular syphilis. Neurosyphilis may involve tabes dorsalis, general paresis, and meningeal symptoms. At the cardiovascular level, it can affect the aorta and cause aneurysms or aortic insufficiency. In addition, inflammatory granulomas or syphilitic gummas may form in the skin and other organs, with the ability to cause significant tissue destruction. Immunocompromised individuals, especially those co-infected with HIV, are at increased risk for rapid progression and severe complications in early stages. Gummous syphilis is a manifestation of tertiary syphilis that affects the skin, skeleton, and other internal organs, producing destructive granulomas. Cutaneous gummas may ulcerate and cause deformities, while bony gummas may cause intense pain and compromise bone structure (12).

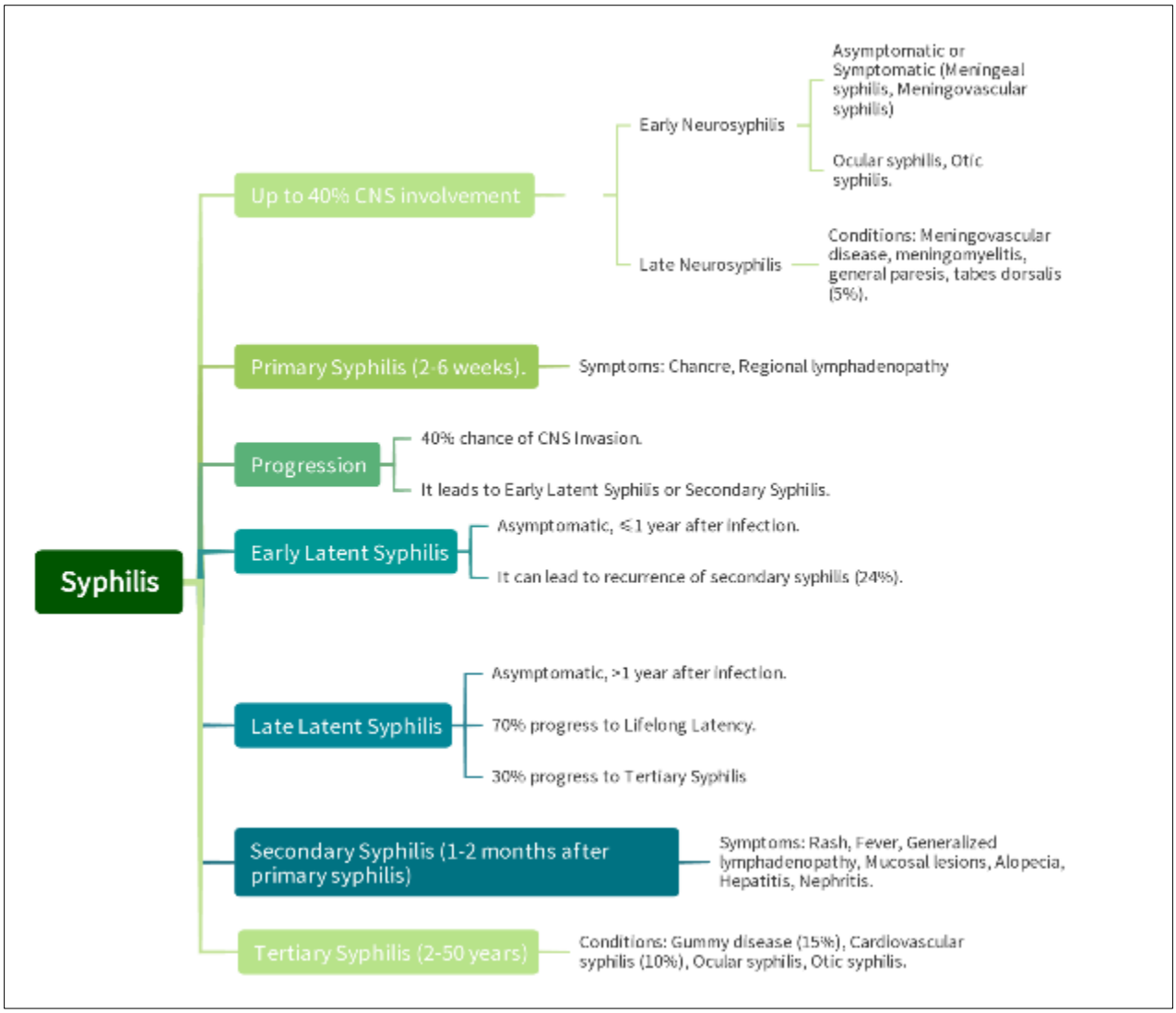

Figure 1 Natural history of the disease

There are also atypical manifestations such as ocular and otic involvement. Ocular syphilis can appear at any stage, and its presentations range from anterior uveitis, retinitis, and chorioretinitis to optic neuritis. Syphilitic uveitis is the most common manifestation and can progress to vision loss if not treated properly. Syphilitic otitis media is another rare presentation that can cause sensorineural hearing loss, tinnitus, or vertigo. Like ocular involvement, it can occur at any stage of the infection and tends to be bilateral (1).

8. Diagnostic approach

It relies primarily on serologic testing, due to the difficulty of culturing *T. pallidum*. There are two types of tests: nontreponemal and treponemal.

- **Nontreponemal tests (such as RPR and VDRL):** These tests detect antibodies that respond to lipids released from damaged cells during infection. They are valuable both for initial diagnosis and for monitoring disease activity and response to treatment, as antibody titers often decline after effective therapy. However, nontreponemal tests can give false positives in conditions such as autoimmune diseases or viral infections (12).
- **Treponemal tests (FTA-ABS, TPPA):** These tests detect specific antibodies against T. pallidum and, unlike nontreponemal tests, they usually remain positive for life. Treponemal tests are primarily used to confirm diagnoses of active or past infection, but are not useful for monitoring after treatment (12).

- **Darkfield microscopy and PCR:** darkfield microscopy allows direct visualization of treponema in exudates from active lesions such as chancre. Although PCR is not common in routine settings, it can be useful in the direct detection of the pathogen in syphilitic lesions (1).

In patients with suspected neurosyphilis, cerebrospinal fluid (CSF) analysis is essential, as this condition can appear at any stage of the disease and produce various neurological symptoms. Typical findings include pleocytosis, increased CSF protein, and in some cases, reactive CSF serologic tests (1).

By applying the above mentioned serologic studies we can make a diagnostic algorithm:

When starting by performing a treponemal test we will apply the reverse sequence algorithm, while when starting by performing a non-treponemal test we will apply the traditional algorithm. In high prevalence settings, a non-treponemal test (RPR or VDRL) is often started due to its low cost and ease of monitoring treatment response. (12)

8.1. Interpretation of the initial test

- **If the test is non-treponemal and is positive:** Proceed with a confirmatory treponemal test, such as FTA-ABS or TPPA, which has high specificity and confirms the diagnosis.
- **If the test is treponemal and is positive:** Continue with a non-treponemal test to obtain titers, which are used to monitor treatment. If the latter is negative, it could initially be considered a prozone reaction, which merits repeating a second and different treponemal test, which in case it is positive could be a case of treated or untreated syphilis of long standing and if it is negative, it could be a false positive (12).

When neurosyphilis is suspected, a lumbar puncture must be performed to evaluate the presence of pleocytosis and protein levels in the cerebrospinal fluid (CSF). A positive CSF for VDRL along with neurological symptoms confirms the diagnosis. In immunocompromised patients, such as those with HIV, a more exhaustive evaluation may be necessary due to the possibility of atypical presentations and rapid disease progression (12). As a follow-up after treatment, non-treponemal tests are used to monitor the effectiveness of treatment. A four-fold decrease in the titer (two dilutions) is indicative of an adequate response, while a persistent or increasing titer may suggest reinfection or therapeutic failure (1).

8.2. Treatment

Penicillin G remains the drug of choice for all stages of syphilis, given its proven effectiveness and the absence of significant resistance of *T. pallidum* to this antibiotic, unlike many other pathogenic bacteria (12).

- **Primary, secondary, and early latent syphilis:** For these phases, the standard recommendation is a single dose of 2.4 million units of intramuscular benzathine penicillin, which has been shown to be highly effective, regardless of the presence of HIV co-infection (12).
- **Late latent syphilis of unknown duration:** In these cases, a series of three doses of 2.4 million units of benzathine penicillin is indicated, administered at weekly intervals to ensure complete elimination of the bacteria and prevent progression to tertiary syphilis (12).
- **Neurosyphilis:** Infection in the central nervous system requires a more intensive regimen. Intravenous aqueous penicillin G (18-24 million units per day) is administered in divided doses every 4 hours for 10 to 14 days to ensure adequate levels of the drug in the CSF and to eradicate the pathogen (12).
- **Alternatives for penicillin allergy:** In allergic patients, especially those who are not pregnant, doxycycline (100 mg twice daily for 14 days) is an alternative in primary and secondary syphilis. For pregnant women with penicillin allergy, desensitization is recommended because of the unique effectiveness of penicillin in preventing congenital syphilis (12).

The sustained efficacy of penicillin in treating syphilis has been instrumental in controlling this infection worldwide. However, the prevalence of syphilis has increased in certain groups, especially among men who have sex with men (MSM) and people co-infected with HIV, suggesting the need for additional control and prevention strategies (12).

9. Severity and prognosis

The prognosis of syphilis depends largely on early detection and treatment. Without treatment, the disease can lead to severe and irreversible complications, such as neurosyphilis and cardiovascular syphilis, which can be life-threatening (13).

Neurosyphilis can present at any stage of the disease and may cause early or late neurological symptoms such as syphilitic meningitis, tabes dorsalis, and general paresis. Factors such as diplopia are associated with a poor prognosis in neurosyphilis (14)(15).

Ocular syphilis, although rare, can cause permanent vision loss if not treated in time. Early detection and appropriate treatment are crucial to prevent irreversible visual loss (16).

10. Conclusion

Syphilis, a sexually transmitted infection, remains a significant public health challenge. Early detection and appropriate treatment are essential to prevent serious complications such as tertiary syphilis and mother-to-child transmission.

Implementation of prevention, diagnosis, and treatment strategies that include sexual education, condom use, and regular testing in at-risk populations are fundamental measures today. In addition, the importance of treating sexual partners to prevent reinfection and spread of the disease is emphasized.

The standard treatment remains penicillin, which is highly effective when administered correctly. However, it is crucial to ensure universal access to and adherence to treatment, especially in vulnerable populations such as pregnant women and their partners.

In conclusion, a coordinated and sustained approach to combat syphilis should be proposed, prioritizing education, prevention and access to treatment to reduce its impact on public health.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflicts of interest.

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