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Syphilis

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1. Introduction

Also known as lues venereum, syphilis is an infect-contagious chronic systemic disease, which is, in the majority of times, sexually transmitted. It is caused by the bacterium, *Treponema pallidum.* The illness is characterized by periods of activity between latency, becoming systemically worse throughout its different periods of virulence (1-5).

2. History

The name "syphilis" was first proposed by the physician and writer Girolamo Fracastoro who wrote about the disease in 1530, but it only became a medical term by the nineteenth century. He had published three epic books, in which he makes reference to a mythic Greek shepherd, *Syphilus,* whom *Apollo* had cursed with such an ailment (6).

The actual origin of this venereal condition is unknown. The first well described epidemic of the disease is dated from the fifteenth century. This European epidemic came about after the year of 1495, when the French, accompanied by the Spanish, invaded Italy. After the invasion, a strange and gruesome disease began to spread with sores, ulcers and skeletal pain, followed by physical incapacity and death. It then became known as the French disease. Of course, other names also followed, such as the Spanish disease, Italian, and so on (2-10).

It is not however, certain if this was syphilis' first appearance in the world; the pre-Colombian theory speculates that the bacterium was imported to Europe by sailors who went to America and many authors have observed bone deformity and treponemal lesions found in excavations and observations of the prehistoric period in different sites in America (9,10).

The Old World theory, states that Treponema has been around for thousands of years, but, like other living things, it suffered under nature's force and had to adapt through evolution. This theory is based on observations of diseases depicted throughout history and artefacts which seem to be in favour of different diseases caused by other species of spirochete bacterium. For example, it could have been misdiagnosed as leprosy for a long time. If this is true, its origin would mix with human history, far beyond a possible pinpoint in a timeline. Both theories remain inconclusive and are, as yet, not proven definitely one way or

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the other. What is true is that, even with such opposing theories, the *Renaissance* was a time of sexual freedom that helped the spread of sexual diseases (9,10). But, the new world theory or Columbia theory postulates that, since Columbus originated from continental Europe, where there was misleading evidence of syphilis, the origins could not be from Europe. Instead, his voyages contributed to the transmission, since his crew might have been infected on the voyages to the New World. Hence, the origin remains a mystery.

The discovery of the etiological factor of the disease – *Treponema Pallidum* – was of great importance. In 1905, in Hamburg, Germany, the zoologist Fritz Richard Schaudinn and the dermatologist Paul Erich Hoffmann presented the medical community with the discovery of the bacterium. Besides the natural controversies and disappointments of a new scientific discovery, it didn't take long for the world to recognize the new fact about the disease. From this point, research was made possible, helping the understanding of the pathology behind the bacterium (7-10). Another landmark for the classification of disease was the work developed by Wassermann in 1906, which led to serological test for syphilis. Treatment for the disease using arsenic-benzene was introduced by Paul Ehrlich in 1910, but it was only after the discovery of penicillin, and its introduction as treatment in 1943, that syphilis diminished its incidence and prevalence. A more recent discovery was the genomic sequence of the *Treponema pallidum* that can lead to a better understanding of the pathophysiology of the disease (10).

Another point in history that should be mentioned is the Tuskegee Syphilis Experiment. From 1932 until 1972 the US Public Health Services (PHS) left 399 black men untreated with diagnosed syphilis. Between those years, patients were given ineffective medicine (even aspirin) in order to keep track of the pathophysiology. Even with the cure for the disease accessible to all, these people were denied treatment with penicillin (11).

Many ethical issues have been exposed with this experiment, but the experiment took 30 years to finally end and many medical notes were revealed regarding the different phases of syphilis.

2.1 Epidemiology

It is a globally prevalent disease, most commonly found in cities. It does not have any predilection for race or sex, but it has been found to be more common among young people. From the 1960s there have been a growing number of syphilis cases because of sexual freedom, from use of birth control pills and higher rates of tourism and homosexuality (1,2,4).

There has been an expansion on the latent form of syphilis because of misdiagnoses and mistreatment of the disease. The fact that a person uses the antibiotics does not mean correct treatment, since the appropriate dosage must be applied. Hence many people go direct to the latent period of syphilis without the cure, with a high probability of recurrence (1,2,5,8).

With the advent of AIDS (Acquired Immunodeficiency Syndrome), atypical form of lues, with a more severe evolution of the disease, has been observed. Patients with other sexually transmitted diseases (STD) have been shown to have associated syphilis, for example, soft chancre (12-15%), donovanosis (45%), gonorrhoea (1-4%) and condyloma acuminatum (5%). This is the reason for the importance of screening patients with STDs for lues (1,2,8,12).

2.2 Pathophysiology

The causative agent of syphilis, *Treponema pallidum*, comes from a family of bacteria that are present in animals and insects without any harm to them, living in the digestive system of the animals. It is a gram-negative bacterium, spiral shaped (8 to 20 spirals), measuring from 4 to 10 μm in length to 0,25 μm in width. Except for its more irregular and delicate spirals, the bacterium is undistinguishable from others spirochetes. It is an obligate parasite of humans (1-8).

The initial multiplication of the parasite is intense, as there is an absence of antibodies and cellular immunity. They attach to cells of the mucosa by ligands on their surface, the adhesins, that facilitate bacterial adhesion to the host´s cells. The bacteria secrete hyaluronidase that will destroy the polysaccharide that holds animal cells together, making its penetration possible. It will need free iron and will bond to lactoferritin, lipoproteins, mucopolysaccharides, proteoglycans or glycosaminoglycans, that are necessary to its development and its protection and as they mix with these substances, the host will recognize the microorganism as itself (7).

There is no natural immunity against syphilis. The inoculation in healthy individuals will always cause the disease, by inducing a humoral and cellular response. The immune response to syphilis involves production of antibodies to a wide range of antigens, including non-specific antibodies and specific treponemal antibodies. The first demonstrable humoral response is the production of anti-treponemal IgM at the end of the second week, and IgG at approximately four weeks after the exposure. The cellular immunity will come after, exteriorized by disseminated infection (5-7).

With the development of the humoral and cellular immunity, the bacteria are gradually destroyed, living only in a few tissues. This is the latent phase of the disease, which can go for an undetermined period. They can remain inside the tissues or be eliminated through a biological cure. The microorganisms can be reactivated, when there is a decline in immunity efficiency, thus reinfecting the host (5-9).

T. pallidum cannot be cultured in the laboratory and therefore it is impossible to investigate it by using the conventional techniques. It does not live outside mammalian cells. It is researched through the inoculation of the bacteria inside rabbit or monkey cells.

It is contagious during the recent phase of the disease. Syphilis is transmitted primarily by sexual contact and the next most common is transfer across the placenta. Human contact, blood transfusion & accidental inoculation have also been reported as routes of transmission but are of minor importance. The bacterium penetrates the body through the mucosa or microabrasion on skin. Within a few hours of inoculation, it enters the lymphatics and blood, producing infection long before the appearance of the primary lesion. The concentration of *T. pallidum* in the blood of a person with the disease is around 10^7 per gram of tissue before the first lesions. The median incubation time is 21 days, ranging from 10 to 90 days. Studies in rabbits have shown that spirochetes can be found in the lymphatic system 30 minutes after primary inoculation (1-10,12-14). Congenital syphilis is contracted from an infected mother via transplacental transmission of T. pallidum at any time during pregnancy or at birth.

2.3 Primary syphilis

The primary lesion appears in the site of inoculation, persisting for 4 to 6 weeks, healing spontaneously. It is normally a single, painless papule, with a reddish halo around it, presenting a discrete serosity, that becomes indurated, which can erode (protosyphiloma). It measures from a few millimetres to 2 centimetres. The lesion can be painful if it is presented extragenital. It normally appears on the penis of heterosexual men. Lesions in homosexual men, are present in the anal canal, rectum or extragenital – perianal or perioral, for example. In women, the lesions are most commonly observed in the cervix and labia. Presence in the cervix can lead it to being undiagnosed. Extragenital lesions can appear on the lips, tongue, tonsil, nipple, fingers and anus. They usually heal within 4 to 6 weeks (ranging from 2 to 12 weeks); it does not leave any scar tissue. The lesion is highly contagious. If the protosyphiloma appears in a place that has been already inoculated with another pathogen, and presents a characteristic lesion, such as anal genital herpes or even anal fissures, the lesion can take the morphology of the first lesion. That is why every person with a genital ulcerated lesion should be tested for syphilis (1-6,8,15,16).

In relation to the primary lesion, other forms include:

Decapitated syphilis: syphilis that does not present with the primary lesion. Normally the infection occurs by transfusion or in patients that during the infection were using antibiotics that obscured the chancre, although the dosage was insufficient to eradicate the pathogen (1,17,18).

Chancre of Rollet: the association of a hard chancre (syphilitic) with a soft chancre, from *Haemophilus ducreyi* (chancroid) (1, 17,18).

Chancre Redux: Chancre redux is the presence of a gumma, reappearing at the site of the initial chancre, and "pseudochancre redux" is one solitary gumma on the penis (1,17,18)

A satellite bubo also appears 1 week after the primary lesion. Bubo is a lymphatic gland responsible in the drainage of the area containing the lesion. They become enlarged nonsuppurative and painless. From the affected gland, liquid can be aspirated for further diagnosis when the primary lesion does not have enough substance. When the lesion is anal or within the external genitalia, the nodes appear at the inguinal region. Rectal chancre usually cause perirectal lymphadenopathy, while lesions in the vagina or cervix result in iliac or perirectal adenopathy. This condition may persist for months, even after the primary lesion disappears (1-3,5, 6, 17,18).

Differential diagnosis: soft chancre and herpes are the basic pathologies that could be misdiagnosed, since both present with genital eruption.

2.4 Secondary syphilis

After 6 to 8 weeks of healing of the chancre, systemic manifestation and skin lesions begin to appear. Though, 15 to 25% of patients with secondary syphilis may still have the primary lesions, and up to 45% will have the lesion associated with AIDS. About 25% may not remember having a primary lesion. Some will take a few months for the disease to florid again, while others will never go through the secondary phase of syphilis (1-3,12, 18,19).

Symptoms include low-grade fever, nontender adenopathy, hyporexia, malaise and rash. Other symptoms that are less common are ophthalmia, arthralgia, iritis and other eye lesions, including pupillary abnormalities, optic neuritis, uveitis and retinitis pigmentosa. Acute meningitis may occur, but is rare; 30% of patients will only have proteins and cells present in the CSF, with only mild headache. Also gastrointestinal involvement, nephropathy and hepatosplenomegaly can occur (1-3,18).

The initial lesions are usually non-pruritic, with a wide aspect range, symmetric, and usually cover the entire body.

The skin lesions, *syphilides*, are very common. They consist of macular, papulosquamous, and sometimes pustular. Often, the different types of lesions may occur simultaneously (20). Initial lesions are bilateral, round macules measuring between 5 to 10mm in diameter, distributing on the trunk and proximal extremities. They are usually very discrete. After days or weeks, red papules also appear. These lesions will cover palms and soles, including face and scalp. After a few weeks, papular syphilides or papulosquamous (psoriform), and rarely pustulosis, appear. Biopsy shows numerous plasma cells with mononuclear infiltration and *endarteritis obliterans*. This endarteritis can lead to *papulosquamous syphilides* because of the isquemia and may finally lead to necrosis – *pustular syphilides.*

In black individuals, facial and anal lesions take on annular and circinated configurations ("elegant syphilids") (17,18).

Oral mucosa is also affected and the lesions are known as mucosal plaques. The plaques are multiple, erosive, asymptomatic, measuring about 1 centimeter, being usually of a round shape (17).

Follicular syphilides are the involvement of hair follicles that will lead to *alopecia areata*. On the head, there is usually loss of hair on the temporoparietal and occipital regions. It can affect the beard, eyebrows and eyelids. The alopecia is reversible and temporary; it ends after the control of the infection (1,18).

In intertriginous body areas, which are warm and moist, like the perineum and axillae, lesions will coalesce and erupt, becoming larger, moist, of pink colour or white, that is called *condyloma lata* or *flat condyloma*. These lesions have a high concentration of spirochetes and are the most infectious lesions in this phase. Laboratory techniques have shown a smaller concentration of the bacteria in the other lesions, suggesting that the rash is a direct consequence of the infection (17,20).

Differential diagnosis: skin lesions should be considered from drug usage and viruses. Mucous lesions have to be differentiated from candida, Lichen planus and leucoplasias. The condyloma from the genital and perianal area should be distinguished from the condyloma accuminatum.

The presentation of secondary syphilis is so wide that this disease can be thought as secondary diagnosis for any dermatitis that presents itself in an atypical manner.

2.5 Latent syphilis

Latent syphilis is diagnosed when serologic tests are positive, with normal CSF examination and absence of any clinical manifestation. It evolves from the secondary syphilis being

untreated. It is suspected when there is a history of primary or secondary lesions, history of exposure, or a congenital case from a mother without a prior diagnosis. There is a possibility of headaches, different skin coloration and alopecia, because of mistreatment of secondary syphilis (1,2,5,8).

Early latent syphilis is the infection after primary or secondary phase have subsided, during the first year of infection, while late latent syphilis is diagnosed when the manifestations appears more than 1 year after infection. This period is variable; a patient can present at any moment presenting either secondary or tertiary syphilitic signs. There are still doubts as to what is the real outcome of the latent syphilis, since more than 50% may never present with another syphilitic lesion; although a spontaneous cure is controversial (1,2).

2.6 Late syphilis

Late or tertiary syphilis will appear in about one-third of untreated patients. Lesions will appear after 3 to 15 years of remission. The manifestations will appear as neurosyphilis, cardiovascular, cutaneous and others. And the most common manifestation of tertiary syphilis is aortitis (1,2,5,8,17).

2.7 Neurosyphilis

Symptoms begin after 1 year of infection for meningeal syphilis, between 5 to 10 years for meningovascular syphilis, 15 to 20 years for general paresis and 25 to 30 years for tabes dorsalis. The syndrome is nothing more than a chronic meningo-vasculitis, capable of producing vascular and parenchymal lesions on the brain and the spinal cord. It is not well known why some cases spontaneously resolve, evolve to asymptomatic neurosyphilis or to the symptomatic presentation. Nowadays, signs and symptoms are incomplete and mixed because of the antibiotic treatment (1,21).

Meningeal syphilis: 25% of patients will show the meningeal involvement as the first sign of syphilis. Clinical presentation alterations include headache, neck stiffness, nausea and vomiting. The main neurological alteration includes cranial nerve palsies, especially II, VI, VII e VIII, seizures and changes in mental status. Neurosensory deafness occurs in up to 20% of cases. Syphilitic hydrocephaly presents with intracranial hypertension, appearing from 3 to 7 months after the initial infection (1-3,21,22).

Meningovascular syphilis: involves practically any area of the central nervous system, being traditionally subdivided in cerebrovascular and spinal cord. The lesions are caused by ischemia, secondary to endarteritis, which is the result of vascular wall infiltration from lymphocytes and plasmocytes in small and medium arteries. Symptoms related to neurosyphilis are comparable to atherosclerotic disease. Manifestations may include hemiparesis, aphasia and seizures. The initial symptoms may be acute or may follow general symptoms, like headache, insomnia and humor changes. In older patients, these alterations may be mistaken for encephalic accident. In younger people, there is a mandatory screening for the disease (21,22).

Meningovascular syphilis is rare and involves a wide range of aspects, being associated with the cerebral disease. It clinically presents with alteration on sphincter function, legs paraparesia and weakness. Pain and paresthesia of the legs are common (1,21,22).

General paresis: is a rare, progressive and chronic meningoencephalitis, which will eventually evolve to dementia. The presentation is a consequence of multiple damage to the brain, which includes personality changes, affection disorders, hyperactive reflexes, Argyll Robertson pupils (small pupils that do not react to light, but reacts to accommodation), illusions, deliriums, hallucinations, alterations on recent memory, thinking capacity and speech. These signs may be confused with many psychiatric diseases with neurological signs. If not treated, the patient will become apathetic, hypotonic, demented and physically incapable, finally leading to death after 4 to 5 years of evolution. Treatment will stop the spread of the disease, but will not recover the damage already present (15,21-23).

Tabes dorsalis: Symptoms appear because of the demyelination of the posterior columns, dorsal ganglia and dorsal roots. Symptoms include ataxia, paresthesia, bladder disturbances, impotence, areflexia, Charcot's joints (trophic joint degeneration) loss of position, deep pain, alteration on temperature sensation, loss of pain sensation, that will finally result in perforation and ulceration of the feet, from the lack of sensation and optic atrophy. There is a history of terrible pain in this phase of the disease, although it is actually attributed to the heavy metals used for treatment in the past before the antibiotic treatment (21-23).

2.8 Cardiovascular syphilis

Among the lesions, the most common is the syphilitic aortitis. On the non-treated syphilis, aortitis can manifest after 10 to 40 years, after the initial sexual contact. The ascending aorta is the most targeted by the disease 50% of the cases, followed by the aortic arch, the descending aorta and the abdominal aorta, coronary ostia and aortic valve lesions (1,14, 24-29). Presently this entity is very rare.

The main cause of death, in about 80% of the cases, is sacular aneurism rupture, when it is not treated surgically (1,14, 24-29).

After infection, the *T. pallidum* can be observed on the aorta's wall, initially on the tunica adventitia and at the lymphatic vessels. This is one of the reasons for the spirochete's tropism for the ascending aorta, since the latter is rich in lymphatic vessels (1,15,17,18,24-29).

The vasa vasorum suffers an obliterative endarteritis process, media necrosis (mesoarteritis) and plasmocitary infiltrate. Consequently, the elastic tissue of the aorta is destroyed and substituted by scar tissue. The inflammatory process can go on for a long time and it can be found in the patient up to 25 years after the first contagion (1,15,17,18,24-29). The clinical features can be of angina pectoris, when there is coronary ostia obstruction, dyspnoea when there is aortic regurgitation. Although the most common clinical feature is thoracic pain, secondary to fast luetic aneurysm expansion. When the lesion is present only at the aorta, the patient may be asymptomatic (1,15,17,18,24-29). Differential diagnosis: hypertensive cardiomyopathy, rheumatic carditis, cardiac insufficiency, and coronary atherosclerosis.

2.9 Cutaneous syphilis

The cutaneous involvement of the secondary syphilis is rare and may appear as nodular syphilids and gumma. The nodules are firm, grouped, with tendency to a circinated disposition among them. With the progression, they tend to present with central cure and external progression. They are usually present on the face and back, although they can be present on any part of the body (1-7,15,16,18).

The gumma is the progression of the nodules that get larger and become necrotic and ulcerated, leading to adherent and caseous material. They are very destructive and painless. These can destroy the palate and uvula (15,17,18).

Differential diagnosis: pharmacodermias, tuberculosis, cancer, paracoccidiomicosis, *american tegumentary leishmaniasis, lupus and rosacea.*

2.10 Congenital syphilis

Without adequate treatment, pregnant women can infect the foetus, either transplacentary or during labour. Generally the more advanced the pregnancy, the chance of transmission decreases. Lesions usually occur after the fourth month of pregnancy, when the foetus begins to develop an immunologic system. This suggests that the disease depends on a response from the body rather than a direct effect from the *T. pallidum* (1,30,31).

The risk of congenital infection is 75 to 95% when syphilis is early and untreated in the mother. The risks drop to 35% when the maternal syphilis has more than 2 years of duration. The damage to the foetus can be prevented if treatment begins before the 16th week of pregnancy. Foetal loss can be as high as 40% when left untreated, another 30% may die shortly after birth; premature labour or congenital syphilis are other possible outcomes (31-35).

When the baby is born alive, only fulminant congenital syphilis is apparent at birth, and these babies have a very poor prognosis. Most babies are born apparently healthy (about two-thirds), from a serologic-positive mother. Live-born infants with congenital syphilis may be divided into early signs – appearing in the first 2 years of life – and late signs – appearing after 2 years, over the first two decades of life. Congenital syphilis can be clinically similar to other pathologies, such as toxoplasmosis, herpes simplex, cytomegalovirus and rubella, as well as sepsis, blood incompatibility and other neonatal disorders (1,31)

2.11 Early congenital syphilis

The manifestations of the early disease occur in the first two years of life. Most of symptomatic infants will have hepatomegaly, with normal liver function, but jaundice may be present, from hepatitis; usually associated with high hepatic enzymes. Splenomegaly may also be present in about 50% of cases. Liver disease may cure slowly or even worsen after treatment (1,13,34).

Mucocutaneous lesions are present in up to 70% of patients. They may be present at birth or appear within the first weeks of life. These lesions generally are compatible to the secondary syphilis, being more infiltrated. The typical lesions constitute a small red maculopapular lesion, affecting hands and feet more severely. Desquamation and crusts will be present after 1 to 3 weeks. Snuffles will appear because of the involvement of the nasal mucous membrane – syphilitic rhinitis, appearing in the first week of life. In syphilitic pemphigus, there is a discharge that can vary from blood tinged to purulent, when bacterial infection occurs. This secretion is rich in spirochetes; being highly infectious. Condyloma lata may be present, along with mucous patches. Fissures occur around the lips, nostrils and anus. Thrombocytopenia may cause petechiae (1,13,31,33,34). Bone involvement is present in 60 to 80% of these infants. The lesions are commonly symmetric and multiple. Periostitis and demineralization occur in long bones and osteochondritis affects the joints:

Parrot's pseudoparalysis: generally the bone lesions are very painful, leading the newborns to avoid movement with the affected area (36,37).

Wimberger sign: metaphyseal demineralization or destruction of the upper medial tibias are seen radiographically (36,38).

Usually within the first six months of life, the bone lesion will resolve spontaneously. Neurosyphilis is observed in 40 to 60% of babies in this phase.

2.12 Late congenital syphilis

Late syphilis occurs after 2 years of age with untreated syphilis, corresponding to the late acquired syphilis in the adult, because of the similarities of the lesions, as nodular syphilides, gumma and periostitis. In 60% of cases, the infection remains subclinical. Some lesions are characteristic of this phase (1,15,30,34):

Interstitial keratitis is the most common and serious lesion of this phase. Both eyes are normally affected; the patient presents with photophobia, pain and less visual acuity. Optic atrophy may also be present. Treatment will not affect the evolution of the manifestation (1,13,17,18).

Clutton's joints are painless synovitis, affecting knees. The radiologic finding is an increase in the articular space (1,3,13).

Bone involvements are periostitis of long bones, mainly tibia - that becomes bigger in size and presents an anterior curvature (Saber shins) (1,13,34).

Cranial nerve lesion is frequent , specially related to the VIII pair, which will gradually evolve to deafness (1,2,13).

Asymptomatic neurosyphilis is present in approximately 33% of the patients and 25% will display clinical neurosyphilis after the sixth year of age.

Characteristic stigmata presented in late congenital syphilis: Hutchinson's teeth: centrally notched, widely spaced, peg-shaped upper central incisors and "mulberry molars" - poorly developed teeth, present after the sixth year of life. The Hutchinson's triad includes the teeth lesion, interstitial keratitis and deafness. Facies is also abnormal and may include frontal bossing, saddle nose and curved maxillae. Linear scars at mouth and nose angles from secondary bacterial infection also appear (Rhagades) (1,2,13,34). Rarely, syphilis is found in children that that been sexually abused, thus it will behave as regular syphilis; going through each of the phases. Sexual transmission should be assumed unless another mechanism is identified. If precautious are not used, these children can transmit to healthcare providers that are unaware of the contagiousness.

2.13 Diagnosis

In the diagnosis of syphilis, apart from detailed clinical history and physical examination, microscopy and serologic tests are the most important aspects in diagnosis and monitoring treatment (15).

Dark field microscopic examination of the exudate present in lesions, such as chancre of primary syphilis and condyloma latum in secondary, is needed. If a single motile

microorganism characteristic of syphilis is verified, it will be sufficient for diagnosis. Anal and oral lesions should not be evaluated through dark field since it is hard to differentiate the pathogen from other common bacteria present in these sites. A direct fluorescent antibody *T. pallidum* (DFA-TP) test is also available – it can be used for rectal/anal and oral and genital lesions. The most reliable method for detection is the rabbit infectivity testing (RIT), where the serum is inoculated into the animal and will provide definitive evidence of *T. pallidum*. However, the use of RIT for diagnostic procedure is impractical (1-3,13,39).

Serologic tests are divided between non-treponemal and treponemal tests. Non-treponemal tests are useful for screening, while treponemal tests are used as confirmatory tests.

Non-treponemal serologic tests: Detection of non-specific treponemal antibody. They detect and measure IgG and IgM against cardiolipine-lecithin-cholesterol antigen complex. They include Venereal Diseases Research Laboratory (VDRL) and rapid plasma reagin (RPR) tests. In these, the antibody is detected by microscopic or by macroscopic flocculation of antigen suspension. The limitation of the non-treponemal serologic tests is the lack of sensitivity in dark ground microscopic examination for positivity in primary and late syphilis (3,8,15).

The PRP and VDRL are both equally sensitive and may be used for initial screening or quantification of the antibody; the titter will reflect the disease's activity. A specific rise in the titter will be seen during the evolution of early syphilis. A persistent fall following treatment of early syphilis gives evidence of adequate response to therapy. PCR and VDRL are equal in sensitivity and may be used for the initial screening and quantitation of the serum antibody (3,815).

Treponemal: detects specific antibodies to cellular components of the bacterium. Treponema pallidum haemagglutination assay (TPHA), fluorescent treponemal antibody-absorbed test (FTA- ABS), enzyme immunoassay tests (EIA) and Polymerase Chain Reaction (PCR).

In TPHA, purified *T. pallidum* antigens are fixed into red cells to detect specific anti-treponemal antibodies from the patient's serum. If another particle from the patient's serum is attached, other than red blood cells, it is called Treponemal Pallidum Particle Agglutination (TPPA) test. FTA- ABS is an observer-dependent test that detects the presence on anti-treponemal antibodies microscopically, that were fixed with the treponema's antigen. Both agglutination assays and the FTA- ABS are very sensitive, although it may give false-positive results in up to 2% of the general population (15,39-41).

In the EIA chromogenic end products are measured from enzymatic reactions on antigen-antibody complex. These chromogenes are read in a spectrophotometric device. Other antigens can be used, like cardiolipin, purified treponemal antigen or recombinant treponemal antigen. In the case of cardiolipine usage, the test is known as non-treponemal test. Purified and recombinant treponemal antigen is the most available EIA tests. The EIA tests has the advantage of being more objective and automated, requiring less work. PCR is most useful where the treponema serologic tests are limited: in primary, early congenital syphilis and neurosyphilis (15,41-44).

The non-treponemal tests are non-reactive in approximately 15 to 25% of primary syphilis (RPR is positive in approximately 85% of primary syphilis and 98% in secondary, while VDRL is positive in 80% and 95%, respectively), hence the diagnosis should be confirmed by using either FTA- ABS or by repeating VDRL after 1 to 2 weeks of the initial negativity of

the first test. In secondary syphilis, virtually all non-treponemal and treponemal tests are reactive; TPPA is positive in 75% and FTA- ABS in 85% in primary syphilis, while both are positive in 100% of the secondary syphilis. Non-reactivity virtually excludes the disease in the secondary phase, in a patient with the mucocutaneous lesions (1-3,5,15,39).

Titters of non-treponemal antibody reflect disease activity – a fourfold decrease suggests adequate therapy, whereas an equal increase indicates activity (treatment failure or reinfection). Within a year, the patient will show test negativity after adequate treatment of primary syphilis and within 2 years of secondary syphilis. Although a small percentage of patients that receives adequate therapy will remain positive, even with low titters (1-3).

About 1% of patients will have false-positive response in non-treponemal tests, although it will rarely exceed 1:8 titters. The antibody reacts with more than 200 non-*T. Pallidum* antigens. It can occur in some viral infections, such as varicella, measles and HIV; some systemic diseases – systemic lupus erythematosus, lymphoma, malaria, tuberculosis, hepatitis and endocarditis. A few patients will have high antibody quantity levels in serum, resulting in excess of free antibodies. This can be interpreted as false-negative – the prozone effect. It can be avoided by serial dilutions of the serum (1-3,15,39,45).

The diagnosis of neurosyphilis can be challenging, as about 25% of patients will present a non-reactive non-treponemal serologic test. Therefore, cerebrospinal fluid CSF examination is crucial for clinical evidence suggesting neurosyphilis. Cell count, protein analysis and VDRL titter are needed. With lymphocytosis, elevated CSF proteins are present. A reactive VDRL is diagnostic of neurosyphilis, but its negativity does not exclude the disease, since only 30% will have this test reactive in neurosyphilis. However, the treponemal test is highly sensitive; a non-reactive test almost always excludes neurosyphilis. Lumbar puncture should be performed in evaluation of late latent syphilis, syphilis of unknown duration, suspicion of neurosyphilis (neurologic signs and symptoms), in late complications other than symptomatic neurosyphilis or suspected treatment failure. In HIV patients, some authors believe that routine CSF examination should be done, since some patients coinfected have shown *T. pallidum* in the CSF even with completed standard treatment for syphilis (1-3, 21-23).

Studies have shown that sexually transmitted diseases (STD), such as syphilis, are associated with an increased risk for HIV acquisition. Initial serologic responses for early syphilis have shown to be equally present in HIV-positive and negative patients. Reports concerning false-positive and false-negative results in HIV-positive patients raise concern on serology. A biopsy to direct visualization and special staining should be considered. CSF evaluation should also be considered, but the magnitude of neurosyphilis presented in this population is unknown. It is difficult to diagnose neurosyphilis in HIV-positive patients, since there are similarities in CSF abnormalities in both syphilis and HIV. Hence clinical evaluation has great effect in appropriateness of this exam (1-3,15).

Early congenital syphilis is generally suspected on maternal serologic test, routinely done in the 3rd trimester and during delivery. Positive tests lead to a more thorough investigation; VDRL and PRP are used to titer the serum. Cord blood should not be used because of low specificity and sensitivity; instead dark field microscopy or fluorescent antibody tests are used to analyse the placenta and umbilical cord. Infants with positivity in serologic tests should also have the CSF analysed; long bone x-rays and liver function tests are indicated (31,32).

Diagnosis is confirmed through direct visualization of the spirochete. Serology in neonates can be false-positive because of transplacental IgG transfer. The positivity can be considered highly probable if neonatal titer is more than four times the maternal titer. Neonates with low titers should be considered with the illness if present with clinical manifestations, since acquired disease can be transmitted through the placenta before development of antibodies. Any positive non-treponemal test should always be confirmed with a specific treponemal test, but no delays on treatment should be considered if neonates are symptomatic or have a high risk for infection (31-33).

3. Treatment

Penicillin is considered the drug of choice for all stages of syphilis. Treatment is based on staging the disease; the longer the course of the disease, the longer the treatment, as *T. pallidum* has a slow bacterial replication.

Penicillin is the only drug used for neurosyphilis, congenital syphilis or during pregnancy. There is no evidence of bacterial resistance to penicillin, although there has been persistence of the disease after full treatment.

3.1 Recommendations with penicillin treatment

Primary or secondary syphilis – single dose of penicillin G benzathine 2.4 million units (IM).

In some countries will indicate 4.8 million units divided in two doses, with 1 week interval, for secondary syphilis is recommended.

Early latent syphilis – single dose of penicillin G benzathine 2.4 million units (IM) .

Late latent syphilis or latent syphilis of unknown duration - penicillin G benzathine 7.2 million units (IM) divided in 3 doses of 2.4 million units each at 1 week intervals.

Asymptomatic neurosyphilis (HIV negative) – penicillin G benzathine 7.2 million units (IM) divided in 3 of 2.4 million units each at 1 week intervals *plus* aqueous penicillin G or procaine penicillin G 9 million units (IM) in doses of 600,000 units/day for 15 days.

Symptomatic neurosyphilis or asymptomatic neurosyphilis (HIV positive) - aqueous penicillin G 2.4 million units (IV) every 4 hours for 10 to 14 days (some will consider adding oral penicillin to complement) *or* Procaine penicillin G 2.4 million (IM) plus probenecid 500 mg orally 4 times per day, both for 10 to 14 days.

Pregnancy - treatment appropriate to the stage of syphilis is recommended.

4. Congenital syphilis

For infants with confirmed or highly probable disease aqueous penicillin G 100,000 to 150,000 units/kg/day, administered a dose of 50,000 units /kg/dose (IV) every 12 hours during the first 7 days of life; every 8 hours thereafter for a total of 10 days *or* procaine penicillin G 50,000 units/kg/dose (IM) daily for 10 days.

Infants with normal physical examination and treponemal serologic titer, the same level or less than fourfold the maternal titer (with mother not treated, inadequately treated or with

less than 4 weeks of treatment) aqueous penicillin G 100,000 to 150,000 units/kg/day administered 50,000 units /kg/dose (IV) every 12 hours during the first 7 days of life; every 8 hours thereafter for a total of 10 days *or* procaine penicillin G 50,000 units/kg/dose (IM) daily for 10 days *or* Penicillin G benzathine 50,000 units/kg-dose (IM) in single dose.

Infants with normal physical examination and treponemal serologic titer at the same level or less than fourfold the maternal titer (mother was treated *adequately* with no signs of reinfection or relapse) penicillin G benzathine 50,000 units/kg-dose (IM) in single dose.

Infants with normal physical examination and treponemal serologic titer at the same level or less than fourfold the maternal titer (with adequate mother treatment and mother's serological titer low and stable) NO treatment is required *or* penicillin G benzathine 50,000 units/kg-dose (IM) in single dose if follow-up is uncertain.

Children with syphilis aqueous penicillin G 200,000 to 300,000 units/kg/day administered 50,000 units/kg every 4 to 6 hours for 10 days (1,2,5,6,8, 14-18,29,31,34,35, 46).

5. Penicillin allergy

Penicillin is the drug of choice for neurosyphilis, congenital syphilis or in pregnant woman; HIV-positive patients should also be considered for this treatment. No other treatment has shown effectiveness as an alternative, consequently desensitization should be done (1,16,47).

5.1 Desensitization

Patients with positive skin tests for penicillin determinants can be desensitized. This procedure is safe and can be performed either IV or orally. The oral procedure is usually safer to perform. Patients should be in hospital for this procedure, since severe IgE mediated allergic reactions can occur. The entire desensitization is completed between 4 to 12 hours, after this period the first dose of penicillin is administered (1-3,16-18,47).

5.2 Alternatives to penicillin

Primary and secondary syphilis, non-pregnant penicillin allergic patients can be treated with alternative drugs.

Ceftriaxone, tetracycline, erythromycin, doxycycline and *azithromycin* have shown effectiveness against treponema in clinical trials, however the recommendation for their usage is restricted as an alternative to penicillin, since new studies have shown treatment failure with some drugs (1,2,5,6,8,14-18,29,31,34,35,46,48).

6. Jarisch-Herxheimer reaction

After treatment initiation, the dying bacteria release inflammatory molecules that can trigger a cytokine cascade, which can lead to this phenomenon. Symptoms include myalgia, fever, headache, tachycardia, increased respiratory rate, hypotension and increased circulating neutrophil count. Also exacerbation of current syphilitic lesions can occur, normally as rash and chancre. This reaction occurs in approximately 50% of patients with primary syphilis, 90% with secondary syphilis and 25% with early latent syphilis. It develops within 2 hours of treatment, with peak temperature at 7 hours and usually clears within 24 hours. The

etiology is unclear, although studies have demonstrated induction of inflammatory mediators by treponemal lipoproteins. Management involves resting and aspirin. Patients should be informed of this possible aggravating side effect. Early labour and foetal distress have been reported as obstetric complications, although syphilis treatment should not be delayed. Obstetric care is mandatory if there is a decreased in foetal movement or uterine contractions are observed (1-3,17,18).

6.1 Surgery

Surgery is considered for cardiovascular lesions to treat aortic and coronary lesions (14,26-29,49,50).

6.2 Syphilis prevention

Sexually transmitted diseases are prevented through safe sex. Patient counselling should also advise not to share needles with others in the case of drug use, and only use clean needles.

Pre-natal care is important to prevent the spread of syphilis. At risk mothers should be screened. Screening is also advocated to city populations with high risks (1,2).

Although circumcision helps to prevent some sexually transmitted diseases, syphilis is not prevented (51).

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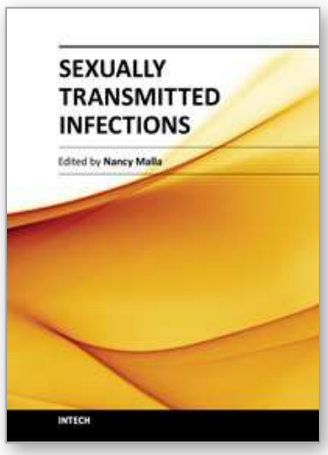

Sexually Transmitted Infections

Edited by Prof. Nancy Malla

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Sexually transmitted infections (STIs) are infections that are spread primarily through person to person sexual contact. There are more than 30 different sexually transmissible bacteria, viruses and parasites. STIs lead to high morbidity and complications. This book entitled as Sexually Transmitted Infections is not a text book but provides useful information for general reference work for physicians, researchers and students interested in the subject. Each chapter is abundant in tips useful to general readers as well. It also includes the Introductory chapter providing an overview with special emphasis on syndromic approach to the management of STIs in clinical setting.

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