A Review on the Diagnosis and Treatment of Syphilis

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Abstract. Syphilis is a multi-phase sexually transmitted disease through contacting with a partner infected by syphilis or from a gravida to her newborn congenitally. The reappearance of syphilis is a severe public health concern, particularly because syphilis lesions would boost the chance of acquiring and spreading human immunodeficiency virus (HIV) infection. A dose of benzathine penicillin G (BPG) through intramuscular injection is the current treatment for syphilis, which is the optimal treatment for all stages of syphilis. Although some alternatives such as doxycycline and ceftriaxone are also evidently effective, the optimal therapy is still BPG, especially in latent syphilis and pregnancy. Because of the clinically significant azithromycin resistance, this second-line medication is no longer used routinely. Currently, macrolide resistance is the only antibiotic resistance with clinical evidence. Even though still no vaccine is published for syphilis, syphilis is a promising disease for vaccine development. The vaccine for syphilis is currently under research. This paper contained information about the pathological process, symptoms, diagnosis of syphilis, and effective treatment using antibiotics. The review also discussed future vaccine directions.

Keywords: Syphilis, STI, Clinical Manifestations, Diagnosis, Treatment, HIV.

1. Introduction

One of the common sexually transmitted infection (STI) is syphilis, which is treatable and caused by bacterial pathogen. The re-emerge of syphilis occurred in recent years despite well-established treatment and preventative strategies. With more than 11 million new cases detected each year, syphilis remains a worldwide health issue [1]. Syphilis is caused by the spirochetal Gram-negative bacterium Treponema pallidum subspecies pallidum (\textit{T. pallidum}) [2]. \textit{T. pallidum} is considered a concealed pathogen due to its structural characteristic, with the absence of lipopolysaccharides and only a tiny amount of surface-exposed proteins on the outer membrane, which results in challenges for the immune system to control the infection. (Tudor et al., 2022) Syphilis is mainly transmitted via sexual contact, including vaginal, anogenital, and orogenital interactions. For venereal syphilis, which accounted for most of the new cases, the spirochetes can penetrate the mucous membrane, to which the \textit{T. pallidum} would adhere with the epithelial cells and extracellular matrix components [2]. Syphilis could also infect via vertical transmission during pregnancy. For congenital syphilis, caused by in utero transmission, spirochetes undergo transplacental passage, infecting the fetus around 9 to 10 weeks of gestation [2]. Other transmission routes include blood products and organ donations, which the transmission through non-sexual contact is infrequent, with only a few cases being recorded in the past [3].

Although the WHO indicates that more than 90% of syphilis diagnoses take place in low-income developing countries, a recurrence of the disease appeared in several economically developed countries, such as the UK, the US, Canada [4, 5]. Syphilis has had a considerable influence on several high-risk populations. In the United States, the incidence of early stage syphilis has increased more than three times from 2000s, owing mainly to a rise in male prevalence. Males accounted for 86 percent of all syphilis cases in 2018, and more than half of syphilis cases involved sex with men [6]. In the UK, the majority group of syphilis cases remains the men having sex with men (MSM) from 2011 to 2019 [7]. The rise in infected cases in the United States appears to be caused by many
sociodemographic factors. High-risk sexual behaviour occurs across persons due to a general decrease in concerns about infection mortality and overall confidence in the availability of therapy and cure [8]. The popularity of the epidemic and increased rates of methamphetamine use have most certainly contributed to the increase in STIs [9]. In addition, the reported incidence of the first two stages of syphilis among young women aging from 15 to 19 years increased by 34.4% between 2017 and 2018 [8]. The reproductive age group has the most significant prevalence of syphilis in women, which is 15-44. The rise in primary and secondary incidence in women is indicated by increasing congenital syphilis cases and infant mortality [10]. Youth, low socioeconomic level, insufficient prenatal care and drug addiction are potential risk factors for syphilis transmission during pregnancy [10]. Syphilis continues to become a public health issue worldwide, significantly since it raises the risk of developing and transferring HIV [5].

Clinical symptoms would appear during both phases of primary and secondary syphilis, and the infection could be diagnosed through serological testing. Luckily, treponema showed a sensitive response to penicillin, which antibiotic treatments could be used to cure the early stages of syphilis. The patient would undergo a tertiary phase if no treatment was taken instantaneously, in which the organism would attack the central nervous system, leading to cardiovascular syphilis, neurosyphilis, and late benign syphilis [11].

However, although syphilis could be easily diagnosed and treated, it still shows a high prevalence globally. The use of screening tests and treatment services are far not enough to reduce the incidence rate. Since humans are considered the only reservoir for *T. pallidum*, an effective vaccine development will overcome the difficulties that public health is facing in eliminating the infections and mitigating the burden of syphilis. [12]

Therefore, scientifically proven diagnostic and therapeutic methods are required. This review will focus on the pathogenesis, diagnosis and treatment of syphilis. Hopefully, this review will help all physicians caring for patients with syphilis to systematize current treatments.

2. Pathogenesis

As mentioned in the introduction, *T. pallidum*’s unique structure characteristics are considered a “stealth” pathogen. The organism can penetrate the junctions between cultivated umbilical vein endothelial cells, which are assumed to get access to tissue parenchyma after hematogenous dispersion by “interjunctional invasion” after attaching to the arterial endothelium [13]. In this case, the spirochaetes use motility to navigate the pathway of *T. pallidum* through intercellular connections; this organism will quickly spread throughout the body. During the secondary syphilis stage, a large number of spirochaetes in the epidermis and superficial dermis will allow infection to spread through microscopic abrasions formed through sexual activity. The blood-brain barrier can be penetrated in approximately 40% of patients with diagnosed early stages of syphilis, which will result in catastrophic neurological diseases [13].

The adaptive immune response would be triggered when *T. pallidum* multiplies and undergo recurrent episodes of dissemination. Dendritic cells pick up the organisms and transport them to draining lymph nodes, where they deliver homologous treponemal antigens to naive B cells and T cells. At this point, CD4+ T cells, CD8+ T cells, natural killer cells, and activated macrophages will be identified to fight the inflammation [13].

3. Clinical presentations

3.1. Primary syphilis

As shown in Figure 1, there are multiple stages of syphilis. After direct contact with *T. pallidum*, an overlapping clinical stage would occur within 9 to 90 days, while the primary stage usually starts with an average of 21 days. Symptoms that appear during primary syphilis are distinguished by a papule that could develop into an ulcer or chancre at the bacterium’s entrance location. Common
locations include anogenital areas, rectum, cervix, and mouth. In most cases, the chancre has a diameter of 0.5 to 2 cm, is observed to be hard or elastic, and may accompany regional lymphadenopathy. This stage usually takes 4 to 6 weeks to recover. Rare manifestations of HIV coinfection appear with numerous or painful ulcers [14].

3.2. Secondary syphilis

Four to ten weeks after the ulcer has healed, the second stage is entered. However, the first two stages would likely overlap. During secondary syphilis, a maculopapular rash is the most common symptom, which affects the palms and soles in 50-70% of individuals. Other signs include myalgia, fever, weight loss, alopecia and generalized lymphadenopathy [14].

3.3. Latent syphilis

If without proper treatment, the patient would enter the latent stage, which usually happens after three months of secondary syphilis, and the symptoms would revert. At this point, the illness remains dormant and non-infectious. The early latent disease is possible that symptoms relapse in the first two years of the latent period, but the late latent disease is uncommon to happen after two years [15].

3.4. Tertiary syphilis

Signs and symptoms of tertiary infection may appear after the latent stage, usually after 15 to 30 years; this stage is considered the final stage of syphilis, in which severe complications would occur. However, it is common for patients to enter this stage due to the extensive use of proper antibiotics. Tertiary illness includes gummatous (affecting skin, bones, and organs), cardiovascular disease (aortic dilatation and regurgitation), and neurological disease. Moreover, neurosyphilis could happen during any stage, mainly influencing the vasculature, cranial nerve and eyes [14].

![Figure 1. Different Stages of syphilis [16]](image)

4. Syphilis diagnosis

4.1. Direct Observation

The rabbit infectivity test (RIT) is a sensitive approach to diagnosing syphilis. In this test, contaminated tissue or fluid is injected into the rabbit’s testicles [10]. As *T. pallidum* is unable to be constantly cultured in vitro, and injection of rabbits is time-consuming and costly, the medical history, clinical signs, and direct visualization tests are used to diagnose early-stage syphilis [8]. For example, darkfield microscopy with a sensitivity of 32-81% and a specificity of 82-100% is typically employed to detect *T. pallidum* [17]. The direct visualization approach examines the exudate of the lesion by darkfield microscopy and is regarded as one of the most accurate ways for early syphilis diagnosis. On the other hand, dark-field microscopy cannot be utilized for oral infections. In addition, PCR has
been reported to be more diagnostically accurate than darkfield detection in initial lesions, which is mostly used in research laboratories [10].

4.2. Nontreponemal antibody tests

One form of syphilis serological test (STS) is nontreponemal antibody testing. The Venereal Disease Research Laboratory (VDRL) slide test and the rapid plasma reagin (RPR) card test are mostly used for screening [8], and both of them are effective. The assays assess the existence of nonspecific antibodies which can respond to the antigen particles, the cardiolipin-cholesterol-lecithin produced by the host when suffering acute and chronic illness [10]. Non-treponemal findings are classified as reactive or non-reactive, and titers are provided if reactive. Titers for RPR are typically greater than those for VDRL [8]. For consistency, the same laboratory should employ the same nontreponemal test to track titers, and when tracking titers, one test should be used from start to completion [10].

4.3. Treponemal Antibody Tests

Treponemal STS is a test based on the antibodies of serum immunoglobulin M (IgM) or immunoglobulin G (IgG) to treponemal antigens, which can be natural or recombinant. T. pallidum particle agglutination assay (TPPA), fluorescence treponemal antibody absorption assay (FTA-abs) and T. pallidum haemagglutination assay (TPHA) are now a few of the tests available [8]. These tests are described as qualitative, reactive and non-reactive. The tests have a range of 97 to 99 % of accuracy and can detect infection as soon as the chancre emerges [10]. Since these tests are more costly and harder to administer, their application in screening is limited. Automated treponemal enzymes, as well as chemiluminescent immunoassays (CIA), have recently been developed [10].

People who test positive for treponemal STS frequently stay positive throughout the rest of their lifetime despite they have received treatment. Therefore, it cannot be used to measure a patient's response to antibiotic therapy. As a result, non-treponemal STS is employed as a quantitative test to check antibiotic medication efficacy [18].

5. Treatments

5.1. Benzathine Penicillin G

Syphilis treatment is chosen according to the phase of acquired syphilis and other clinical evidence as shown in Figure 2. T. pallidum is still particularly susceptible to penicillin, an antibiotic drug that inhibits bacterial cell wall formation [19]. The majority of the data is supportive of the utilization of parenteral penicillin, and it is still the preferred therapy [19]. As a primary agent for managing latent and all periods of syphilis presentations, the choice of benzathine, aqueous solutions of procaine, or crystalline aqueous solutions, route of administration, dose and period of treatment should be considered [18]. Additionally, the phase and symptoms of syphilis and other therapeutic concerns such as pregnancy, HIV condition, and the age are all essential when deciding the treatment for syphilis patients. Early in the 1950s, benzathine penicillin G (BPG) investigations for syphilis in early stages indicated high cure rates and nearly no needs for additional treatment [19]. The standard therapy is one dose of 2.4 million units of BPG through intramuscular injection. Treponemal medication levels in the blood may be maintained for 7 to 10 days and help treat uncomplicated early syphilis [6]. According to the study, there was no significant difference between a single BPG injection and several injections of penicillin in the effectiveness of syphilis treatment in early syphilis [19]. Only in situations when patients are allergic to penicillin or they reject parenteral treatment are other medications indicated [20].

There is limited high-quality data to advise advanced syphilis therapy. It is hypothesized that advanced syphilis may need additional penicillin therapy because treponemal tend to regenerate more slowly into the later phases of syphilis, although the reliability of this theory has not been adequately tested [19]. BPG and procaine penicillin are first choice treatments for latent syphilis and unknown
Syphilis stage [19]. However, compared to early syphilis, the period of therapy is prolonged. Latent syphilis is treated with 2.4 million units of BPG three times a week. Although seven days is the optimal dose interval, non-pregnant people can tolerate up to 10 days [6]. Cerebrospinal fluid (CSF) test is necessary for patients with neurological presentations before the treatment. As detectable quantities of BPG in the cerebral fluid are not achieved in people with neurosyphilis or eye or ear syphilis, they are given an intravenous aqueous solution of penicillin G [6]. However, in some cases, clinicians will treat patients with neurological symptoms using aqueous penicillin G when CSF result is negative.

**Figure 2.** The flowchart of suggested treatments for syphilis [19]

### 5.2. Alternative treatments: Non-penicillin

Desensitization and penicillin treatment are suggested for people who shows penicillin allergy. Alternative antibiotics should only be employed when penicillin treatment is either brutal or completely contraindicated [6]. In the studies of the 1950s, tetracycline was shown to be beneficial in treating early syphilis. Briefly, retrospective studies revealed that oral doxycycline has similar effects on treating syphilis cases compared to BPG [19]. Most experiments adopted 100mg oral doxycycline twice daily for 14 days, with a serologic response rate ranging from 83% to 100%. Doxycycline has the additional advantage of being effective against other sexually transmitted illnesses [6]. However, compared to the recommended single-shot injection of intramuscular BPG with compliance concerns, doxycycline necessitates multi-day therapy. As a result, doxycycline is regarded as a feasible alternative to BPG in treating syphilis.

Furthermore, investigations using intramuscular ceftriaxone to treat early syphilis have shown equivalent effectiveness to BPG. Most research utilized parenteral injection of 1 to 2 g once a day for a period of 10 to 15 days. The serology result indicated a response rate of 65 to 100% [6]. More than one parenteral dose is needed per day in ceftriaxone therapy, which is more complex and costly than 2.4 million units of BPG. Ceftriaxone is also effective in treating other concurrent sexually infected illnesses.

### 5.3. Syphilis Treatment during Pregnancy

Syphilis during pregnancy is still an issue all over the world. Congenital syphilis is one of the most prevalent newborn illnesses resulting in baby mortality [21]. If a pregnant mother has syphilis and is not treated correctly, the fetus has an 80 percent risk of being infected [22]. As a result, all women during pregnancy should be checked for syphilis throughout the first trimester. Women at high risk of infection should be tested again at 28 weeks of pregnancy and during delivery [6]. The current agreed therapy for treating pregnancy-acquired syphilis is BPG with intramuscular injection in a dosage of 2.4 million units. In the control of congenital syphilis, benzathine penicillin G has a success
rate of 98.2 percent [21]. An urgent is needed for alternative syphilis treatment during pregnancy; however, insufficient clinical data was displayed to support the usage of other antibiotic drugs except for BPG [21]. Amoxicillin has comparable structural properties to penicillin and has demonstrated promising outcomes. Amoxicillin may be chosen because of its high oral bioavailability; nevertheless, pregnant individuals may require more doses of amoxicillin, and the ideal dosage is still unknown [23, 24]. Alternative medications such as third-generation cephalosporins should also be investigated. However, there is insufficient evidence showing that ceftriaxone effectively cures syphilis in pregnancy. To appropriately address the increased frequency of maternal and congenital syphilis in the setting of a global scarcity of BPG, alternative therapies for syphilis in pregnant women should be identified [21]. Pregnant women should be prioritized in syphilis therapy research. Furthermore, investigations on pregnant patients require funding.

5.4. Antibiotic resistance

Oral azithromycin has previously been identified to be helpful to treat early syphilis. In the mid-1990s and early 2000s, Uganda, the United States, and Canada employed azithromycin to manage syphilis [5]. Several incidences of adverse events following azithromycin therapy were documented in individuals with syphilis in San Francisco, California, between 2002 and 2003 [25]. The mutation was obtained from a patient who was previously demonstrated to be highly resistant and cross-resistant to erythromycin [5]. These mutations appear as A2058G or A2059G mutations in 23S rRNA in T. pallidum. A real-time triple PCR detection technique has been developed for treponemal A2058G and A2059G mutations [26]. This test may assist clinicians in deciding how to treat people with penicillin allergies in the early stages of syphilis. Currently, the only clinically meaningful resistance in T. pallidum is macrolide resistance.

5.5. Patients with HIV

Since syphilis may increase the risk of developing and transferring HIV, multiple treatment procedures have been investigated for syphilis patients with HIV co-infection. A clinical trial that targeted HIV co-infection proved that using azithromycin can prevent opportunistic infection result in improved serological consequences [27]. During the early stages of syphilis, a rise in cell amount and protein concentration in the cerebrospinal fluid are discovered more commonly in HIV acquired patients than patients without HIV, and there has been an indication that neurosyphilis symptoms in early stages are more prevalent for HIV co-infection patients. To specifically treat in the early stages, enhanced treatment is suggested by some studies. Prospective observational research which included 573 participants used a last-observed-carried-forward data analysis strategy to explain the missing data. The study showed a result of 67.1% serological response rate of patients who received one dose of penicillin G, and 74.8% of serological response rate of a patient who received the enhanced treatment (3 doses) [28] This study successfully showed a clinically significant difference to prove the effectiveness of enhanced treatment [13]. However, some researchers failed to prove the efficacy of enhanced treatment, which using a single dose of penicillin G results in no significant difference from using multiple doses. As a result, the findings were inconclusive, but many physicians still prefer to prescribe enhanced treatment for syphilis patients with HIV co-infection.

6. Limitations and future directions

Currently, there is no effective syphilis vaccine available. Syphilis can only affect humans, which indicates that it has no animal reservoirs or environmental reservoirs; this factor resulted in that syphilis being an ideal disease to develop a vaccine. As the global incidence of syphilis remains high, which showed an urgent need to develop a vaccine. An effective syphilis vaccine will resolve many challenges that global public health is facing and will also play an essential role in eliminating syphilis around the world. It may reduce the risk of transmission, including regular infections, HIV infections, and congenital infections [12].
Limited research has been done in developing a syphilis vaccine since penicillin G is considered the gold standard treatment, and it has a high accessibility rate. Moreover, a challenge that arises during vaccine development is to consider the related immune response and compensatory clearance mechanisms for HIV co-infection patients, which to achieve comprehensive protection for the target population [12].

A cohort study on the white rabbit showed two possible syphilis vaccine candidates that may effectively inhibit the separation of *T. pallidum*. Tp0136 and Tp0663 immunization proteins can prevent pathogen dissemination in the local areas and also to the distant organ sites at early stages. Tp0136 represented a strong reaction to the serum antibodies with the infected rabbit, while Tp0663 requires further studies [29].

7. Conclusion

As a sexual infectious illness, syphilis remained at an increasing rate of prevalence globally, which is still a challenge for public health control. The early stages of syphilis are infectious but can be treated easily; current antibiotics treatments can also target different populations. Latent stages of syphilis are non-infectious and could only happen if no treatment occurs; such a situation is rare but would result in irreversible consequences. Syphilis elimination has been considered a persistent goal for many countries; with the current diagnostic and therapeutic challenges, vaccine development is imperative for disease management. The elimination would also benefit from reducing HIV transmission, but there is still a long way to go, and further research and investigation are required to overcome the current challenges.

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