Syphilis: a mini review of the history, epidemiology and focus on microbiota

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INTRODUCTION

Syphilis is a chronic systemic infectious disease caused by the spirochaete bacterium Treponema pallidum (Treponema treponeme). In recent decades there has been a drastic increase in cases of syphilis, with a relative increase in scientific interest in this regard. However, the data concerning the study of microbiota in syphilis are few and very scattered. This brief review provides a quick update on the disease, with particular attention to the role of the microbiota, an aspect not always adequately considered in the evaluation of the pathology. The usual coexistence of different sexually transmitted diseases in the same patients led us to delve also into the possible role of the microbiota in the pathogenesis of syphilis; indeed, not all sexual contacts lead to infections, suggesting that host immunity and local microbiota could modulate the history of sexually transmitted disease. In both males and females, alteration of the microbiota may be involved in syphilis as well as in the other sexually transmitted diseases. Finally, since 9% of the total proteome of T. pallidum is spent for transportome, the latter may provide essential nutrients, making T. pallidum able to adapt to a diverse range of microenvironments and stresses in the human host.

HISTORY AND EPIDEMIOLOGY

The origin of syphilis has been controversial and there are many theories that try to explain it. One of them is the "Columbian Hypothesis", which claims that syphilis was brought from the New World to Europe in 1493 by Christopher Columbus and his sailors, but the possibility that the sailors were already infected from the get-go cannot be ruled out (Menicanti et al., 2016). Another theory assumes that syphilis was present in Africa and was brought by slaves to Spain and Portugal (Anteric et al., 2014), and yet another one that syphilis was present for a long time in the old and new worlds and that, depending on the geographical area, four different syn-
Syphilis

Over the centuries, everyone writing about syphilis noticed its connection with the sexual act. For this reason, the first restrictions concerned prostitution, from weekly medical examination to a notification requirement to the health authorities in the 20th century (Tognotti, 2009; Anteric et al., 2014; Ghanem et al., 2020). Syphilis surveillance began in 1941 and the highest case count occurred in 1946 (94,957) (Centers for Disease Control and Prevention, 2015). However, syphilis incidence decreased following the introduction of effective antimicrobial treatment, without disappearing, and declined markedly during the HIV/AIDS crisis because of changes in sexual behaviours. Although the disease was declared nearly eradicated in 1998, the incidence rate of syphilis has been increasing worldwide since 2000: 6.3 million cases per annum are recorded, with an increase of more than 150% in some high-income countries in the last ten years (Beale et al., 2021)

In 2016, the WHO estimated about 12 million new cases worldwide, mainly on the Asian and African continents (Menicanti et al., 2016). The Centers for Disease Control and Prevention recorded an increase of 81% from 2014 to 2018. In 2018, in the US, men accounted for 86% of all patients with syphilis and more than half of men reported having sex with men (MSM); 42% of those men were infected with the human immunodeficiency virus (HIV), which underlines the trend toward co-infection between sexually transmitted diseases (Centers for Disease Control and Prevention, 2019) Also in Europe and China an increase among MSM is reported (Spiteri et al., 2019; Tao et al., 2020). Although the distribution trend mainly involves MSM and people engaging in high-risk sexual activity (Wong et al., 2005), recently, a new outbreak in developed countries is also involving heterosexual men and women (Spiteri et al., 2019; McNamara et al., 2020). It is important to consider that in recent years there have been changes in sexual behaviour; with increased exposure to the risk of STDs resulting from improved treatments for AIDS and increased finding of partners via Internet through mobile dating applications (Thomas et al., 2016). This new aspect makes disease epidemiology and control more complex and difficult.

**MICROBIOLOGY**

*Treponema p. pallidum* is a member of the order Spirochaetales, family Spirochaetaceae, and genus *Treponema*, which includes four human pathogens and at least six human non pathogens (Santacroce et al., 2020). *Treponema p. pallidum* is a slow-growing, motile spirochete bacterium, 0.10 to 0.18 μm in diameter and 6 to 20 μm in length, with a long spiral shape (Norris et al., 1995). It is a microaerophilic bacterium that survives for short time outside the infected organism. It is closely related (>99% DNA
homology) to other pathogenic strains of *T. pallidum*, such as *T. p. pertenue*, which causes yaws, *T. carateum*, which causes pinta and *T. p. endemicum*, which causes endemic syphilis or bejel (Giacani et al., 2014). The causative agent of syphilis was identified by Schaudinn and Hoffmann in 1905 (Kojima et al., 2018). It actively reproduces in the rabbit testis and cannot be cultured in vitro (Menicanti et al., 2016, Forrestel et al., 2020), and is easily destroyed at a temperature of 41.5° C (Santacroce et al., 2020). The transmission of venereal syphilis, which is the oldest known Sexually Transmitted Disease (STD), can be through sexual contact, including oral and anal contact, between the skin or mucous membrane of an uninfected person and someone with active primary or secondary lesions. The risk of transmission after sexual exposure is estimated at approximately 33% (Hook et al., 1992). Furthermore, there are forms similar to sexually acquired syphilis which are transmitted, more rarely, by transfusion of unscreened blood or blood products, artificial insemination, organ or bone marrow transplantation, or through indirect transmission by infected materials (Menicanti et al., 2016). Mother-to-child transmission of spirochaetes can lead to congenital infection at any time during pregnancy if an acquired syphilis infection is not identified and adequately treated (Galvis et al., 2020; Ghanem et al., 2020; Hussain et al., 2021; Tudor et al., 2021).

**CLINICAL FEATURES**

*Treponema p. pallidum* infection presents several clinical manifestations depending on the stage and the timing of the disease. Acquired syphilis is known to be divided into three stages. Primary syphilis occurs 3 to 90 days after exposure to the infection and the clinical presentation is a solitary painless and ulcerated nodule (chancre), localized at any site of inoculation, genital (vagina, penis) or non-genital (perineum, anus, rectum, oral mucosa, nipples or fingers), often accompanied by regional lymphadenopathy (Clement et al., 2014; Menicanti et al., 2016, Forrestel et al., 2020). Checres, which are 0.5 to 3-cm indurated pink-red painless nodule, can appear at any site in direct contact with an infected lesion, and typically has a clean base. Chancres can easily ulcerate and the ulcer, with raised borders, shows an exudate rich in treponemes; therefore it is highly contagious. After 3-6 weeks, the

![Figure 1](image-url) - Maculopapular lesions spread over the abdomen (A) and trunk in a patient with secondary syphilis (B); Hematoxylin & Eosin 40X shows the presence of a lichenoid plasma cells infiltrate, with focal epithelioid granulomas (C); immunohistochemistry (400X) revealed the presence of Spirochete bacteria (D).
primary lesion resolves spontaneously and heals with restitutio ad integrum (Clement et al., 2014; Hook et al., 2017; Ghanem et al., 2020; Tudor et al., 2021) or, sometimes, with a modest scar atrophy (Menicanti et al., 2016). Sometimes it may not be identified if it is in a non-visible area (rectum or vagina) or if the patient has taken antimicrobial drugs during the incubation phase. Satellite adenopathy initially presents with swelling of a single and then multiple lymph nodes. The lymph nodes appear hard, mobile and indolent in this phase.

Secondary syphilis (Figure 1) appears around 3 to 12 weeks from the disappearance of the chancre but can be concurrent. This stage consists of several muco-cutaneous signs, such as papulo-squamous or macular rash on trunk, scaly plaques on palms and soles, alopecia, condyloma lata and mucous patches. The secondary lesions are 3-10 mm red-brown maculopapular eruptions and appear about 60-90 days after exposition, and could be characterized by marginal collarette of scales (Biett collarette). Palmoplantar involvement is common in this phase (40-80% of cases), but any organ system could be affected. This results in a variety of clinical manifestations, such as low-grade fever with diffuse lymphadenopathy, headache, myalgia, arthralgia, pharyngitis and hepatosplenomegaly. The clinical picture of this stage, having a broad spectrum of differential diagnosis with polymorphic and atypical clinical features, gave the name “great imitator” to syphilis. In this phase, the central nervous system (with meningism or meningitis), liver, kidney and eye can also be involved (Ghanem et al., 2020). Because of the high load of spirochetes, primary and secondary lesions are highly contagious, thus forming the sexually transmissible stages of infection. Untreated primary or secondary syphilis is followed by a latent stage that can be discriminated in early or late latent phase, according to the onset of one year or less and over one year. The latent stage is characterized by positive serologic tests, but negative clinical manifestations, and can persist throughout life, while in a minority of cases it occurs in the tertiary period (15-25% of untreated patients) (Tudor et al., 2021; Ghanem et al., 2020).

Tertiary syphilis (Figure 2) can occur after 1 year and up to decades of latency. The manifestations include gummatous disease with infiltration and destruction of any organ. In this phase there are few tertiary mucocutaneous lesions, which are classified as nodulo-ulcerative or gummatous. These granulomatous lesions could colligate by draining necrotic material rich in treponemes and can invade deeply into bones and other organs. The most dramatic effect is on the cardiovascular system, with aortic aneurism, aortic insufficiency, myocarditis, carotid ostial stenosis, peripheral arterial obliterans disease and valvulopathy (Menicanti et al., 2016; Ghanem et al., 2020; Clement et al., 2014). Regarding cutaneous manifestations, a dermoscopic description of the cutaneous lesions has been performed for secondary syphilis (Marthur et al., 2019), helping clinicians in the diagnosis with this non-invasive method. Herein, we also present

**Figure 2** - Ulcerative and necrotic painless lesions with mild peripheral erythema in a patient with tertiary syphilis (A, B); the dermoscopy of one sub-ocular lesion at 10X showed an erythematous background with hyperkeratotic follicular openings and a central necrotic area, with crusts (C).
dermoscopic images of a patient with neurosyphilis, tertiary syphilis and multiple papulo-necrotic lesions on the face, characterized by erythematous border and central necrotic area. The dermoscopic images show the presence of an erythematous background with hyperkeratotic follicular openings and a central necrotic area, with crusts (Figure 2).

Syphilis may also involve the nervous system with meningomyelitis, meningovascular disease, and, later, tabes dorsalis and paresis. Neurosyphilis can be divided into early or late neurosyphilis. The first one can occur due to central nervous system invasion during primary and secondary stages with meningitis, meningovascular disease, cranial nerve defects or stroke (Clement et al., 2014). The late stage usually involves the brain and the spinal cord with: progressive paralysis, emotional lability, weakening of intellectual functionality, memory impairments, impaired judgment and affectivity, paranoia, sensory and motor coordination disturbances (Ghanem et al., 2020). Tabes dorsalis is characterized by motor coordination and sensitivity disorders (Menicanti et al., 2016), lightning pains, ataxia, bladder disturbances, visceral crises and rectal incontinence (Ghanem et al., 2020).

Mother-to-child transmission of T. p. pallidum can cause congenital infection and can induce several antenatal and perinatal occurrences depending on the time of transmission (Galvis et al., 2020; Ghanem et al., 2020; Hussain et al., 2021; Tudor et al., 2021).

Most infants with congenital syphilis are infected in utero, but the new-born can also be infected by contact with an active genital lesion at the time of childbirth (connatal syphilis) (Santacroce et al., 2020). Recognition of congenital syphilis is difficult because of its non-specific presentation. Moreover, syphilis is mostly known as a sexually transmitted disease in adults and for this reason it is not often considered in differential diagnosis of children with suspicious symptoms (Keuning et al., 2020), although fetal deaths attributed to syphilis are still frequent (Kojima et al., 2018).

Congenital syphilis causes abortion, stillbirth, intrauterine growth restriction, nonimmune hydrops, prematurity, perinatal death or other congenital disorders (Cooper et al., 2018). More than half of new-borns are asymptomatic at birth. Thus, early congenital syphilis is defined by the onset of symptoms or signs before the age of two, including vesicular (pemphigus syphiliticus) or maculopapular rash prominently distributed on the palms and soles, hepatosplenomegaly, generalized lymphadenopathy, thrombocytopenia, anaemia, leukopenia/leucocytosis, fever, rhinitis, bulging fontanels, seizures or cranial nerve palsies. Skeletal lesions are typically symmetric, involving long bones, like destruction of tribal tubercle (Wimberg sign) and periostitis of the metaphysis with pseudoparalysis of Parrot (Galvis et al., 2020; Keuning et al., 2020; Hussain et al., 2021).

Congenital syphilis should be considered in the differential diagnosis of an infant presenting undefined skin abnormalities (Keuning et al., 2020). The late congenital disease is not contagious and is diagnosed in patients older than 2 years of age. It can have several presentations, including peg-shaped upper central incisors (Hutchinson teeth) and molars with many small cusps (Mulberry molars), nasal cartilage destruction (Saddle nose), frontal bossing (Olympian brow), bowing of the tibia (Saber shins), sterile joint effusion (Clutton joints), eighth nerve deafness, interstitial keratitis and morbilliform rash. The simultaneous presence of interstitial keratitis, eighth nerve deafness and Hutchinson’s teeth is known as Hutchinson’s triad.

Accordingly, routine screening is recommended at the first prenatal visit and during the third trimester and delivery in high-risk women (Keuning et al., 2020).

**DIAGNOSIS**

Diagnosis is based on the detection of Spirochetes by direct examination of the material with dark-field microscopy or by direct immunofluorescence on exudate of muco-cutaneous lesions of primary/secondary syphilis. The first technique is the most used and is the one used for the diagnosis of primary syphilis. Diagnosis is also usually carried out by serological tests, classified as non-treponemal and treponemal. These techniques, associated with clinical evaluation and possibly with direct examination of the exudate with dark-field microscopy, are used for the diagnosis of secondary syphilis and are the only ones indicated for the diagnosis of early latent syphilis or late syphilis. The standard screening algorithm begins with a non-treponemal test [e.g., a Rapid Plasma Reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test] that detects serum antibodies to cardiolipin. These tests are positive after the development of the primary lesion, and search for antibodies produced against antigens released from the tissues due to the pathogenic action of treponema (Ghanem et al., 2020; Tudor et al., 2021). They are the only tests useful in the follow-up phase because they can highlight the activity of the infection and monitor the response to treatment. However, they are not very specific and therefore always need to be associated with a treponemal test. Reactivity is then confirmed with the use of highly sensitive and specific treponemal tests that detect serum antibodies to T. pallidum, such as Treponema pallidum Haemagglutination Assay (TPHA) and the Treponema pallidum Particle Assay (TPPA) that are positivized 40-50 days after infection.

IgM + IgG immunoenzymatic reactions are very early, already positivizing from the second (IgM) and fourth week (IgG) after infection. Treponemal tests remain reactive despite the treatment history there-
fore are not useful for follow-up (Menicanti et al., 2016; Ghanem et al., 2020; Tudor et al., 2021).

**THERAPY**

Intramuscular (IM) penicillin G benzathine remains the first-rate therapy which is administered in different dosages depending on the type of syphilis. Resistance to penicillin has not been observed in *T. pallidum* (Ghanem et al., 2020).

Alternative therapies include doxycycline or erythromycin orally or ceftriaxone IM or intravenously (IV). To avoid the Jarisch-Herxheimer reaction, which is an immune-mediated self-limited reaction following therapy, it can be useful to premedicate with steroids IM (Galvis et al., 2020; Ghanem et al., 2020; Hussain et al., 2021; Tudor et al., 2021).

**ROLE OF MICROBIOTA AND COINFECTIONS**

Since the early 2000s, the prevalence of syphilis around the globe has begun to increase again. According to epidemiological data, the cause is to be found in the high incidence of HIV (McNamara and Yingling, 2020). In fact, in patients affected by HIV, co-infections with STD frequently coexist due to their shared sexual transmission. Indeed, according to recent studies, syphilis infection increases the risk of HIV transmission by at least 3-fold. The reasons for this derive not only from the habits of patients with STD, such as disregard for HIV infection, the ease of finding sexual partners and the sexualized drug use (chemsex), but also from some pathogenetic characteristics of both syphilis and HIV (Donnadieu-Rigo et al., 2020; Gilbert et al., 2021). In fact, syphilis causes epithelial and mucosal breaches and induces immune activation with an increase in activated CD4 lymphocytes, leading to facilitated HIV transmission and then causing a decline in CD4 count, with rapid progression to Acquired Immuno-Deficiency Syndrome (AIDS). Furthermore, the presence of HIV induces greater susceptibility to syphilis, atypical clinical presentation, resistance to treatment and frequent recurrences (Behara et al., 2021; Gilbert et al., 2021). Nevertheless, the coexistence of different STDs in the same patient also led us to examine the possible role of the microbiota. In fact, not all sexual contacts lead to infections, suggesting that host immunity and local microbiota could modulate the history of STDs. Mehta S.D. et al. studied genital ulcer disease in male patients, detecting Herpes Virus (HSV) or *syphilis treponeme* in 37.3% of the cases. Therefore, the microbiota was analysed: sequences corresponding to *Prevotella* spp. were most abundant, then, in order, *Anaerospaera* spp., *Anaerococcus* spp., *Porphyromonas* spp., *Fusobacterium* spp., *Sneathia* spp., *Peptophilus* spp. and *Dialister* spp. Bacterial diversity was greater in genital ulcers of unknown aetiology than in STD-associated ones. Furthermore, *Anaerococcus* spp. and *Parvimonas* spp. were more often detected in ulcers of unknown aetiology, and *Enterobacter* spp. was detected more frequently in STD-related ones (Mehta et al., 2012). The interaction between microbiota and STD also concerns the female host. According to Tamarelle et al., vaginal microbiota is either dominated by one of four species of *Lactobacillus* (*L. crispatus, L. iners, L. gasseri* and *L. jensenti*) or characterized by a paucity of *Lactobacillus* spp. and a diverse set of strict and facultative anaerobes. Perhaps vaginal microbiota could impact on STD and also be impaired by it. Lactobacillus species are thought to be protective against STDs through competition, production of lactic acid that lowers pH, and production of target-specific bacteriocins. Furthermore, strict and facultative vaginal anaerobes seem to produce nitrosamines, cytokines and inflammatory mediators that are thought to lower barriers to infections (Tamarelle et al., 2018).

Another aspect to consider in this delicate interaction between host and *T. pallidum* is the mechanisms that *T. pallidum* employs to gain nutritional benefits from its host. Buyuktimkin et al. (2018) hypothesize that despite its small genome size (~1.1 Mbp), 9% of the total proteome of *T. pallidum* is spent for transport proteome. This transportome provides essential nutrients, also enabling *T. pallidum* to adapt to a diverse range of microenvironments and stresses in the human host (Buyuktimkin et al., 2018).

**CONCLUSION**

Unfortunately, data are not yet sufficient to understand the mechanisms underlying the response between *T. pallidum* and host. Improved knowledge on the role of the muco-cutaneous microbiota can lead to a successful prevention strategy against a new spread of syphilis and maybe against all STDs as well.

**References**


