www.jcimcr.org

JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Review Article

Open Access, Volume 2

Syphilis and pregnancy: Review

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Received: Apr 16, 2021

Accepted: May 17, 2021

Published: May 20, 2021

Archived: www.jcimcr.org

Abstract

Syphilis is a disease that has not been eradicated in part due to inadequate management of antibiotic therapy which is selected according to the stage of the disease and to the misuse of the type of penicillin. Treatment of this disease should be done to prevent it´s chronic complications, to avoid infecting sexual partners and the fetus in a pregnant woman. Syphilis in pregnancy causes increase in the rate of recurrent abortions and neonatal morbidity and mortality, that´s the main reason why early detection and treatment without delay is extremely important. Pregnancy alters immunity, so the serological diagnosis can provide false positives, with the use of inverse algorithms these results may decrease, by increasing the sensitivity of the tests. Today, after 69 years since the advent of penicillin, it has become the drug of choice for any stage of syphilis and in pregnant women; if the patient has allergy, desensitization is indicated either orally or intravenously and other antibiotic shouldn´t be used because of the security offered by penicillin in the cure rate and in the reduction of congenital syphilis.

Keywords: Syphilis; Pregnancy; Inverse algorithms.

Introduction

Syphilis is as old as Latin America, this is based on the historical reviews of famous people such as Martin Alonso Pinzón who was one of the companions of Cristobal Colon in his quest to find another way to India with the subsequent discovery of Abya Yala who would have contracted syphilis while traveling. Hitler during his last days of life would have experienced encephalitis, dizziness, chest pain, perhaps unequivocal symptoms of tertiary syphilis or like Beethoven where it is speculated that due to his promiscuous behavior he had contracted syphilis and his deafness was the effect of this disease [1].

Since time immemorial, syphilis has been treated based on countless elements that, rather than causing the cure of the disease, caused the destruction of tissues, this is how the use of arsenic, iodides, Salvarsán and mercury is exemplified, the latter being most widely used hence the well-known phrase "A night with Venus leads to a life of mercury" [2].

Epidemiology

According to the World Health Organization, it is estimated that the incidence of syphilis is 12 million new cases each year, of which 90% are concentrated in developing countries. According to figures from Galban E. in << Situation of Syphilis >> in 20 countries of Latin America and the Caribbean, our country had reported in 2006, a total of 4068 distributed cases of 1885 syphilis and 110 of congenital syphilis numbers exceeded only by Argentina, Bolivia and Brazil [3].

According to reports from the Ministry of Public Health in 2007, there are 124 cases of congenital syphilis and 1,438 cases of primary syphilis, both values per 100,000 inhabitants, finding the Sierra region as the one with the highest prevalence [4].

Etiology

Syphilis is a sexually transmitted disease caused by the spirochete Treponema pallidum, a 10 x 0.2 ug gram negative corkscrew-shaped microaerophilic bacterium with a covering called the periplast, which has the ability to become coated with host elements such as IgG, transferrin and glucose hiding from the opsonization of Th1 lymphocytes, hence its systemic inflammatory response, absent in its first stage [5].

Transmission occurs through microabrasions in the vaginal and penile epithelium where the bacteria are inoculated into the epidermis and by the action of hyalorudinase they invade the tissue layers from superficial to deep, helped by their shape, emulating the act of opening the cork of a Cabernet Sauvignon. of 82. At least approximately 57 spirochetes are needed for the inoculum to cause the ulcer or hard chancre [6,7].

Symptoms

The full range of symptoms and signs of syphilis should be classified according to stage.

Primary syphilis

From contagion (sexual intercourse) a period of 10 to 90 days is expected, which is the incubation time for the formation of the genital ulcer, which in 80% of cases in immunocompetent people is unique while in 47% of the cases. Cases can be bilateral or multiple but associated with HIV infection. The ulcer can measure 0.5 to 1.5 cm in diameter with a clean bottom and regular raised edges, it is not painful due to early re-epithelialization before the resolution of the ulcer, allowing the nerve fillets not to be exposed. There is a spontaneous cure after 1 to 6 weeks [10]. The diagnosis is made with direct identification of T. pallidum through dark field microscopy. At this stage the person is considered infective [9].

Secondary syphilis

It appears 3 to 6 weeks after the ulcer and is characterized by the hematogenous dissemination of the treponema thanks to the invasion by tissue layers (thanks to its corkscrew shape and hyalorudinase) generating generalized bodily manifestations such as non-pruritic maculo-papular lesions located on the trunk, extremities, palms of the hands and soles of the feet as well as flat grayish eruptions in the mouth, pharynx, larynx, genitals and anus known as condyloma lata. All these manifestations can be considered as secondary and some of them have eponyms such as the "Biet's Collar" which are a scaly collarette that unites erythematous lesions such as a rosary or the "crown of Venus" where the crusty lesions located on the Hair implantation falls out and leaves whitish spots resembling a crown. At this stage the patient is considered a source of infection [11,15,16].

Thanks to the action of adaptive immunity exemplified by the Th1 and Th2 lymphocytes, they will activate the macrophages, which will eliminate the treponemes and if it does not receive treatment, syphilis will go to the next stage characterized by the absence of symptoms but with positive serology [12,13].

Early latent syphilis

After the elimination of the treponemes by immunity and without antibiotic therapy, syphilis is not eliminated because the patient may no longer have symptoms but the T. pallidum will replicate very slowly or will be deposited in the CSF and aqueous humor. The characteristic of this phase is that there are no florid symptoms but there are positive serological tests (positive VDRL - reactive FTA-Abs). It is called early because the infection occurred within the previous 12 months and the patient is considered infectious [13,16].

Late latent syphilis

It has the same pathophysiological characteristics as the early latent with the difference that the exposure occurred more than 12 months ago, at this stage the person is not considered infectious but the risk of developing tertiary syphilis (aortitis, gums) increases exponentially. Syphilis in latent state, whether early or late, due to its absence of symptoms, there is a greater risk of not being treated and for this reason, a greater risk of transmission to the fetus in a pregnant woman. At this stage the person is not infectious [12,14,16].

It is worth mentioning that there is an additional subclassification known as latent syphilis of unknown duration, the characteristic of which is not knowing the exact time of the possible contagion or less than 1 year or greater than 1 year, so for treatment purposes this subclassification will be handled as if was a late latent stage [14,15].

Tertiary syphilis

According to the CDC 2015, tertiary syphilis should only be considered when there is involvement of the cardiovascular system with endarteritis, aortic aneurysm, coronary stenosis, myocarditis, and gums on the skin or viscera, but neurosyphilis should not be included at this stage. It is an asymptomatic persistent chronic infection that appears 3 to 20 years after infection. At this time patient is not considered infectious. In both late latent and tertiary syphilis, treatment is the same and lasts for 3 weeks due to slow replication of the spirochete [16,17].

Neurosyphilis

During the replication of T. pallidum, its soma has a characteristic in its composition that is the possession of two MCP (methyl accepting chemotaxis protein) type 1 and 2 proteins, which guide the bacteria to locate in the inguinal lymph nodes along with their small size it can cross the blood-brain barrier and infect cerebrospinal fluid, forming neurosyphilis. There may be two types: Asymptomatic where we will only find CSF abnormalities (> 5 white blood cells, > 40-50 mg / dl of proteins, reactive VDRL) 25 and symptomatic, which can be early with basilar meningitis onset (LV involvement, VII, VIII) or meningovascular and late syphilis with paresis together with tabes dorsalis (posterior column demyelination, paresthesias, ataxia, fecal incontinence and impotence) [18,19].

Diagnosis

The certainty of syphilis only based on the clinical picture is very unspecific and sensitive, so we used serological tests.

There are two types of tests:

Direct

Which detect the microorganism itself, are, for example, dark field microscopy, direct immunofluorescence of mono or

polyclonal antibodies specific for T. palludim and the infectivity test in rabbits.

Indirect

Non-treponemal and treponemal tests [20].

We will not concentrate on the tests that are the most frequent in use in our country.

Non-treponemal tests: They are of the IgG or IgM type that target an antigen called Reagin (T. pallidum + cardiolipin-cholesterol-lecithin). They are quantitative tests (titles) that allow us to define if the infection is past or present, effectiveness of the treatment or possible reinfection.

They become positive after 10 to 20 days after the ulcer. Examples of these tests are the VDRL or RPR which have a sensitivity of 78% for primary syphilis, 100% secondary syphilis, 95% and 71% for latent or tertiary syphilis respectively [20,21].

When treating by dilutions, the minimum value of 1:2 is considered to be a reactive test and the variability of the concentrations indicates the effectiveness of the treatment, so if we have a 1:8 VDRL with a following control of 1:34 (elevation of two dilutions or 4 times its value) indicates treatment failure or reinfection, but if the dilution decreases two dilutions or 4 times its value (example decreases from 1:64 to 1:16) it indicates effectiveness of treatment with remission of the disease [23]. In a patient with a history of adequately treated syphilis, an increase of one dilution or 2 times its value can be considered as a result of a variation in the test and has no clinical significance [10-16].

Treponemal tests: They use antibodies directed at the body itself of Treponema pallidum for this reason they are known as confirmatory tests, among the great diversity of tests are FTA Abs (fluorescent anti-treponemal absorbed antibodies), FTA Abs DS (same as FTA Abs but double staining), TPHA (T. palliduim hemagglutination), MHA-TP (T. pallidum Microhemagglutination), Western Blot and TPI (T. pallidum immobilization test). The FTA Abs is an indirect immunofluorescence test that uses T. pallidum obtained from rabbit testes as antigens; its result is only expressed as reactive or non-reactive because it is a qualitative test that becomes positive earlier at 7 or 10 days after the ulcer. 24 Its sensitivity is 84% for primary syphilis and 100% for secondary syphilis as well as latent [21,22,25].

Below we show you all the possible results of the combination of VDRL and FTA Abs with their respective interpretation.

Table 1: Possible results of syphilis diagnostic tests and their interpretation (Taken and adapted from the Centers for Disease Control. Sexually Transmitted Diseases. Treatment Guidelines 2006) [10].

Test/result	FTA Abs negative	FTA Abs positive
VDRL negative	- No Sifilis - Syphilis in incubation period - Very early primary syphilis since FTA Abs positive 7-10 days and VDRL 10-20 days after the ulcer	- Very early primary syphilis since FTA Abs positive 7-10 days and VDRL 10-20 days after the ulcer - Secondary syphilis with prozone phenomenon, which is the excessive amount of Ac or Ag without formation of the Ag-Ac complex - Syphilis already treated - Falsely negative VDRL or FTA Abs falsely positive for HIV infection or immunocompromised
VDRL positive	- False positive VDRL such as pregnancy, old age, autoimmune diseases, or vaccines - FTA Abs falsely negative in HIV infection	- Syphilis diagnosis - Lyme's desease - Endemic treponemal non-sexually transmitted disease such as Yaws, begel or pinto

Treatment

As mentioned above, syphilis has been a very old disease and the forms of treatment have varied enormously without showing adequate results until the advent of the antibiotic era where countless drugs were used that promised adequate effectiveness until Steven J. Norris in 1988 compared all these drugs, finding that penicillin G had the lowest MIC (minimum inhibitory concentration) with only 0.0005 ug/ml and a MBC (minimum bactericidal concentration) of 0.0025, surpassing erythromycin, tetracycline and spectinomycin [26].

After this, multiple studies were conducted which concluded that Penicillin G is the P drug for the treatment of syphilis. It should be noted that after receiving the dose determined for each stage of syphilis, a control should be done every 6 and 12 months in primary and secondary syphilis, in addition to a control every 6,12 and 24 months in case of early or late latent syphilis [10,16].

Penicillin is an antibiotic formed by an active nucleus called 6-aminopenicillanic acid. Within the group of natural penicillins are type G is the only one for parenteral administration and type V which is only for oral administration as it is resistant to degradation by gastric acids, its mechanism of action is the selective inhibition of transpeptidation for the synthesis of murein, a fundamental element in the stability of the bacterial cell membrane [27].

There are several types of penicillin G.

Benzathine penicillin G: Whose bioavailability is 30 days, it is used as a treatment for syphilis because its mechanism of action is achieved at low levels but for prolonged periods [28,29].

Crystalline or aqueous penicillin G: Treatment of neurosyphilis by better penetration to the meninges, generating rapid effects at a high serum concentration and it is only for intravenous administration [28].

Procaine penicillin G: Identical meningeal penetration as crystalline, only the effect persists for hours and is only for intramuscular use when the intravenous route is not accepted or cannot be used [27,28].

Jarisch-herxheimer reaction

After placing the penicillin, a sudden death of thousands of spirochetes can occur due to the inhibition of transpeptidation in the synthesis of the bacterial cell wall that will cause an increase in intracellular pressure, generating the lysis of the bac-

Table 2: Treatment by stage of syphilis. (Taken and adapted from the Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2015.) [10].

Syphilis Stage	Man or non-pregnant woman	Pregnant woman	Possible infectious or infected partners
Primary	Benzathine penicillin G 2400000 IU intramuscular single dose or Doxycycline 100 mg orally every 12 hours for 14 days Tetracycillin 500 mg every 6 hours for 14 days Ceftriaxone 1gr intramuscular or intravenous every day for 10 days	Benzathine penicillin G 2,400,000 IU intramuscular single dose (a second dose could be added in a week in patients at risk)	3 previous months
Secundary	See primary syphilis	See primary syphilis	6 previous months
Early latent syphilis	See primary syphilis	See primary syphilis	12 previous months
Late latent syphilis	Benzathine penicillin G 2,400,000 IU intramuscular every week for 3 weeks or Doxycycline 100 mg orally every 12 hours for 4 weeks Tetracycillin 500 mg every 6 hours for 4 weeks	Benzathine penicillin G 2,400,000 IU intramuscular every week for 3 weeks	More than 12 previous months
Latent syphilis of unknown duration	See late latent syphilis	See late latent syphilis	Couple with VDRL> 1:32 consider treatment
Tertiary syphilis	See late latent syphilis	See late latent syphilis	See late latent syphilis
Neurosífilis	Crystalline penicillin G 18-24 million IU intravenous daily divided 3-4 million IU every 4 hours for 14 days or Procaine penicillin G 2400000 IU intramuscular + Probenecid 500 mg orally every 6 hours for 14 days	Crystalline penicillin G 18-24 million IU intravenous daily divided 3-4 million IU every 4 hours for 14 days or Procaine penicillin G 2400000 IU intramuscular + Probenecid 500 mg orally every 6 hours for 14 days	See late latent syphilis

teria with the consequent release of LPS (lipopolysaccharides) into the bloodstream with the activation of endogenous pyrogens (IL6, IL1, TNF, INF) causing the exacerbation of the signs and symptoms of syphilis within 24 hours (2-8 h more frequently). In a pregnant woman this increase in prostaglandins will produce premature labor and risk of loss of fetal well-being [10,28].

In the following section we present the treatment of the different stages of syphilis according to the CDC 2015 Sexually Transmitted Diseases Guide [16].

Congenital syphilis

Transmission to the fetus by active disease occurs when RPR> 1/8 or 5 years without treatment, the passage of T. pallidum occurs after 12-16 weeks generating intrafetal infection that can be reflected by obstetric examination as hepatomegaly, hydrops and anemia.

The risk of fetal infection was categorized as 50% in primary syphilis, 67% secondary syphilis, and 83% in early latent syphilis, hence the importance of treatment in the asymptomatic phase [16,30].

The CDC recommends maternal screening for syphilis in early pregnancy and in the third trimester, while the WHO recommends early in pregnancy and after 20 weeks [30].

Treatment for definite or highly probable congenital syphilis is Crystalline penicillin 100,000 - 150,000 IU administered 50,000 IU / kg / dose IV every 12 hours for the first 7 days then every 8 hours for a total of 10 days [10].

Allergic to penicillin

It has been determined that once there is an exposure to an allergen and as a consequence a severe anaphylaxis according to the theory of tolerance, the person would stop being allergic but this can occur in 90% of cases, but in approximately 10% of cases. Individuals with a history of severe allergic reactions to penicillin remain allergic because penicillin-specific IgE decreases its expression.

It has been shown that the most effective drug in syphilis is penicillin regardless of the patient's allergic status or not, therefore, if we are facing this scenario, desensitization should be carried out, it can be oral or intravenous [16].

The oral form uses a Penicillin V potassium in a concentration of 400000IU/5ml, we use three solutions, the first consisting of 1 ml of Penicillin V potassium + 79 ml of water and we make them ingest 16 ml for 5 times every 15 min, the second solution With 2 ml of penicillin + 14 ml of water, take 5 ml every 15 min for 5 occasions and the third, undiluted penicillin, take 1 ml every 15 min for 5 occasions; thus, the patient is desensitized with the precaution of maintaining the therapeutic dose without interruption. The intravenous form has the same principle where the dose is doubled every 15 min using Dextrose in 5% water [31].

Algorithms

For dozens of years, diagnostic algorithms have been used for the management of syphilis, the most recommended is the traditional one where a non-treponemal test is used as screening and if this is reactive, it will be confirmed with a treponemal test. Reverse algorithms have been introduced 6 years ago in order to eliminate the low Positive Predictive Value that the traditional algorithm had, starting with a treponemal test, then a non-treponemal test and ending with a treponemal test other than the initial one. There is a study carried out in 5 laboratories in the USA where they verified the percentage of discordance

between the two treponemal results and it was determined that there were 31.6% false positives with the use of the reverse algorithm [32,33].

According to the CDC 2015, it is recommended to perform either the traditional algorithm or the reverse, taking care to use two different treponemal tests when the latter is put into practice [32].

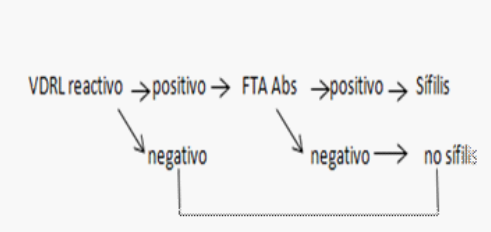

Table 3: Traditional algorithm scheme (Taken and modified from CDC. Syphilis testing algorithms using treponemal tests for initial screening 2008).

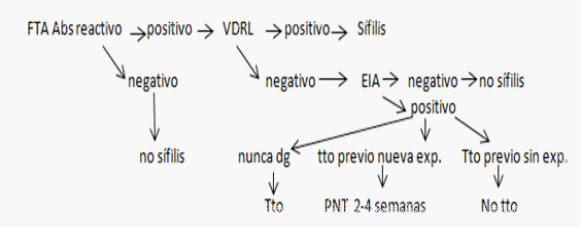

Table 4: Inverse algorithm scheme (Taken and modified from CDC. Syphilis testing algorithms using treponemal tests for initial screening 2008.

Conclusions

The management of syphilis is based on determining the stage of the disease since the duration of treatment depends on that, the drug of choice based on multiple scientific studies is benzathine penicillin G, in patients who have an allergy to this drug the desensitization and no other antibiotics are recommended. Prompt treatment of syphilis during pregnancy lowers the risk of congenital syphilis. VDRL is the only test that shows us the effectiveness of the treatment or a possible reinfection through its titration. Similar utility in the diagnosis of syphilis during pregnancy exhibits the traditional algorithm as the reverse.

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